Drug Utilisation Patterns and Factors Influencing Prescribing Choice of Antidiabetic Drugs Among Patients with Type 2 Diabetes Mellitus in Scotland, 2010-2020: a population-based, multi-study project

FATEMA MOHAMMAD ZAKI KHALED MAHMOUD

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Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS)

The University of Strathclyde

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Declaration

This thesis is the result of the author's original research. It composed by the author and has not been previously submitted for examination which has led to award of the degree.

Signed:

Date:

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"In the name of Allah, the most Gracious, the most Merciful"

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Publications and Poster Presentation

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2. Mahmoud, F., Mullen, A., Mueller, T., Yasin, H., Abutheraa, N., & Kurdi, A. (2022). The Association of Patients' demographics with glucose-lowering drugs prescription among patients with type 2 diabetes mellitus: a systematic review and meta-analysis of observational studies. Poster presented at the ICPE conference, Copenhagen, Denmark.

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List of abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetic Association
ADDs	Antidiabetic Drugs
ADP	Antidiabetic Drug Prescribing
AGEs	Advanced Glycation End Products
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
CAD	Coronary Artery Disease
CCB	Calcium Channel Blockers
CCI	Charlson comorbidity index
CHI	Community Health Index
CHIAG	Community Health Index Advisory Group
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Collaboration
CPRD	Clinical Practice Research Datalink
CRD	Chronic Renal Disease
CVDs	Cardiovascular Diseases
DARTS	Diabetes Audit and Research in Tayside Study
DDDs	Defined Daily Doses
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
DN	Diabetic Neuropathy
DPP4-Is	Dipeptidyl Peptidase-4 Inhibitors
DQA	Data Quality Assurance
DR	Diabetic Retinopathy
DUR	Drug Utilisation Research
ED	Erectile Dysfunction
eDRIS	Electronic Data Research and Innovation Service
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESRC	Economic and Social Research Council
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FFA	Free Fatty Acid
FH	Family History
FM	Family Medicine
GDM	Gestational DM
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLP1-RA	GLP-1 Receptor Agonists
GPs	General Practitioners
GPs	General Practitioners

GROS	General Register Office for Scotland
HDL	High-Density Lipoprotein
HF	Heart Failure
HSC-PBPP	Public Benefit and Privacy Panel for Health and Social Care
HTN	Hypertension
ICD-10	International Classification of Disease codes, 10th edition
IDF	International Diabetes Federation
IG	Information Governance
IGT	Impaired Glucose Tolerance
IHD	Ischemic Heart Disease
IR	Insulin Resistance
IRS-1	Insulin Receptor Substrate 1
ISD	Information Services Division
LDL	low-Density Lipoprotein
LOCF	Last Observation Carried Forward
LRT	Likelihood Ratio
MA	Meta-analysis
MAR	Missing at Random
MCAR	Missing Completely at Random
MCCD	Medical Certificate of the Cause of Death
MCN	Managed Clinical Network
Mesh	Medical Subject Heading
MI	Myocardial Infarction
MNAR	Missing Not at Random
MODY	Maturity-onset Diabetes of the Young
NHS	National Health Service
NHS NSS	NHS National Services Scotland
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NRS	National Records of Scotland
OPCS-4	Office of Population Censuses and Surveys procedural codes, 4th revision
OR	Odds Ratio
P&CFS	Practitioner & Counter Fraud Services
PAC	Privacy Advisory Committee
PHS	Public Health Scotland
PIA	Privacy Impact Assessment
PICO	Population, Intervention, Comparison, and Outcomes
PIS	Prescribing Information System
PMM	Predictive Mean Matching
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Review
PVD	Peripheral Arterial Disease
RCTs	Randomised Controlled Trials
ROS	Reactive Oxygen Species
RVE	Robust Variance Estimation
RWD	Real-World Data

SCI-Diabetes	Scottish Care Information-Diabetes
SE	Standard Error
SGLT2	Sodium-Glucose Transporter 2
SGLT2-I	SGLT2- Inhibitor
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple deprivation
SIMD-D	SIMD Decile
SIMD-Q	SIMD Quintile
SIPBS	Strathclyde Institute of Pharmacy and Biomedical Sciences
SLC47A1	Solute Carrier Family 47 Member 1
SLCO1B1	Solute Carrier Organic Anion Transporter Family Member 1B1
SMBG	Self-Monitoring of Blood Glucose
SMD	Standardised Mean Difference
SMR	Scottish Morbidity Records
SMR00	Scottish Morbidity Records Outpatient Attendance dataset
SMR01	Scottish Morbidity Records General/Acute Inpatient and Day Case dataset
SR	Systematic Review
SU	Sulfonylurea
T21DM	Type 1 DM
T2DM	Type 2 DM
TG	Triglyceride
TZDs	Thiazolidinediones
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
UR	Urban-rural
USA	United State
Vd	Standard Deviation Variance
VIF	Variance Inflation Factor
VPN	Virtual Private Network
WHO	World Health Organization

Abstract

Introduction: Multiple pharmacological treatment options are currently available for managing type 2 diabetes mellitus (T2DM) with variable safety and extra-glycaemic profiles. However, clinical guidelines mostly do not have a clear treatment algorithm for the optimal selection of antidiabetic drugs (ADDs) as alternative first-line and add-on therapy.

Methods: This thesis comprised multiple studies. First, a systematic review and meta-analyses (SRMA) of observational studies investigating factors associated with prescribing ADDs was conducted to identify the gap in this area of research. Second, retrospective cohort studies were performed using linked routinely collected data of patients with T2DM who received ADD between Jan/2010 and Dec/2020 to describe the ADD prescribing patterns and factors influencing ADD prescribing/selection at drug initiation and first-intensification. Data were analysed using descriptive statistics and multinominal logistic regression as appropriate.

Results: The identified factors in the SRMA were mapped into four categories; demographic, socioeconomic, clinical, and prescriber factors. Patient age, sex, baseline HbA1c, body mass index (BMI), and kidney problems were the most frequently studied factors. Between 2010 and 2019, 145909 new ADD users with T2DM were identified in Scotland, with around 91% (N=132382) of patients receiving a single ADD. Of those, metformin was the most often prescribed monotherapy (89.7%). Of 145909 new ADD users, 50731 patients were started on metformin (N=46730) or SU (N=4001) monotherapy and intensified with additional ADD(s) between Jan/2010 and Dec/2020. Most initial-metformin (98.4%) and initial-SU users (97.3%) were intensified with single ADD. SU (48.3%) was the most common first-intensifying monotherapy after initial metformin but was replaced by SGLT2-I in 2019. Metformin was the most frequently added monotherapy to initial SU (75%). Nevertheless, there was a significant increase in prescribing newer antidiabetic classes (SGLT2-I, DPP4-I), opposite to older ones (SU, insulin, thiazolidinedione). Moreover, multiple clinical (e.g., HbA1c, BMI, etc.) and non-clinical (e.g., age, sex) factors were associated with ADD selection, yet the extent and direction of association varied by antidiabetic class.

Conclusions: An overall increase in prescribing newer antidiabetic classes compared to older ones was observed. Some identified factors associated with the prescribing choice were consistent with the variability in drug characteristics, but others (particularly baseline cardiovascular disease) showed inconsistent results.

Thesis structure

This thesis describes the prescribing pattern and factors influencing the prescribing choice of antidiabetic drugs for patients diagnosed with type 2 diabetes mellitus at drug initiation and the stage of first drug intensification in Scotland using multiple national record-linked datasets. Additionally, it summarises the published literature that examined factors associated with antidiabetic medication prescribing using a systematic review and meta-analysis approach. This thesis consists of six chapters:

Chapter one: provides a clinical background on type 2 diabetes mellitus and discusses the principles of drug utilisation research and its application in the area of antidiabetic drugs.

Chapter two: is a systematic review and meta-analysis that summarises, classifies, and quantifies factors associated with antidiabetic drug prescribing, both at the initiation and intensification stages.

Chapter three: describes the technical process in terms of data request, access, preparation, and cleaning and provides details about data sources and variables used in this project.

Chapters four and five: present prescribing patterns of antidiabetic drugs among patients diagnosed with type 2 diabetes mellitus across Scotland over time and explore factors associated with the selection of antidiabetic drugs at both drug initiation (Chapter 4) and stage of first intensification (Chapter 5). They also describe the baseline characteristics of patients diagnosed with type 2 diabetes who received one or more antidiabetic drugs in Scotland at both stages of treatment.

Chapter 6: summarises the findings and discusses the strength and limitations of this work and indicates its implication on clinical practice and future research.

1 Chapter 1: Background

The purpose of this chapter is to provide a clinical background relevant to the studied disease of interest and discuss the principles of drug utilisation research (DUR). It begins with the disease definition and epidemiology, then briefly summarises diabetes pathophysiology, its related risk factors, and the potential consequences of the disease. In addition, it describes the management of type 2 diabetes, including details about the available antidiabetic drugs (ADDs) as well as the treatment algorithms described in the current clinical guidelines with a specific focus on the recent evidence related to the newer ADDs. Moreover, it introduces the principles of DUR and its current application on ADDs.

1.1 Definition of diabetes mellitus

Diabetes mellitus (DM) is derived from a Greek word, Diabetes, for a siphon which means to pass through as a description of passing much urine, and a Latin word, mellitus, for sweet *(Sapra and Bhandari, 2020).* DM is a common chronic progressive metabolic disorder characterised primarily by persistent elevation in serum glucose level as a consequence of decreasing insulin production and/or increasing insulin resistance, causing impairment in the carbohydrate, protein, and fat metabolism *(Kharroubi and Darwish, 2015).*

1.2 Classification and epidemiology of diabetes mellitus

DM is classified into several categories; type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (GDM), and other types of diabetes of specific causes such as maturity-onset diabetes of the young (MODY), disease of the exocrine pancreas, and drug or chemical induced DM *(American Diabetes Association, 2019).* The two main types of diabetes are T1DM which accounts for around 5-10% of patients with DM, and T2DM, which occurs in the majority of diabetic individuals (~90%) *(Sapra and Bhandari, 2020, Kharroubi and Darwish, 2015).*

DM is a disease that affects all nations, according to the International Diabetes Federation (IDF). In 2021, around 537 million adults aged 20-79 years were

diagnosed with diabetes worldwide, which is projected to rise to 643 million by 2030 and to 783 million by 2045 *(International Diabetes Federation, 2021, Sun et al., 2021).* Additionally, it was estimated that globally, around 240 million people living with diabetes are undiagnosed, and 541 million are expected to have impaired glucose tolerance (IGT) in 2021 *(International Diabetes Federation, 2021)*. Nonetheless, the prevalence of diabetes varies across age, sex, geographical region, and world income level. Generally, the prevalence of diabetes increases by age; in which the lowest prevalence was noticed among the 20-24 years age group (2.2% in 2021), and the highest prevalence was among people aged 75-79 years (24.0% in 2021) *(Sun et al., 2021).* Also, referring to the IDF report 2021, diabetes was slightly more prevalent among men than women (10.8% vs. 10.2% aged 20-79 years) *(Sun et al., 2021).*

Regarding the regional differences according to the IDF regions classification, at age 20-79 years, the highest comparative prevalence was observed in the Middle East and North Africa (MENA) Region, while it was lowest in the Africa Region (18.1% vs. 5.3%) *(Sun et al., 2021).* Plus, it was higher in urban than rural areas (12.1% vs. 8.3%). About 81% of diabetic people live in low- and middle-income countries, yet the greatest relative increase in the prevalence of diabetes between 2021 and 2045 is estimated to be in the middle-income countries compared to the high- and low-income ones (21.1% vs. 12.2% and 11.9%, respectively) *(Sun et al., 2021).* Recent statistics showed that 4.9 million people were diagnosed with DM in the United Kingdom (UK), where the number of patients has doubled over the past 15 years, with around 90% of patients having T2DM *(Diabetes UK, 2021).* The number of individuals with diabetes in the UK is expected to be 5.5 million by 2030 if no actions are implemented *(Diabetes UK, 2021).* In Scotland alone, the Scottish diabetes survey reported 317,128 patients living with DM in 2020, of which 87.8%(278,239) had T2DM *(The Scottish Diabetes Data Group, 2020).*

Diabetes is considered a major cause of mortality, which accounted for 12.2% of global all-cause mortality in 2021 among people aged 20-79 years, excluding the risk associated with the COVID-19 pandemic *(International Diabetes Federation, 2021).*

Diabetes also has an impact on global health expenditure; for instance, the global diabetes costs for adults aged 20-79 years have increased from USD 232 billion in 2007 to USD 966 billion in 2021 *(International Diabetes Federation, 2021)*. In the UK, at least 10% of the entire annual budget (around £10 billion) of the National Health Service (NHS) in both England and Scotland was spent on diabetes, and 80% of the diabetes budget was spent on treatment of diabetes complications *(Diabetes UK, 2021, Colhoun and McKnight, 2020).*

1.3 Pathogenesis of T2DM

The main difference between T1DM and T2DM is the underlying cause. T1DM is mainly resulted from complete insulin deficiency due to autoimmune destruction of the pancreatic β-cells of Langerhans; on the other hand, the cause of T2DM is related to the development of insulin resistance with variable degrees of β-cell dysfunction based on the stage of the disease *(American Diabetes Association, 2019).*

Post glucose ingestion, any disturbance in the balance between glucose production and uptake mostly causes hyperglycaemia. Under normal circumstances, to maintain a normal glucose level, this elevation in blood glucose concentration results in, firstly, inhibiting endogenous glucose production and increasing its uptake by the muscle in a dose-dependent manner independent from insulin secretion *(Cersosimo et al., 2018b)*. Secondly, stimulating insulin secretion from the pancreatic β-cell, which has several insulin-mediated actions, including; 1- enhances glucose uptake by the liver, gut, and peripheral tissues, 2- suppresses endogenous glucose synthesis by inhibiting glucagon, a peptide hormone secreted from pancreatic alpha cells which stimulates glucose production by the liver through glycogenolysis and gluconeogenesis, and 3- inhibits lipolysis (fat metabolism) leading to a lower level of free fatty acid (FFA) which causes by itself inhibition in glucose production and stimulation of glucose uptake by the muscle *(Cersosimo et al., 2018b)*. Defects in any step of this process contribute to developing hyperglycaemia and T2DM. Accordingly, multiple organs and tissues play a role in the pathogenesis of hyperglycaemia and T2DM, including the pancreas, liver, muscle, adipose tissue, brain, gut, and kidney, as demonstrated in Figure 1.1

(Cornell, 2015). All organs and tissues contribute to the development of the disease by intermediating insulin resistance and/or insulin deficiency. The role of insulin resistance, insulin deficiency, and other factors in the development of T2DM are discussed below.

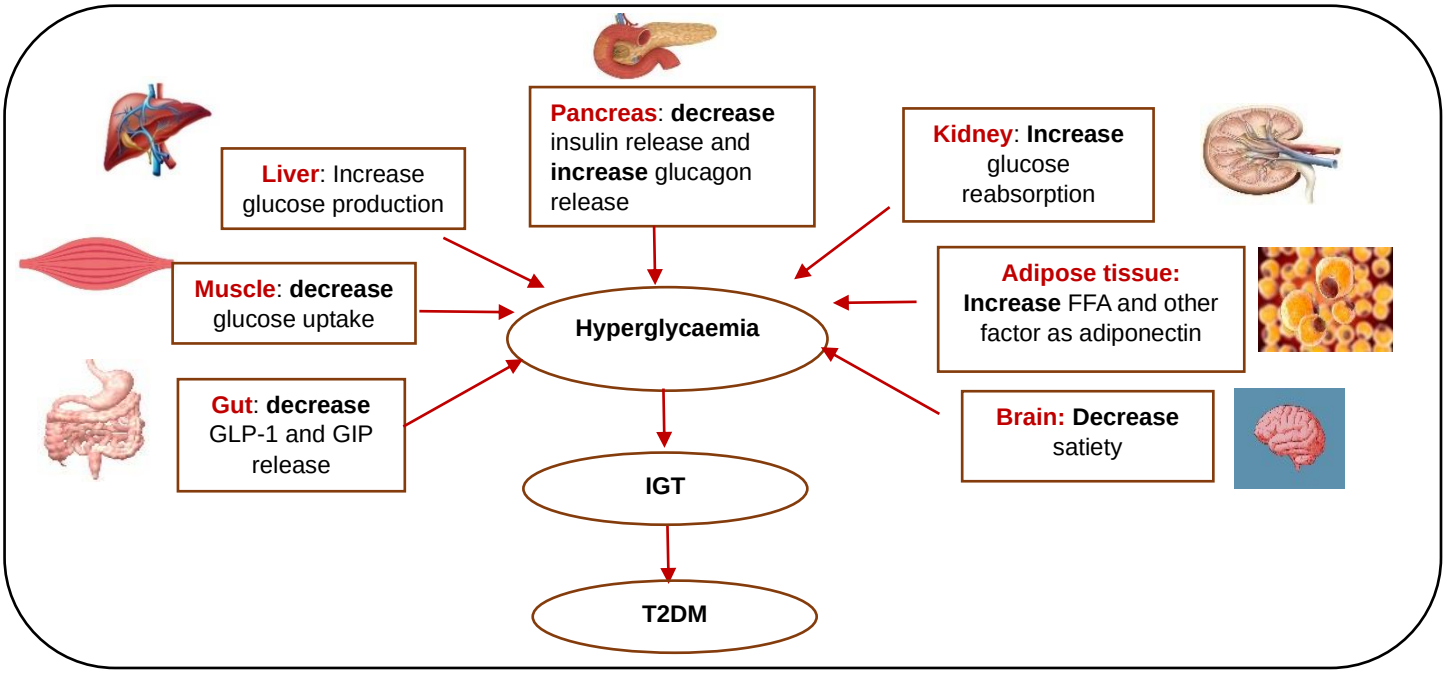

Figure 1.1: Schematic presentation of the pathogenesis of hyperglycaemia and type 2 diabetes. IGT; impaired glucose tolerance, T2DM; type 2 diabetes mellitus, FFA; free fatty acid, GLP-1; glucagon-like peptide-1, GIP; glucose-dependent insulinotropic polypeptide.

1.3.1 Insulin resistance

Insulin resistance represents the impaired ability of certain tissues to uptake glucose and suppress endogenous glucose production in response to insulin release at a particular concentration *(Cersosimo et al., 2018b)*. Initially, after the start of Insulin resistance, several mediators are stimulated as a response to reduced insulin sensitivity, including adipose-related hormones, FFA, and gut-derived glucagon-like peptide-1 (GLP-1), which in turn stimulate the pancreatic β-cells to release more insulin thus maintaining an euglycaemic (Normal glucose) state *(Pilar Durruty, 2019, Cersosimo et al., 2018b).* However, this compensatory mechanism progressively worsens over time which initially causes a slight elevation in plasma glucose level

leading to the development of IGT and eventually T2DM when the glucose level is constantly elevated *(Cersosimo et al., 2018b, Pilar Durruty, 2019)*. Prediabetes or IGT usually starts several years before the development of T2DM *(Cersosimo et al., 2018b, Pilar Durruty, 2019).*

Insulin resistance is mainly manifested in the liver, muscle, and adipose tissue. Usually, body muscle is responsible for controlling the postprandial or post-meal glucose level by increasing glucose uptake after carbohydrate intake to be stored as glycogen by activating glycogen synthase enzyme in response to insulin release *(Pilar Durruty, 2019, Cersosimo et al., 2018b)*, while the liver mainly controls fasting glucose level, which is responsible for providing glucose supply overnight to meet the metabolic need of the brain and other organs. In T2DM, the liver produces more glucose than normal due to insulin resistance, increasing the supply of glucose precursors (e.g., lactate), increasing FFA oxidations, and increasing hepatic enzymes activity *(Pilar Durruty, 2019, Cersosimo et al., 2018b).* All eventually cause hyperglycaemia; the contribution of each organ in the development of hyperglycaemia is illustrated in Figure 1.2.

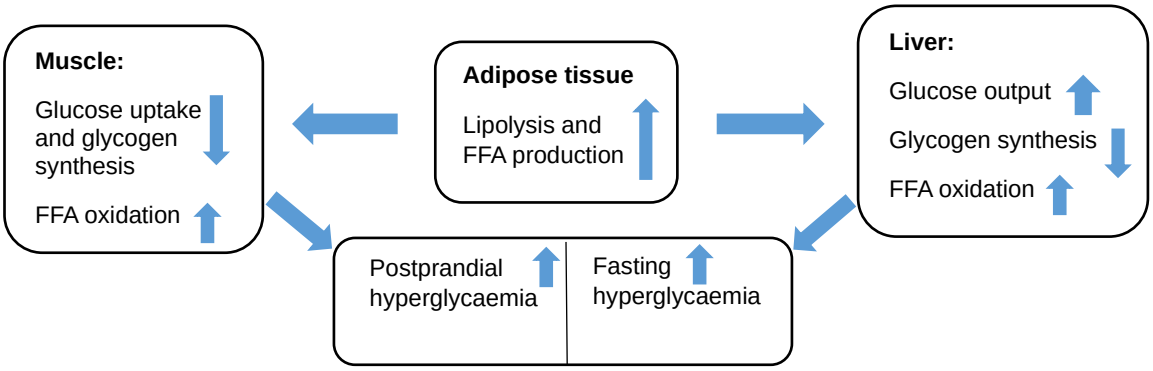

Figure 1.2: The role of insulin resistance in the liver, muscle, and adipose tissue in the development of hyperglycaemia. FFA; free fatty acid.

1.3.2 Pancreatic β-cell dysfunction

Insulin is secreted from β-cells islets of Langerhans in biphasic manners; the first is the peak lasting for about 10 minutes, followed by a plateau phase lasting 2-3 hours. Both phases are reduced in T2DM *(Pilar Durruty, 2019, Meier and Bonadonna, 2013).* This reduction in insulin release could be related to abnormalities in the β-cells' function and mass *(Meier and Bonadonna, 2013).* These abnormalities could have resulted from two underlying causes: firstly, cellular apoptosis due to glucotoxicity (persistent elevation in glucose level), lipotoxicity (elevation in FFA), and elevation in the islets amyloid polypeptide (Amylin), which released concomitantly with insulin and its accumulation promotes apoptosis. Secondly, the occurrence of the initial cellular defect increases the demand on the remaining β-cells leading to more cellular exhaustion, creating a vicious circle *(Meier and Bonadonna, 2013, Pilar Durruty, 2019).* The initial defect in the β-cell function is correlated to multiple factors, including obesity, gene defects, and age *(Cornell, 2015, Meier and Bonadonna, 2013)*. The progressive decline in insulin secretion is the main factor that mediates the transition of IGT to T2DM.

1.3.3 Others

Other factors contribute to the development of T2DM, including the reduction in the secretion of incretin hormones from the gut like GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are released after a meal, and they are responsible for stimulating around 60% of insulin release and inhibiting glucagon secretion *(Meier and Bonadonna, 2013).* Furthermore, hyperglycaemia could be driven by an elevation in the glucagon level because of the reduction in incretin hormones and the development of alpha-cells insulin resistance, which make glucagon less responsive to the insulin inhibitory effects *(Pilar Durruty, 2019).* Additionally, glucose reabsorption by the kidney into the circulation through sodium-glucose transporter 2 (SGLT2) in T2DM exceeds the normal situation *(Meier and Bonadonna, 2013).*

1.4 Risk factors for T2DM

The identification of disease risk factors is vital for improving disease screening and addressing appropriate measures to prevent the development of the disease and its associated complications. Each cause of T2DM, insulin resistance and insulin deficiency, results from a complex interaction of several genetic and environmental risk factors; the greater number of risk factors an individual has, the more likelihood to develop T2DM *(Olokoba et al., 2012, Bi et al., 2012)*. The impact of those risk factors is summarised in Table 1.1 *(Olokoba et al., 2012, Bi et al., 2012, American Diabetes Association, 2019).* Although some factors are not modifiable – e.g., genetic factors – many can be modified and controlled, particularly lifestyle-related ones *(Bi et al., 2012, Olokoba et al., 2012)*

Table 1.1: Risk factors of type 2 diabetes mellitus.

Lifestyle factors	Description
1- Physical inactivity	Indirect (negative) association (dose-dependent)
2- Cigarette smoking	Direct (positive) association (dose-dependent)
3- Obesity	Overweight/obese; BMI ≥ 25kg/m2
4- Alcohol consumption	Heavy consumption ≥ 50g/day (U-shaped association)
5- Diet	High energy Western diet (high in refined carbohydrates, salts, and trans-saturated fat and low in fibre) is associated with T2DM risk
Genetic	
1- Ethnicity	African-Caribbean and South Asians in the UK Non-Hispanic black population and Hispanic Americans in the USA
2- Family history	Diagnosis in 1st-degree relatives
Others	
1- Medical conditions	Hypertension, metabolic syndrome, Cushing syndrome, thyrotoxicosis, chronic pancreatitis, pheochromocytoma, polycystic ovary syndrome.
2- Medications	Antipsychotic, anti-infective (as fluoroquinolone), antihypertensive (as beta blocker, thiazide diuretics), glucocorticoids.
3- Age	The risk increases with increasing age

1.4.1 Lifestyle factors

The increasing prevalence of T2DM globally in a short term suggests the significant role of environmental factors since genes have not changed over this short period. The most striking factors are low physical activity, consuming an energy-dense diet, and obesity *(Kolb and Martin, 2017).*

- Diet:

Consuming a Western diet, characterised by a high content of refined carbohydrates, salts, and trans-saturated fat and low in fibre, increases the risk of T2DM directly and indirectly by promoting obesity. In contrast, the intake of some minerals and micronutrients such as vitamin D, anti-oxidants, and magnesium are associated with a lower risk of T2DM *(Mambiya et al., 2019).*

- Physical activity:

A sedentary lifestyle means spending much time doing activities that require consuming low energy, such as watching television (TV) and sitting while working or communicating *(Rockette-Wagner et al., 2015).* Such behaviours, particularly watching TV, are significantly associated with the incidence of T2DM. According to the 2017 report from the British Heart Foundation, around 20 million adults in the UK were physically inactive. Only 67% of males and 55% of females met the recommended physical activity level (at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity activity per week) in England and Scotland *(Diabetes UK, 2021).* A meta-analysis (MA) showed that a longer duration of sedentary time was associated with a 112% higher risk of diabetes *(Wilmot et al., 2012).* On the other hand, doing physical activity has an overall non-linear inverse association with diabetes incidence at all levels of activity; more vigorous activities were linked with a greater reduction in diabetes risk (26% risk reduction with 150 min/week of moderate activity vs. 36% with 300 min/week) *(Smith et al., 2016).*

- Obesity:

Obesity is defined as having a body mass index (BMI, kg/m^2) value equal to or greater than 30 kg/m^2. Obesity is a key risk factor in developing metabolic diseases,

primarily T2DM, in which around 86% of patients with T2DM are obese or overweight *(Saboor Aftab SA, 2014)*. A study revealed that an increase in body weight by 1 kg per year for ten years is related to a 49% higher risk of T2DM in the following ten years (Saboor Aftab SA, 2014). According to the 2017 OECD report, the UK was rated amongst the 10% of countries with the highest rates of obesity *(Baker, 2019).* In Scotland, 29% of people aged ≥ 16 years were overweight or obese *(Baker, 2019)*.

The mechanism that links obesity with T2DM is not completely understood. Obesity is associated with insulin resistance that is initially compensated by β-cell secretion of an adequate amount of insulin to overcome the reduction in insulin sensitivity and maintain a normal glucose level *(Al-Goblan et al., 2014)*. As described previously, T2DM develops when β-cells are no longer able to do this compensation *(Al-Goblan et al., 2014).* So, the development of T2DM by obesity requires the presence of β-cell dysfunction *(Al-Goblan et al., 2014)*.

Furthermore, that could be linked to several factors, including *(Al-Goblan et al., 2014)*:

1- The release of more hormones, cytokines, adiponectin, leptin, pro-inflammatory mediators, and FFA from adipose tissues in obese individuals to control body metabolism; all contribute to the development of insulin resistance.
2- The pattern of fat distribution: female type or central obesity is more linked to insulin resistance, and it is associated with higher secretion of adiponectin and FFA.
3- The progressive decline in β-cells that is mediated by genetic susceptibility, glucotoxicity, and lipotoxicity.

- Other lifestyle risk factors:

Smoking has a dose-dependent relation with the risk of T2DM, in which current smokers have a 49% higher risk of developing T2DM compared to non-smokers *(Bi et al., 2012).* This association can be explained partially by the impact of nicotine on β-cell dysfunction and cell apoptosis as well as the tendency of a smoker to gain

weight when quitting, especially in the abdominal area, which is an important mediator of T2DM *(Bi et al., 2012)*.

A MA showed that alcohol consumption had a U-shaped association with T2DM; heavy alcohol consumption (50 g/day) was associated with a higher risk of T2DM, while moderate alcohol intake reduced the incidence of T2DM by 30% (22g/day for men and 24 g/day for women) *(Baliunas et al., 2009).* The association of moderate alcohol intake with a lower incidence of T2DM could be mediated by promoting insulin sensitivity, reducing inflammatory mediators, reducing low-density lipoprotein (LDL), and increasing high-density lipoprotein (HDL) *(Pietraszek et al., 2010).* In contrast, heavy intake may increase the risk of T2DM by causing a defect in the liver function, increasing the risk of pancreatitis, and increasing the intake of energy diet, promoting obesity; all are key mediators of T2DM *(Bi et al., 2012).*

1.4.2 Genetic factors

Environmental factors play a significant role in the development of T2DM. Nevertheless, it was found that individuals with the same environmental exposure have a different tendency to develop T2DM, suggesting a strong genetic component of T2DM as indicated in family and twin studies *(Omar, 2013, Mambiya et al., 2019).* For example, having one parent with T2DM increases the risk of having the disease by 40%, and the risk may increase to around 70% if both parents have T2DM *(Prasad and Groop, 2015, Omar, 2013)*. This suggests that individuals with a family history (FH) of first-degree relatives with T2DM are three times more likely to have T2DM *(Omar, 2013, Prasad and Groop, 2015)*. Additionally, part of the variability in the risk of T2DM among different ethnic groups could be related to genetic differences. For instance, in the UK, the prevalence of T2DM is 3-5 times higher in minority ethnic groups (African-Caribbean and South Asian) compared to the White population *(Goff, 2019).* Moreover, in the USA, T2DM is more prevalent among non-Hispanic Black and Hispanic Americans compared to non-Hispanic White and Asian Americans *(Golden et al., 2019).*

T2DM is polygenetic in nature, with more than 100 genetic variants having been identified to be linked with T2DM *(Dorajoo et al., 2015)*. Some genetic loci have been

suggested to contribute to the pathogenesis of T2DM by disturbing pancreatic β-cell function, insulin secretion, or insulin action *(Sun et al., 2014).* The advances in genetic studies assist researchers in examining the impact of pharmacogenomics on drug response and achieving glycaemic control *(Mambiya et al., 2019)*. Several genetic polymorphisms are associated with a patient's response to ADDs, like *Insulin Receptor Substrate 1* (*IRS-1)* variant with sulfonylurea, *Solute Carrier Family 47 Member 1* (*SLC47A1)* with metformin, and *Solute Carrier Organic Anion Transporter Family Member 1B1* (*SLCO1B1)* with repaglinide *(Sun et al., 2014, Dorajoo et al., 2015)*.

1.5 Diagnosis and screening of T2DM

Around one-quarter to one-third of patients are free of symptoms for a long period before being diagnosed with T2DM and thus tend to have more complications at the time of disease diagnosis *(Diabetes UK, 2021, American Diabetes Association, 2019).* Since early diagnosis and treatment initiation may decrease the burden and complications of the disease, guidelines of the UK National Institute for Health and Care Excellence (NICE) and the American Diabetic Association (ADA) have recommended conducting screening for asymptomatic adults at high risk for developing T2DM *(American Diabetes Association, 2019, National Institute of Health and Care Excellence, 2021)*. For screening and diagnostic purposes, it is recommended to use the following tests: fasting blood glucose test, HbA1c, and oral glucose tolerance test *(American Diabetes Association, 2019, National Institute for Health and Care Excellence, 2012).* Confirming a diagnosis of T2DM requires the presence of hyperglycaemic symptoms such as polyuria, polydipsia, blurred vision, and polyphagia, in addition to one abnormal approved plasma glucose test *(American Diabetes Association, 2019)*. However, one test is not enough in asymptomatic patients and an additional abnormal glucose test on another day is needed to confirm a T2DM diagnosis *(American Diabetes Association, 2019)*. The diagnostic criteria of prediabetes and T2DM are presented in Table 1.2 *(World Health Organisation, 2006, American Diabetes Association, 2019).*

Table 1.2: Diagnostic criteria for prediabetes and T2DM *(World Health Organisation, 2006, American Diabetes Association, 2019)*

Diabetes stage/diagnostic criteria	Fasting blood glucose (FBG)*	HbA1c**	Oral glucose tolerance test (OGTT)***
Prediabetes	100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)	5.7–6.4%(39–47 mmol/mol)	140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)
T2DM	≥126 mg/dL (7.0 mmol/L)	≥6.5%(48 mmol/mol)	≥200 mg/dL (11.1 mmol/L)

*Fasting; no calories for 8 hours, **; not recommended in some conditions such as sickle cell disease, pregnancy, glucose-6-phosphate dehydrogenase deficiency, haemodialysis, or erythropoietin therapy, ***; using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

1.6 Diabetes-related complications

People with T2DM are at high risk of developing serious health problems. These long-term complications are classified into microvascular and macrovascular complications *(Papatheodorou et al., 2018)*. The pathogenesis of these complications is complex, but both are related to the exposure of cells to persistent hyperglycaemia. Hyperglycaemia contributes to the development of complications through several pathways *(Chawla et al., 2016)*:

1- It causes direct tissue injury and endothelial damage, activating monocytes, thus inducing the release of inflammatory mediators.
2- It modifies the LDL molecules into more atherogenic ones, enhances the release of reactive oxygen species (ROS) and pro-inflammatory mediators as nuclear factor-κB, as well as promotes the formation of advanced glycation end products (AGEs); AGEs are non-enzymatic glycated plasma proteins, which accumulate in the cells leading to structural and functional disruption.
3- Induces oxidative stress by increasing the formation of ROS through DNA and protein destruction, as well as inhibiting anti-atherogenic enzymes like nitric oxide synthase.

All pathways mentioned above cause an alteration in the blood flow, protein deposition, and coagulation which eventually promote the development of atherogenesis in the small (microvascular) and large (macrovascular) blood vessels

leading to organ dysfunction *(Chawla et al., 2016).* A number of large-scale randomised controlled trials (RCTs), such as the United Kingdom Prospective Diabetes Study (UKPDS), revealed that diabetes-related complications could be prevented or delayed by achieving adequate glycaemic control *(Holman et al., 2008, Patel et al., 2008).* However, these studies showed a greater impact of intensive glycaemic control on reducing microvascular complications compared to macrovascular ones *(Holman et al., 2008, Patel et al., 2008).* Consistently, a prospective observational study (UKPDS 35) revealed a strong association between glycaemic control and diabetes-related complications, reporting that a reduction in HbA1c by 1% was associated with a 21% reduction in any end point related to diabetes and death, 14% reduction in myocardial infarction (MI), and 37% reduction in microvascular complications *(Stratton et al., 2000).*

1.6.1 Microvascular complications

Microvascular complications are mainly manifested by diabetic nephropathy, neuropathy, and retinopathy. Diabetic nephropathy or diabetic kidney disease (DKD) is defined as the reduction in the estimated glomerular filtration rate (eGFR) (< 60 ml/min/1.73m2) and/or increment in the urinary albumin excretion (> 30 mg/g of creatinine) over at least three months after excluding other causes of kidney disease *(Faselis et al., 2020).* DKD affects around 25% of the diabetic population, and diabetes accounts for more than 50% of end-stage renal disease (ESRD) cases *(Faselis et al., 2020).* Since the onset of T2DM is insidious, it is recommended to assess the kidney function at the time of T2DM diagnosis and yearly thereafter *(Faselis et al., 2020).* According to the UKPDS, albuminuria was detected in 38% of patients with T2DM over a median of 15 years, with around 29% developing renal impairment. Hypertension (HTN) is an independent risk factor for DKD; thus, both the reduction in HbA1c and blood pressure are associated with improved albuminuria and kidney function *(Faselis et al., 2020)*.

Diabetic retinopathy (DR) is the most common cause of blindness worldwide, affecting around one-quarter of patients with T2DM *(Faselis et al., 2020)*. The prevalence of DR is strongly associated with HTN and dyslipidaemia *(Faselis et al.,*

2020). Referring to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the progression of DR was decreased with intensive glycaemic and lipid control but not intensive blood pressure control *(Chew et al., 2010).* However, UKPDS-38 found that tight blood pressure control reduced the risk of DR progression by 34% *(UK Prospective Diabetes Study Group, 1998b)*.

Lastly, diabetic neuropathy (DN) affects the sympathetic and/or para-sympathetic nervous system, prevalent in about 20% of patients with T2DM at the time of disease diagnosis and 50% within ten years of disease duration *(Faselis et al., 2020).* Glycaemic control is the most promising method to reduce DN progression, yet the result of studies are conflicting *(Faselis et al., 2020)*. In addition, DN is a risk factor for foot ulcers, amputation, and sexual dysfunction *(Faselis et al., 2020)*. A MA showed that the global prevalence of foot ulceration in T2DM was 6.4%, and it was associated with age, diabetes duration, BMI, HTN, smoking, and DR *(Zhang et al., 2017)*. Furthermore, erectile dysfunction (ED) was three times higher among patients with T2DM, where at least 50% of patients with T2DM developed ED within ten years of disease diagnosis *(Faselis et al., 2020).*

1.6.2 Macrovascular complications

Macrovascular complications represent largely cardiovascular diseases (CVDs), including MI, stroke, heart failure (HF), and peripheral arterial disease (PAD). CVD is the major cause of mortality and morbidity among the diabetic population, responsible for more than half of diabetic deaths *(Kosiborod et al., 2018b).* According to the DISCOVER study program, the prevalence of macrovascular complications among patients with T2DM was 12.7%, ranging from 4.1% in South-East Asia to 18.8% in Europe *(Kosiborod et al., 2018b)*. Multiple RCTs such as ACCORD and UKPDS revealed that intensive glycaemic control was associated with a higher risk of hypoglycaemia and mortality without significantly reducing cardiovascular risk *(Holman et al., 2008, Patel et al., 2008).* Since CVDs are multifactorial, several factors should be addressed (e.g., dyslipidaemia, HTN, obesity, insulin resistance, albuminuria, and smoking) to reduce the incidence of the disease and the associated mortality *(Martin-Timon et al., 2014).*

1.7 Management of T2DM

Treatment goals of T2DM include preventing or delaying the progression of diabetes-related complications, limiting the emergence of medication side effects like hypoglycaemia, and improving patients' quality of life *(Davies et al., 2018).* All organizations have recommended following a patient-centred approach with the engagement of both healthcare professionals and patients in deciding treatment plans and setting treatment goals *(The Scottish Intercollegiate Guidelines Network, 2017, Davies et al., 2018, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2022).* During the first visit, a comprehensive assessment of a patient's medical status should be performed to set a patient-specific treatment goal and formulate an appropriate management plan, including the presence of complications and other comorbidities, hypoglycaemic risk, and all diabetes risk factors *(American Diabetes Association, 2022).*

Glycaemic control can be assessed based on the HbA1c value, which reflects the average glycaemic status over around three months and is a strong predictor for the risk of diabetes complications. The targeted HbA1c level should be determined and weighted for the glycaemic and extra-glycaemic benefits against the risk of hypoglycaemia and associated mortality for each patient. Previous evidence did not support the benefit of intensive glycaemic control on reducing cardiovascular outcomes and related mortality *(Gerstein et al., 2008, Holman et al., 2008, Zoungas et al., 2014, Duckworth et al., 2009, The ADVANCE Collaborative Group, 2008)*. Accordingly, guidelines have suggested a general goal of HbA1c of < 7% for non-pregnant adult patients. Nevertheless, it is recommended to tailor the goal for the individual patient considering several factors like having comorbidities, cardiovascular risk, hypoglycaemic risk, life expectancy, and, most importantly, patient preference *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. For instance, a goal of 6.5% is considered more appropriate at disease diagnosis for patients with long life expectancy and low risk of hypoglycaemia. In contrast, the target should be relaxed for patients with limited life expectancy, multiple comorbidities, and a high risk of

consequences from hypoglycaemia *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021)*. Since hyperglycaemia characterises T2DM, it is fundamental to manage glucose levels by starting a patient-specific lifestyle modification and appropriate medical therapy early after disease diagnosis *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017).*

1.7.1 Non-pharmacological approach

Self-management and lifestyle changes are cornerstones for successful glycaemic control and preventing complications in patients with T2DM *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021)*. It involves providing structured patient education at the time of diagnosis and follow-up visits about healthy nutrition, physical activity, weight management, complications screening, and glucose self-monitoring *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021).* A healthy diet that is low in carbohydrates (13-33% of total energy), low in fat (20-35% of total energy), high in fibre (> 14 g/ 1000Kcal), and low in sodium (<2300 mg/d) is very beneficial in managing weight, glucose level, blood pressure, and lipid level of patients with T2DM *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017)*. Furthermore, regular physical activity, aerobic and resistance types, positively affect glucose levels and other metabolic factors *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016)*. Thereby, patients with T2DM are recommended to perform physical activity for approximately 30 minutes per day of moderate-intensity activities for five days per week or at least every second or third day *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016)*. Weight reduction, smoking cessation, and alcohol moderation (not > 40 g/d for males and not > 24 g /d for females) can also improve glucose level and other cardiovascular risk factors *(The Scottish Intercollegiate Guidelines Network, 2017)*.

Patients' self-monitoring of glucose is crucial for guiding treatment adjustment and preventing complications, particularly hypoglycaemia *(The Scottish Intercollegiate Guidelines Network, 2017).* In addition, healthcare professionals must regularly perform several tests to monitor glycaemic status and diabetes-related complications, including HbA1c every 3-6 months, and approximately an annual assessment of renal functions, lipid profile, and eye examination *(National Institute of Health and Care Excellence, 2021).*

1.7.2 Pharmacological approaches:

Despite the proven beneficial effect of lifestyle changes on glycaemic control, it is difficult for patients to keep on lifestyle interventions for a long time. Because of the progressive nature of diabetes, the addition of antidiabetic medications is essential for most patients with T2DM *(Marin-Penalver et al., 2016)*. ADDs are classified based on their mechanism of action into insulin sensitisers, insulin secretagogues, alpha-glucosidase inhibitors, and SGLT2- inhibitors (SGLT2-Is) *(Marin-Penalver et al., 2016)*; Figure 1.3 illustrates the sites of action of all ADDs. Table 1.3 summarises the characteristics of antidiabetic classes.

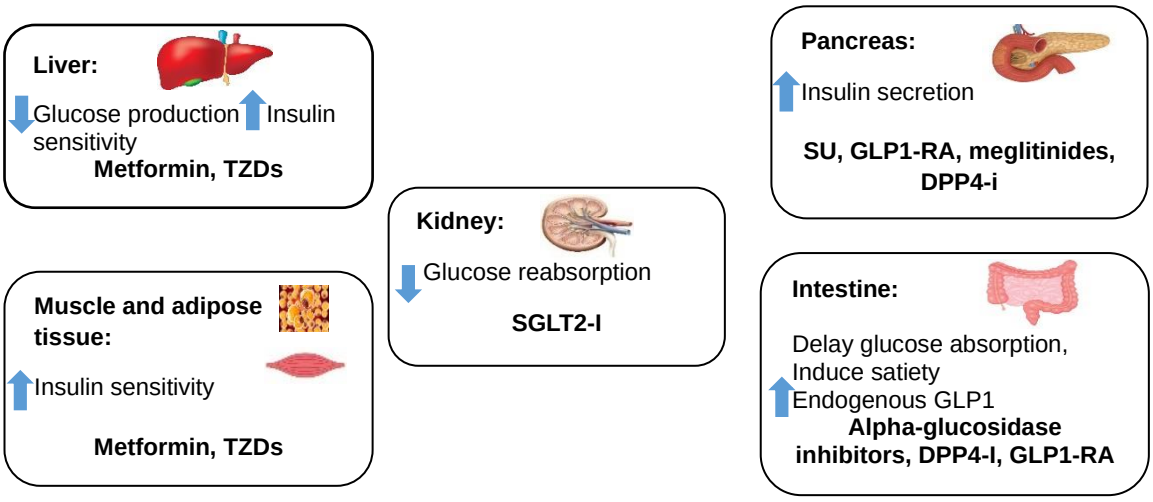

Figure 1.3: Sites of action of antidiabetic drugs. TZDs; thiazolidinediones, SU; sulfonylurea, DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

1.7.2.1 Insulin sensitisers

Insulin sensitisers, biguanide and thiazolidinediones (TZDs), enhance the sensitivity of circulating insulin to its receptors without influencing the amount of insulin secretion *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017).* Metformin is the only currently available biguanide that reduces blood glucose via complex molecular mechanisms by inhibiting glucose production in the liver and enhancing insulin sensitivity *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017).* Metformin is considered a drug of choice for newly diagnosed patients with T2DM, especially for overweight and obese patients because of its weight-neutral to weight-loss effect *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017)*. Nonetheless, metformin is not recommended in case of renal impairment or with conditions causing volume depletion because of the high risk of lactic acidosis *(American Diabetes Association, 2021).* TZDs promote insulin sensitivity by activating the nuclear receptor PPAR*γ,* which has a role in obesity and insulin resistance *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017)*. Currently, the only commercially available TZD in the UK is pioglitazone, while rosiglitazone is no longer used because of the warning alert related to rosiglitazone-associated cardiovascular risk issued in May 2007 *(The Scottish Intercollegiate Guidelines Network, 2017)*. Pioglitazone is contraindicated for patients with stage III-IV HF, with an active or history of bladder cancer, at a high risk of fractures, or with severe hepatic impairment *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017).*

1.7.2.2 Insulin secretagogues

Insulin secretagogues include sulfonylurea (SU), meglitinides, GLP-1 receptor agonists (GLP1-RAs), and dipeptidyl peptidase-4 inhibitors (DPP4-Is). The older groups, meglitinides and SU, stimulate insulin secretion by promoting the closure of ATP-sensitive potassium channels in the membrane of pancreatic β-cells causing cell depolarization and calcium level elevation, which ultimately lead to insulin secretion *(Marin-Penalver et al., 2016).* SU and, to a lesser extent, meglitinides are associated with weight gain and hypoglycaemia, particularly among elderly patients, those with

renal or hepatic impairment, and those with hypothyroidism *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016).* On the other hand, the newer antidiabetic groups (GLP1-RA and DPP4-I) stimulate insulin secretion differently. GLP1-RA mimics the action of endogenous GLP-1 incretin hormone *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016),* which is released from the gut in response to food to stimulate insulin secretion, inhibit glucagon action, slow glucose absorption, and suppress the appetite *(The Scottish Intercollegiate Guidelines Network, 2017).* Accordingly, GLP1-RA mimics the endogenous hormone with more prolonged action because of its lower affinity to the DPP-4 enzyme, responsible for the degradation of the endogenous GLP-1 incretin hormone *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016)*. Likewise, DPP4-I increases the activity of endogenous GLP-1 hormone by inhibiting DPP-4 enzyme. Both DPP4-I and GLP1-RA should not be prescribed for patients with a history of pancreatitis and GLP1-RA should not be used in severe renal impairment, while DPP4-I is contraindicated in severe hepatic impairment *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016)*.

GLP1-RA and DPP4-Is have a lower risk of hypoglycaemia and a more favourable effect on body weight compared to SU *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016)*. GLP1-RAs were found to have a weight-loss effect which could be driven by the glucagon extra-pancreatic effects, including slowing gastric emptying and inducing early satiety *(Andrikou et al., 2019, Ard et al., 2021)*. In addition, large cardiovascular outcome studies have shown a potential cardioprotective effect of GLP1-RA in terms of reducing the risk of non-fatal MI, non-fatal stroke, cardiovascular mortality, and HF hospitalisation, yet these effects were more prominent among patients with established CVD *(Giugliano et al., 2021, Zelniker et al., 2019b)*. The cardiovascular benefits of GLP1-RA could be mediated directly by their anti-atherosclerotic and anti-inflammatory effects, along with modifying cardiovascular risk factors such as promoting weight loss and improving abnormal lipid profiles *(Andrikou et al., 2019)*. Moreover, a reduction in macroalbuminuria has been observed among patients with T2DM who were treated with GLP1-RA

(Giugliano et al., 2021, Zelniker et al., 2019b). Albuminuria is a strong predictor of renal function, and the renal protective effects of GLP1-RA might be driven by their benefits in improving blood pressure, body weight, and glucose levels *(Greco et al., 2019)*. All GLP1-RAs are available in injecTable form except semaglutide oral formulation, which became available in Scotland in 2020 *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016).*

1.7.2.3 Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (e.g., acarbose) bind to alpha-glucosidase enzyme with higher affinity than carbohydrates, thereby delaying the absorption and digestion of carbohydrates, and thus reducing postprandial glucose levels *(Marin-Penalver et al., 2016).* The most common side effects of alpha-glucosidase inhibitors are gastrointestinal-related, including flatulence and abdominal pain; hence, they are contraindicated for patients with chronic intestinal disorders *(Marin-Penalver et al., 2016).*

1.7.2.4 Sodium glucose co-transporter-2 inhibitor (SGLT2-I)

SGLT2-I is the newest class of ADDs that was introduced into the UK market in 2013 *(Ramzan et al., 2019).* SGLT2-Is act independently from pancreatic cells, inhibiting glucose reabsorption from the kidneys and increasing urinary excretion by blocking the activity of SGLT2 protein, which is located in the renal-proximal tubule and responsible for approximately 97% of glucose reabsorption from the kidneys *(The Scottish Intercollegiate Guidelines Network, 2017, Marin-Penalver et al., 2016)*. SGLT2-Is have shown a modest reduction in HbA1c by around 0.5% to 1% *(Zelniker and Braunwald, 2018),* yet they are associated with a low risk of hypoglycaemia as their mechanism in glucose reduction is independent of insulin secretion *(Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017).* In addition, this class has the advantage of promoting weight loss (around 1-3 kg), which could be resulted from enhancing fat metabolism (lipolysis) as well as reducing the required insulin dose and the associated hyperphagia *(Lee et al., 2018, Pereira and Eriksson, 2019)*. The weight loss effect of SGLT2-Is is dose-dependent, and it increases when

combined with other drugs with weight-lowering effects, such as GLP1-RA *(Pereira and Eriksson, 2019).*

Furthermore, several clinical trials and observational studies revealed that SGLT2-Is have a protective effect against cardiovascular and renal outcomes, including MI, stroke, HF, cardiovascular death, all cause-mortality, albuminuria, serum creatinine, and the need for renal replacement therapy *(Zelniker et al., 2019a, Kosiborod et al., 2018a, Kosiborod et al., 2018c, Seidu et al., 2018, Zheng et al., 2021)*. Cardiovascular protective effects of this class could be mediated directly by reducing vascular resistance and improving myocardial function as well as indirectly by decreasing blood pressure through its natriuretic effects and reducing the level of uric acid, body weight, and oxidative stress *(Rabizadeh et al., 2019)*. Additionally, its renal benefits could be linked to their natriuretic effects that cause a reduction in the intra-glomerular pressure, which may lead to an initial transient decrease in the eGFR, in addition to its favourable effects on blood pressure, body weight, and blood glucose, which are important contributing factors of renal disease *(Rabizadeh et al., 2019)*. Nevertheless, SGLT2-Is are currently not recommended with low eGFR of < 60 (ml/min/1.73m2) because of their limited efficacy in reducing glucose level at this stage of kidney function *(The Scottish Intercollegiate Guidelines Network, 2017).*

Table 1.3: Features of antidiabetic drugs *(Marin-Penalver et al., 2016, International Diabetes Federation, 2017, The Scottish Intercollegiate Guidelines Network, 2017)*

Feature	Metformin	Sulfonylurea	TZD	DPP4-I	SGLT2-I	GLP1-RA	Alpha-Glucosidase Inhibitors
Hypoglycaemic risk	**Low**	**Moderate-high**	**Low-moderate**	**Low-moderate**	**Low**	**Low**	**low**
Weight	**Loss** or **neutral**	**Gain**	**Gain**	**Neutral**	**Loss**	**Loss**	**Neutral**
Adverse effects	**- Mainly;** GI as diarrhoea, nausea. -Lactic acidosis risk; not common	**Mainly,** hypoglycaemia	**Mainly**, Fluid retention Other: increase fracture risk and bladder cancer risk.	Well-tolerated, may cause: Headache, nausea, and rash. **Rare**: pancreatitis	Mainly, genital mycotic infections Others: UTI, increase risk of fracture. DKA, and peripheral amputation	-Mainly GI - Injection site reactions	Mainly GI; flatulence, abdominal pain, nausea
Major CV benefit and HF	**Benefit,** mortality and MI risk but not stroke or PAD.	**Neutral**	**Neutral** Increase HF hospitalization risk	**Neutral** Risk of HF hospitalization increased with saxagliptin	**Benefit**; decrease CV death, incidence of MI and stroke.	**Benefit**, Liraglutide decrease CV death, rate of MI and stroke but not HF	**Neutral**
Other advantages	Favourable effect on lipid profile		Favourable effect on lipid profile.		-Decrease blood pressure. -Favourable effect on lipid profile - Renal protective effect	-Decrease blood pressure -Favourable effect on lipid profile	
In CKD stage 3a,3b	3a; Dose reduction 3b; Contraindicated	With caution, higher risk of hypoglycaemia	No renal adjustment	Need dose reduction except linagliptin	Do not initiate	No renal adjustment	No renal adjustment
In CKD stage 4, 5	Contraindicated	Not recommended except glipizide and gliclazide; lower hypoglycaemic risk	No renal adjustment	Need dose reduction except linagliptin	Contraindicated	Contraindicated	Contraindicated

GI; Gastrointestinal, CV; cardiovascular, HF; heart failure, MI; myocardial infarction, PAD; peripheral arterial disease, CKD; chronic kidney disease, UTI; urinary tract infection, DKA; diabetic ketoacidosis., TZD; thiazolidinedione, GLP1-RAs; GLP-1 receptor agonists, SGLT2-I; sodium-glucose transporter 2 inhibitors, DPP4-Is; dipeptidyl peptidase-4 inhibitors .

1.7.3 Treatment guidelines

Several clinical guidelines have been developed, providing recommendations on the management strategy of T2DM. The international (IDF) and national (NICE, The Scottish Intercollegiate Guidelines Network (SIGN), ADA) guidelines have recommended metformin as the drug of choice for T2DM management in the absence of contraindication and catabolic/hyperglycaemic symptoms *(International Diabetes Federation, 2017, The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021).* This recommendation was made based on the results of clinical trials such as UKPDS 34, which showed the superiority of metformin over the conventional treatment with SU and insulin in overweight patients in terms of glycaemic control (7.4% vs. 8%), all-cause mortality (36%, p=0.011), and risk of MI (39%, P=0.01) (UK Prospective Diabetes Study Group, 1998a). Thereby, the choice of metformin as a first-line therapy in almost all guidelines is related to its general safety, tolerability, effectiveness, low cost, and favourable impact on body weight, CVD risk, and mortality *(American Diabetes Association, 2021).* If a patient is initially presented with hyperglycaemic (polyuria, polydipsia, blurred vision) or catabolic (weight loss, ketosis) symptoms, sulfonylurea or insulin should be started until symptoms resolve *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021).* ADA has also recommended introducing insulin early in the treatment in case of extremely high glucose level manifested by an HbA1c value of > 10% or blood glucose level of ≥ 300 mg/dL *(American Diabetes Association, 2021).*

Despite the fact that the majority of patients with T2DM are usually started on monotherapy, some individuals need to be initiated on combination therapy. The IDF and ADA guidelines recommended considering initiating dual therapy for patients presenting with an HbA1c value that is 1.5-2% above the target *(International Diabetes Federation, 2017, American Diabetes Association, 2021).* In addition, because of the progressive nature of the disease, most patients require additional drug therapy to maintain the targeted glycaemic control since with time,

insulin secretion from the pancreas decreases, and body tissues become less responsive to insulin *(American Diabetes Association, 2021)*. Nevertheless, there is no consensus in the clinical guidelines regarding the selection of additional ADDs when patients do not achieve glycaemic control after 3-6 months of initial therapy or for selecting an alternative therapy in case of contraindication or poor tolerance to metformin *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021)*. Treatment guidelines have recommended considering several drug- and patient-related factors, such as the presence of comorbidities, hypoglycaemic risk, drug side effects, drug cost, drug effect on body weight, and patient preferences for deciding the optimal ADDs for an individual patient *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021)*. For example, if a patient has established CVD, is at high risk for CVD, has HF, or has chronic kidney disease, guidelines have recommended either SGLT2-Is or GLP1-RA with proven cardiovascular and renal benefits, considering other patients factors such as the baseline renal and hepatic function *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021).*

Moreover, some patients, especially those with long-standing diabetes, eventually need to add a third therapy with an oral or injectable ADD, where the selection primarily depends on the value of BMI, the risk of hypoglycaemia, and cost *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021)*. The available injectable ADDs are GLP1-RA and insulin, yet it has been stated that adding a third oral therapy or an injectable GLP1-RA is preferred over insulin addition whenever possible, related to the lower risk of hypoglycaemia, lower need for glucose monitoring, and better extra-glycaemic profile of some of the non-insulin ADDs *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021)*. Table 1.4 highlights the similarities and differences in T2DM management as recommended by the SIGN, NICE, and ADA guidelines. The

three guidelines shared the same recommendation of using metformin as a first-line therapy for newly diagnosed patients with T2DM. However, there are some variabilities across the guidelines regarding the choice of alternative initial monotherapy, initial dual therapy, and intensifying therapy. The ADA guideline provided more definitive recommendations compared to the SIGN and NICE guidelines. For instance, the SIGN guideline has recommended SU as the first alternative therapy to initial metformin, and the other antidiabetic classes are recommended if SU is contraindicated. In contrast, in the NICE and ADA guidelines, SU was not preferred over the other antidiabetic classes as an alternative therapy to first-line metformin. Neither SIGN nor NICE guidelines have stated when dual therapy should be used as a first-line therapy for T2DM management. In addition, there is no clear guidance in the treatment algorithm of the SIGN guideline regarding the conditions where insulin should be used as first-line therapy. Additionally, baseline BMI guides the selection of injectable drugs as a third-line therapy according to the SIGN guideline (Table 1.4).

Table 1.4: Type 2 diabetes treatment according to ADA, SIGN, and NICE guidelines *(The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021).*

Feature	ADA	SIGN	NICE
1- First line (monotherapy);	**Metformin**	**Metformin**	**Metformin**
A- If osmotic or catabolic symptoms present	Consider **insulin**	Consider **sulfonylurea**	Consider **sulfonylurea or insulin.**
B- If metformin is contraindicated or not tolerated	Any class based on patients feature	**Sulfonylurea:** If it is contraindicated, consider DPP-4 inhibitors, pioglitazone or SGLT2 inhibitors	**Sulfonylurea (SU), DPP-4 inhibitors or pioglitazone.** SGLT2 inhibitors only if; 1- DPP4-i otherwise prescribed. 2- Pioglitazone and SU are contraindicated.
C- Insulin	A1C> 10% or blood glucose ≥ 300 mg/dL (16.7 mmol/L)	No clear recommendation	Start insulin-based regimen if HbA1c ≥ 9%.
2- First line (dual therapy)	Consider if patients presenting with HbA1c 1.5-2% above their target	No clear recommendation	No clear recommendation
3- Second line (first intensification; dual therapy): HbA1c not at goal after 3-6 months	-If patients have established or at high risk of ASCV, has established kidney disease, or HF; consider **SGLT2-i or GLP1-RA.** -Otherwise; guide based on patients' profile	Guide based on patients' profile; **SU, SGLT2-i, DPP4-i, or pioglitazone**	**SU, DPP4-i, or pioglitazone.** SGLT2-i only if SU is contraindicated or high risk of hypoglycaemia.
4- Third line (second intensification; triple therapy): HbA1c not at goal after 3-6 months	-Guide based on patients' profile, additional oral therapy, or injectable drugs.	Add oral agent from different class or injectable agent; If BMI >30, add GLP1 agonist. If BMI <30, add basal insulin.	metformin + SU + either pioglitazone or DPP4 inhibitor or Insulin based regimen. GLP1-RA, SGLT2-I for specific condition

1.8 Utilisation and treatment patterns of antidiabetic drugs

1.8.1 Drug Utilisation Research (DUR)

DUR is a broad area of research including multiple descriptive and analytical methods for quantifying and evaluating prescribing, dispensing, and consumption of drugs, as well as evaluating the interventions to optimise the quality of these processes *(Wettermark et al., 2016)*. DUR focuses on several aspects of medication utilisation, including medical (benefits/risks), social (appropriateness of drug use), and economic (cost of drug treatment) aspects.

DUR is also linked with other scientific disciplines, such as clinical pharmacology. While clinical pharmacology research focuses on examining the efficacy and safety of medicines in clinical trials under an ideal, strict, and controlled situation, DUR evaluates the effectiveness and risks of medications as well as the appropriateness of use and cost of drug based on real-world data (RWD) *(Wettermark et al., 2016)*. RWD represents all data related to a patient's health status and health care delivery, which may be collected from various sources, including electronic health records, disease registries, claims databases, pharmacy data, health insurance data, etc. *(Ramamoorthy and Huang, 2019)*. Although RCTs are considered a gold standard for obtaining clinical evidence, they include strict inclusion/exclusion criteria. They also require more intensive monitoring and a controlled treatment plan, limiting the applicability of their findings to clinical practice and possibly creating variability in the observed results compared to the real-world setting *(Liu et al., 2019, Ramamoorthy and Huang, 2019, Wettermark et al., 2016).* In addition, certain research questions such as those related to prescribing patterns and factors influencing the prescribing choice of medicines cannot be answered by conducting RCTs.

The importance of using RWD has been recognised by multiple regulatory bodies, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). However, the variability in the features of RWD sources, the ability to obtain comprehensive longitudinal data, as well as the potential for selection and confounding bias challenge the validity of using RWD to generate

clinical evidence *(Liu et al., 2019, Ramamoorthy and Huang, 2019).* Nevertheless, using data that is reliable and aligns with the studied research question, as well as implementing new study designs and proper analytical approaches, increase the validity of the findings of a study using RWD *(Liu et al., 2019, Ramamoorthy and Huang, 2019)*.

1.8.2 Prescribing pattern of antidiabetic drugs for patients with T2DM

ADDs are currently receiving attention in DUR because of the increasing number of new antidiabetic classes, changes in treatment guidelines, the emergence of new adverse reactions, the differences in the health insurance policy across countries, and the recent evidence regarding the cardiovascular/renal benefits and risks of ADDs. As a result, a change in the utilisation and prescribing patterns of ADDs over time and across countries is expected. Accordingly, several studies have been conducted in different countries to evaluate the utilisation trend of antidiabetic medications for patients with T2DM *(Hampp et al., 2014, Mata-Cases et al., 2016, Chu et al., 2017, Christensen et al., 2016, Torre et al., 2015)*. Most of these studies reported an increase in the overall use of ADDs for T2DM management, and this might be related to the increasing prevalence of T2DM even in young individuals and the current availability of more treatment options *(Christensen et al., 2016, Filion et al., 2009).* For instance, a USA study identified a 42.9% rise in the prescription of ADDs between 2003 and 2012 *(Hampp et al., 2014)*. Similarly, in Denmark, the annual prevalence of ADDs increased more than two times between 1999 and 2014 (from 19 to 41 per 1,000 inhabitants). In the UK, the prescription rate increased from 9.6 prescriptions/patient-year in 2000 to 14.8 prescriptions/patient-year in 2006 *(Filion et al., 2009)*.

Moreover, multiple studies evaluated the prescribing patterns of initial ADDs for newly diagnosed patients with T2DM in clinical practice. These studies showed a significant rise in metformin use over time, which surpassed SU and became the most commonly prescribed monotherapy for newly diagnosed patients with T2DM *(Christensen et al., 2016, Filion et al., 2009, Sharma et al., 2016, Wilkinson et al., 2018a, Desai et al., 2012).* A global study, including 37 countries, showed that metformin

accounted for 57.9% of all first-line ADDs. However, metformin accounted for 77% of the initial prescriptions in the USA in 2016, more than 80% in Germany in 2009, and around 89% of the first-line ADDs in the UK in 2017 *(Wilkinson et al., 2018a, Montvida et al., 2018, Geier et al., 2014)*. A study conducted across European countries reparteed that prescribing metformin as a first-line therapy ranged from 65% in Italy to 88% in the UK *(Overbeek et al., 2017)*. Conversely, the use of SU as an initial monotherapy has declined over time, as observed in the USA, Germany, and the UK *(Wilkinson et al., 2018a, Montvida et al., 2018, Geier et al., 2014)*; for instance, SU prescription as an initial monotherapy has fallen from 20% in 2005 to 8% in 2016 in the USA, and from 48.43% to 5% between 2000 and 2017 in the UK *(Montvida et al., 2018, Wilkinson et al., 2018a)*. A similar decline in SU use was observed in Taiwan and Denmark, yet the stage of treatment was not stated *(Ou et al., 2017, Christensen et al., 2016).*

The use of TZDs as an initial monotherapy increased early after their license until 2007, when a warning alert was issued about rosiglitazone-associated cardiovascular risk *(Leal et al., 2013, Stewart et al., 2009)*. Consequently, several utilisation studies reported a significant decline in rosiglitazone use after this safety alert *(Montvida et al., 2018, Sharma et al., 2016, Chu et al., 2017, Leal et al., 2013, Stewart et al., 2009)*. The newer classes of ADDs (DPP4-I, SGLT2-I, and GLP1-RA) were less commonly prescribed as a first-line therapy for newly diagnosed patients with T2DM, where DPP4-I was the most frequently used among the newer ADDs *(Montvida et al., 2018, Sharma et al., 2016, Wilkinson et al., 2018a).* A rise in the prescription of DPP4-I as first-line therapy was observed in the USA, Taiwan, Europe, and the UK *(Sharma et al., 2016, Wilkinson et al., 2018a, Overbeek et al., 2017, Ou et al., 2017, Montvida et al., 2018)*; it has increased from 3.7% to 19.6% between 2009 and 2012 in Taiwan *(Ou et al., 2017).* Additionally, a study across Europe showed that DPP4-I use significantly increased in France (0% to 27%), Spain (0% to 9%), and the UK (<1% to 9%), with limited use in Italy (2%), and the Netherlands (4%) *(Overbeek et al., 2017)*. These studies also revealed that the proportional share of GLP1-RA as initial therapy was very low. However, the change in the use of SGLT2-I as first-line

therapy over time was not frequently investigated *(Montvida et al., 2018)*. The proportional use of insulin as a first-line therapy among newly diagnosed patients was variable by country; for instance, two studies in the UK reported that only 1.7% and 0.6% of patients were started on insulin in 2013 and 2017, respectively, compared to 10% in the USA in 2016 as mentioned in Montvida et al. *(Wilkinson et al., 2018a, Montvida et al., 2018, Sharma et al., 2016)*.

As stated previously, a small proportion of patients could be initiated on combination therapy, and with longer disease duration, patients mostly require adding one or more ADDs to maintain glycemic control *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021)*. Previous studies showed that prescribing patterns of ADDs at the stage of drug intensification after initial antidiabetic therapy have changed over time, with metformin+SU identified as the most commonly prescribed combination regimen in the majority of studies *(Montvida et al., 2018, Wilkinson et al., 2018a, Sharma et al., 2016, Overbeek et al., 2017).* However, a global study conducted in 37 countries identified a combination regimen of metformin and DPP4-I (25.3%) as the most commonly prescribed second-line therapy, followed by a combination of metformin and SU (21.3%) *(Nicolucci et al., 2019)*. Nevertheless, it was indicated that the proportional share of TZD and SU as add-on therapy has declined over time *(Montvida et al., 2018, Wilkinson et al., 2018a, Sharma et al., 2016)*. In spite of the reduction in the use of SU over time, it remained the most popular intensifying therapy in certain countries, particularly the USA *(Sharma et al., 2016, Montvida et al., 2018)*.

Likewise, the use of newer ADDs at the stage of drug intensification has generally increased over time with variability in the rate and proportion of drug use by countries *(Wilkinson et al., 2018a, Montvida et al., 2018, Kim et al., 2019a, Overbeek et al., 2017)*. For example, the utilisation of DPP4-I and SGLT2-I as a first intensifying therapy after initial metformin was higher in the UK compared to the USA (42.4% and 21.7% in 2017 versus 20% and 7% in 2016), while there was a greater consumption of GLP1-RA and insulin in the USA compared to the UK (7% and 17% in 2016 versus 1.8% and 0.9% in 2017) *(Wilkinson et al., 2018a, Montvida et al., 2018)*.

Additionally, it has been reported that prescribing practices of the add-on ADDs differed by regions within the same country; for instance, in the UK, the proportional use of DPP4-I and SGLT2-I was higher in Northern Ireland and Wales (45% and 46%, 18% and 13% respectively) compared to England and Scotland (36% and 30%, 9% and 12% respectively) *(Wilkinson et al., 2018a)*.

1.8.3 Factors associated with the prescribing choice of antidiabetic drugs for T2DM management

With the availability of several treatment options with different mechanisms of action, side effects, and extra-glycemic benefits, selecting a particular combination regimen may lead to different outcomes. Along with the absence of clear recommendations on the choice of the most appropriate antidiabetic combination as an initial or add-on therapy in clinical guidelines, prescribing choice of ADDs as a first-line therapy alternative to metformin or as add-on therapy is expected to vary over time and across countries. Therefore, the selection of the optimal ADDs could be influenced by several clinical and non-clinical factors, including patient demographics, clinical characteristics, socioeconomic status, etc. *(American Diabetes Association, 2021)*. These factors arise from the differences in the effectiveness, cardiovascular and renal benefits, adverse reactions, hypoglycaemic risk, weight-change effects, and cost of the available antidiabetic classes. These differences were discussed in section 1.7.2 and summarised in Table 1.3. In summary, almost all classes of ADDs except insulin have a relatively similar glycaemic reduction effect, yet they vary in their side effects, drug cost, risk of weight gain and hypoglycaemia, as well as renal and cardiovascular benefits. The newer antidiabetic classes are known to have more favourable effects on body weight and cardiovascular/renal outcomes.

The differences in the benefits and risks of ADDs emphasize the importance of studying the impact of these features on the selection of ADDs. Consequently, the association of several factors related to patient demographics (e.g., patient age, sex, and ethnicity), socioeconomic status, and clinical characteristics, including co-existing diseases, concomitant medications, glycaemic status, kidney function, BMI,

and lipid profile with the prescribing choice of ADDs was investigated in some previous studies *(Heintjes et al., 2017, Chu et al., 2017, Geier et al., 2014, Grabner et al., 2015, Wilkinson et al., 2018c)*. For instance, it has been reported that older age and reduced kidney function were associated with the prescribing choice of older classes of ADDs, particularly SU, and inversely associated with the use of newer antidiabetic groups such as SGLT2-I and GLP1-RA *(Morita et al., 2019, Heintjes et al., 2017, Geier et al., 2014, Wang et al., 2019, Fujihara et al., 2017, Brouwer et al., 2012, Abdelmoneim et al., 2013)*. Moreover, being overweight/obese was negatively associated with prescribing of medications causing weight gain (e.g., SU and insulin), yet directly associated with the use of drugs with weight neutral to weight loss effects *(Morita et al., 2019, Heintjes et al., 2017, Fujihara et al., 2017)*. However, the influence of sex, ethnicity, socioeconomic status, and clinical factors such as cardiovascular diseases, microvascular complications, and others was much less frequently evaluated, especially with the newer classes of ADDs, and the results of studies that investigated their effect were inconsistent *(Heintjes et al., 2017, Chu et al., 2017, Geier et al., 2014, Grabner et al., 2015, Wilkinson et al., 2018c)*.

1.9 Thesis rationale

Based on all previous evidence, there is a clear consensus in national and international guidelines regarding the optimal first-line therapy for patients diagnosed with T2DM, with metformin recommended as a drug of choice. However, multiple treatment options can be prescribed or added to achieve adequate glycaemic control for patients who cannot tolerate metformin or have metformin contraindications and after failing the initial therapy. Still, there are no definite recommendations around the selection of initial alternative therapy or intensifying therapy for T2DM management, where clinical guidelines recommend following a patient-centred approach. The absence of a clear treatment algorithm in clinical guidelines, the availability of multiple treatment options for T2DM management with variable safety and extra-glycaemic benefits, especially after the introduction of newer antidiabetic classes, as well as the differences in the healthcare policy and medications access across countries create a debate and variability among

prescribers regarding the choice of ADDs at both stages of drug initiation (alternative to metformin) and intensification; thus, making the choice of ADDs could be highly variable over time and across countries. In addition, this indicates that the prescribing decision is a product of multiple interlinked clinical and non-clinical factors.

The variability in prescribing patterns and physician prescribing practices has led to growing concerns regarding the potential differences in health outcomes, utilisation of resources, and healthcare expenditure. Therefore, conducting prescribing patterns research is important for evaluating the rational use of drugs, as well as explaining the extent of drug use and physician compliance with the regional and national clinical guidelines, thus maximizing the effective use of resources *(Jain et al., 2015).* Furthermore, factors influencing prescribing decisions are a vital input to clinical practice guidelines and healthcare policy, which could also possibly advise the regulation of the pharmaceutical market. The fundamental and vital position of physicians makes studying factors influencing the prescribing decision of tremendous value. Accordingly, investigating the prescribing patterns of ADDs at the treatment initiation and intensification, the possible factors influencing the prescribing decision, and the agreement of prescribing process with guideline recommendations provide crucial information for prescribers and policymakers to understand the most commonly used ADDs of all available classes and which characteristics (patients, prescribers, and drug) are associated with the use of a particular antidiabetic class. That information can highlight potential systematic differences in the strategies that prescribers follow to select the optimal treatment option for patients with T2DM, which is highly important for proper understanding and interpretation of subsequent outcomes research, and in turn, could inform the need for optimising the clinical practice to improve patient outcomes. Moreover, exploring factors influencing the prescribing decision could assist in guiding and rationalising the process of patient care and healthcare expenditure, as well as highlighting the differences in medication access across regions and the related

inequalities of receiving treatment. That underlines the importance of studying prescribing pattern practice and factors influencing decision-making in each country.

Given the prevalence, the progressive nature, and the health and economic burden of T2DM, as well as the importance of implementing an appropriate patient-specific treatment plan, multiple prior studies described the change in the prescribing pattern of ADDs for T2DM management and presented some of the factors that were found to be associated with the prescribing choice of ADDs. Nevertheless, few studies have examined the prescribing patterns of ADDs over time in the UK, and no studies have been published so far in Scotland at a national level in that regard. The most recent published study in the UK was conducted by Wilkinson and colleagues, which examined the prescribing trend of ADDs at drug initiation and stage of first drug intensification between 2000 and 2017 using the Clinical Practice Research Datalink (CPRD). CPRD covers around 7% of the UK population, including a small number of GPs from Scotland *(Wilkinson et al., 2018a).*

However, previous studies, including the UK studies, mostly examined old antidiabetic classes with a very limited investigation of the newer groups, particularly SGLT2-I; the last antidiabetic class introduced into the market. In addition, knowing that a number of patients would be treated with a combination regimen at the stage of drug initiation and intensification, no extensive data is available on the change in the prescribing patterns of combination regimens as a first-line and add-on therapy, especially with the presence of multiple treatment options with different extra-glycaemic benefits. Furthermore, most previous studies that examined prescribing patterns of first-intensifying therapy after an initial ADD focused on initial metformin users, while studies investigating the prescribing pattern after an initial SU (the second most commonly prescribed initial therapy) are scarce.

Studies investigating factors associated with the prescribing decision of ADDs are scarce globally and not thoroughly and comprehensively explained. Similar to prescribing pattern studies, previous studies that explored factors influencing the

prescribing choice of ADDs mostly examined the selection of single ADDs, mainly the older groups. However, very limited research studied factors influencing the choice of newer classes and combination regimens at drug initiation and first intensification. Although recent guidelines strongly recommended considering the presence of CVD and renal disease for selecting the optimal antidiabetic therapy, the influence of baseline CVD and renal disease on the choice of ADD in clinical practice was not comprehensively investigated. Moreover, limited studies examined the influence of other factors, including clinical and socioeconomic, as the majority of studies discussed the demographic factors, primarily patient age and sex.

Accordingly, studies that thoroughly investigate prescribing trends and drug utilisation of ADDs, as well as factors influencing the prescribing decision, including both monotherapy and combination regimens, at the stage of drug initiation and intensification in clinical practice in Scotland are required. Using multiple datasets that cover the entire population of Scotland who were registered with General Practitioners (GPs) and over a long study interval, including recent years, provides a reliable, representative, and valuable data source to address the previously discussed gaps in this area of research. This could indirectly reflect the prescribing practice of ADDs in Scotland and the agreement of prescribing process with the local and national guideline recommendations as well as the updated evidence on the differences in the characteristics of ADDs.

Aims and objectives:

The aims of this thesis were to comprehensively understand and investigate the change in prescribing patterns of ADDs over time and explore factors influencing the prescribing choice of ADDs in clinical practice. The objectives of this thesis were to

1- Conduct a systematic review and meta-analysis to identify, summarise, and quantify factors that were reported in the literature to have an association with the selection of ADDs prescribed for patients with T2DM to identify the gaps in the literature and understand which factors were more frequently studied, and how much each factor is weighted in prescribing decision making.

2- Examine the utilisation/prescribing pattern of ADDs, including both initial and subsequent intensifying therapy over the period of 2010-2020, using record-linked datasets at a national level in Scotland to assess the potential change in the utilisation of the older classes after the introduction of newer ones.

3- Describe the characteristics of the population of Scotland who were diagnosed with T2DM and treated with at least one ADD in the primary care setting over the study period.

4- Comprehensively explore factors influencing the prescribing choice of ADDs at both drug initiation and stage of drug intensification following the results of the SR and MA (objective 1), using national record-linked datasets in Scotland to explore which factors have an impact on the prescribing decision of ADDs among patients with T2DM in clinical practice in Scotland, including a wide range of data related to patient demographics, clinical characteristics, and socioeconomic information.

2 Chapter 2: Factors associated with antidiabetic drugs prescribing among patients with type 2 diabetes mellitus: A systematic review and meta-analysis of observational studies

2.1 Introduction

Given the recommendations of clinical guidelines to follow a patient-centred approach for selecting the optimal ADDs for patients with T2DM, the differences in the safety and extra-glycaemic benefits (e.g., cardiovascular, renal, and weight loss) of the available ADDs, and the variability in healthcare policy across countries, the prescribing choice of ADDs could be linked to several clinical and non-clinical factors *(American Diabetes Association, 2021, Davies et al., 2018, Marin-Penalver et al., 2016, The Scottish Intercollegiate Guidelines Network, 2017, National Institute of Health and Care Excellence, 2021)*. Multiple observational studies evaluated the association of several factors with antidiabetic drug prescribing (ADP) in clinical practice, including patient age, sex, ethnicity, socioeconomic status, BMI, HbA1c, renal function, microvascular/macrovascular complications, and other comorbidities *(Wilkinson et al., 2018c, Heintjes et al., 2017, Chu et al., 2017, Geier et al., 2014, Grabner et al., 2015)*.

Nevertheless, no previous studies extensively quantified the association of these factors with the prescribing selection of various ADDs or categorised these factors to explore which category has the most impact on decision-making, particularly following the introduction of newer ADDs. The introduction of newer ADDs provides prescribers not only with wider treatment alternatives for T2DM but also with ADDs that may have independent cardiovascular and renal benefits. Generally, factors associated with drug prescribing in clinical practice may indirectly reflect prescriber adherence to guideline recommendations and specific drug features. Accordingly, this emphasises the significance of studying which and how factors contribute to decision-making in clinical practice in a systematic and structural way to assess the process of patient care and understand the possible predictors of drug prescribing *(Davari et al., 2018).*

A systematic investigation of factors associated with ADP is still lacking. Therefore, this systematic review (SR) and meta-analysis (MA) aimed to summarise, classify, and quantify factors associated with ADP both at drug initiation and intensification stages.

2.2 Method

The SR and MA are presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, Appendix S.2.1 *(Moher et al., 2009)*. The protocol is registered in the international prospective register of systematic review (PROSPERO) (Registration number: CRD42020173917).

2.2.1 Search strategy

The search strategy was guided using the Population, Intervention, Comparison, and Outcomes (PICO) approach *(Thomas J, 2020)*. Accordingly, three main concepts were included in the search strategy corresponding to the population (patients with T2DM), intervention (ADDs), and outcome (factors associated with ADP). Then the search strategy was developed using the synonyms of each concept in free text and Medical Subject Heading (Mesh) forms.

Medline/PubMed, Embase, Scopus, and Web of Science databases were searched from January 2009 until the search date (April 2020). The time interval of the search strategy started from 2009 to ensure the inclusion of the newer antidiabetic groups in the majority of retrieved studies since the newer ADDs, DPP4-I and SGLT2-I, were introduced from 2009 onwards. To ensure literature saturation, additional searches were performed on ProQuest and Open Grey (http://www.opengrey.eu/) databases to retrieve any other relevant articles, theses, and unpublished literature. A supplementary search was conducted in January 2021 to cover the period between April 2020 and January 2021 (the date of starting data analysis), and it included the following:

- Screen the reference lists of included articles.
- Activate the alert function of the searched databases like Web of Science for any newly published relevant papers.

- A hand search of the following journals: Diabetes Research and Clinical Practice, BMJ Open Diabetes Research & Care, Journal of Endocrinology, and The Lancet Diabetes and Endocrinology.
- Conduct an updated search on the Medline database for any newly published relevant articles.

Experienced researchers and an academic librarian at the University of Strathclyde independently reviewed the search strategy. The search strategies for all databases are available in Appendix S.2.2

2.2.2 Eligibility criteria

Eligible studies included those that evaluated factors associated with ADP among adult patients with T2DM in the primary care or outpatient setting and published in English. The hospital setting was excluded since hospitalised patients are more vulnerable to developing hypoglycaemia or hyperglycaemia, a situation where oral ADDs are not recommended, and insulin is the preferred treatment option alongside close glucose monitoring *(Marín-Peñalver et al., 2016)*. Only quantitative observational studies were included from peer-reviewed journal articles and unpublished literature. Table 2.1 summarises the inclusion and exclusion criteria.

Table 2.1: Study inclusion and exclusion criteria

Category	Inclusion criteria
Language	English
Publication year	Jan 2009 to April 2020
Publication type	Studies reported factors associated with antidiabetic drug prescribing or provided patient or prescriber characteristics at or prior to the prescription of antidiabetic drugs.
Methodology	Quantitative observational study designs
Diabetes type	Only type 2 diabetes mellitus
Patients	Adult patients who were prescribed any of the following antidiabetic groups: Biguanide (metformin), Sulfonylurea (SU), thiazolidinedione (TZD), Dipeptidyl-peptidase 4 inhibitors (DPP4-I), sodium-glucose transporter2 inhibitors (SGLT2-I), Glucagon-Like peptide receptor agonist (GLP1-RA), and insulin
Category	**Exclusion criteria**
Language	Other than English
Publication year	Published before January 2009
Publication type	Reports, commentaries, editorials, book chapters, systematic reviews, and meta-analysis
Patients	Studies on children, adolescents, pregnant or breastfeeding women
	Studies included types of diabetes other than T2DM, such as type 1 DM or gestational diabetes
Outcome	Studies did not clearly state that factors were collected at baseline
	Studies conducted in the inpatient setting
	Studies without relevant outcomes (e.g., switching medicine, discontinuation)
	Studies had not specified the type of antidiabetic groups being studied

2.2.3 Study selection

The search results from all databases were imported to the EndNote reference software, where the primary reviewer removed duplicates. Two stages of study selection were conducted using the Covidence software (https://www.covidence.org/): initial screening of titles and abstracts of the bibliographic database search results where studies that met the above inclusion criteria were identified and then progressed onto full-text screening. A total of 20% of included studies was validated by two independent reviewers (a 10% random subset for each) at each step of title/abstract and full-text screening. The degree of agreement between reviewers was calculated as a percentage and categorised into

poor (<70%), fair (70-79%), good (80-89%), and excellent (>90%) *(Watkins and Pacheco, 2000)*. Lastly, a final list of eligible articles was produced as a consensus of all reviewers, with the reasons for exclusion recorded at the full-text screening step.

2.2.4 Data extraction

Data extraction was done using an Excel spreadsheet, and the initial extraction form was created following Cochrane recommendations for collecting data which was modified as appropriate and piloted on 10% of included studies. The items of the extraction form are presented in Table 2.2. The primary reviewer extracted all relevant data from all included studies. In addition, two independent reviewers validated a total of 20% of included studies. The identified factors were classified into four categories: demographic factors, clinical factors, socioeconomic factors, and prescriber-related factors. These categories were initially informed by the literature on factors affecting physicians' prescribing decisions in general *(Sharifnia et al., 2018)* and by piloting 10% of included studies.

Table 2.2: Extracted items from included studies

Field	Items
Study details	**Identification**: author, publication year, sponsor source, country **Method**: design, data source, ascertainment of T2DM diagnosis, study duration, analysis method
Population	Age, sex, comorbidities, socioeconomic status, diabetes duration, lab values as HbA1C and renal function
Intervention	Antidiabetic drugs involved, stage of treatment, and stage definition
Outcome	Outcome definition, sample size, identified factors grouped into categories, type of effect measures (odds ratio or others)

2.2.5 Quality assessment

Several tools are available to appraise the risk of bias or evaluate the methodological quality of the primary studies. The selection of the most appropriate tool relies primarily on the study design *(Ma et al., 2020)*. Among these tools, the most commonly used one for cohort studies is the Newcastle-Ottawa Scale (NOS), which has the advantage of being Adaptable according to the study subject *(Ma et al., 2020)*. NOS contains eight items that appraise the quality of a

study based on three main perspectives: the selection of study group, the comparability of studied groups, and the ascertainment of outcomes. The quality of a study was judged in this tool using a star system; each item can get a maximum of one star, except the comparability section can get a maximum of two stars *(Wells et al., 2000)*. Accordingly, each study can get a final score that ranges from 0 to 9. However, thus far, no universal threshold has been established for categorizing the NOS; hence the score was categorized by applying the following thresholds for converting the NOS to the standards of the Agency for Healthcare Research and Quality (AHRQ) as reported in previous systematic reviews *(Robinson et al., 2021, Sharmin et al., 2017)*:

- Good quality: studies got 3 or 4 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome/exposure domain.
- Fair quality: studies got 2 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome/exposure domain.
- Poor quality: studies got 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain

A detailed description of the applied decision rules of the NOS is presented within Appendix S.2.3. Based on the outcome and exposure in this study (factors associated with ADP and ADDs, respectively), the fourth item in the selection domain of the NOS was considered to be not relevant (NR) since all factors were present at the start of the study. Furthermore, the second item in the outcome domain was considered not relevant since factors were required to be the most recent before or at the time of drug prescribing; thus, no follow-up was needed. Consequently, after discussion, it was decided to award the star of these two items for all studies instead of deleting them to follow the same scoring categorisation scheme applied in previous studies.

For assessing the quality of cross-sectional studies, an adapted tool of NOS was used in this study, which was also applied in several previous systematic reviews *(Chang et al., 2020, Modesti et al., 2016)*. The modified tool is composed of seven items on the

same perspectives as the original tool, which evaluates the adequacy of study design, recruiting strategy, response rate, representativeness of the sample, reliability of the result, and appropriateness of statistical analyses. This tool uses a staring system to judge the quality of the study, where each study can get a maximum score of ten and a minimum of zero. Scores of nine to ten were considered as very good and seven to eight as good, while five to six stars were rated as satisfactory and zero to four as unsatisfactory (Appendix S.2.3). Since there is no universal threshold for categorising the score of the adapted NOS, the cut-off categorisation was determined based on previous literature *(Chang et al., 2020, Modesti et al., 2016)*. The primary reviewer carried out the quality assessment of included studies, and two independent reviewers validated a random 10% of included studies.

2.2.6 Data synthesis

The choice of the synthesis method (MA or narrative synthesis) for each of the identified factors was determined based on, firstly, the number of studies examining the association of the individual factor with each class of ADDs; and secondly, the variability in the measurement or definition of the studied factors across included studies. For instance, despite macrovascular diseases being frequently investigated, they were not consistently examined among included studies because they were presented using several concepts or measures (e.g., ischemic heart disease, cerebrovascular disease, heart failure, and peripheral vascular disease). Therefore, fewer studies reported each disease per antidiabetic group, where conducting a MA would have been less applicable and unreliable. As a result, only narrative synthesis was utilised to summarize the result of macrovascular diseases association with ADP. Data synthesis using MA included age and sex (demographic factors), as well as glycaemic status, obesity, and renal function (clinical factors). On the other hand, narrative synthesis was used to summarise the results of all other factors.

2.2.6.1 Meta-analyses

MA is an established statistical technique that combines the results of multiple independent primary studies addressing a specific research question *(Mikolajewicz and Komarova, 2019).* It started to be applied in medical research in the late 1970s, but its use exponentially increased over time *(Haidich, 2010)*. While narrative synthesis focuses more on statistical significance, MA focuses on both the direction and magnitude of the result. Accordingly, conducting MA has the advantage of improving the statistical power, and the precision of the results since combining the samples of individual studies will produce a larger overall sample size and, thus, a higher precision. Additionally, it can be used to assess the degree of conflict among studies investigating a specific research question as well as to explore and quantify the possible reasons for different study results *(Haidich, 2010).*

In the current study, a quantitative synthesis was generated for the following factors: sex, age, glycaemic status (HbA1c), obesity, and renal function by conducting a separate MA for the individual factor; thus, a total of five meta-analyses were performed.

Applied meta-analysis model

In the MA, each study is given a weight as a measurement of study precision to generate a valid overall estimate that is representative of all included studies *(Mikolajewicz and Komarova, 2019, Michael Borenstein, 2009a).* The most commonly used weighing scheme is the inverse of variance weighting since it acts as a measure of both the sample size and variance; studies with larger sample size and smaller standard error get a higher weight as they are considered more reliable *(Mikolajewicz and Komarova, 2019, Michael Borenstein, 2009a).* The inverse-variance weighting scheme is widely used in two models of MA: the fixed-effect model and the random-effect model *(Mikolajewicz and Komarova, 2019, Michael Borenstein, 2009a).*

The fixed-effect model assumes that all studies originated from one homogenous population with a common true effect size, and the heterogeneity between studies is assumed to be zero *(Michael Borenstein, 2009a, Mikolajewicz and Komarova, 2019, Cheung, 2015).* Therefore, the only assumed variance is the one related to the intra-

study variability or sampling error, which is defined as the deviation of each study's effect size from the true effect size of that study's population that occurs as a result of the sampling procedure (i.e., all studies sampled their participants from the same target population) *(Michael Borenstein, 2009a, Mikolajewicz and Komarova, 2019, Cheung, 2015)*. Accordingly, this model can be applied when the goal of MA is to compute the overall effect size that would be generalised only to other examples of the same population's characteristics or when there is a justification for considering all studies to be identical.

On the contrary, the random effect model allows for heterogeneity among studies by assuming that each study comes from a different population, so having different true effect sizes *(Michael Borenstein, 2009a, Mikolajewicz and Komarova, 2019, Cheung, 2015).* Based on the above assumption of the random-effect model, two sources of heterogeneity exist in each study. The first one relates to between-study variance, representing the deviation of the true effect size of each study from the average true estimate of all included studies, whereas the second one relates to the sampling error *(Mikolajewicz and Komarova, 2019, Michael Borenstein, 2009a).* These two errors correspond to two levels in the MA; hence the random-effect model can be treated as a two-level MA *(Fernández-Castilla et al., 2020).* The random-effect model is usually preferred over the fixed-effect one since the results from the random-effect model can be generalised to the subsequent research. In contrast, the fixed-effect results can be extended only to studies included in the analysis *(Mikolajewicz and Komarova, 2019, Michael Borenstein, 2009a).*

Besides the assumption of the normal distribution of the measured outcome, one of the critical assumptions in the conventional MA (i.e., two-level random effect model and one-level fixed effect model) is the independency of effect sizes from included studies *(Cheung, 2019).* Still, in various research, the effect sizes within primary studies could be statistically dependent *(Cheung, 2019).* Multivariate effect size is a typical example of dependent effect size, including examining multiple treatment groups in comparison to a similar or shared control group where some participants are used to calculate the effect size of all treatment groups *(Cheung, 2014, Cheung,*

2019). In this MA, several studies reported more than one effect size for each examined factor as they assessed the outcome on multiple antidiabetic groups. The included participants were used for calculating the effect sizes of all groups since the investigated antidiabetic groups were compared to each other. That created a level of dependency among effect sizes reported per study; hence the conventional MA could not be applied as the ignorance of dependence would bias the results and underestimate the associated standard error, which might lead to an inflated level of significance *(Cheung, 2014).*

In the current MA, a three-level MA model was applied as an approximation to the multivariate model by introducing the type of antidiabetic group as a variable representing different effect sizes within studies. The three-level MA is an extension of the conventional random-effect model, which incorporates a third variance component into the model that represents the heterogeneity of within-study outcomes *(Van den Noortgate et al., 2015).* As a result, three variance components are introduced into the model. The first one relates to the sampling variance for each effect size (level-1), the second one represents the variance within study outcomes (level-2), while the third one relates to the variance between-study outcomes (level-3) *(Van den Noortgate et al., 2015).* Accordingly, this model consists of three regression equations that are combined into one formula, as shown in equation 1 *(Van den Noortgate et al., 2015).*

$$djk = Y00 + u0k + vjk + rjk \ldots \text{equation 1}$$

djk: estimate of true effect size of included studies; jk represents the effect size j in study k, Y00: overall population effect, u0k: within-study variance on level-2, vjk: between-study variance on level-3, rjk: the residuals which represents the deviation of effect sizes of multiple outcomes from their corresponding population estimate.

The three-level MA assumes that the residuals at each level are independent of each other, of those at different levels, and the regression coefficient. Also, it assumes that the residuals are normally distributed with study-related and outcome-related variance *(Van den Noortgate et al., 2015).* The following parameters are estimated from the three-level model using the maximum likelihood estimation

procedure: the regression coefficient, which represents the overall effect size, within-study variance, and between-study variance *(Van den Noortgate et al., 2015).*

As stated previously, the primary source of dependency among effect sizes in this MA is examining the outcome of multiple antidiabetic groups within each study, which was observed among several primary studies. Therefore, each antidiabetic group was assigned a specific identification number (*group_id*), which was used to define the second level (level-2) of the three-level MA model to represent within-study (between-outcomes) variance. Moreover, each study was assigned a specific id number (*study_id*) to define the higher level (level-3) of the three-level model. However, two of the included studies, Montvida et al. *(Montvida et al., 2018)* and Ou et al. *(Ou et al., 2017)*, reported two effect sizes for each antidiabetic group since it evaluated the outcome at two stages of treatment. Nonetheless, the effect sizes were considered independent; thus, each stage of treatment was assigned a different study_id number *(Ou et al., 2017, Montvida et al., 2018)*. Also, in Saine et al., the outcome was tested using four different datasets; hence the result from each dataset was coded with a different study_id number *(Saine et al., 2015).*

Coding and computation of effect sizes for meta-analysis

In the majority of included studies, the reported data on the distribution of certain factors among antidiabetic groups were presented either in the form of odds ratios (OR) or frequency data, so it was agreed to use the OR as a measure of effect size in the present MA. OR is an association measure between specific exposure and outcome, which is defined as the odds of an outcome in the exposed group over the odds of the outcome in the non-exposed group *(Michael Borenstein, 2009c).* The odds represent a ratio of the probability that an outcome will occur in one group to the probability that the outcome will not occur in that group *(Michael Borenstein, 2009c).* The null value of OR is one, indicating the absence of difference in the outcome between the two groups *(Michael Borenstein, 2009c).* The natural log of OR was used in the analyses since the sampling distribution of the logOR is more likely to be normally distributed, a vital assumption in MA *(Bland and Altman, 2000, Higgins JPT, 2021).*

Studies to be included in the MA were required to report the investigated outcome as OR or to provide baseline data essential for OR calculation. When only baseline or descriptive data was provided, the following formula of a 2 X 2 contingency Table was used for OR computation *(Michael Borenstein, 2009c).*

	Outcome	No-outcome
Group 1	A	B
Group 2	C	D

OR= (A*D) / (B*C) … equation 2

The standard error (SE) and variance are usually incorporated in the MA as an index of the precision of effect sizes. Study variance represents the square of SE of logOR ((SElogOR)^2), which was calculated using the 95% confidence interval (CI) if it was reported, as illustrated in equation 3. Otherwise, equation 4 was followed to calculate the SE of logOR using the frequency data *(Michael Borenstein, 2009c).*

SE log OR = (ln upper limit CI – ln lower limit CI) / 3.92 … equation 3

SE log OR = square root of: (1/A) + (1/B) + (1/C) + (1/D) … equation 4

Furthermore, some studies reported baseline data as a continuous variable, such as mean age, mean HbA1c value, and mean BMI. In that situation, the standardized mean difference (SMD) using Cohen's d (the difference in the mean outcome between groups over the pooled standard deviation of the two groups) and its associated variance (Vd) were calculated, as shown in equations 5 and 6, respectively *(Michael Borenstein, 2009d).* The values of d and Vd were then converted to logOR and its variance by applying equations 7 and 8 *(Michael Borenstein, 2009b).*

$$d = (\text{Mean in treatment group} - \text{mean in control group}) / \text{SD pooled}$$

$$\text{Pooled standard deviation (SD pooled)} = \sqrt{((n1-1) * (S1^2)) + ((n2-1) * (S2^2))) / (n1 + n2 - 2)} \quad \text{... equation 5}$$

$$Vd = ((n1+n2) / (n1*n2)) + ((d^2) / (2 (n1 + n2))) \quad \text{... equation 6}$$

S1: SD of group 1 and S2: SD of group 2, n1: sample size of group 1 and n2: sample size of group 2

$$\text{Log OR} = d * (\pi/\sqrt{3}) \quad \text{... equation 7}$$

$$\text{V of Log OR} = Vd * (\pi^2 / 3) \quad \text{... equation 8}$$

For all studies that required calculation of OR, all calculations were performed manually, as well as using the online Practical Meta-Analysis Effect Size Calculator, which was developed by David B. Wilson *(Wilson)* to validate the manual calculations.

Effect sizes manipulation: data was manipulated in two situations

1- The presence of differences in the reference group

Besides the importance of having effect sizes expressed with the same kind of measure (i.e., OR in this case), it is also crucial to ensure that all effect sizes examined the studied factor in the same direction to get a reliable overall estimate. For instance, all included studies in the MA of age reported the data in one direction (older to younger), except Wang and colleagues' study *(Wang et al., 2013a)*, which assessed the outcome in the opposite direction; younger to older (< 65 years compared to >=65 years) *(Wang et al., 2013a)*. For the purpose of making all pooled studies in the same direction, switching in the reference group was done by taking the reciprocal of the original OR as described in equation 9. The value of SE of logOR is not affected by switching the reference group as reflected from equation 4 (SElogOR = SElogOR switch).

$$\text{As } OR = A*D/B*C \text{ then } OR_{switch} = B*C/AD. \text{ So, } OR_{switch} = 1/OR \quad \text{... equation 9}$$

2- The outcome factor was not reported as binary

Additionally, data that was reported in more than two categories were reconstructed into binary data to achieve one effect size per antidiabetic group per study. Two methods were suggested to achieve this: first, using baseline frequency data whenever it was available to reconstruct the categories of the studied factor into binary, then computing the crude OR and its associated variance *(Wilkinson et al., 2018c, Saine et al., 2015, van den Boom et al., 2020, Nicolucci et al., 2019).* And second, aggregating within-antidiabetic group effect sizes following Gleser & Olkin's (1994) procedure for aggregating dependent effect sizes *(Olkin, 1994).* However, the latter method requires prior knowledge of the correlation (r) level among aggregated effect sizes. As a result, the first approach was followed whenever the baseline data was available. Studies that did not report the baseline data and did not provide sufficient information for aggregating the effect sizes were excluded from MA *(Desai et al., 2012, Hartmann et al., 2020, Liu et al., 2017, Zaharan et al., 2014, Payk et al., 2015).*

Heterogeneity and model fitness

The statistical heterogeneity represents the diversity or spread of the investigated outcome among included studies. As stated in section 2.7.1, in addition to the sampling error (level-1) and between-study heterogeneity (level-3), the three-level model contains another source of variability representing within-study or between-outcomes heterogeneity (level-2).

Cochran's **Q** is a traditional method for assessing the variability among included studies in MA, which measures the deviation of each study's effect size from the overall estimate weighted by the inverse of study variance *(Cheung, 2015).* Since the value of Q depends mainly on sample size and the number of effect sizes (K), its use is limited *(Cheung, 2015).* Therefore, in the present MA, Higgins & Thompson's I^2 test statistic was conducted, a commonly used heterogeneity test that shows how much, in percentage, the observed value of Q exceeds the expected one when there is no heterogeneity among included studies *(Cheung, 2015).*

In the three-level MA, heterogeneity (I^2) distribution was measured over the three levels, producing three I^2 values. According to the 75% rule described by Hunter and Schmidt (1990), the heterogeneity was considered substantial if the sampling variance (level 1) contributed to less than 75% of the total heterogeneity *(Hunter, 2015).*

A log-likelihood-ratio test was performed to evaluate whether the three-level (full) model fits the variability in data better than the two-level (reduced) model *(Harrer et al., 2021, Assink and Wibbelink, 2016).* This test additionally indicates whether the variance between outcomes and between-study is significant. Two separate one-sided log-likelihood-ratio tests were performed, one for each level. In this test, the null hypothesis states that there is no difference between the full and reduced model; thus, the variance component of the tested level was fixed to zero *(Harrer et al., 2021, Assink and Wibbelink, 2016).* Accordingly, the model was reduced to two levels, and the importance of accounting for within-study variance (H0:V2 (level2)=0) and between-study variance (H0: V3 (level3) = 0) was evaluated *(Harrer et al., 2021, Assink and Wibbelink, 2016).* Lower values of fit indices of the Akaike information criterion (**AIC**) and the Bayesian Information Criterion (**BIC**) in the full model compared to the reduced one reflect a better performance of the full model *(Cheung, 2015).* Likewise, a significant value of the likelihood ratio value (LRT) comparing the two models (p-value < 0.05) indicates that the full model has a better fit to the variability in data compared to the reduced one, and it has a better estimation of the overall estimate, rejecting the null hypothesis *(Harrer et al., 2021, Assink and Wibbelink, 2016)*. That, in turn, shows that the amount of variability within-study (the level-2 reduced model) and between-study (the level-3 reduced model) is significant.

Moderator or sub-group analyses

The possible moderating effect of several variables related to study characteristics on the overall estimate was assessed by conducting an omnibus test for moderator analysis *(Assink and Wibbelink, 2016).* The null hypothesis (Ho) in the omnibus test assumes that the regression coefficients of all subgroups of the tested variable are

equal to zero, while in the alternative hypothesis (Ha), at least one of the regression coefficients is not equal to zero *(Assink and Wibbelink, 2016).*

In the present MA, several variables were examined for their impact on the overall estimate, including the type of antidiabetic groups, the stage of treatment at which the outcome was assessed (initiation, intensification, or not specified stage of treatment), quality of the study, type of analysis test used (adjusted vs. un-adjusted), study design, study duration, and year of publication. Additionally, the overall estimate was computed initially, including all studies that measured the outcome using continuous or categorical data since they examined the outcome in the same direction using the same effect measure. Subgroup analyses were conducted to assess if there was any significant difference in the overall estimate of studies by the type of outcome variable. Furthermore, some studies that reported the outcome as a categorical variable used a different categorisation method. Therefore, a subgroup analysis was performed to investigate the difference in the overall estimate according to the categorization scheme.

A P-value of < 0.05 indicates that the overall estimate varies significantly among the subgroups of the tested variable, and this variable contributes to the overall estimate. Additionally, the overall estimate of included studies within the subgroup of each variable was computed using a three-level model. However, two-level random effect models were used to compute the overall estimate by antidiabetic class since only one effect size is reported per antidiabetic group within the individual study.

Publication bias, outliers, and influential cases

Publication bias is a type of reporting bias in a MA that results from missing studies that are either unpublished or missed because of non-comprehensive searching *(Page et al., 2021, Hopewell et al., 2005).*

The funnel plot is a traditional visual method for assessing the presence of publication bias, which is a scatter plot of study effect sizes plotted on the x-axis against a measure of study size (typically, SE) on the y-axis *(Page et al., 2021, Sterne et*

al., 2005). No publication bias is considered if the plot shows a symmetric inverted funnel shape *(Page et al., 2021, Sterne et al., 2005).* Nevertheless, the asymmetry in the funnel plot could occur due to reasons other than publication bias; hence, the funnel plot should not be used alone as a diagnostic tool for publication bias *(Page et al., 2021, Sterne et al., 2005).*

In the present MA, a contour-enhanced funnel plot was performed. It is a funnel plot with contour lines representing the level of statistical significance (p-value), which helps in inspecting whether the area of missing studies is related to the statistical significance. That, in turn, determines if the asymmetry in the funnel plot is associated with publication bias or other sources *(Page et al., 2021).* The study effect sizes (logOR) were plotted on the x-axis against their related SE (SElogOR) on the y-axis. As the visual inspection of the funnel plot asymmetry is highly subjective, multiple statistical tests have been developed to assess the presence of asymmetry in the funnel plot. These tests include Egger's test, which introduces a regression model for a study effect size against its standard error. Limited evidence is available regarding the performance of these test statistics in the three-level model *(Sterne and Egger, 2005)*. Nonetheless, an extended Eggers' test that accounts for dependency among effect sizes has been proposed in a simulation study *(Fernández-Castilla et al., 2021)*. In the current MA, Egger's test was extended to be applied to the three-level model by introducing the SE of logOR as a moderator in the three-level model.

Moreover, the outliers can be detected by comparing 95%CI of the effect size to 95%CI of the overall estimate. Accordingly, the effect size was considered an outlier when its CI did not overlap with the CI of the pooled estimate *(Viechtbauer and Cheung, 2010)*. In this MA, the number of outliers was measured for each identified factor, and it was plotted as a histogram to display the distribution of outliers around the pooled estimate.

Nevertheless, not all outliers exert a substantial impact on the pooled estimate. Hence the presence of influential cases was investigated *(Viechtbauer and Cheung,*

2010). In the current MA, Cook's distance (D) was used to assess the presence of influential cases. It is considered a representative way to measure the impact of effect sizes on the overall fit from two aspects; the change in the pooled estimate when a certain case is removed and the change in the distance of one observation from the others. The larger Cook's D value, the greater the influential effect of the study *(Viechtbauer and Cheung, 2010)*. However, multiple cut-off points have been proposed to decide whether the study should be considered an influential case *(Cook, 1977)*. A value of >= 4/n (n: the number of effect sizes) was used as a cut-off point in our MA. Also, Cook's D values were plotted as a scatter plot to facilitate the interpretation of the results.

Sensitivity analysis

A sensitivity analysis was conducted to evaluate whether the results would be significantly influenced by the presence of outliers, which was examined by calculating the overall estimate after excluding the outliers to check how much these outliers would bias the pooled estimate.

Software

All analyses were conducted using the following packages in R software: metafor, forestplot, ggplot2, and dmetar packages. Details about the R syntax of all performed tests are described in Appendix S.2.3.

2.2.6.2 Narrative synthesis

When MA was not applicable, a narrative synthesis was conducted following the guidance of the Economic and Social Research Council (ESRC) Methods Programme *(Popay et al., 2006).* Multiple tools or techniques that are suggested in the ESRC guidance were used in this SR. Firstly, tabulation of the results, in which Tables were created to summarise the directions and magnitude of association of each studied factor with each antidiabetic group. Secondly, a textual description and grouping/clustering techniques were used, in which the results were summarized in text, and the outcome was grouped/clustered into four categories: demographic factors, clinical factors, socioeconomic factors, and prescriber-related factors.

2.3 Result

2.3.1 Study selection

From a total of 2331 identified studies that had title/abstract screened, 96 full articles were examined for inclusion, and 35 studies met all inclusion criteria for extraction and synthesis. Five studies were added after conducting a supplementary search from April 2020 until January 2021; thus, a total of 40 studies were included in the final review (Figure 2.1). The percentages of agreement between reviewers at the stages of title/abstract and full-text screening were 93.8% (excellent) and 85.7% (good), respectively. The disagreement was mostly related to the reason for exclusion, not the decision of inclusion or exclusion. All conflicts were resolved by discussion.

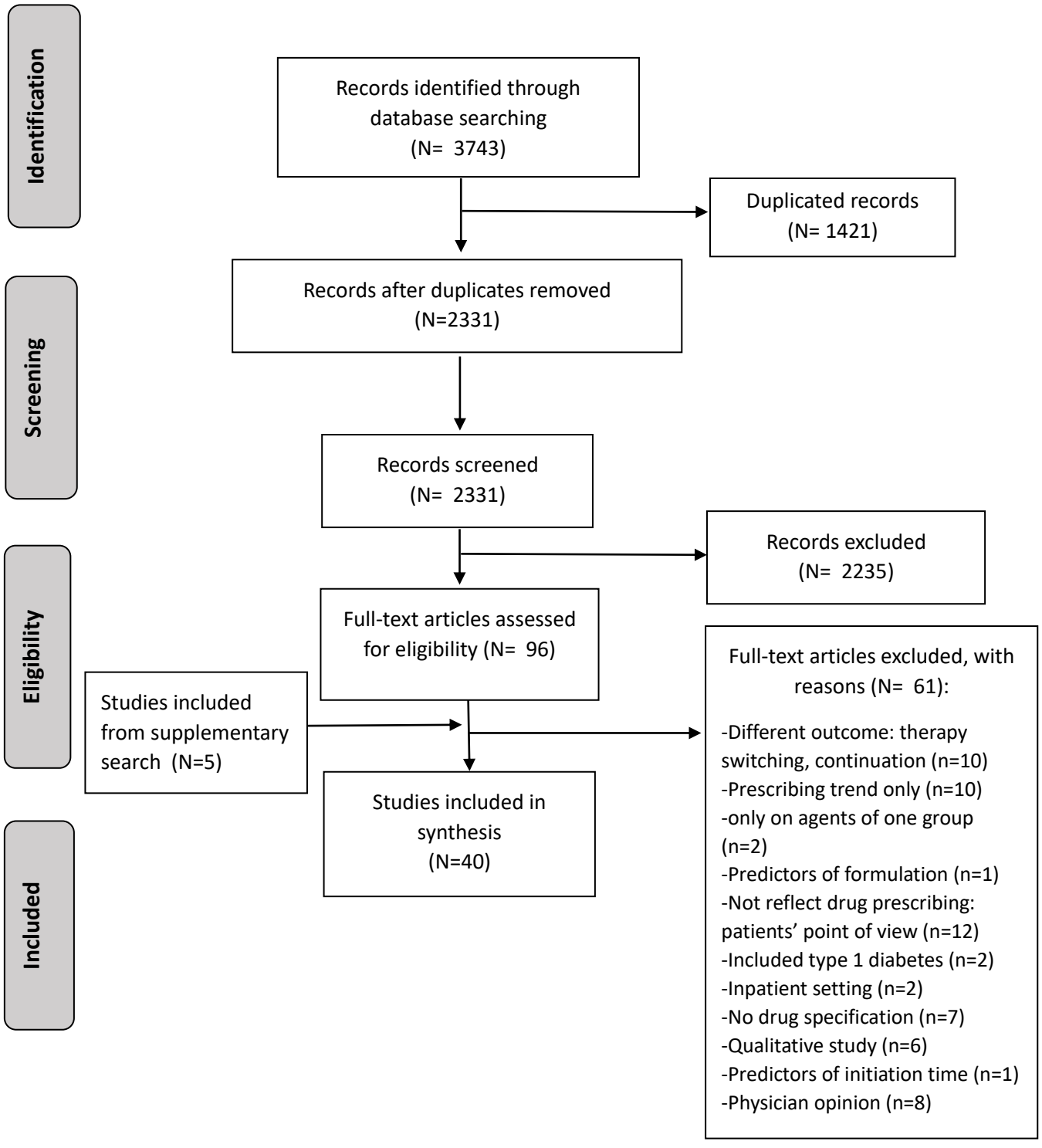

Figure 2.1: PRISMA flow chart of screening process to identify relevant studies (Jan 2009 - Jan 2021)

2.3.2 Study characteristics

All included studies were published from 2009 to 2020, with more than two-thirds (n=33, 82.5%) published from 2013 and onwards; Table 2.3 *(Ackermann et al., 2017, Arnold. et al., 2018, Arnold et al., 2018, Dhanaraj et al., 2013, Fujihara et al., 2017, Gentile et al., 2018, Hartmann et al., 2020, Heintjes. et al., 2017, Katakami et al., 2020, Kim et al., 2019a, Korytkowski et al., 2014, Kostev et al., 2014, Levin et al., 2014, Liu et al., 2017, Longato et al., 2020, Montvida et al., 2018, Moreno Juste et al., 2019, Nicolucci et al., 2019, Ou et al., 2017, Payk et al., 2015, Saine et al., 2015, van den Boom et al., 2020, Wang et al., 2013a, Whyte et al., 2019, Wilkinson et al., 2018c, Yu et al., 2017, Zaharan et al., 2014, Zoberi et al., 2017, Grimes et al., 2015, Abdelmoneim et al., 2013, Grabner et al., 2015, Geier et al., 2014, Morita et al., 2019).* About 90% (n=36) of articles were of cohort study design *(Arnold. et al., 2018, Arnold et al., 2018, Cai et al., 2010, Fujihara et al., 2017, Gentile et al., 2018, Grimes et al., 2015, Hartmann et al., 2020, Heintjes. et al., 2017, Hirsch et al., 2011, Katakami et al., 2020, Kim et al., 2019a, Korytkowski et al., 2014, Kostev et al., 2014, Levin et al., 2014, Liu et al., 2017, Longato et al., 2020, Montvida et al., 2018, Moreno Juste et al., 2019, Nicolucci et al., 2019, Ou et al., 2017, Stargardt et al., 2009, van den Boom et al., 2020, Wang et al., 2013a, Whyte et al., 2019, Winkelmayer et al., 2011b, Yu et al., 2017, Zaharan et al., 2014, Zhang et al., 2010, Zoberi et al., 2017, Abdelmoneim et al., 2013, Brouwer et al., 2012, Desai et al., 2012, Geier et al., 2014, Wilkinson et al., 2018c, Grabner et al., 2015, Morita et al., 2019),* while only three studies were cross-sectional *(Dhanaraj et al., 2013, Payk et al., 2015, Saine et al., 2015),* and one was a multiple case-comparative study *(Ackermann et al., 2017).*

In addition, more than one-third of studies (n=15; 37.5%) originated from the United States *(Ackermann et al., 2017, Arnold. et al., 2018, Arnold et al., 2018, Cai et al., 2010, Hirsch et al., 2011, Korytkowski et al., 2014, Levin et al., 2014, Montvida et al., 2018, Payk et al., 2015, Yu et al., 2017, Zhang et al., 2010, Zoberi et al., 2017, Brouwer et al., 2012, Desai et al., 2012, Grabner et al., 2015).* Five articles were cross-national *(Hartmann et al., 2020, Heintjes. et al., 2017, Nicolucci et al., 2019, Saine et al., 2015, Stargardt et al., 2009),* and the other 20 studies were conducted in the United Kingdom (n=4, *(Grimes et al., 2015, Whyte et al., 2019, Wilkinson et al., 2018c, Zaharan et*

al., 2014)), Japan (n=3, *(Fujihara et al., 2017, Katakami et al., 2020, Morita et al., 2019)*), Italy (n=3, *(Gentile et al., 2018, Longato et al., 2020, Moreno Juste et al., 2019)*), Germany (n=3, *(Kostev et al., 2014, van den Boom et al., 2020, Geier et al., 2014)*), Canada (n=2, *(Wang et al., 2013a)*), Taiwan (n= 2, *(Liu et al., 2017, Ou et al., 2017)*), Austria (n=1*, (Winkelmayer et al., 2011b)*), Korea (n=1, (Kim et al., 2019a)), and India (n=1, *(Dhanaraj et al., 2013)*).

The total number of participants from the included studies was 5,327,502 adult patients with T2DM, excluding one study that reported the number of visits rather than the number of patients *(Payk et al., 2015).* Oral ADDs were examined in almost 90% of studies (n=36), whereas the injectable drugs were evaluated in about half of included studies (n=21, 52.5%). Among antidiabetic groups, the most frequently examined ones were SU (n=21), metformin (n=20), and DPP4i (n=19); SGLT2-I was the least studied group (n=11). Only 29 studies stated at which stage of treatment the outcome was observed: whether at the initiation (n=14) or intensification (n=15) stage. Furthermore, the outcome in more than half of the studies (n=23, 57.5%) was reported as OR[95%CI]. Tables 2.3 and 2.4 provide detailed information about the characteristics of included studies and descriptions of the studied outcome, respectively.

2.3.3 Quality assessment results

Cohort studies

Utilising NOS and following pre-specified decision rules (section 2.2.5), the quality score of included cohort studies and a multiple-case comparative study ranged from 5 to 9, with the majority of studies (n=29/37, 78.4%) rated as good. Regarding the selection of study groups, only five studies did not describe the representativeness of the included cohort. Among articles that reported the representativeness of their sample (n=32), 16 were somewhat representative of their studied population. The participants who were prescribed different ADDs were selected in each study using the same source of data and under the same inclusion/exclusion criteria. All studies also ascertained the exposure of cohorts to ADDs using medical, prescribing, or dispensing records. Moreover, eight out of 37 studies did not adjust for the possible

confounders in the analyses of the study outcome. Consequently, the quality of these studies was rated as poor following the grading system described in section 2.2.5. Lastly, the outcome has been ascertained using medical or pharmacy records in all studies, yet only 11 studies adjusted for missing data in their analyses. Appendix S.2.5 contains the results of the quality assessment of cohort studies

Cross-sectional studies

Of the three cross-sectional studies, two were rated very good (Payk. et al. 2015, Saine et al. 2015) and one satisfactory *(Dhanaraj et al., 2013)*. Dhanaraj et al. (2013) did not describe the representativeness of their sample and did not provide any calculation or justification for the sample size; they also did not adjust for possible confounders. All three studies provided detailed descriptions of the ascertainment of exposure and outcome. Full information about the quality assessment of cross-sectional studies is available in Appendix S.2.5.

Table 2.3: Characteristics of the 40 studies which were eligible for inclusion

Author, year, country	Study design/ duration	Data source	# Of Participants/ Age/ Sex	Antidiabetic drug studied	Comparison group	Stage of treatment	Analysis method
(Winkelmayer et al., 2011b), Austria	Retrospective cohort/ 1/2007 - 6/2008	Insurance claims data	39,077 patients / 19 -100 years; mean 63.4 years/ F: 50.4%	Metformin	Other oral hypoglycaemic (SU, TZD, alpha-glucosidase inhibitor, DPP4-I, combination, others)	initiation	multivariable logistic regression
(Abdelmoneim et al., 2013), Canada	Retrospective cohort/ January 1998- December 2010	Administrative drug insurance database	31,421 patients / >=65 years; mean: 74.8 years / F: 49%.	Metformin	SU monotherapy	initiation	multivariable logistic regression models
(Brouwer et al., 2012), United States	Retrospective cohort/ Jan 1998- Dec 2009	Vendor-based electronic health records	1972 patients / >21 years; median: 54 years/ F: 52.5%	metformin, SU	metformin vs. SU, TZD, combination. SU vs. combination	initiation	multinomial regression model
(Liu et al., 2017), Taiwan	Retrospective cohort/ January 2006- December 2010.	The National Health Insurance Research Database (NHIRD)	28,640 patients/ >=20 years; mean: 57.4/F: 47.3%	Non-metformin prescriptions: SU, glinides, TZD, alpha-glucosidase inhibitors, and DPP4-I)	Metformin Prescription	Initiation	Logistic regression
(Wang et al., 2013a), Quebec, Canada	Dynamic historical cohort study/ January 2003 - December 2011	Electronic health records and the evidence scale from the Evidence-Practicality-Conformity questionnaire	1279 patients/ >=18 years, 53.4% >=65 years/ F: 50.8%	Metformin	non metformin (SU, TZD, others: acarbose, repaglinide, Sitagliptin)	Initiation	Multivariate generalized estimating equation analysis

(Geier et al., 2014), Germany	Retrospective cohort/June 2003-December 2009	Disease Management Programs for type 2 diabetes and pharmacy dispensing claims data	10,657 patients/ 40- 79 years; mean: 61.47 years/ F for 51%	Metformin	SU	Initiation	Multiple logistic regression
(Fujihara et al., 2017), Japan	Retrospective cohort/Dec 2009 - Mar 2015	The Japan Diabetes Clinical Data Management Group	2666 patients/ >=20 years; overall mean: 60.9 years/F: 35.9%	Metformin, DPP-4Is	Sulfonylureas	initiation	Multinomial logistic regression analysis
(Desai et al., 2012), United States	Retrospective cohort/ Jan 2006-Dec 2008	Prescription claims data	254,973 patients /18-100 years; mean: 58.2 years/ F: 47.3%	Metformin	Not clear (non-metformin)	initiation	multivariable logistic models
(Grimes et al., 2015), Ireland	Retrospective cohort/Jan 2008-Dec 2009	pharmacy claims database	20947 incident users of antidiabetic agents/ >=40 years/ F:42.1%	Metformin	SU	initiation	Adjusted logistic regression
(Cai et al., 2010), United States	Retrospective cohort/ Jan 2006 - June 2008	The Ingenix claims database	240426 patients/ 26-88 years; mean: 54.4/ F: 44.8%	Sitagliptin	non- Sitagliptin oral antidiabetics	not specified	Chi-square statistics
(Saine et al., 2015), United States and United Kingdom	Cross-sectional/ THIN: October 2009 -September 2012, US Medicare: August 2009 - December 2011, HIRD: August 2009 -July 2012	UK: (CPRD), (THIN), US: Medicare, (HIRD)/	UK: 43,466, US: 631,273/ Mean: UK: 58.8, US:67.6 years/ F: UK: 42.4%, US:55%	Saxagliptin	Compared to other oral antidiabetic	not specified	Conditional logistic regression

(Wilkinson et al., 2018c), United Kingdom	Retrospective cohort/ January 2014- July 2017	the UK Clinical Research Datalink (CPRD)	14,149 individuals/ >=18 years; Mean: 60 years/ F: 40.3%	SGLT2 inhibitors, DPP-4 inhibitors	SU	1st intensification	Multinomial logistic regression
(Grabner et al., 2015), United States	Retrospective cohort/ Jan 2011-Sep2013	Administrative claims data; HIRD	Overall: 27790 patients/ >=18 years; mean 55.03years/ F:39.4%	Canagliflozine	DPP4i	Intensification not specified level	Multivariable logistic regression
(Ou et al., 2017), Taiwan	Retrospective cohort/ 2011-2012	National health insurance database	32724 patients / ≥ 20 years	DPP-4i	Other antidiabetic drugs include SU, metformin, TZD, and acarbose	1st and 2nd intensification	Multiple logistic regression
(Stargardt et al., 2009), Finland, France, Germany, Norway, Poland, Spain, and the UK	Retrospective cohort/ June 2006 and February 2007	Clinical records of office-based physicians or health centres	1218 patients: 891; added SU 327 added TZD/ >=30 years; Mean: SU, TZD: 61.0, 57.8 years	TZD	SU	1st intensification	probit regression analysis
(Payk et al., 2015), United States	cross-sectional study/ 2003 to 2004 and 2007 to 2010	National Ambulatory Medical Care Survey (NAMCS)	7042 visits, weighted, represented an extrapolated national estimate of 280,733,405 patients visits/ >=18 years; Mean: 61.6 years/F: 52%	SU	Not clear which is the comparison group	Not specified	weighted sampling, A multivariate logistic regression model

(Zhang et al., 2010), United States	Retrospective cohort/ October 1, 2006 - June 2008	Electronic medical record (EMR) database	41836 patients/ >=30 years; Mean overall: 60.08	Sitagliptin	Non-Sitagliptin (SU, Metformin, TZD)	Not specified	Adjusted logistic regression analysis
(Morita et al., 2019), Japan	Retrospective cohort/ October 2012-September 2016	Diagnosis Procedure Combination (DPC) administrative database	224761, For metformin and DPP4i users only: 74935.658	DPP4i	Metformin	Initiation	Univariate logistic regression
(Kim et al., 2019a), Korea	Retrospective cohort/ 2014-2016	The National Patient Sample data (HIRA-NPS)	3609 patients/>=20 years/ F:48.9%	older (SU, TZD) or newer agents (SGLT2I, DPP4-I)	Newer group vs. older group	1st Intensification	Logistic regression analysis
(Heintjes. et al., 2017), Netherlands, Italy, Spain, United Kingdom	Retrospective cohort/ 5 years: 2007 to 2011 (ES, IT, and NL) or 2008 to 2012 (UK)	population-based databases in each country	485,570 patients/ >=18 years	metformin, SU, TZD, DPP4i, and 'other' (e.g., alpha-glucosidase inhibitors and meglitinides), or the injecTable classes of GLP-1ra or insulin.	1st line SU were compared to the other antidiabetic monotherapy; in 2nd line each combination (metformin+SU, metformin+DPP4i, metformin+TZD) compared to other second line combination	initiation and intensification; 1st line, 2nd line, 3rd line, 4th line	Poisson Regression
(Nicolucci et al., 2019), 38 Countries	Prospective cohort/December 2014 - June 2016	Standardized electronic case report form, and electronic health records in Canada, Denmark, France, Norway, and Sweden	14,668 patients/ ≥18 years; mean: overall: 57.5 years/ F: 46.1%	DPP4i, SGLT2i, GLP1-RA	SU	1st intensification (second line)	Firth logistic regression

(Hartmann et al., 2020), Germany, Austria, Switzerland, and Luxemburg	Retrospective cohort / 2000-2017	the DIabetes Versorgungs-Evaluation (DIVE) registry and the Diabetes-Patienten-Verlaufsdokumentation (DPV) database	4770 patients/ > 18 years; median: BOT initiated, OAD w/o insulin, GLP w/o insulin: 64.0, 62.6, 55.3 years/ F: overall:45.7%	GLP1- RA, basal insulin, oral drugs (Metformin, SU, glinides, DPP-4i, SGLT-2i, alpha glucosidase inhibitors)	Not clear	1st Intensification	multivariable linear and logistic regression models
(Longato et al., 2020), Italy	Retrospective cohort / Jan 2014-Sep 2018	Administrative claims data	12996 patients/ calculated mean for both groups: 62.84 years/ F: 36.8%	SGLT2-I and GLP1-RA	SGLT2-I vs. GLP1-RA	Not specified	Chi-square, standardized mean difference, or many Whitney
(Ackermann et al., 2017), United States	Multiple case-comparative study design/ January 2011- June 2015	Administrative database	77744 patients/ >=18 years, 25.7% >=65 years/ F: 43.1%	DPP4-I, GLP1-RA, SGLT2-I, SU, TZD	Compared to each other	1st intensification	Multinomial logistic regression
(Whyte et al., 2019), England	Retrospective cohort/ January 2012-December 2016	Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database	49,380 patients/ >= 18 years; Mean: 68.7 years/ F: 43.9%	SGLT2-I, GLP1-RA, metformin, insulin, SU, DPP4-I, , TZD	Not clear	Not specified	Logistic regression, mixed effects model
(Arnold et al., 2018), United States	Retrospective cohort/ Not stated	the Diabetes Collaborative Registry (DCR)	157,551 patients/ ≥18 years; Mean: 68.1 years/ F:42.8	SGLT2-I, GLP1-RA, metformin, insulin, SU, DPP4-I, TZD	Not clear	Not specified	Possion regression
(Arnold. et al., 2018), United States	Retrospective cohort/ 2013-2016	the Diabetes Collaborative Registry (DCR)	456,106 patients/ Mean: 67.6 years	SGLT2-I, GLP1-RA, metformin, insulin, SU, DPP4-I, TZD	Not clear	Not specified	Possion regression

(Zaharan et al., 2014), Ireland	Retrospective cohort/ 2008–2012	National pharmacy claims databases	From all regions: 524305, >=16 years	Metformin, SU, TZD, GLP1-RA, DPP4-I	Not clear what is the comparison group	Not specified	Adjusted logistic regression
(Zoberi et al., 2017), United States	Retrospective cohort/ July 2008-July 2013	Electronic medical records; Primary Care Patient Data (PCPD) Registry	Patients; Overall: 1952/ >=18 years Mean: Overall:59.3 years. F: 60.76%	Non-metformin, Insulin	Metformin, non-insulin	Not specified	Chi-square for independent sample t-tests
(Montvida et al., 2018), United States	Retrospective cohort/ 2005-2016	Centricity Electronic Medical Records	1st line: 1,023,340 patients 2nd line: 357482 patients	GLP1-RA, SGLT2-I, metformin, insulin, TZD, DPP4-I, SU	each one to the others	Initiation and intensification	descriptive only
(Katakami et al., 2020), Japan	Prospective cohort/ September 2014 -December 2015	collected data from clinics and hospitals	1806 patients/ mean:61.7 years/ F;38.4%	Metformin, SU, alpha-glucosidase inhibitors, TZD, glinides, DPP4-I, SGLT2-I, GLP1-RA, insulin	To each other	intensification	Firth logistic regression models
(Kostev et al., 2014), Germany	Retrospective cohort/ January 2003-December 2012	The Disease Analyzer database	10, 223 patients/ > 40 years; Mean for both groups: 65.69 years/F for both groups: 49.7%	Insulin	non-insulin	Initiation intensification	A multivariate Cox regression model for insulin

(Dhanaraj et al., 2013), India	Cross-sectional/June 2007 - March 2009	Data collected by doing laboratory analysis and assessing the presence of diagnosis at time of meeting in outpatient clinic	1185 patients/ mean age: 55 years/ F: 49%	Metformin, SU, insulin, pioglitazone	To each other	Not specified	Univariate logistic regression
(Yu et al., 2017), United States	Retrospective cohort/November 2014- February 2016	Practice Fusion cloud based ambulatory EHR platform	11,053 patients / ≥18 years; Mean overall: 61.26 years/ F: 51.5%	GLP-1-RA or basal insulin	GLP-1-RA versus basal insulin	Intensification; Not specified level of intensification	Boosted regression models (GBM), logistic regression model
(Levin et al., 2014), United States	Retrospective cohort/ January 2000 - March 2011	IMPACT, a managed care database	51,771 patients/ ≥18 years; Mean overall: 55.6 years/ F:40.2%	Insulin, GLP1-R	Oral antidiabetic	Intensification; Not specified level of intensification	t-test or chi square
(Gentile et al., 2018), Italy	Retrospective cohort/ 2004 - 2011	electronic medical records of database on diabetes centers (DC)/	All 366955; sample size included in the model 4 (N=44611)/ >= 18 years; mean: 65 years/ F: 44.2%	Insulin	Non-insulin	Intensification; Not specified level of intensification	Cox proportional hazard model
(Korytkowski et al., 2014), United States	Retrospective cohort / June 2005- November 2011	Electronic health records	1892 patients/ calculated mean age for all groups: 54.78 years/ F: 48.95%	Insulin, GLP1-RA	Oral antidiabetic	Intensification	t-test or chi square

(Hirsch et al., 2011), United States	Retrospective cohort/ October 1,2005, - January 2008	Electronic medical records	190, 444 patients; Sample size for multivariable model was 51048/ >= 18 years; mean: 62.4 years/ F: 51.9%	Exenatide	Non-exenatide	Not specified	Cox proportional hazard regression
(van den Boom et al., 2020), Germany	Retrospective cohort/ Jan 2014-Dec 2018	Disease Analyzer database (IQVIA)	10497 patients/18-90years, mean overall:63.6 years/ F overall: 45.9%	Insulin	Oral antidiabetic	Initiation	multivariable logistic regression model
(Moreno Juste et al., 2019), Italy	Retrospective cohort/ January 1 and December 31, 2016.	Administrative database	12753 patients / calculated mean age for all monotherapy groups: 63.9 years/ F: 45.76%	Metformin, SU, DPP4-I	To each other and others monotherapy	Initiation	t-test or chi square

SU; sulfonylurea, DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors, HIRD; the Health Core Integrated Research Database, CPRD; Clinical Practice Research Datalink, THIN; The Health Improvement Network,

Table 2.4: Description of the outcome of the 40 studies which were eligible for inclusion stratified into four categories of factors affecting prescribing decisions

Author	Outcome definition	Patients-related	Clinical-related	Socioeconomic	Prescriber-related	Reported as
(Winkelmayer et al., 2011b)	Associations of metformin initiation versus any other oral hypoglycaemic medication.	patient age, sex		Socioeconomic status	age, sex, speciality	OR, 95%CI
(Abdelmoneim et al., 2013)	Predictors of new monotherapy users	Age, sex	Microvascular (neuropathy, retinopathy, nephropathy) and macrovascular complications (as ischemic heart disease (IHD), cerebrovascular disease, heart failure (HF), peripheral vascular disease (PVD)), comorbidities (as hypertension (HTN) and dyslipidaemia)			OR, 95%CI
(Brouwer et al., 2012)	Factors influencing the selection of initial oral hypoglycaemic medication	Age, sex, race,	Glycaemic status (HbA1c), Serum creatinine			probability ratio, 95%CI
(Liu et al., 2017)	Factors associated with non-metformin prescription as initial antidiabetic therapy.	Sex, age		Income level, medical facility features; accreditation level, ownership, location.	Age, sex, speciality	OR, 95%CI
(Wang et al., 2013a)	Predictors of starting metformin and the influence of guideline adherence on starting of oral hypoglycaemic agents	Age, sex	Comorbidities (renal and cardiovascular disease (CVD))		Sex, practice experience	OR, 95%CI
(Longato et al., 2020)	The difference in the baseline	Age, sex	HTN, dyslipidaemia, microvascular and macrovascular complications,			%/mean, p value

	characteristics between patients newly initiated SGLT2-I vs. GLP1-RA		comorbidities		
(Geier et al., 2014)	Predictors of Metformin vs. SU initiators	Age, sex, smoking status	obesity, HbA1c, diabetes duration		OR, 95%CI
(Fujihara et al., 2017)	Factors that influence the choice of each of 3 hypoglycaemic agents prescribed as initial monotherapy	Age, sex	Diabetes duration, body mass index (BMI), HTN, HbA1c		OR, 95%CI
(Desai et al., 2012)	Predictors of Receiving Metformin as Initial Oral Hypoglycaemic Therapy	Age, sex	Comorbidity	Income, Drug insurance cover	OR, 95%CI
(Grimes et al., 2015)	Socio-demographic factors association with initiation of metformin or SU	Age, sex			OR, 95%CI
(Cai et al., 2010)	Characteristics of patients prescribed Sitagliptin vs. other oral antidiabetics	Age, sex	retinopathy, neuropathy, nephropathy, CVD (as HF, stroke, myocardial infarction (MI), PVD), other comorbid diseases (HTN), obesity		%, P value
(Saine et al., 2015)	Determinants of saxagliptin use	Age, sex, Smoking	HbA1c, obesity, nephropathy, neuropathy, retinopathy, CVD, PVD, cerebrovascular disease		OR, 95%CI N, % for age and sex
(Wilkinson et al., 2018c)	characteristics associated with the class of antidiabetic drug prescribed	Age, sex, Ethnicity, smoking	HbA1c, BMI, Kidney function (eGFR), CVD, retinopathy	SES	OR, 95%CI

(Grabner et al., 2015)	Baseline Characteristics with Initiation of Canagliflozin vs. DPP4-I		HbA1c, microvascular complications, dyslipidaemia, Obesity			OR, 95%CI
(Ou et al., 2017)	Factors associated with the choice of DPP4-I rather than other antidiabetics	Age, sex	Comorbidities (HTN, dyslipidaemia, stroke, coronary artery disease (CAD), heart failure (HF))			Estimates, SE
(Stargardt et al., 2009)	Predicted probabilities of adding glitazone or sulfonylurea to metformin	Age, history of diabetes in family	History of macrovascular complication, HbA1c, weight		Speciality, years of experience	predicted probability, P value
(Payk et al., 2015)	Predictors of SU use	Age, sex, race		payment type	Speciality	OR, 95%CI
(Zhang et al., 2010)	Baseline characteristics of initiating Sitagliptin monotherapy compared to non-Sitagliptin monotherapy	Age	HbA1c, obesity, Microvascular conditions, Chronic renal disease, CVD			OR, 95%CI
(Morita et al., 2019)	Patient characteristics associated with the selection of DPP4-I versus metformin	Age, sex,	Renal disease, HbA1c, obesity, microvascular complications, CAD, and stroke			OR, 95%CI
(Kim et al., 2019a)	the influencing factors in the selection of second oral antidiabetics added to metformin	Age, sex	CVD, renal failure, HF, dyslipidaemia	Insurance, institution	speciality	OR, 95%CI

(Heintjes. et al., 2017)	Factors associated with the choice of treatment at intensification	Age, sex, smoking status	macrovascular complication, renal function, HbA1c, obesity			RR, 95%CI
(Nicolucci et al., 2019)	Factors associated with second-line treatment choices in patients prescribed metformin	Age, sex, Education, Health	Obesity, microvascular/macrovascular complications, diabetes duration, HbA1c, chronic kidney disease	Insurance coverage, employment status	Physician speciality	OR, 95%CI
(Hartmann et al., 2020)	Predictors of treatment escalation after metformin monotherapy failure	Age, sex	HbA1c, diabetes duration, microvascular/macrovascular disease, chronic kidney disease, obesity			OR, 95%CI
(Ackermann et al., 2017)	Correlates of type 2 diabetes second line medication selection	Age, sex, race/ethnicity	HbA1c, obesity	Insurance	speciality	Probability%, 95%CI
(Whyte et al., 2019)	Disparity exists in drug prescribing	Ethnicity, sex		socioeconomic status		OR, 95%CI
(Arnold et al., 2018)	The association of the variable of interest with the likelihood of being prescribed a glucose-lowering medication	Age	Obesity, Kidney function, CAD			Relative Risk / 5 years, 95%CI
(Arnold. et al., 2018)	Glucose-Lowering Medication Use in T2D and HF		Heart failure			Relative Risk, 95%CI
(Zaharan et al., 2014)	Variations in the prescribing of oral antidiabetic drug	Age, sex				OR, 95%CI

(Zoberi et al., 2017)	Characteristics of patients with diabetes by non-metformin prescription and by insulin prescription	Age, sex, Race, Smoking	HbA1c, obesity, Microvascular complications, CVD, Cerebrovascular disease, Hyperlipidaemia, HTN		%, P value
(Montvida et al., 2018)	Patient characteristics according to antidiabetic therapy prescribed	Age, sex, ethnicity	HbA1c, obesity, CVD, chronic kidney disease		N, %
(Katakami et al., 2020)	Factors associated with the selection of second-line treatment	Age, sex	HbA1c, obesity, renal function (eGFR), CVD		OR, 95%CI
(Kostev et al., 2014)	Predictors of Insulin Initiation in Metformin and Sulfonylurea Users	Age, sex	Kidney function (eGFR), comorbidities (HTN, stroke, HF, Hyperlipidaemia)	Diabetologist care	HR, 95%CI; insulin
(Dhanaraj et al., 2013)	Choice of antidiabetic drug therapy and influencing factors	Age, sex, family history of diabetes	Obesity, HbA1c, microvascular complications, comorbidities, diabetes duration, serum creatinine.		OR, 95%CI
(Yu et al., 2017)	Factors that may predict choice of first injectable therapy.	Age, sex, ethnicity, smoking status	HbA1c, obesity, cardiovascular disease, chronic kidney disease, dyslipidaemia, HTN		OR, 95%CI %, p value for some variables
(Levin et al., 2014)	Baseline Characteristics of patients with T2DM who added OAD, insulin, or GLP-1)	Age, sex	HbA1c, HTN, Dyslipidaemia, HF, Microvascular complications (neuropathy, nephropathy, retinopathy), MI, PVD.		%, P value

(Gentile et al., 2018)	Predictors of initiating insulin therapy	Age, sex,	Diabetes duration, HbA1c, obesity, retinopathy, kidney function (eGFR)			HR, p value
(Korytkowski et al., 2014)	Baseline characteristics of T2DM patients according to intensifying drugs	Sex, age, race	Obesity, HbA1c			Mean or %, p value
(Hirsch et al., 2011)	Predictors of Exenatide Use	Age, sex	Obesity, HbA1c, diabetes duration,	payer type		HR, 95%CI
(van den Boom et al., 2020)	Factors associated with the probability of receiving insulin	Age, sex	HbA1c, PAD, stroke, MI		practice specialty	OR, 95%CI
(Moreno Juste et al., 2019)	Difference in the baseline characteristics among antidiabetics new users	Age, sex	microvascular/macrovascular complications	Area of living		Mean or %, p value

OR; odds ratio, CI; confidence interval, eGFR; estimated glomerular filtration rate

2.3.4 Synthesis of factors associated with antidiabetic drug prescribing

Factors associated with ADP were classified into four categories; demographic, clinical, socioeconomic, and prescriber-related factors, as displayed in Table 2.4. The most frequently studied ones were demographic factors, particularly age (n=38/46, 82.6%) and sex (n=36/46, 78.3%), in addition to clinical factors, primarily macrovascular complications (n=23, 50%), glycaemic status (n=22, 47.8%), and obesity (n=21, 45.7%). This section is divided into two parts; the first presents the findings of meta-analyses applied to five identified factors as described previously, and the second part provides the results of narrative synthesis for the remaining factors.

2.3.4.1 Meta-analysis results

This section provides the results of meta-analyses, which were conducted to quantify the association of the following factors with ADP: age, sex, obesity, glycaemic control, and kidney function. Within each factor, the following subsections were discussed: firstly, the number of included studies and the overall estimates stratified by antidiabetic class, the type of the outcome variable (continuous vs. categorical), and the outcome's categorization scheme. The second subsection includes the results of model fitness tests of the three-level MA and the heterogeneity of included studies. The third subsection contains the result of subgroup/moderator analyses investigating the possible influence of several study characteristics on the overall estimates. The last one provides the results of publication bias, outliers, and influential case assessment.

Studies included and the overall estimate

Patient sex

Out of the 40 eligible studies, 36 assessed the association of patient sex with ADP, and all except one *(Heintjes et al., 2017)* were included in the MA. Heintjes et al. (2017) was excluded since the outcome was not reported as OR and due to insufficient statistical data required for OR calculation necessary for MA *(Heintjes. et al., 2017)*. Therefore, 35 studies were finally included that contributed to 96 effect

sizes. The most frequently studied groups were DPP4-I, metformin, and sulfonylurea accounting for 20, 16, and 15 of the total effect sizes, respectively. The remaining 45 effect sizes were related to insulin (K=13), GLP1-RA (K=12), TZD (K=10), and SGLT2-I (K=10).

The result of the three-level MA showed that sex had almost no association with ADP, including all antidiabetic groups (pooled estimate: 0.998 [95%CI: 0.857-1.164]), yet a subgroup analysis identified a significant difference in the result according to the examined antidiabetic group (p=0.001). It revealed that sex had only significant associations with GLP1-RA and TZD prescription. Female patients were more likely to be treated with GLP1-RA compared to male patients (pooled estimates: 1.379 [95%CI: 1.189-1.599]) yet significantly less likely to get a TZD prescription (pooled estimate: 0.909 [95%CI: 0.844-0.979]). Being female had a weak albeit non-significant association with the choice of other antidiabetic groups; they had a weak positive association with the prescription of insulin and SGLT2-I (Pooled estimates: 1.070 [95%CI: 0.989-1.159]] and 1.019[95%CI: 0.922-1.127], respectively), while a weak negative association with the prescription of DPP4-I, metformin, and SU (0.985[95%CI: 0.953-1.018], 0.992[95%CI: 0.903-1.089], and 0.926[95%CI: 0.851-1.009], respectively). Figure 2.2 presents the forest plot of patient sex of all included studies categorized according to the antidiabetic group.

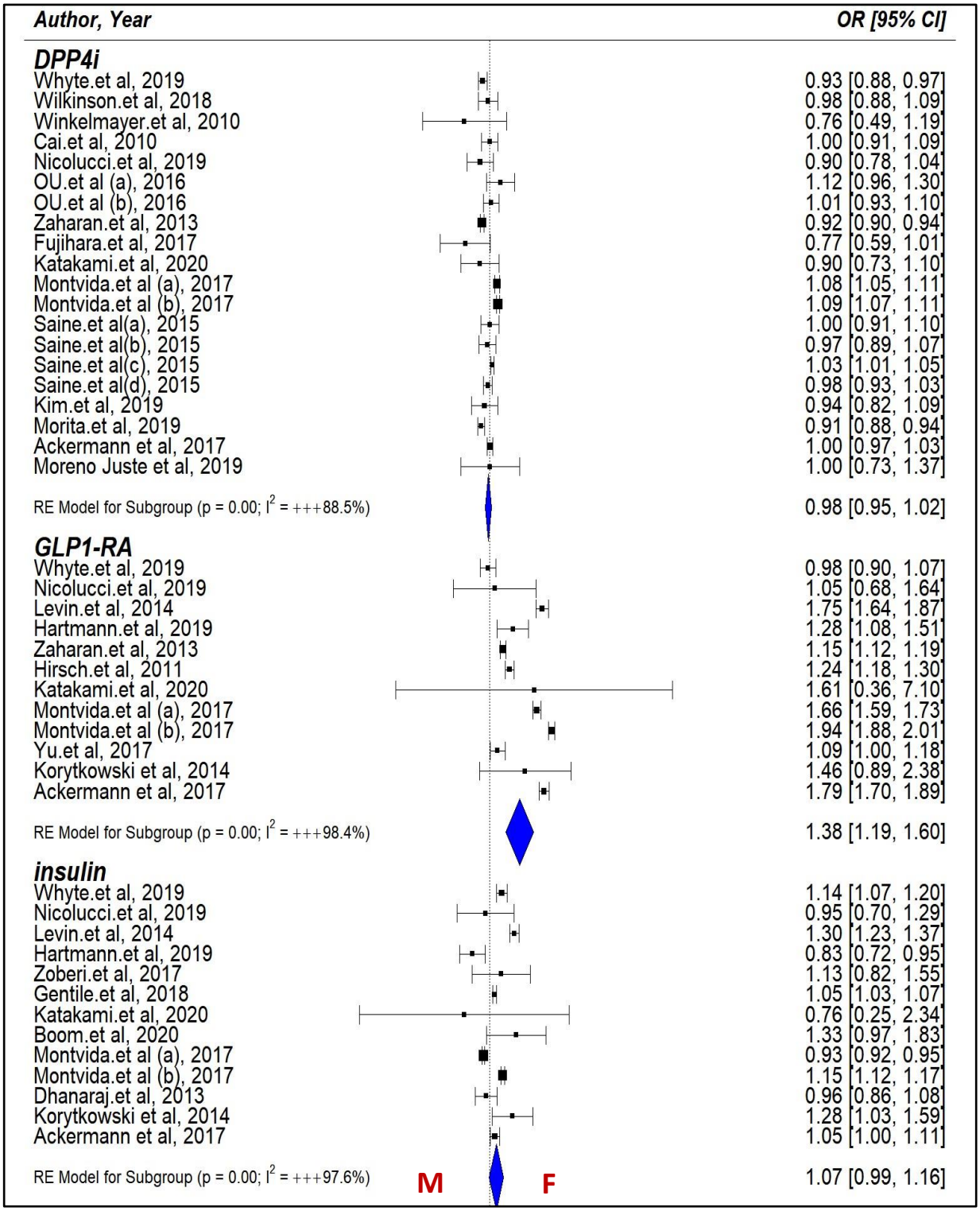

Figure 2.2*:* Forest plot of sex association with antidiabetic drugs prescribing as overall and per antidiabetic group. OR: odds ratio; CI: confidence interval; DPP4i: dipeptidyl peptidase 4 inhibitor; GLP1-RA: glucagon like peptide receptor agonist; SGLT2i: sodium glucose transporter 2 inhibitor; SU: sulfonylurea; TZD: thiazolidinedione.

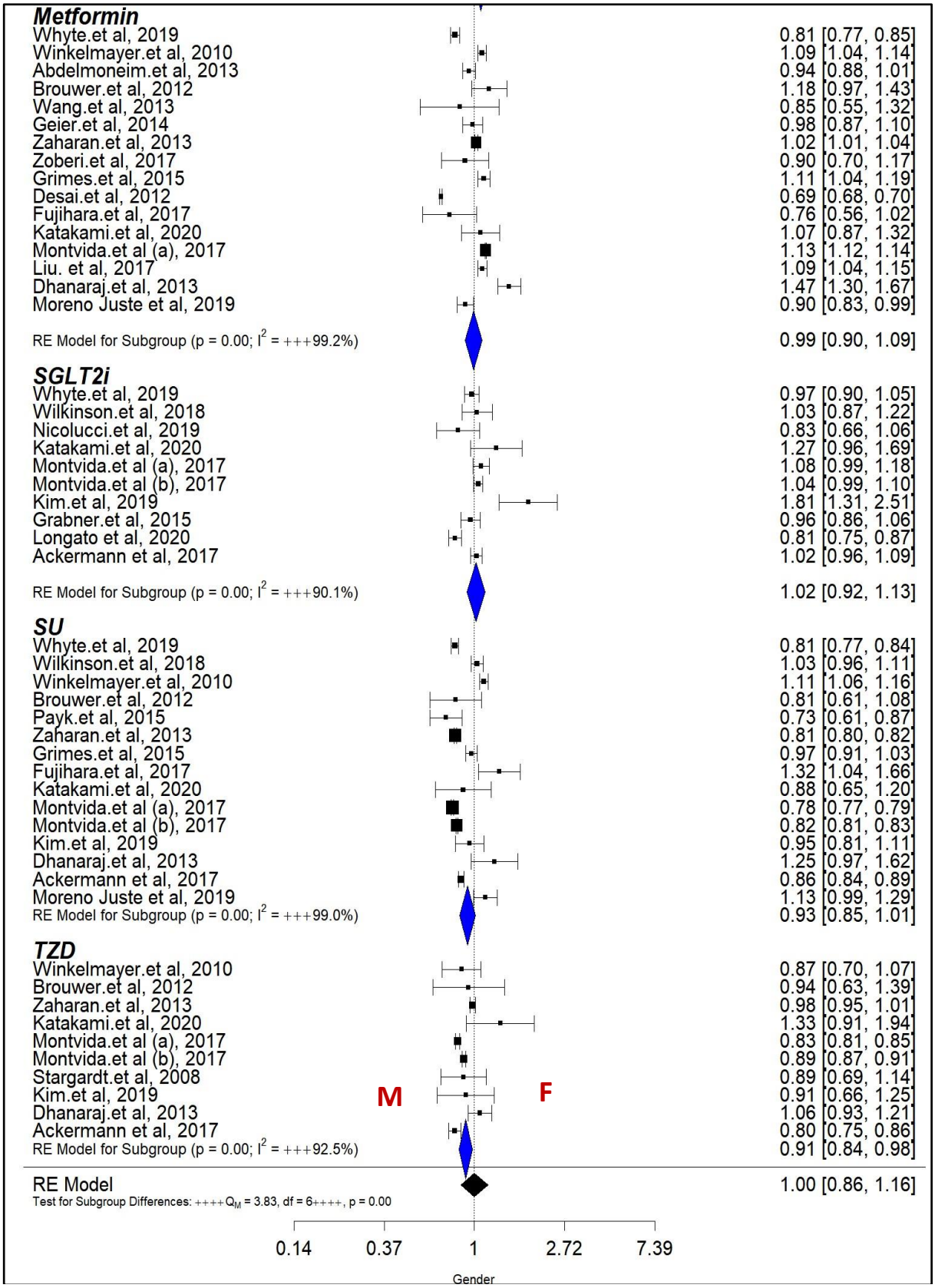

Figure 2.2: Continued.

Patient age

Age association with ADP was evaluated in 38 studies, and 31 were included in the MA, contributing to 88 effect sizes. Of the seven excluded studies, two did not report the outcome in the form of OR or provide adequate baseline data for OR calculation *(Heintjes. et al., 2017, Kostev et al., 2014)*. The other five studies did not present age as binary or provide sufficient data to aggregate or reconstruct age categories into binary *(Hartmann et al., 2020, Liu et al., 2017, Payk et al., 2015, Zaharan et al., 2014, Desai et al., 2012).*

Overall, including all studies reporting the outcome as binary or continuous from all antidiabetic groups, it was found that older age had a non-significant negative association with ADP (pooled estimate: 0.933[95%CI: 0.659 -1.319]). However, a subgroup analysis showed a significant difference based on the investigated antidiabetic group (p< .0001). It revealed that SU prescription had the strongest positive association with patient age, which was 51% more likely to be prescribed for older patients than their counterparts (pooled estimates: 1.510 [95%CI: 1.295-1.762]). In contrast, patients at an older age had an overall significant negative association with the prescribing of GLP1-RA (pooled estimate: 0.524 [95%CI: 0.399 - 0.688]), SGLT2-I (pooled estimate: 0.573 [95%CI: 0.417 - 0.788]), and metformin (pooled estimate: 0.704 [95%CI: 0.607-0.816]). Patient age had an overall non-significant positive association with the prescription of DPP4-I (pooled estimate: 1.112[95%CI: 0.981-1.262]), insulin (pooled estimate: 1.042 [95%CI: 0.872-1.244]), and TZD (pooled estimate: 1.065[95%CI: 0.857-1.325]). Figure 2.3 demonstrates the results of the pooled estimate of all included studies overall and per antidiabetic group.

Furthermore, a subgroup analysis was performed to investigate the difference in the overall estimate according to the type of the outcome variable, whether it was calculated based on continuous or binary data. Of the 88 effect sizes, 59 were reported as binary, while 29 effect sizes were examined as a continuous variable. Nevertheless, the analysis showed no significant difference in the overall estimates

between the two subgroups (p = 0.713). For instance, the overall estimate of studies examining age as a continuous variable showed that older patients were 11% less likely to be treated with ADDs than those younger by one year (pooled estimate: 0.892 [95%CI: 0.723-1.099]. The overall estimate of studies presenting age as a binary showed a negative and non-significant result (pooled estimate: 0.889 [95%CI: 0.618-1.279]). Of the 59 binary effect sizes, 29 were categorized into >=65 versus < 65 years, 13 effect sizes were categorised into >=60 versus < 60 years, and 13 effect sizes were categorised into >=70 versus < 70 years. The remaining four effect sizes were extracted from the same study *(Dhanaraj et al., 2013),* where age was categorized into >= 55 versus < 55 years. Nonetheless, no significant difference in the overall estimate according to the categorization scheme (p = 0.942), and all showed a non-significant result. The pooled estimates of studies within each of the four categorization schemes are summarised in Table 2.5. As an example, patients with T2DM aged 70 years or older were almost 25% non-significantly less likely to receive any of the investigated ADDs compared to their counterparts.

Table 2.5: The pooled estimate of the categorisation scheme of age binary data

Categorization scheme of binary age data	# Of effect sizes (Total k=59)	Pooled estimate (OR[95%CI])
>=60 versus < 60 years	13	1.059 [0.613-1.829]
>= 65 versus <65 years	29	1.008 [0.696-1.459]
>=70 versus < 70 years	13	0.747 [0.303-1.843]
>=55 versus < 55 years	4	0.955 [0.985-1.005]

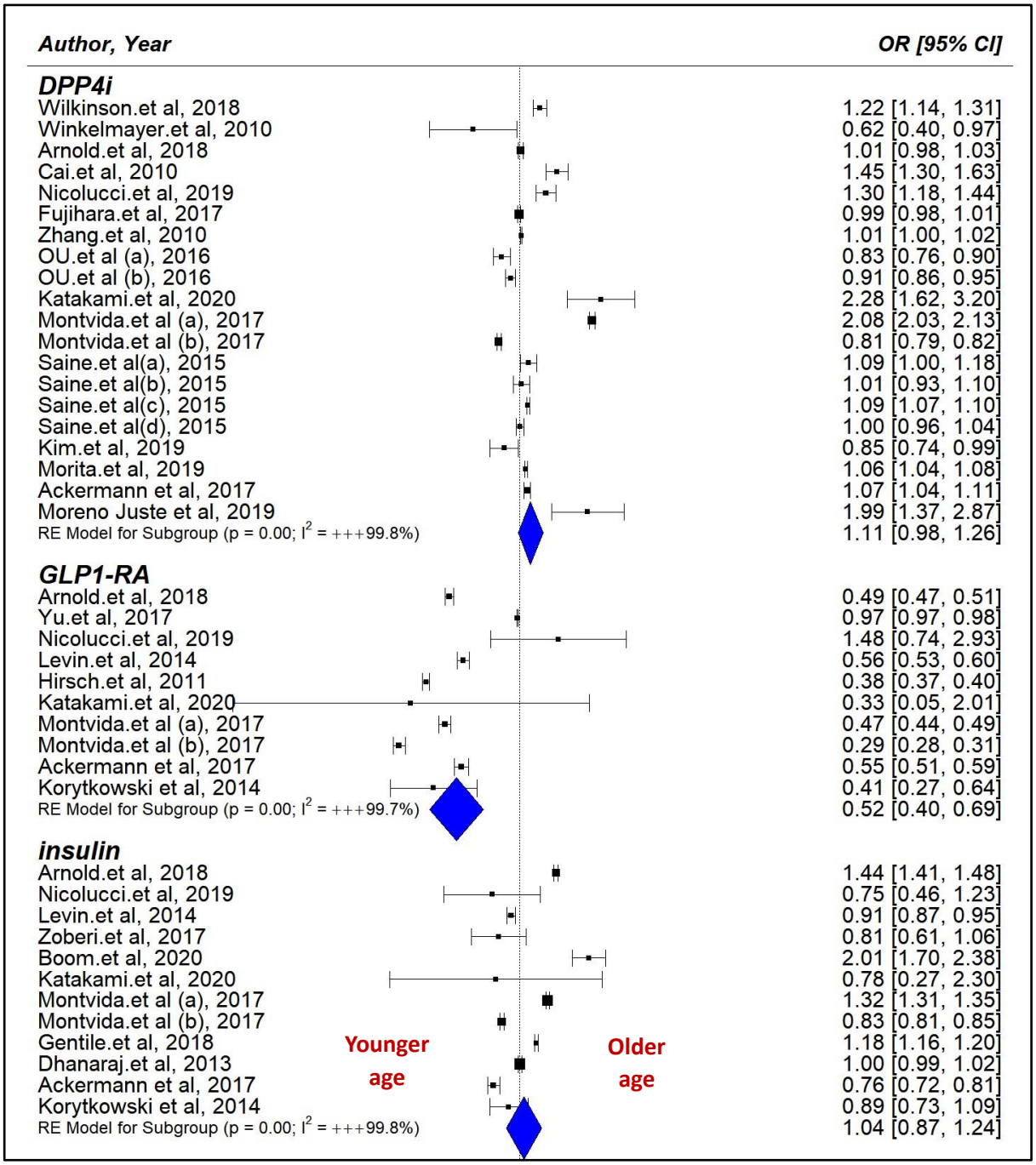

Figure 2.3: Forest plot of age association with antidiabetic drug prescribing overall and per antidiabetic group. OR: odds ratio; CI: confidence interval; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP1-RA: glucagon-like peptide receptor agonist; SGLT2i: sodium-glucose transporter-2 inhibitors; SU: sulfonylurea; TZD: thiazolidinedione.

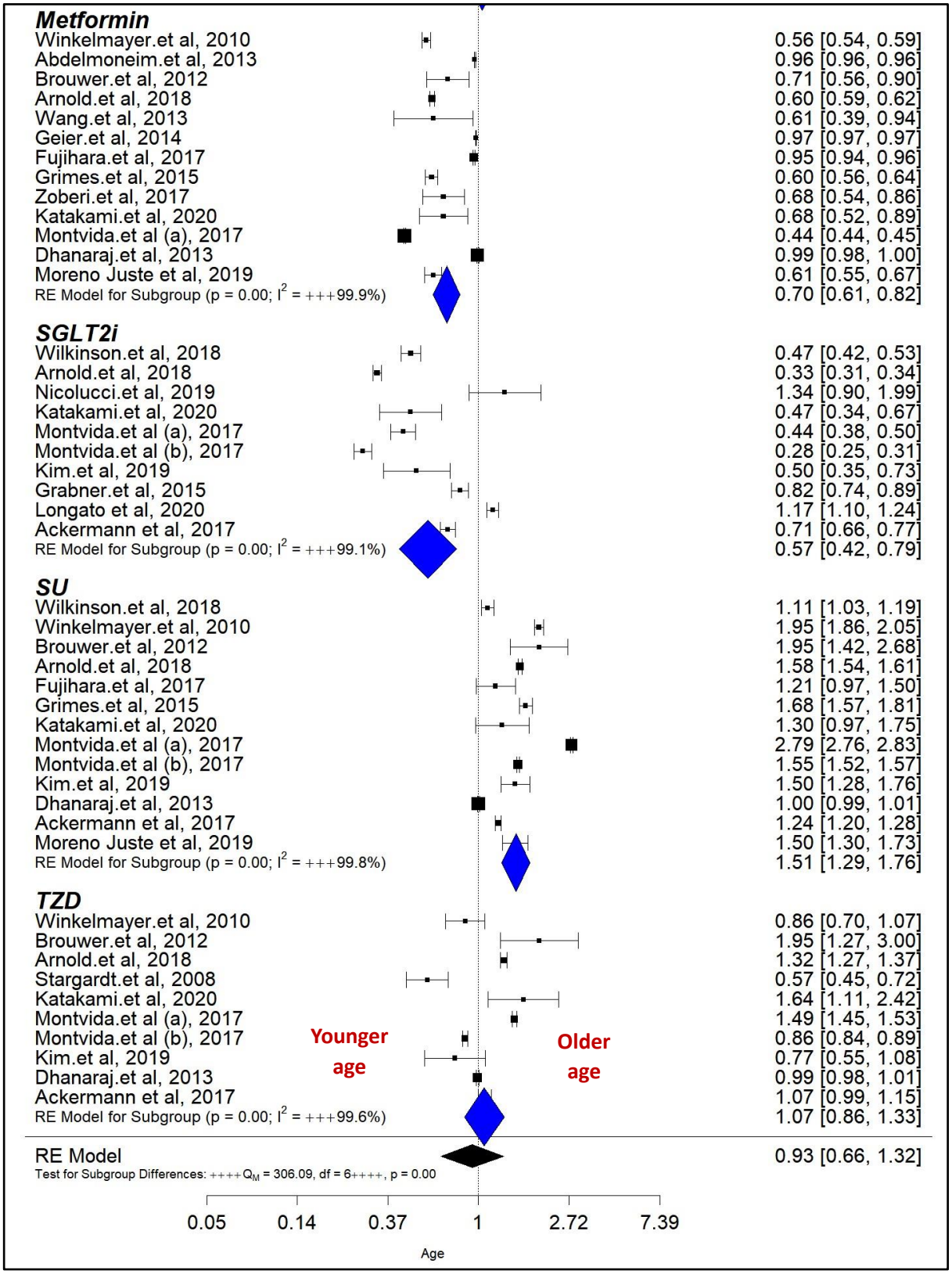

Figure 2.3: Continued.

Obesity (baseline BMI):

The association of obesity with ADP was evaluated in 21 studies. All except one *(Heintjes. et al., 2017)* were included in the MA, contributing to 66 effect sizes from all investigated antidiabetic groups. Heintjes et al. (2017) was excluded because of insufficient data that was required for OR calculation *(Heintjes. et al., 2017)*. The most frequently studied antidiabetic group was DPP4-I which represents 22.7% (k=15) of the total effect sizes. Only four out of the 20 included studies collected obesity data based on the presence of a diagnostic code for obesity, while the majority (16/20, 80%) relied on the collection of BMI data.

The three-level MA revealed that obesity had a non-significant positive association with ADP, including all studies that collected the obesity data as a binary or continuous from all antidiabetic groups (pooled estimate: 1.191[95%CI: 0.847 - 1.673]). Nevertheless, a subgroup analysis showed that the results varied significantly by the assessed antidiabetic group ($p< 0.0001$). It was found that obese patients or patients with higher BMI were 2.35 folds more likely to get GLP1-RA prescription (pooled estimates: 2.349 [95%CI: 1.539-3.587], as well as 1.89 and 1.22 times more likely to receive SGLT2-I and metformin, respectively (pooled estimate: 1.885 [95%CI: 1.326-2.679] and 1.217 [95%CI: 1.079-1.372]). In contrast, they were 24% less likely to be treated with SU (pooled estimate: 0.761 [95%CI: 0.620-0.934]). All other antidiabetic groups had a non-significant association with obesity, as shown in Figure 2.4.

Only 14 out of 66 effect sizes were based on continuous data, in which patients with higher BMI were 1.2% non-significantly less likely to be prescribed antidiabetic drugs than patients with a BMI lower by 1 kg/m^2 (pooled estimate: 0.988 [0.674-1.448]). On the other hand, more than two-thirds of the effect sizes (52/66, 78.79%) were reported as binary, where the pooled estimate revealed a positive and non-significant result (1.333 [95%CI: 0.916-1.939]). Nevertheless, the analysis showed no significant difference in the overall estimates of the two sub-groups ($p = 0.115$).

Among studies that reported the outcome as a binary, the majority of effect sizes (k=32) were categorised into obese (BMI>=30 kg/m^2) versus non-obese (BMI <30kg/m^2). In comparison, 13 effect sizes were categorised into overweight/obese (BMI>=25 kg/ m^2) versus normal/underweight (BMI < 25 kg/m^2), and in only one study *(Katakami et al., 2020)* that contributed to seven effect sizes, the BMI was categorised into >=25 versus 22-25 kg/m^2. Nonetheless, the analysis showed no significant difference in the pooled estimate according to the categorisation schemes (p = 0.067). The pooled estimates of studies within each categorisation scheme are summarised in Table 2.6. For example, it was observed that obese patients were 1.18 folds more likely to be treated with any ADDs compared to non-obese ones.

Table 2.6: The pooled estimate of the categorisation scheme of the binary data related to obesity

Categorization scheme of binary obesity data	**# Of effect sizes (total k=52)**	**Pooled estimate (OR[95%CI])**
Obese (BMI>=30 kg/m^2) vs. non-obese (BMI <30kg/m^2)	32	1.175 [0.855-1.615]
Overweight/obese (BMI>=25 kg/ m^2) vs. normal/ underweight (BMI < 25 kg/m^2)	13	1.545 [0.546-4.369]
BMI >=25 vs. BMI 22-25 kg/m^2	7	1.018 [0.519 -1.996]

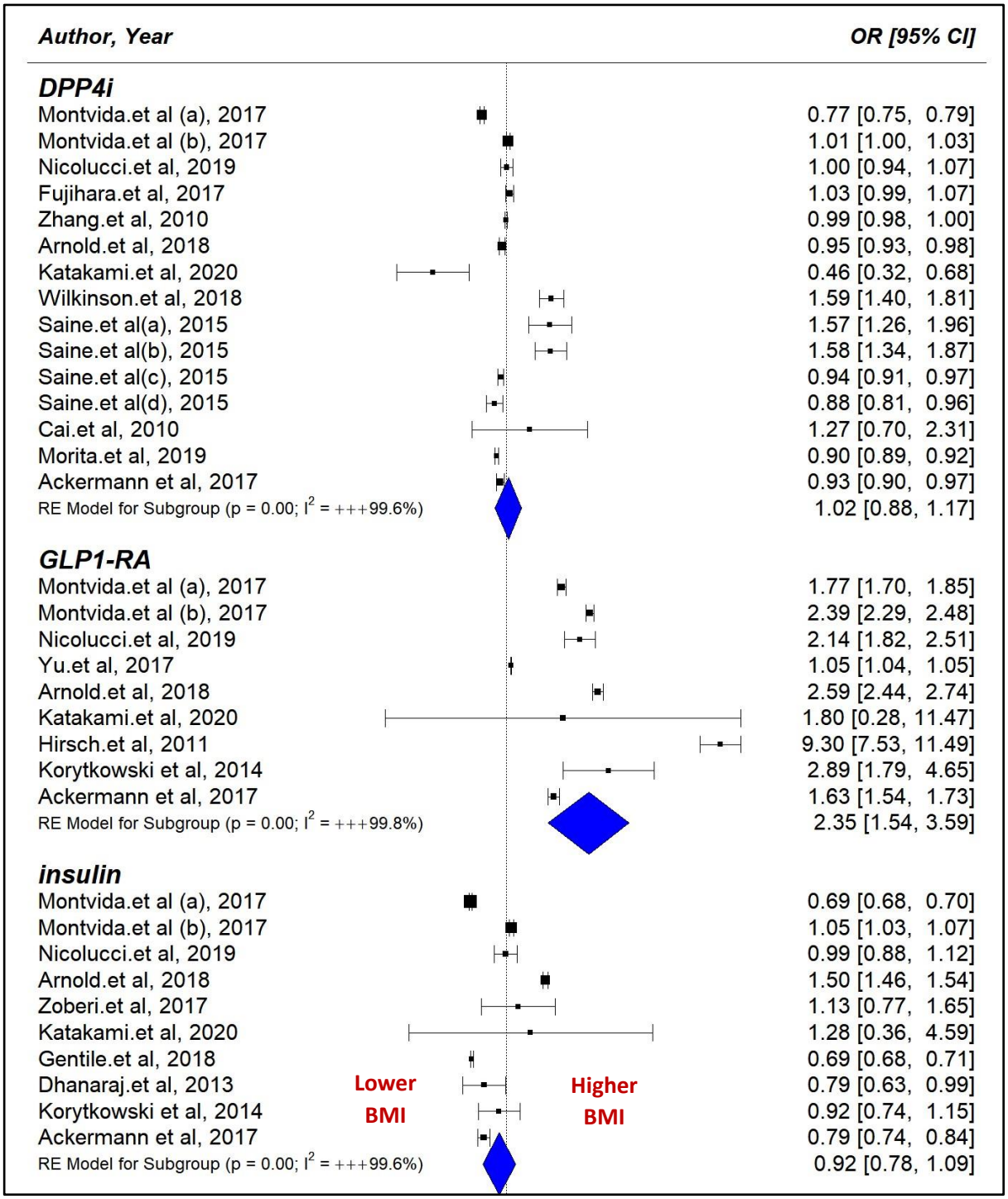

Figure2.4: Forest plot of body mass index (BMI) association with antidiabetic drugs prescribing as overall and per antidiabetic groups. OR: odds ratio; CI: confidence interval; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP1-RA: glucagon-like peptide receptor agonist; SGLT2i: sodium-glucose transporter-2 inhibitors; SU: sulfonylurea; TZD: thiazolidinedione.

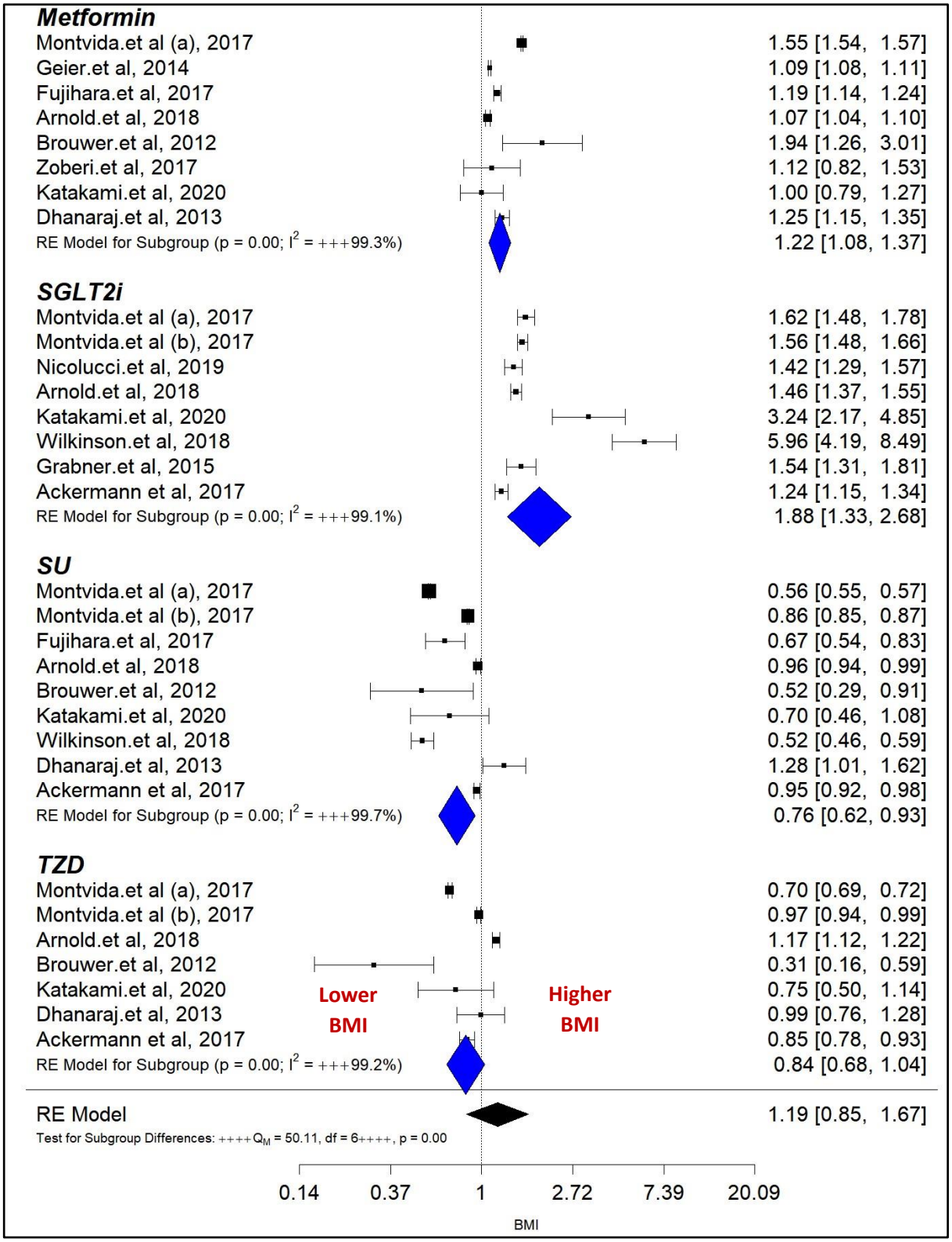

Figure2.4: Continued.

Glycaemic status (HbA1c)

A total of 62 effect sizes from 22 studies were included in the MA measuring the association of HbA1c with ADP. Kostev et al. (2014) and Heintjes et al. (2017) were not included because of insufficient baseline data necessary for OR calculation *(Heintjes et al., 2017, Kostev et al., 2014)*. The most commonly examined antidiabetic groups were insulin (k=12), DPP4-I (k=11), and GLP1-RA (k=10). Of the remaining antidiabetic groups, each metformin, SGLT2-I, and TZD contributed to seven effect sizes, while SU accounted for eight effect sizes. Overall, including all studies that reported HbA1c as continuous or binary from all antidiabetic groups, it was found that higher HbA1c had a weak positive and non-significant association with ADP (pooled estimate: 1.099 [95%CI: 0.811-1.491]). However, a subgroup analysis showed a significant difference according to the investigated antidiabetic group (p = 0.0298). Patients with higher value or category of HbA1C were 2.41 times more likely to get an insulin prescription (pooled estimates: 2.408[95%CI: 1.872-3.097]), yet 26% less likely to be treated with metformin (pooled estimates: 0.735 [95%CI: 0.565 - 0.968]), TZD (pooled estimates: 0.761 [95%CI: 0.592 - 0.978]), and DPP4-I (pooled estimates: 0.820 [95%CI: 0.679 - 0.991]. On the contrary, HbA1c was non-significantly associated with the prescribing choice of SU, SGLT2-I, and GLP1-RA (pooled estimate: 1.221 [95%CI: 0.846-1.763], 0.926 [95%CI:0.745-1.150], and 0.812 [95%CI:0.597-1.104]) as presented in Figure 2.5.

Similar to age and obesity, the subgroup analysis by the type of the outcome variable showed no significant difference in the overall estimate (p= 0.812). Twenty-eight out of 62 effect sizes were calculated from continuous data, where the pooled estimate showed that patients with a higher HbA1c value were only 4.8% more likely to receive any ADDs compared to patients with HbA1c value that is lower by 1% (pooled estimate: 1.048 [95%CI: 0.586-1.874]). The remaining 34 effect sizes were reported as binary and showed a positive non-significant overall estimate (1.115 [95%CI: 0.714-1.739]). Of the 34 binary effect sizes, 13 were categorised into

> 7% versus < 7%, in which patients with HbA1c >7% were 1.5 folds more likely to be prescribed with any ADDs compared to the patients with HbA1c < 7%, but the result was non-significant (pooled estimate: 1.504 [95%CI: 0.335-6.751]. The remaining 21 effect sizes were categorised into > 8% versus < 8%, with an overall estimate of 1.054 [95%CI:0.735-1.511]. Yet, the difference in the overall estimate according to the categorization scheme was non-significant (p= 0.916).

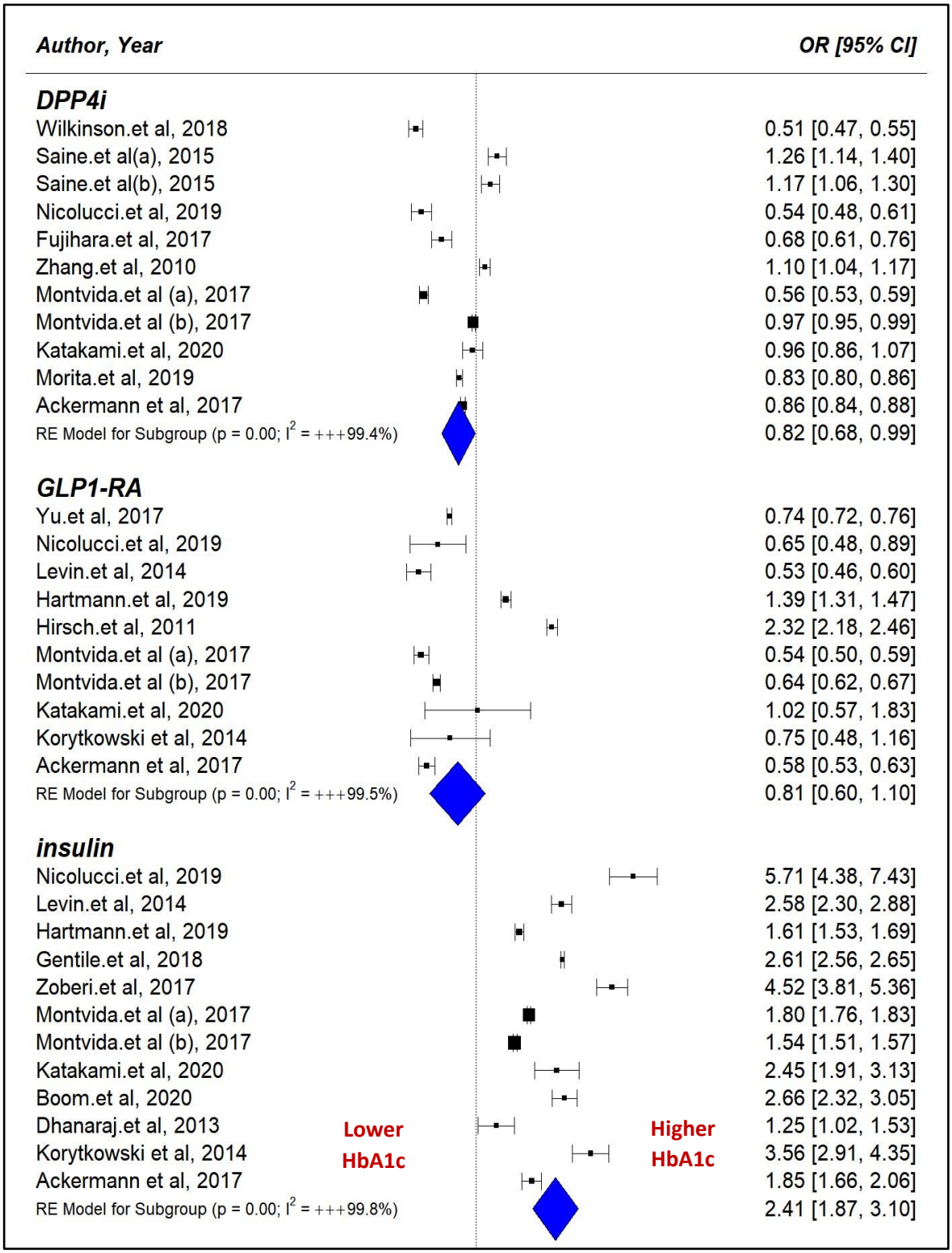

Figure 2.5: Forest plot of HbA1c association with antidiabetic drugs prescribing overall and per antidiabetic groups. OR: odds ratio; CI: confidence interval; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP1-RA: glucagon-like peptide receptor agonist; SGLT2i: sodium-glucose transporter-2 inhibitors; SU: sulfonylurea; TZD: thiazolidinedione.

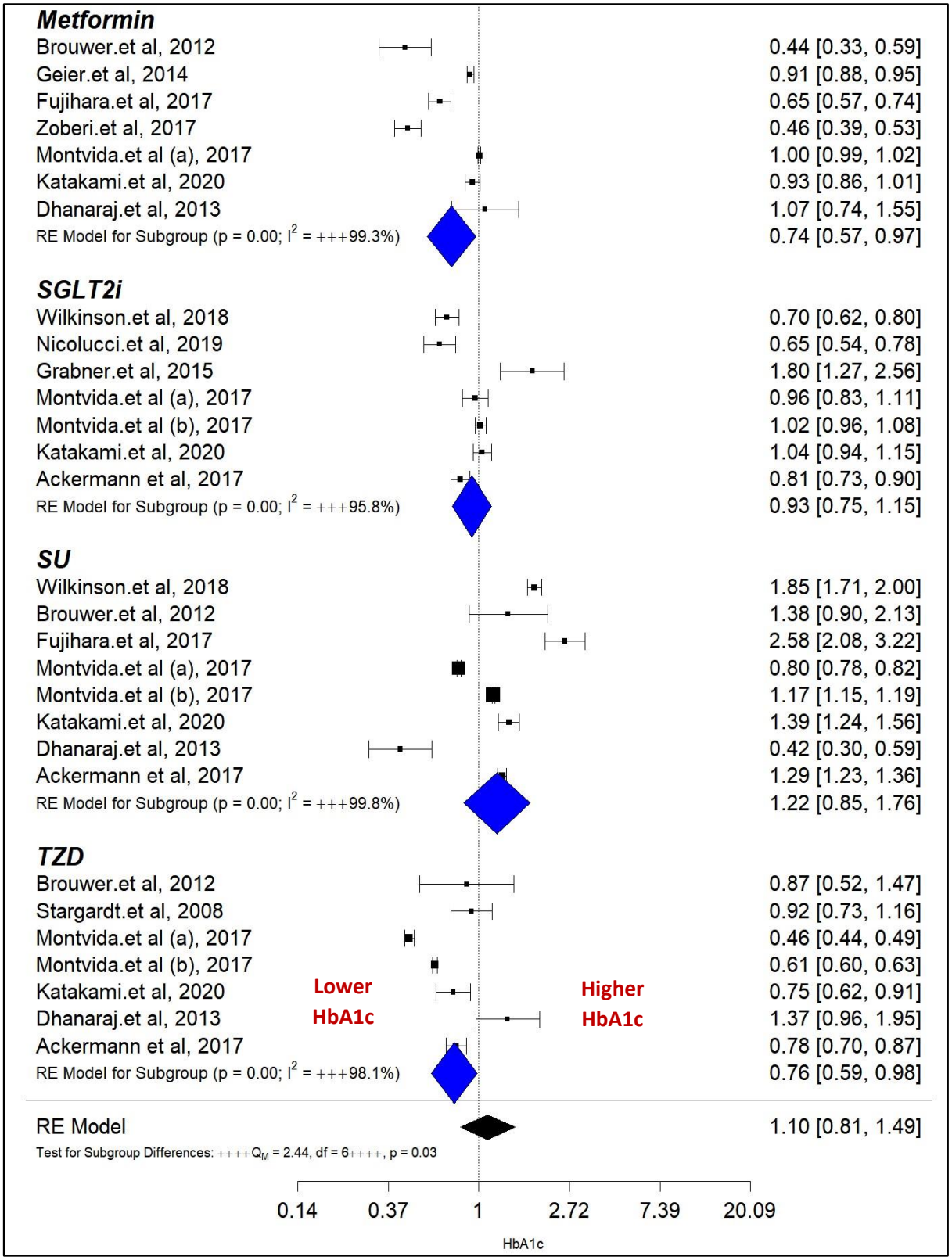

Figure 2.5: Continued.

Kidney function:

A total of 21 studies examined the association of kidney problems with ADP in terms of chronic renal disease (CRD), nephropathy, or based on the eGFR value of < 60 ml/min/1.73 m^2. Only Heintjes et al. (2017) was excluded because of insufficient statistical data that was required for OR calculation *(Heintjes et al., 2017).* Thereby, a total of 20 studies were included in the MA, contributing to 61 effect sizes. The most frequently investigated antidiabetic group was DPP4-I (k=14), followed by insulin (k=10). Of the 20 included studies, nine reported the outcome as CRD (k=28), and six presented it as nephropathy (k=14), while the remaining five studies examined the renal function based on the eGFR (k=19).

The three-level MA showed that, including all antidiabetic groups, patients with kidney problems (either CRD, nephropathy, or eGFR < 60) were non-significantly less likely by 10.5% to receive any class of ADDs (pooled estimate: 0.895 [95%CI: 0.543-1.473]). A subgroup analysis showed a non-significant difference according to the examined antidiabetic group (P = 0.079). Nonetheless, patients with kidney problems were 1.52 and 1.37 times significantly more likely to be treated with insulin (pooled estimates: 1.516 [95%CI: 1.096-2.097]) and DPP4-I (pooled estimates: 1.374 [95%CI: 1.057-1.786]), respectively, yet 61% significantly less likely to be treated with metformin (pooled estimates: 0.387 [95%CI: 0.248 - 0.606]). However, a diagnosis of kidney problem was non-significantly associated with the prescribing choice of SU, TZD, SGLT2-I, and GLP1-RA, as demonstrated in Figure 2.6.

Additionally, a subgroup analysis showed no significant difference in the pooled estimate according to the type of kidney problem (CRD, nephropathy, or eGFR < 60ml/min/m^2, p = 0.286). The overall estimate of studies measuring the kidney problem as CRD revealed that patients with CRD were 36% less likely to receive ADDs than patients without the disease (pooled estimate: 0.640 [95%CI: 0.320-1.279]). Contrastingly, patients with nephropathy were 13% more likely to get ADDs compared to patients without nephropathy, and patients with eGFR of < 60 ml/min/1.73m^2 were 33% more likely to be treated with ADDs compared to their

counterparts (pooled estimate: 1.132 [95%CI: 0.655-1.957] and 1.326[95%CI: 0.547-3.12], respectively).

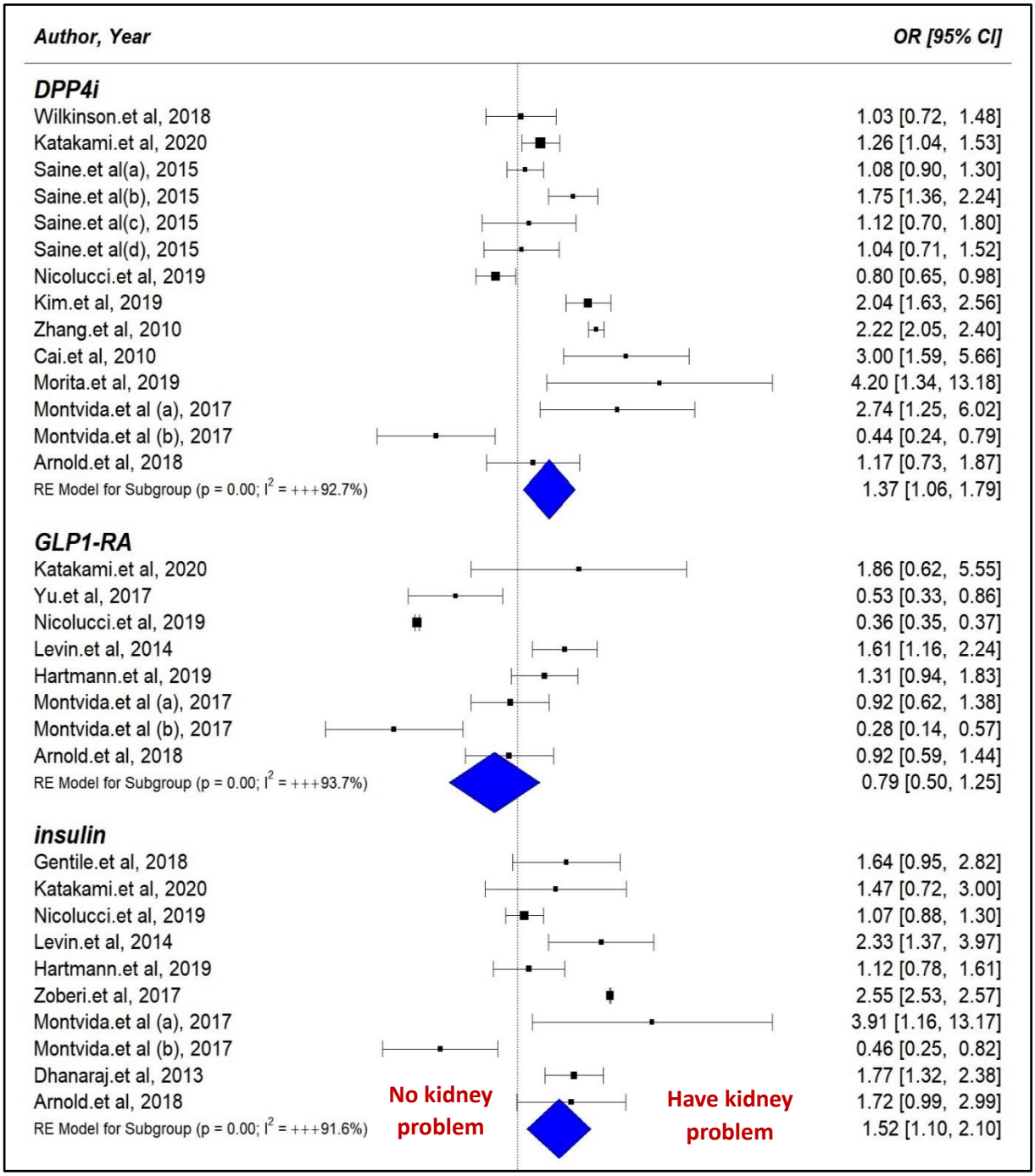

Figure 2.6: Forest plot of kidney problem association with antidiabetic drug prescribing overall and per antidiabetic groups. OR: odds ratio; CI: confidence interval; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP1-RA: glucagon-like peptide receptor agonist; SGLT2i: sodium-glucose transporter-2 inhibitors; SU: sulfonylurea; TZD: thiazolidinedione.

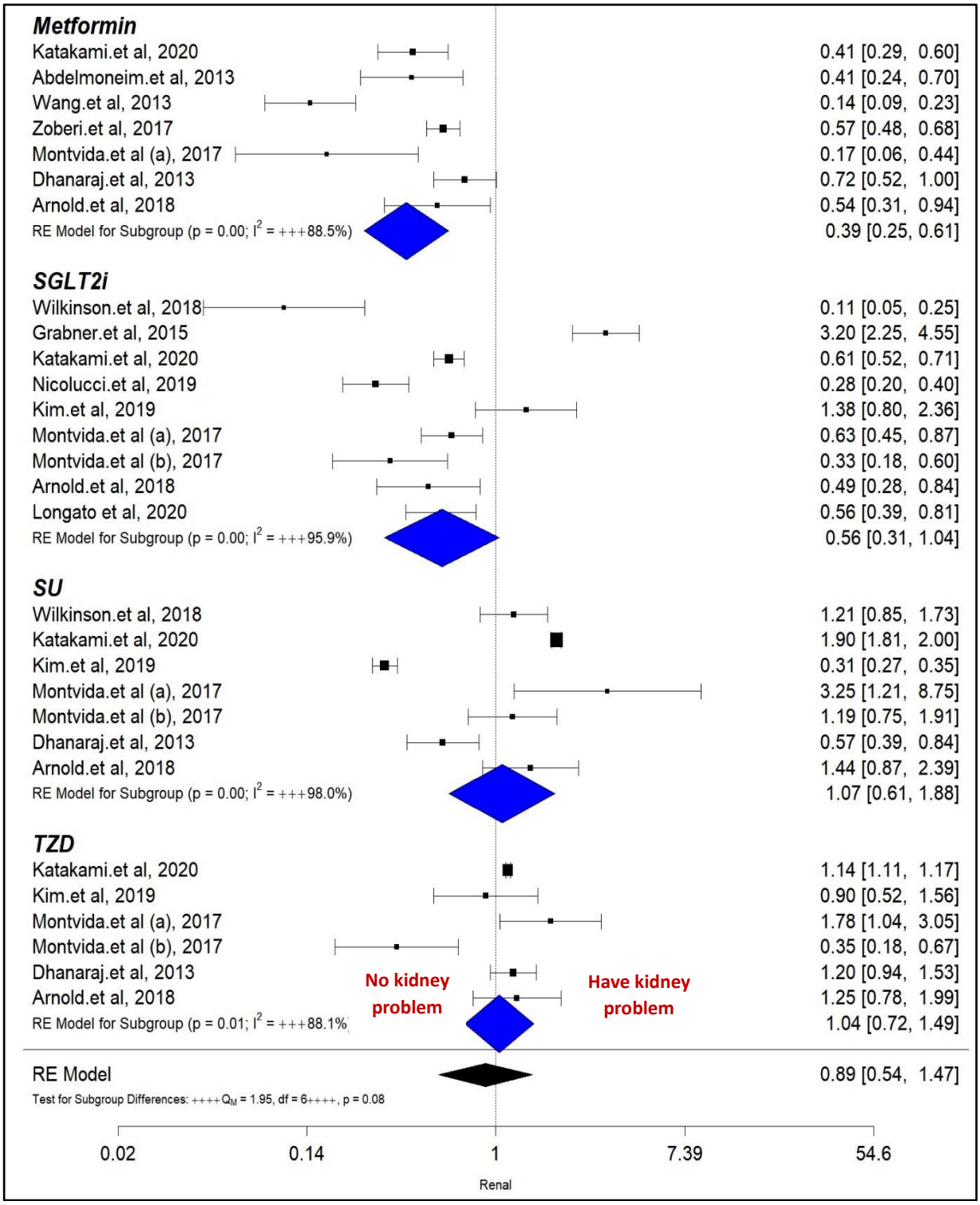

Figure 2.6: Continued.

Heterogeneity and three-level model fitness test:

Table 2.7 presents the overall heterogeneity of the three-level MA model and the distribution of heterogeneity over the third (between-study) and second (within-study) levels. Despite that the overall heterogeneity was high for all studied factors (> 75%), most of the total heterogeneity was related to within-study variance, while between-study variance for all studied factors was < 75%. The results of the log-likelihood ratio test (Table 2.8) indicated that the three-level model had a better fit for variability in data and better estimation of the pooled estimate, as reflected from the lower values of fit indices (AIC and BIC) of the full-model compared to the reduced ones, and the significant value of LRT comparing the two models (p< 0.0001).

Table 2.7: Distribution of heterogeneity among included studies in the meta-analysis of the five quantified factors

Factors	Overall heterogeneity	Between-study variance (level-3)	Within-study variance (level-2)
Sex	99.43%	33.32%	66.11%
Age	99.96%	27.60%	72.36%
BMI	99.94%	51.27%	48.67%
HbA1C	99.79%	49.22%	50.57%
Kidney-related problems	99.73%	52.04%	47.69%

Table 2.8: Model fitness test results of three-level meta-analysis model of the five quantified factors

Factor	Df	AIC	BIC	LRT	Pval
Sex					
Full	3	1201.1740	1208.8356		
Reduced (level- 2)	2	5089.8913	5094.9990	3890.7173	**<.0001**
Reduced (level- 3)	2	7299.1648	7304.2725	6099.9908	**<.0001**
Age					
Full	3	39306.8738	39314.2715		
Reduced (level- 2)	2	58719.6387	58724.5705	19414.7649	**<.0001**
Reduced (level- 3)	2	79296.6636	79301.5954	39991.7898	**<.0001**
Obesity					
Full	3	4437.4977	4444.0209		
Reduced (Level-2)	2	13529.6627	13534.0115	9094.1650	<.0001

Reduced (level- 3)	2	27824.3715	27828.7202	23388.8738	<.0001
HbA1c					
Full	3	2618.1828	2624.5155		
Reduced (level- 2)	2	6224.4123	6228.6340	3608.2294	**<.0001**
Reduced (level- 3)	2	11625.2423	11629.4640	9009.0595	**<.0001**
Renal function					
Full	3	419.4803	425.7633		
Reduced (level- 2)	2	1321.8796	1326.0683	904.3993	**<.0001**
Reduced (level- 3)	2	1253.9828	1258.1715	836.5024	**<.0001**

Df; degree of freedom the number of levels minus 1, AIC; Akaike Information Criteria, BIC; Bayesian Information Criteria, LRT; likelihood ratio test, Pval; P value

Moderator (sub-group) analyses:

Tables 2.9 and 2.10 display the results of moderator analyses of all tested variables and the overall estimate within the levels of each variable. Of the examined variables, only the type of statistical analysis test that was used to measure the outcome (adjusted vs. un-adjusted) had a significant influence on the pooled estimate of the meta-analyses of sex, age, and kidney-related problems ($p< 0.0001$). For instance, in the MA of sex, the overall estimate of studies reporting adjusted values showed an opposite direction of association (0.97[95%CI: 0.86-1.10]) compared to the studies providing un-adjusted data (1.06[95%CI: 0.86-1.31]), yet the association in both sub-groups was non-significant. The moderator analysis in the MA of age showed a significant difference according to the type of conducted analysis test. However, the pooled estimate of studies conducting unadjusted analysis was very close to the one including adjusted data. Nonetheless, both sub-groups showed non-significant overall estimate (0.86[95%CI: 0.76-1.27] vs. 0.85[95%CI: 0.64-1.13], respectively). Lastly, in the renal MA, the overall estimate of un-adjusted effect sizes vs. adjusted effect sizes indicated that patients with kidney problems were 5% and 19% less likely to be treated with any ADDs compared to their counterparts, respectively. Still, the result was non-significant for both sub-groups (0.95[95%CI: 0.59-1.52]) vs. 0.81[95%CI: 0.36-1.86], respectively). On the other hand, there was no significant difference in the pooled estimate by the country of study, stage of treatment, and the other studied variables.

Table 2.9: Results of the moderator analysis of tested variables on the pooled estimate of each quantified factors

Tested variable	Sex	Age	BMI	HbA1C	Kidney problem
Type of outcome variable:					
Continuous	-	29/0.89[0.72-1.10]	14/0.99[0.67-1.45]	28/1.05[0.59-1.87]	-
Binary		59/0.89[0.62-1.28]	52/1.33[0.92-1.94]	34/1.12[0.71-1.74]	
		P=0.713	P=0.115	P=0.812	
Type of analysis test:					
Unadjusted	58/ 1.06[0.86-1.31]	70/ 0.86[0.76-1.27]	45/ 1.30[0.88-1.93]	42/ 1.13[0.77-1.64]	50/ 0.95[0.59-1.52]
Adjusted	38/ 0.97[0.86-1.20]	18/ 0.85[0.64-1.13]	21/ 1.04[0.83-1.31]	20/ 1.10[0.87-1.40]	11/ 0.81[0.36-1.86]
	p< 0.0001	**p< 0.0001**	p = 0.518	p = 0.378	**p< 0.0001**
Stage of treatment:					
Initiation	30/ 0.98[0.79-1.22]	28/ 1.16 [0.66-2.04]	15/0.93[0.61-1.42]	16/ 0.87[0.57-1.34]	11/ 1.35[0.48-3.78]
Intensification	42/ 1.02[0.82-1.27]	40/ 0.85 [0.58-1.25]	31/ 1.02[0.75-1.38]	36/ 1.13[0.84-1.51]	31/ 0.87[0.43-1.75]
Not specified stage	24/ 1.00[0.90-1.12]	20/ 1.04 [0.75-1.45]	20/ 1.57[1.02-2.41]	10/ 1.21[0.57-2.57]	19/ 1.05[0.65-1.70]
	p = 0.520	p = 0.415	p = 0.073	p = 0.179	p = 0.959
Study design:					
Retrospective cohort	70/ 0.99[0.85-1.16]	63/ 0.98 [0.60-1.59]	41/ 1.17[0.79-1.74]	39/ 1.13[0.82-1.57]	42/ 0.97[0.55-1.71]
Prospective cohort	11/ 0.97[0.83-1.13]	11/ 1.04 [0.76-1.42]	11/ 1.10[0.80-1.52]	11/ 1.00[0.52-1.91]	11/ 0.74[0.33-1.66]
Cross-sectional	9/ 0.99[0.79-1.13]	8/ 1.03[0.98-1.09]	8/ 1.14[0.74-1.76]	6/ 1.00[0.58-1.71]	8/ 1.06[0.58-1.92]
Comparative multiple case	6[a] / 1.05[0.78-1.41]	6[a]/ 0.87[0.63-1.20]	6[a]/ 1.03[0.78-1.37]	6[a]/ 0.95[0.62-1.47]	-
	p = 0.9684	p = 0.902	p = 0.799	p = 0.844	p = 0.719
Country					
United States	35/0.95[0.76-1.20]	40/ 0.92[0.56-1.50]	38/ 1.25[0.81-1.93]	32/ 1.18[0.78-1.80]	29/ 1.43[0.72-2.85]
United Kingdom	16/ 1.06[0.91-1.24]	5/ 0.87[0.33-2.35]	3[c]/ 1.69[0.08-34.57]	3[c]/ 0.87[0.17-4.61]	3[c]/ 0.53[0.12-2.38]
Cross-national	11/ 0.97[0.82-1.14]	9/ 0.89[0.60-1.30]	8/ 1.49[0.89-2.51]	9/ 1.39[0.55-3.52]	10/ 0.80[0.38-1.65]
Austria	4[b]/ 1.03[0.85-1.26]	4[b]/ 0.89[0.53-2.23]	-	-	-
Canada	2/ 0.94[0.60-1.46]	2/ 0.81[0.52-1.25]	-	-	2/ 0.24[0.08-0.68]
Germany	2/ 1.10[0.17-7.20]	2/ 1.39[0.68-2.84]	1/ 1.09[1.08-1.11]	2/ 1.55[0.54- 4.44]	-
Taiwan	3/ 1.07[0.96-1.20]	2[c]/ 0.87[0.50-1.54]	-	-	-
Italy	5/ 0.07[0.81-1.16]	5/ 1.18[0.69-2.01]	1/ 0.70[0.68-0.71]	1[g]/ 2.61[2.56-2.65]	2/ 0.94[0.33-2.69]

Japan	10/ 1.05[0.88-1.26]	11/ 0.95[0.64-1.40]	11/ 1.16[0.66-2.06]	11/ 1.05[0.72-1.54]	7[d]/ 1.05 [0.61-1.80]
Korea	4[e]/ 1.08[0.67-1.76]	4[e]/ 0.86[0.42-1.75]	-	-	4[e]/ 0.93[0.24-3.59]
India	4[f]/1.17[0.85-1.60] p = 0.079	4[f]/ 0.10[0.99-1.01] p = 0.763	4[f]/ 1.07[0.75-1.53] p = 0.701	4[f]/ 0.94[0.40-2.22] p = 0.853	4[f]/ 0.98[0.438-2.18] p = 0.242
Quality of study:					
Poor	25/ 1.02[0.82-1.28]	25/ 0.92[0.49-1.75]	19/ 1.15[0.78-1.70]	20/ 1.01[0.69-1.48]	20/ 1.27[0.57-2.58]
Satisfactory	4[f]/ 1.17[0.85-1.60]	4[f]/ 0.10[0.99-1.01]	4[f]/ 1.07[0.75-1.53]	4[f]/ 0.94[0.40-2.22]	4[f]/ 0.98[0.44-2.18]
Good	62/ 1.00[0.90-1.12]	55/ 0.99 [0.70-1.39]	39/ 1.22[0.58-1.75]	36/ 1.18[0.88-1.58]	33/ 0.85 [0.45-1.60]
Very good	5/ 0.87[0.59-1.35] p = 0.6812	4[g]/ 1.05[0.97 -1.13] p = 0.976	4[g]/ 1.18[0.71-1.96] p = 0.649	2[h]/ 1.21[0.76 -1.94] p = 0.685	4[g]/ 1.24[0.80-1.91] p = 0.647
Year of publication	96/ p= 0.9537	88/ p= 0.06	66/ p = 0.080	62/ p= 0.143	61/ p= 0.409

The result presented as the number of effect sizes (K)/ Overall estimate per level (OR[95%CI])/p value. a; only one study; Moreno et al (Moreno Juste et al., 2019), b; 4 effect sizes from one study (Winkelmayer et al., 2011b), c; 3 effect sizes from one study *(Wilkinson et al., 2018c)*; 7 effect sizes from one study (Katakami et al., 2020), e; 4 effect size from one study (Kim et al., 2019a), f; 4 effect sizes from one study (Dhanaraj et al., 2013), g; 4 effect sizes from one study (Saine et al., 2015), h; 2 effect sizes from one study (Saine et al., 2015).

Table 2.10: Results of moderator analysis of categorization scheme of binary data of age, body mass index, and HbA1c meta-analysis

Categorization scheme of binary data	# Of effect sizes (Total k)	Pooled estimate (OR[95%CI])	P value
Age:	59		
≥60 versus < 60 years	13	1.06 [0.61-1.83]	
≥65 versus <65 years	29	1.01 [0.69-1.46]	P=0.942
≥70 versus < 70 years	13	0.75 [0.30-1.84]	
≥55 versus < 55 years	4[a]	0.96 [0.98-1.01]	
Body mass index (BMI):	52		
Obese (BMI≥30 kg/m^2) vs. non-obese (BMI <30kg/m^2)	32	1.175 [0.855-1.615]	P=0.067
Overweight/obese (BMI≥25 kg/ m^2) vs. normal/ underweight (BMI < 25 kg/m^2)	13	1.545 [0.546-4.369]	
BMI ≥25 vs. BMI 22-25 kg/m^2	7[b]	1.018 [0.519 - 1.996]	
Glycaemic control (HbA1c):			
≥ 7 %(≥ 53mmol/mol) vs. < 7%(<53 mmol/mol)	13 21	1.5[0.34-6.75] 1.05[0.74-1.51]	P=0.916
≥ 8%(≥ 63.9 mmol/mol) vs. < 8%(< 63.9 mmol/mol)			

K: effect sizes. a; all from one study (Dhanaraj et al., 2013). b; all from one study (Katakami et al., 2020). OR: odds ratio, CI: confidence interval.

Publication bias and outliers

The Funnel plots (Figures 2.7-2.11) of all quantified factors showed that all studies cluster at the top part of the plots (lower SE, larger sample size). The asymmetry in the funnel plot suggests a possible presence of a publication bias or a small-study bias. The extended Eggers' test showed a significant possibility of asymmetry in the funnel plots for age, BMI, and kidney-related problems ($p< 0.0001$, 0.0013, and < 0.0001, respectively), but the test was non-significant for sex and HbA1c ($p = 0.101$ and 0.329, respectively).

Furthermore, the outliers test showed that 15 out of 96 effect sizes of sex data, 27 out of 88 effect sizes of age data, 18 out of 66 effect sizes of BMI data, and 12 out of 61 effect sizes of renal data were detected as outliers. Moreover, about half of the effect sizes of HbA1c data were recognised as outliers (31/62). The histogram plots of all factors (Figures 2.13-2.16) reflect that the flagged potential outliers are not uniformly distributed around the pooled estimate. The results of the sensitivity analyses (Table 2.11) revealed a close overall OR and narrower but overlapped 95%CI of the pooled estimate after excluding the outliers compared to the pooled estimate with outliers. However, it could not be determined whether the outliers did, in fact, bias the pooled estimate.

Accordingly, a Cook's distance test was measured for all factors (Figures 2.17-2.21). It revealed that none of the effect sizes included in the MA of sex had a Cook's value exceeding 0.04 (4/96); thus, none affected the pooled estimate. In contrast, two effect sizes included in the meta-analyses of age and HbA1c were considered influential cases in the model as they have a distance value of > 0.05 (4/88) and > 0.06 (4/62), respectively *(Zoberi et al., 2017, Hirsch et al., 2011, Dhanaraj et al., 2013, Montvida et al., 2018).* Similarly, among the effect sizes included in the MA of BMI where Cook's distance was computed, only Hirsch and colleagues presented a distance value larger than 0.061 (4/66) *(Hirsch et al., 2011)*. Lastly, three effect sizes included in the MA of kidney-related problems were considered to have an influential effect in the model with a distance value of > 0.07 (4/61) *(Katakami et al., 2020, Kim et al., 2019a).*

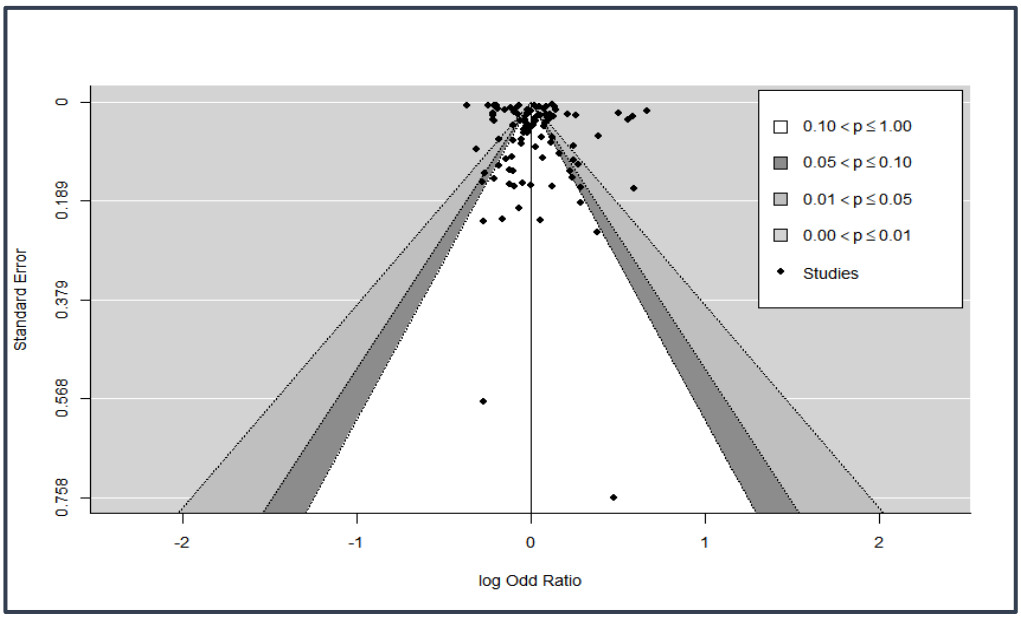

Figure 2.7: Funnel plot of sex association with antidiabetic drug prescription. Y-axis shows the standard error, X-axis shows log odds ratio

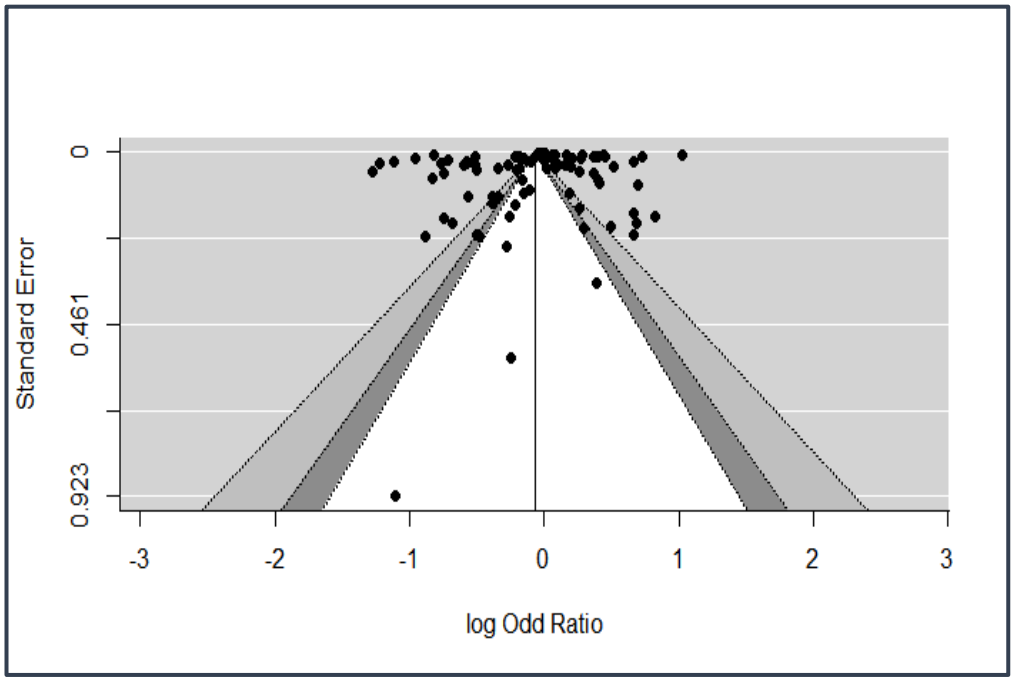

Figure 2.8: Funnel plot of age association with antidiabetic drug prescription. Y-axis shows the standard error, X-axis shows the log odds ratio

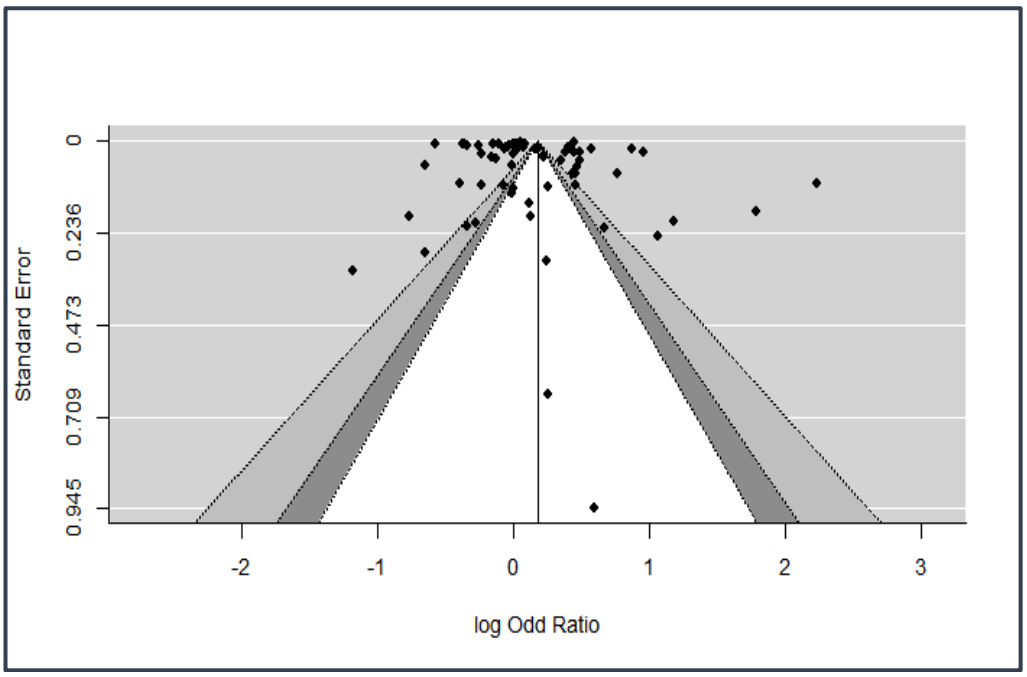

Figure 2.9: Funnel plot of obesity association with antidiabetic drug prescription. Y-axis shows the standard error, X-axis shows log odds ratio

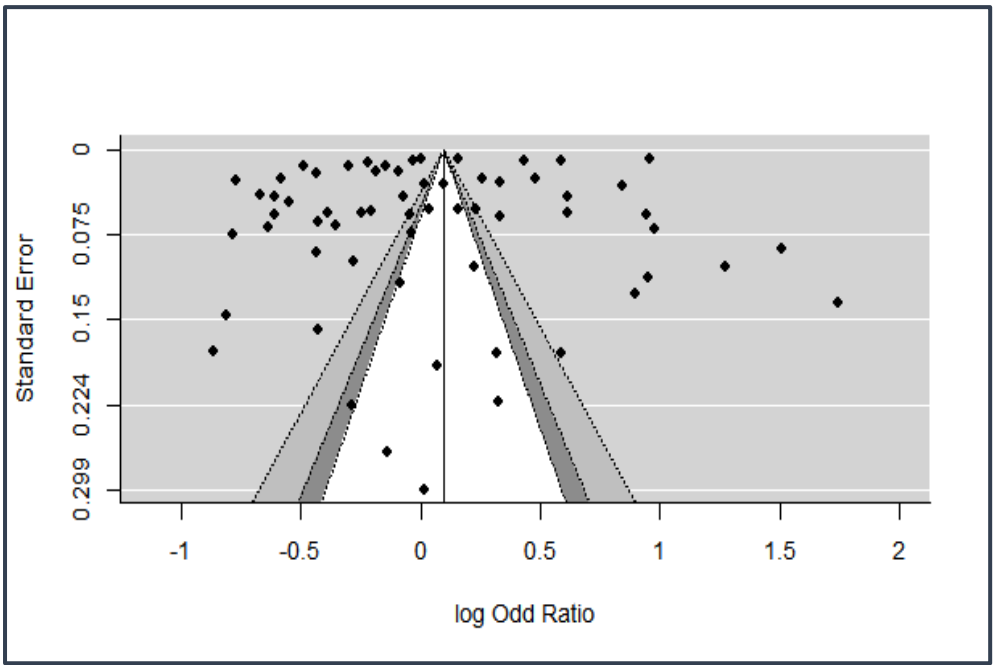

Figure 2.10: Funnel plot of HbA1c association with antidiabetic drug prescription. Y-axis shows the standard error, X-axis shows log odds ratio

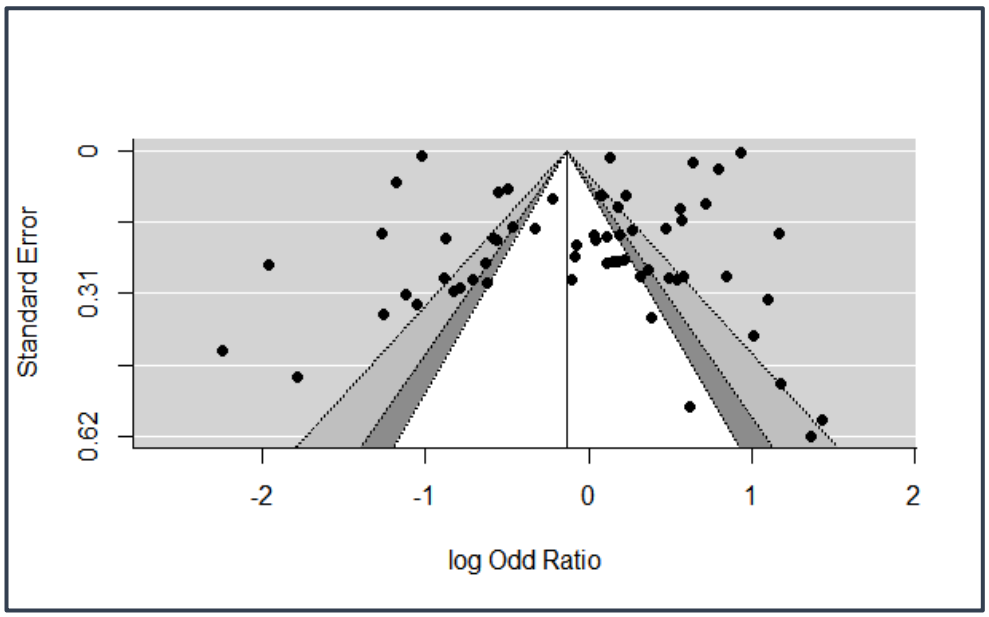

Figure 2.11: Funnel plot of kidney problems association with antidiabetic drug prescription. Y-axis shows the standard error, X-axis shows log odds ratio

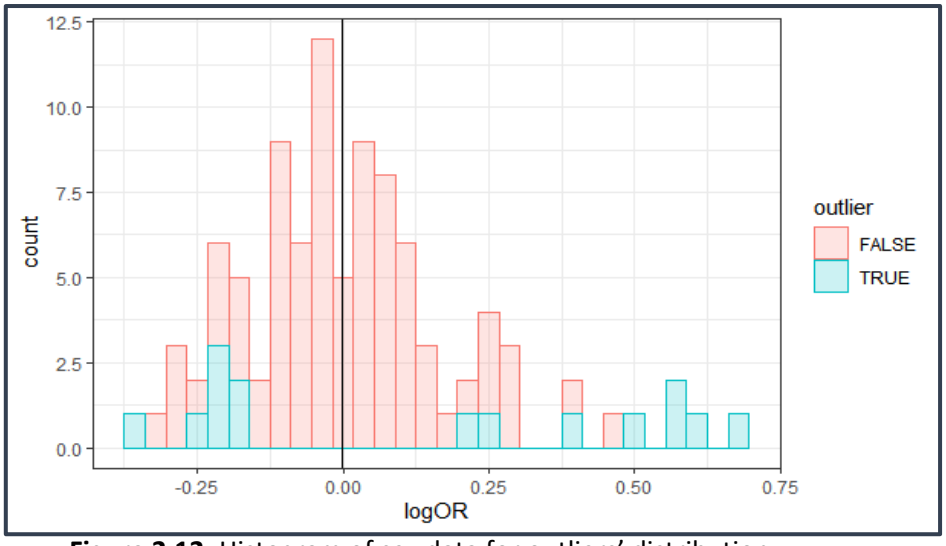

Figure 2.12: Histogram of sex data for outliers' distribution

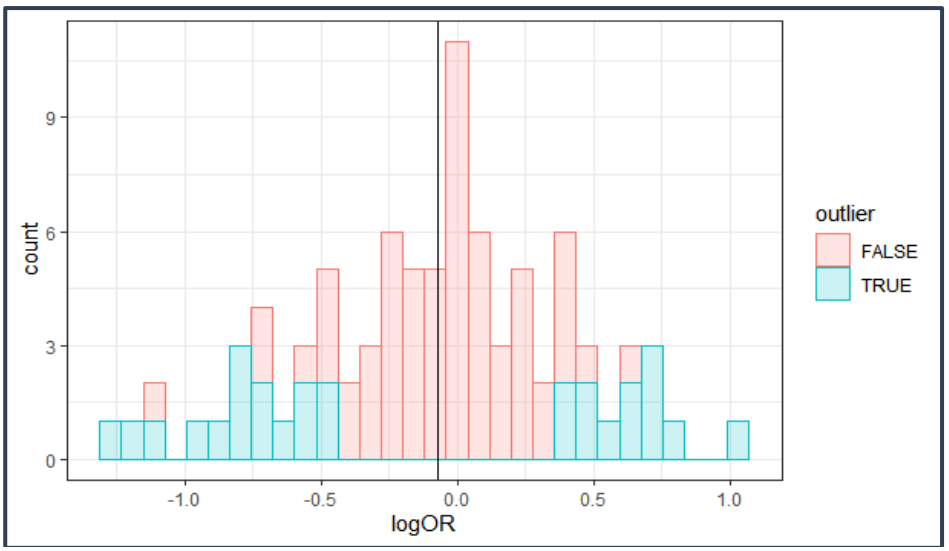

Figure 2.13: Histogram of age data for outliers' distribution

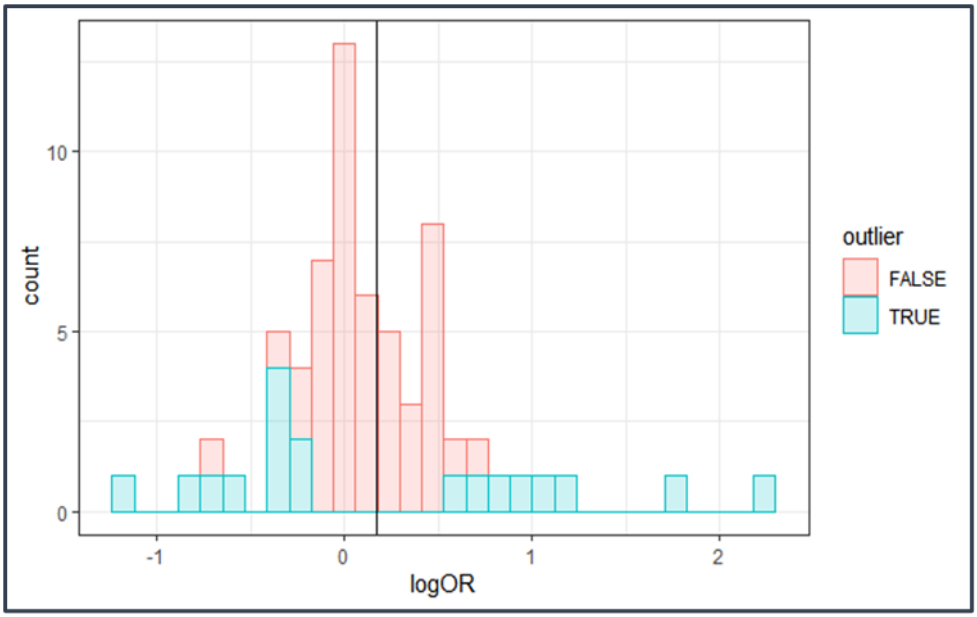

Figure 2.14: Histogram of obesity data for outliers' distribution

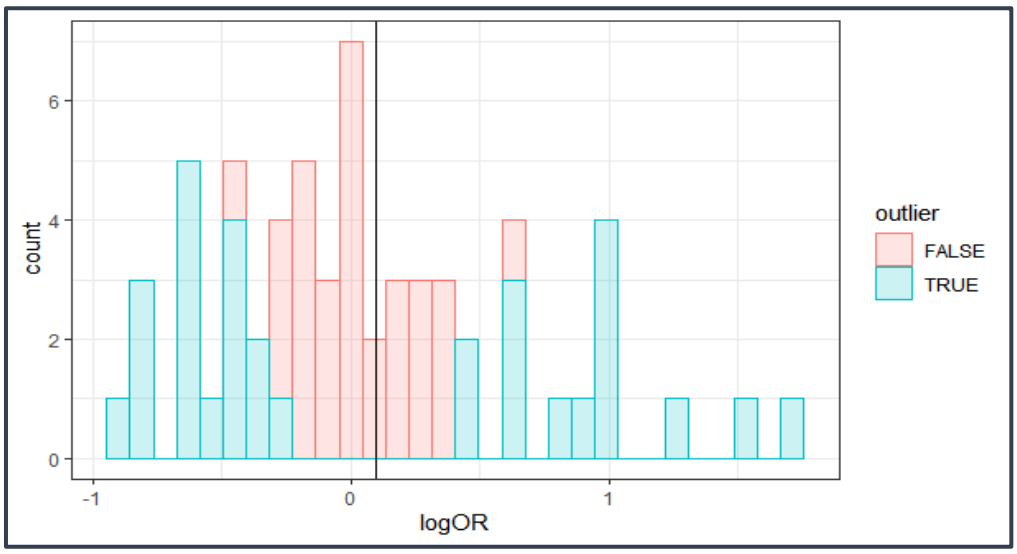

Figure 2.15: Histogram of HbA1c data for outliers' distribution

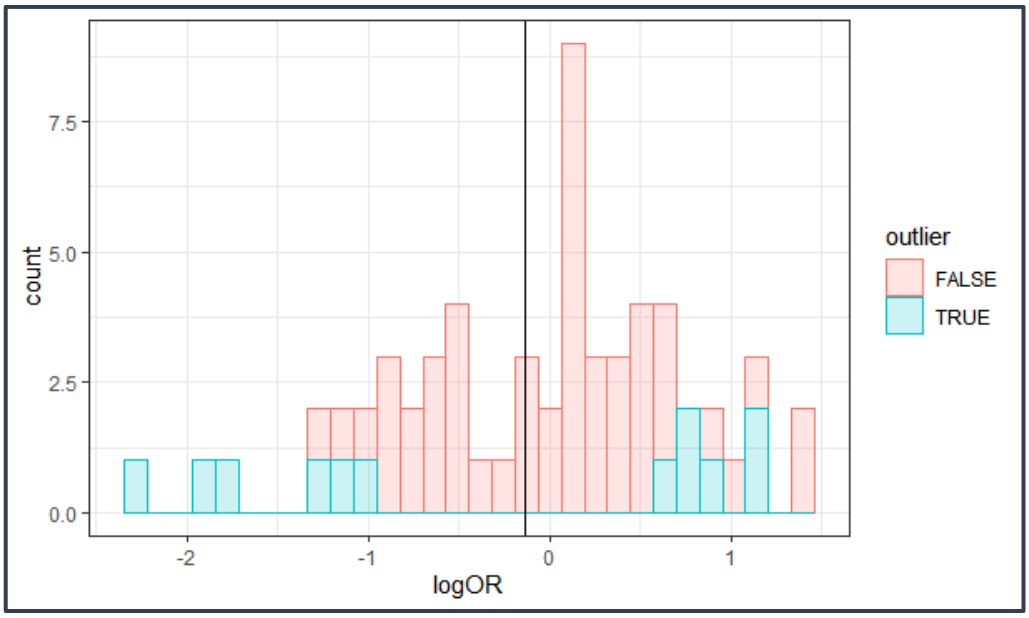

Figure 2.16: Histogram of renal data for outliers' distribution

Table 2.11: The pooled estimate of all quantified factors before and after excluding the outliers

Studied factor	Pooled estimate with outliers	Pooled estimate without outliers
Sex	0.99[0.92-1.07]	1.00[0.86-1.16]
Age	0.96[0.83-1.10]	0.93[0.66 -1.32]
Body mass index	1.21[1.00-1.47]	1.19[0.85-1.67]
HbA1c	1.06[0.88 to 1.29]	1.10[0.81-1.49]
Kidney problem	0.94[0.69-1.29]	0.89[0.54-1.47]

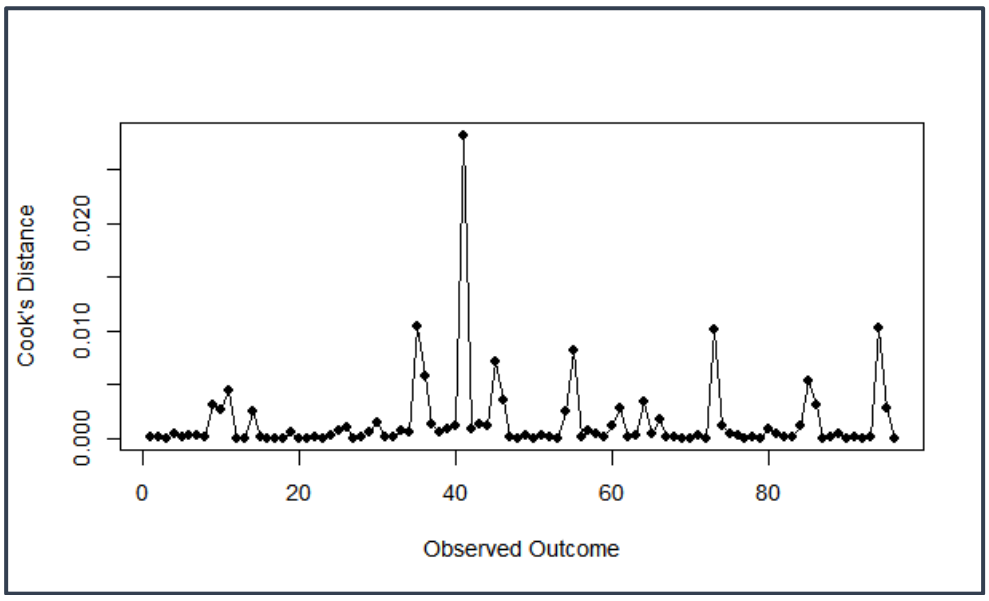

Figure 2.17: Influential observations of sex data by Cook's distance

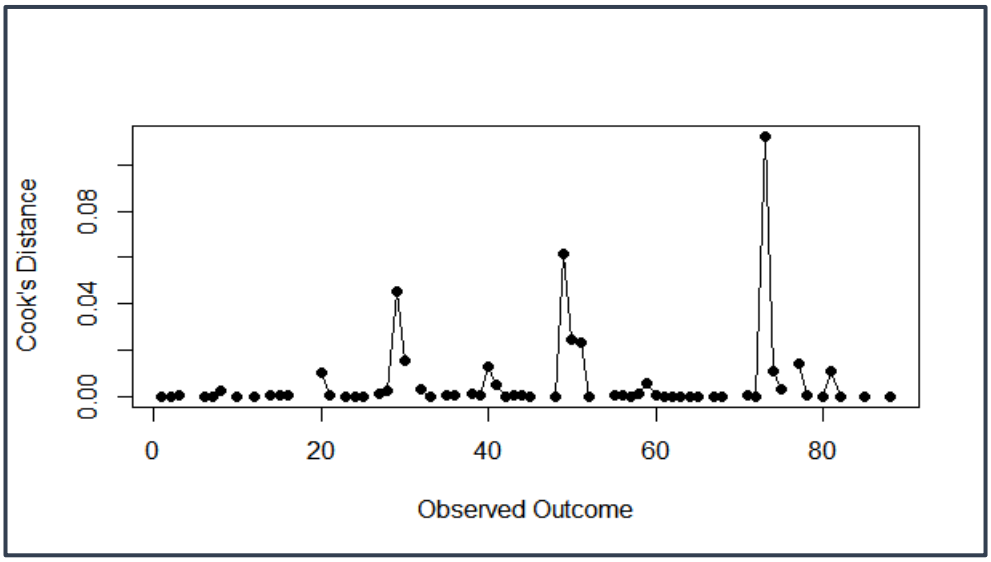

Figure 2.18: Influential observations of sex data by Cook's distance

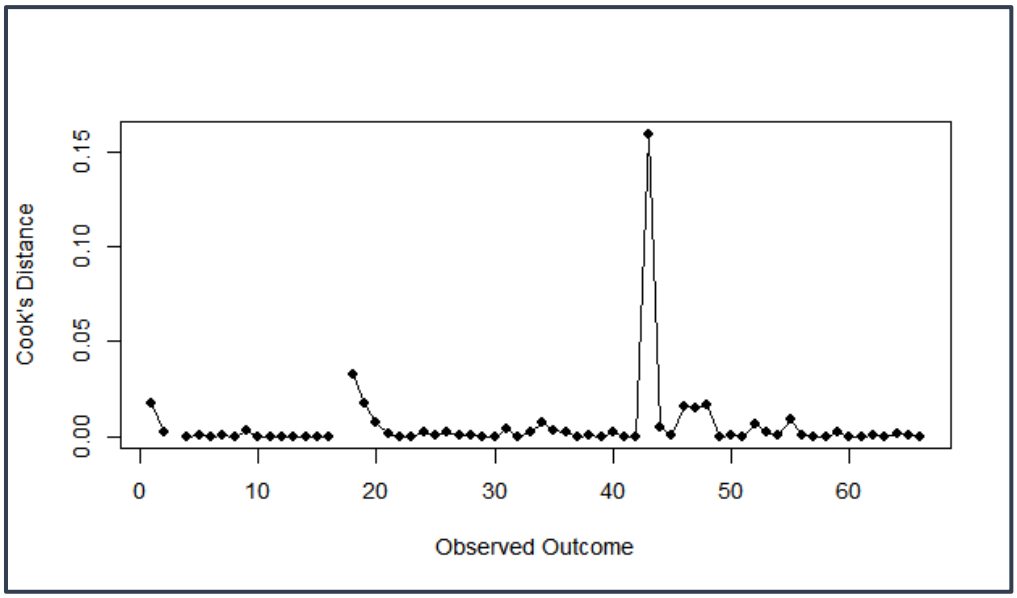

Figure 2.19: Influential observations of obesity data by Cook's distance

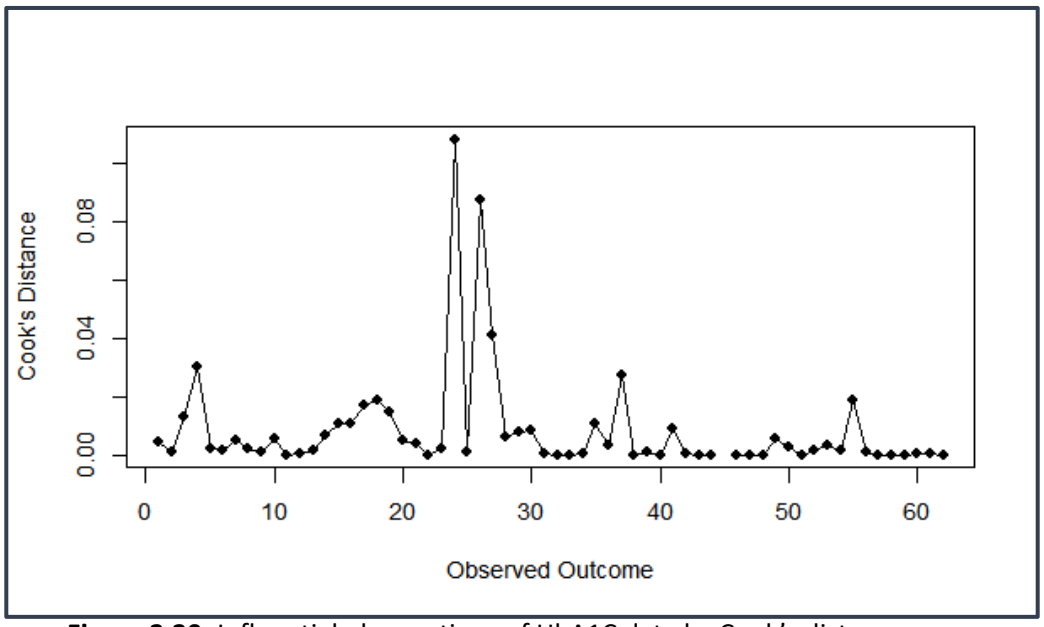

Figure 2.20: Influential observations of HbA1C data by Cook's distance

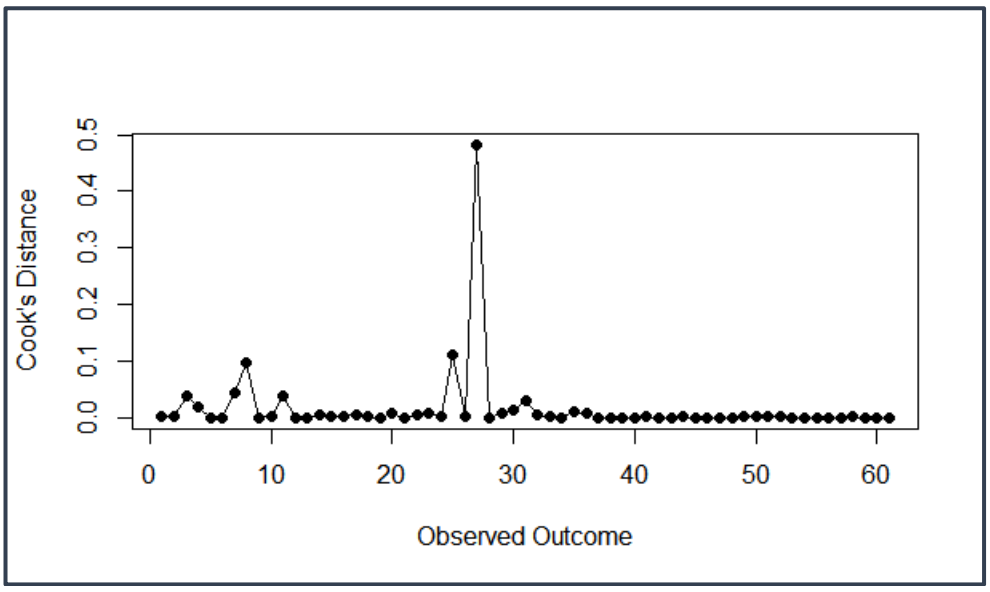

Figure 2.21: Influential observations of renal data by Cook's distance

2.3.4.2 Narrative synthesis

In this part, the results were divided into four subsections based on the category of investigated factors: demographic factors, clinical factors, socioeconomic factors, and prescriber-related factors. Within each category, a summary of the overall direction of association of the individual factor with each antidiabetic group was described, and detailed results on the direction and magnitude of association were summarized in Tables and presented in Appendix S.2.6.

Demographic factors

The following demographic factors were identified from included studies; patient age, sex, ethnicity, educational level, and family history (FH) of diabetes. The patient sex and age were summarized using MA as described in section 2.2.6, and the results were presented in the previous section (2.3.4.1). On the contrary, narrative synthesis was done for the other demographic factors where MA was not a suitable approach due to the limited number of studies that examined each factor per antidiabetic group.

Firstly, the association of ethnicity with the prescribing choice of ADDs was examined in a total of ten studies *(Whyte et al., 2019, Wilkinson et al., 2018b, Yu et al., 2017, Hirsch et al., 2011, Montvida et al., 2018, Ackermann et al., 2017, Korytkowski et al., 2014, Payk. et al., 2015, Zoberi et al., 2017, Brouwer et al., 2012)*. The results varied

according to the investigated antidiabetic groups and compared ethnic groups. SU, GLP1-RA, and insulin were the most frequently studied antidiabetic groups, which were reported in six studies, while TZD was evaluated in only two studies. Four of the ten included studies investigated the remaining antidiabetic groups (metformin, DPP4-I, and SGLT2-I).

It was observed that White patients had a statistically significant positive association with GLP1-RA prescriptions when compared to patients with Asian *(Whyte et al., 2019),* Black *(Whyte et al., 2019, Yu et al., 2017, Montvida et al., 2018, Hirsch et al., 2011, Korytkowski et al., 2014)*, Mixed *(Whyte et al., 2019),* or other ethnic groups *(Whyte et al., 2019, Yu et al., 2017, Korytkowski et al., 2014)*. However, Montvida et al. (2018) reported that GLP1-RA was less likely to be prescribed for White patients compared to Black patients, where the outcome was examined at the stage of first intensification (calculated OR[95%CI] from baseline data: Black to White: 1.389 [1.339-1.443]) *(Montvida et al., 2018)*. In addition, Ackermann and colleagues *(Ackermann et al., 2017)* showed that non-Hispanic Whites were non-significantly less likely by 9.4% to be treated with GLP1-RA compared to Hispanics and Black patients (calculated OR[95%CI] from baseline data: 0.906[0.813-1.009]).

The results of studies investigating SGLT2-I were consistent in terms of the direction of the association. SGLT2-I prescription was positively associated with White ethnicity compared to Asian *(Whyte et al., 2019),* South Asian *(Wilkinson et al., 2018c)*, Black *(Whyte et al., 2019, Wilkinson et al., 2018c)*, Mixed *(Whyte et al., 2019, Wilkinson et al., 2018c),* and other ethnic groups *(Whyte et al., 2019, Wilkinson et al., 2018c)*. Ackermann and colleagues *(Ackermann et al., 2017)* showed a similar result for non-Hispanic Whites compared to Hispanics and Black patients (calculated OR[95%CI] from baseline data: 1.1 [0.971-1.232]). Like GLP1-RA, Montvida et al. *(Montvida et al., 2018)* showed a negative association of SGLT2-I prescriptions at the stage of first intensification for White patients compared to Black ones (calculated OR[95%CI] from baseline data: Black to White: (1.516 [1.426 -1.611]). Regarding the association of ethnicity with the choice of SU for T2DM management, 10 out of 14 effect sizes showed a higher likelihood of prescribing SU for White compared to

non-White patients *(Ackermann et al., 2017, Montvida et al., 2018, Payk et al., 2015, Whyte et al., 2019, Wilkinson et al., 2018b)*. The results of studies that explored the association of ethnicity with the prescription of other antidiabetic groups were less consistent; almost half of the effect sizes showed a positive association, and the remaining revealed negative results, as illustrated in Appendix S.2.6.

Secondly, only five studies assessed the association of smoking status of patients with T2DM with ADP *(Geier et al., 2014, Saine et al., 2015, Wilkinson et al., 2018c, Yu et al., 2017, Zoberi et al., 2017).* Metformin, SU, DPP4-I, and insulin were included in two studies, while GLP1-RA and SGLT2-I were explored only in one study, and TZD was not assessed. All studies except one showed a non-significant association of smoking status with ADP for all examined antidiabetic groups. For instance, in comparison to the non-smokers, the current smokers had a non-significant positive association with the prescription of SU *(Geier et al., 2014, Wilkinson et al., 2018c)*, insulin *(Zoberi et al., 2017),* metformin *(Zoberi et al., 2017)*, and DPP4-I (according to the THIN database in Saine et al. (2015) study *(Saine et al., 2015)*). In contrast, they had a non-significant negative association with SGLT2-I *(Wilkinson et al., 2018c)*, metformin *(Geier et al., 2014)* and DPP4-I prescriptions (according to Wilkinson et al. (2018) study *(Wilkinson et al., 2018c)* and the CPRD database in Saine et al. (2015) study *(Saine et al., 2015)*). Most studies revealed similar findings for the former smokers compared to the non-smokers; detailed results are described in Appendix S.2.6. Nevertheless, the only study with a statistically significant result is the one conducted by Yu and colleagues *(Yu et al., 2017)*. It showed that the current and former smokers were significantly less likely to receive GLP1-RA for T2DM treatment than basal insulin compared to the non-smokers (Calculated OR[95%CI]: current smoker vs. non-smoker: 0.815[0.713-0.931], former smoker vs. non-smoker: 0.887[0.792-0.993])

Lastly, very limited studies assessed the association of other demographic factors with ADP. For example, the level of education was evaluated by Nicolucci and colleagues *(Nicolucci et al., 2019),* which showed that patients with a lower level of education (no formal education, primary education (1-6), or secondary education

(7-13)) were less likely to receive DPP4-I, SGLT2-I, insulin, and GLP1-RA than SU compared to patients who spent >13 years on education. The association was non-significant with insulin prescription at all levels of education and with GLP1-RA prescription for patients at a level of no formal education (Appendix S.2.6).

Additionally, the linkage between diabetes FH and ADP was assessed by Dhanaraj et al. (2013) study *(Dhanaraj et al., 2013) and* Stargardt and Alexander study *(Stargardt et al., 2009)*. Both studies showed that having diabetes FH had a non-significant negative association with pioglitazone prescription. For SU, the results of the two studies were contradictory: Dhanaraj et al. (2013) showed that having diabetes FH was significantly linked to a lower likelihood of receiving SU (OR[95%CI]: 0.03 [0.03–0.04]). On the contrary, the other study showed a non-significant higher probability of receiving SU than pioglitazone for patients having diabetes FH (pioglitazone to SU: Probability estimate [SE]: -0.1340[0.0905], p=0.1389). Furthermore, Dhanaraj et al. (2013) showed that having a history of diabetes in the family was linked to a greater likelihood of getting insulin and metformin prescriptions (OR[95%CI]: 1.76 [1.18–2.64] and 1.10 [0.73–1.67], respectively). Appendix S.2.6 provides detailed information about the direction and magnitude of association of all previously discussed demographic factors with each antidiabetic group.

Clinical factors

The most frequently examined clinical factors in the included studies were glycaemic status (HbA1c), BMI, kidney function, microvascular complications, macrovascular complications, diabetes duration, and other comorbidities like HTN and dyslipidaemia. A narrative synthesis was performed for all clinical factors except BMI, HbA1c, and kidney-related problems, which were quantified using MA since the number of studies investigating the remaining factors did not support the application of MA. Firstly, the association of microvascular complications (neuropathy and retinopathy) with ADP was investigated in 11 studies. All studies evaluated the influence of retinopathy, while nine out of 11 studies included neuropathy. Nephropathy was incorporated in the MA of studies that assessed renal function. Four additional articles examining the association without clearly

stating the type of microvascular complications were discussed in this section as well.

Among all examined antidiabetic groups, only insulin and GLP1-RA showed consistent results in terms of the direction of association with retinopathy. Insulin was assessed in four articles, and all showed a significant positive association of insulin prescription for patients diagnosed with retinopathy *(Dhanaraj et al., 2013, Zoberi et al., 2017, Levin et al., 2014, Gentile et al., 2018).* Also, two studies investigated GLP1-RA, and both revealed that being diagnosed with retinopathy was linked with a lower likelihood of receiving GLP1-RA for T2DM management *(Levin et al., 2014, Longato et al., 2020).* On the other hand, the results were more diverse regarding the prescription of metformin, SU, SGLT2-I, and DPP4-I for patients with retinopathy. For instance, being diagnosed with retinopathy was positively associated with DPP4-I prescription in three studies *(Cai et al., 2010, Saine et al., 2015, Wilkinson et al., 2018b),* while negatively associated in two studies *(Grabner et al., 2015, Morita et al., 2019).*

Regarding neuropathy, the results were consistent for prescribing insulin, SGLT2-I, and SU. It was found that insulin *(Zoberi et al., 2017, Levin et al., 2014, Dhanaraj et al., 2013)* and SGLT2-I *(Longato et al., 2020, Grabner et al., 2015)* were significantly more likely to be prescribed for patients with neuropathy compared to the patients without the disease. SU was less likely to be prescribed for patients with neuropathy; the association was significant in Dhanaraj and colleagues *(Dhanaraj et al., 2013)* but non-significant in Abdelmoneim et al. *(Abdelmoneim et al., 2013).* On the contrary, the results of studies that evaluated the prescribing choice of DPP4-I, metformin, and GLP1-RA for patients with neuropathy were discrepant. As an example, two studies reported positive associations of prescribing DPP4-I *(Saine et al., 2015, Cai et al., 2010)* and metformin *(Abdelmoneim et al., 2013, Morita et al., 2019)* with neuropathy. The other two studies showed the opposite result for DPP4-I *(Morita et al., 2019)* and metformin *(Zoberi et al., 2017, Dhanaraj et al., 2013, Grabner et al., 2015)*. TZD was evaluated only by Dhanaraj and colleagues *(Dhanaraj et al., 2013),* who showed a non-significant positive relation between pioglitazone prescription

and retinopathy, and a non-significant negative association with neuropathy. Detailed information on the direction and magnitude of the association of neuropathy and retinopathy with each antidiabetic class is presented in Appendix S.2.6.

Three studies have not specified the type of microvascular complications. DPP4-I was examined by Zhang et al. *(Zhang et al., 2010)* and Nicolucci et al. *(Nicolucci et al., 2019)*. The former showed that sitagliptin was significantly more likely to be prescribed for patients with microvascular complications (OR[95%CI]: 1.504[1.083-2.089]), but the latter showed an opposite non-significant result (OR[95%CI]: 0.85[0.70-1.02]). Likewise, insulin was evaluated in two studies showing contradictory results *(Nicolucci et al., 2019, Hartmann et al., 2020);* positive and significant according to Hartmann et al. (2020) (OR[95%CI]: 1.54 [1.32-1.80]), yet negative and non-significant based on Nicolucci et al. (2019) (OR[95%CI]: 0.87[0.59-1.28]). For GLP1-RA, both studies *(Hartmann et al., 2020, Nicolucci et al., 2019)* showed a lower likelihood of prescribing GLP1-RA for patients with microvascular complications (OR[95%CI]: 0.66[0.55-0.78] and 0.87[0.59-1.28], respectively). Lastly, SGLT2-I and TZD were reported only in one study, in which SGLT2-I prescribing had a non-significant positive association with the presence of microvascular complications (OR[95%CI]: 1.21[0.88–1.65]) *(Nicolucci et al., 2019)*. Likewise, Stargardt and Alexander *(Stargardt et al., 2009)* revealed a weak positive non-significant association of TZD prescription with a baseline diagnosis of microvascular complications (Calculated OR[95%CI]: 1.013[0.639-1.607]).

Secondly, the relation of baseline diagnosis of macrovascular complications with ADP was examined in 23 studies. Studies that presented the outcome using the general term of CVD (n=12) or macrovascular complications (n=3) were discussed together. Several studies assessed the association of a specific type of CVDs with ADP, mainly ischemic heart disease (IHD) or coronary artery disease (CAD), which was examined in eight studies. Other types of investigated CVDs included cerebrovascular disease (n=9), HF (n=8), and PVD (n=6).

- CVD or macrovascular complications:

Being diagnosed with CVD was found to be negatively associated with metformin prescription in five studies *(Montvida et al., 2018, Zoberi et al., 2017, Wang et al., 2013a, Katakami et al., 2020, Morita et al., 2019),* yet only two studies showed a statistically significant result *(Montvida et al., 2018, Morita et al., 2019)*. Similarly, four out of five studies that examined TZD *(Katakami et al., 2020, Kim et al., 2019a, Montvida et al., 2018, Stargardt et al., 2009)* and GLP1-RA prescriptions for patients with CVD *(Hartmann et al., 2020, Longato et al., 2020, Nicolucci et al., 2019, Yu et al., 2017)* have demonstrated negative associations. The result was statistically significant for GLP1-RA prescription, but only Montvida et al. (2018) showed a statistically significant result for TZD prescription *(Montvida et al., 2018).*

In contrast, most studies examining SU (4 out of 5) and insulin (4 out of 6) showed that patients with CVD or macrovascular complications were more likely to be prescribed SU *(Montvida et al., 2018, Nicolucci et al., 2019, Katakami et al., 2020, Wilkinson et al., 2018b)* and insulin *(Yu et al., 2017, Zoberi et al., 2017, Montvida et al., 2018, Hartmann et al., 2020)*. Lastly, the results of studies investigating DPP4-I were conflicting; a positive association was reported in six studies *(Montvida et al., 2018, Katakami et al., 2020, Kim et al., 2019a, Saine et al., 2015, Zhang et al., 2010, Morita et al., 2019)*. However, a negative association was found in Montvida et al. (2018) when the outcome was assessed at the stage of first intensification *(Montvida et al., 2018)* and in Saine et al. (2015) utilising databases other than CPRD *(Saine et al., 2015)*. Additionally, Wilkinson et al. (2018) and Nicolucci et al. (2019) showed no association (OR=1) of DPP4-I prescription with the presence of CVD *(Wilkinson et al., 2018b, Nicolucci et al., 2019)*.

- CAD or IHD:

All studies that investigated the outcome of SU and GLP1-RA revealed that patients with CAD or IHD were less likely to be prescribed SU *(Abdelmoneim et al., 2013, Dhanaraj et al., 2013, Arnold et al., 2018)* or GLP1-RA *(Arnold et al., 2018, Levin et al., 2014, Longato et al., 2020).* In contrast, DPP4-I was found to be significantly more likely to be prescribed for patients with CAD or IHD *(Arnold et al., 2018, Cai et al.,*

2010, Ou et al., 2017). Similarly, three out of four studies that included insulin showed higher odds of receiving insulin for patients with T2DM with CAD or IHD *(Arnold et al., 2018, Dhanaraj et al., 2013, Levin et al., 2014).* Data on the other antidiabetic groups are illustrated in Appendix S.2.6.

- Cerebrovascular disease or stroke:

Studies examining the association of cerebrovascular disease or stroke with ADP reported negative associations with the prescribing choice of SU *(Abdelmoneim et al., 2013, Dhanaraj et al., 2013),* GLP1-RA *(Longato et al., 2020)*, and TZD *(Dhanaraj et al., 2013)*, still, a positive association was found with insulin *(Kostev et al., 2014, van den Boom et al., 2020, Zoberi et al., 2017)* and SGLT2-I *(Longato et al., 2020)* prescriptions. Some previous studies reported a positive association between cerebrovascular disease or stroke and DPP4-I prescription *(Ou et al., 2017, Cai et al., 2010)*, but other presented a contradictory result *(Saine et al., 2015)*. See also Appendix S.2.6.

- HF and PVD:

A diagnosis of HF was significantly and negatively associated with metformin *(Abdelmoneim et al., 2013, Arnold. et al., 2018)* and GLP1-RA *(Arnold. et al., 2018, Levin et al., 2014, Longato et al., 2020)* prescriptions, yet significantly and positively associated with insulin prescription *(Arnold. et al., 2018, Kostev et al., 2014, Levin et al., 2014).* Moreover, two out of three studies showed that SU was significantly more likely to be prescribed for patients with HF *(Abdelmoneim et al., 2013, Arnold. et al., 2018)*. PVD association with ADP was less frequently studied, in which DPP4-I and GLP1-RA were investigated in two studies, while the other antidiabetic groups were only examined in one study (Appendix S.2.6). As an example, two previous studies showed that insulin was significantly more likely to be prescribed for patients with T2DM who were diagnosed with PVD (OR[95%CI]: 1.940[1.30-2.810] and 2.595[2.226 -3.025], respectively) *(Levin et al., 2014, van den Boom et al., 2020).*

Thirdly, among the other examined comorbid conditions, the most frequently explored ones were HTN (n=12) and dyslipidaemia (n=10). They were mainly investigated with DPP4-I prescriptions, which were included in six studies

investigating HTN and five studies examining dyslipidaemia. While the majority of relevant studies (5 out of 6) reported a negative association of DPP4-I prescription with the presence of HTN *(Saine et al., 2015, Fujihara et al., 2017, Kim et al., 2019a, Ou et al., 2017, Grabner et al., 2015),* two studies *(Saine et al., 2015, Cai et al., 2010)* revealed significant positive results (Appendix S.2.6). In addition, two studies observed lower odds of prescribing metformin for patients with T2DM with HTN *(Fujihara et al., 2017, Zoberi et al., 2017)* relative to one study, reporting an opposite result *(Abdelmoneim et al., 2013).* Furthermore, two out of three relevant studies revealed that a diagnosis of HTN was associated with a higher likelihood of prescribing SU *(Fujihara et al., 2017, Kim et al., 2019a),* GLP1-RA *(Levin et al., 2014, Longato et al., 2020),* and SGLT2-I *(Kim et al., 2019a, Grabner et al., 2015)*. Although three out of four studies presented a positive association of insulin prescription with baseline HTN diagnosis, none showed a statistically significant result *(Levin et al., 2014, Yu et al., 2017, Zoberi et al., 2017)*.

While most studies investigating HTN showed non-significant results, dyslipidaemia had a statistically significant association with ADP in all relevant studies. Overall, patients with dyslipidaemia had lower odds of receiving SU *(Kim et al., 2019a, Abdelmoneim et al., 2013)* and insulin *(Kostev et al., 2014, Levin et al., 2014, Yu et al., 2017)*, but higher odds of being treated with DPP4-I *(Kim et al., 2019a, Ou et al., 2017, Saine et al., 2015)*, SGLT2-I *(Kim et al., 2019a, Longato et al., 2020, Grabner et al., 2015),* and GLP1-RA *(Levin et al., 2014, Yu et al., 2017).* Only two studies explored the likelihood of receiving metformin for patients diagnosed with dyslipidaemia; one study showed a significant positive association *(Abdelmoneim et al., 2013),* yet the other study reported a significant negative result *(Zoberi et al., 2017).* TZD was only examined by Kim and colleagues who reported a non-significant negative association of TZD prescription for patients with HTN or dyslipidaemia *(Kim et al., 2019a).*

Lastly, the association of diabetes duration with ADP was investigated in a total of eight studies (Appendix S.2.6). Of these, four articles evaluated the association of diabetes duration with insulin use, and all reported statistically significant positive

results *(Dhanaraj et al., 2013, Gentile et al., 2018, Hartmann et al., 2020, Nicolucci et al., 2019)*. Conversely, metformin was investigated in three studies, and all revealed that patients with longer diabetes duration were significantly less likely to be treated with metformin *(Dhanaraj et al., 2013, Fujihara et al., 2017, Geier et al., 2014).* About the other antidiabetic groups, the results of studies within each group were diverse. For instance, the association between diabetes duration and GLP1-RA prescription was investigated in four studies. One study showed no association with OR=1 *(Nicolucci et al., 2019)*, while two studies reported positive associations *(Hartmann et al., 2020, Hirsch et al., 2011),* and one presented a negative result *(Longato et al., 2020)*. In addition, DPP4-I was included in two studies; one showed no association between DPP4-I prescription and diabetes duration (OR=1) compared to SU *(Nicolucci et al., 2019),* and the other reported a statistically significant negative result *(Fujihara et al., 2017).*

Socioeconomic factors:

The association of socioeconomic factors with ADP was much less commonly studied compared to the demographic and clinical factors. Socioeconomic factors were divided into those related to the medical facility and factors related to the patients. The former included the type of institution *(Kim et al., 2019a, Liu et al., 2017)* and the ownership of the medical facility *(Liu et al., 2017)*. However, socioeconomic factors related to the patients were assessed using several measures such as income level *(Liu et al., 2017, Desai et al., 2012),* having insurance, the type of insurance *(Hirsch et al., 2011, Kim et al., 2019a, Nicolucci et al., 2019, Payk et al., 2015, Desai et al., 2012)*, the employment status *(Nicolucci et al., 2019)*, area of living *(Liu et al., 2017, Moreno Juste et al., 2019)*, and the deprivation level *(Whyte et al., 2019, Wilkinson et al., 2018b)*. The deprivation level was based on the index of multiple deprivations (IMD), which is an official measure of deprivation in the UK, considering several measures in addition to income levels, such as health, crime, and education *(Noble et al., 2006).*

For instance, according to Liu et al. (2017) study, the ownership of the medical facility had a significant association with metformin prescription, in which public

facilities were more likely to prescribe metformin than for-profit medical facilities (OR[95%CI]: 1.16[1.09-1.24]), but less likely to prescribe metformin compared to not-for-profit facilities (OR[95%CI]: 0.87[0.81-0.94]). Additionally, the income level was examined in two studies, which reported a positive association between income level and metformin prescription *(Liu et al., 2017, Desai et al., 2012)*. However, the number of studies that examined the association of other socioeconomic factors with the prescribing choice of individual ADDs was sparse, and the results were highly diverse. Consequently, an overall conclusion could not be drawn from the available data in that regard. Detailed information on the magnitude of the association of each socioeconomic factor with ADP is presented in Appendix S.2.6.

Prescriber-related factors

The identified prescriber-related factors included prescriber age, sex, speciality, and practice experience. The most frequently studied one was prescriber speciality which was included in 12 studies. Overall, it was reported that Endocrinologists/Diabetologists and prescribers with Internal Medicine speciality were more likely to prescribe metformin *(Liu et al., 2017, Winkelmayer et al., 2011b),* GLP1-RA *(Ackermann et al., 2017, Nicolucci et al., 2019, Yu et al., 2017),* and DPP4-I *(Ackermann et al., 2017, Kim et al., 2019a, Nicolucci et al., 2019, Grabner et al., 2015)* compared to GP or non-specialists. Additionally, four out of five studies showed that Endocrinologists/Diabetologists had a positive association with insulin prescription compared to family medicine (FM) or GP *(Ackermann et al., 2017, Nicolucci et al., 2019, Kostev et al., 2014, van den Boom et al., 2020).*

In contrast, Endocrinologists/Diabetologists were less likely than FM or GP to prescribe SU *(Ackermann et al., 2017, Nicolucci et al., 2019)* and TZD *(Ackermann et al., 2017)*. Similarly, two out of three studies reported a negative association between endocrinology speciality and SGLT2-I prescriptions. Prescriber age and sex were examined only with the prescribing choice of metformin. For instance, two studies showed that metformin was less likely to be prescribed by older prescribers compared to younger ones *(Liu et al., 2017, Winkelmayer et al., 2011b)*. Besides, female prescribers were more likely to prescribe metformin than male prescribers *(Liu et al.,*

2017, Wang et al., 2013a, Winkelmayer et al., 2011b), yet only one study showed a statistically significant result *(Liu et al., 2017).* Furthermore, the association of practice experience with ADP was evaluated in two studies *(Stargardt et al., 2009, Wang et al., 2013a).* Wang et al. (2013) revealed no association between practice experience and the likelihood of prescribing metformin as initial therapy (OR[95%CI]: 1.00[0.96-1.05]) *(Wang et al., 2013a).* However, Stragardt et al. (2009) reported that the length of time the physician had experience in treating T2DM was negatively correlated with the probability of adding glitazone to metformin compared to SU *(Stargardt et al., 2009).*

2.4 Discussion

This SR and MA are the first to systematically assess and quantify the impact of five demographic and clinical factors (age, sex, glycaemic status, BMI, and kidney problems) on the prescribing choice of ADDs in clinical practice, using a three-level MA approach. To our knowledge, no previous review either quantified each factor's impact on ADP; or compared their impact among different antidiabetic groups. This SR and MA aimed to understand and quantify factors associated with ADP among patients with T2DM between 2009 and 2021, in addition to mapping those factors into specific categories.

The findings of the 40 studies investigating factors associated with ADP were synthesized. These factors were categorized into demographic, clinical, socioeconomic, and prescriber-related factors. Among these categories, the most studied are demographic and clinical factors. Of all identified factors, five were synthesized quantitatively using meta-analyses, including age and sex (demographic factors), as well as glycaemic status (HbA1c), BMI, and kidney-related problems (clinical factors). In contrast, narrative synthesis was used to summarise the other factors because of the limited number of studies examining these factors, hindering the application of MA. The first section (2.4.1) discusses factors synthesized using MA, and section 2.4.2 presents factors summarized narratively.

2.4.1 Factors quantified utilising MA

The significant variability in the pooled estimate of sex by class of ADDs could be linked to the differences in the number of studies investigating each antidiabetic class and the pharmacological characteristics of ADDs (mainly their safety and tolerability profile). Sex had the most significant association with prescribing choice of GLP1-RA followed by TZD: female patients were more likely to be prescribed GLP1-RA compared to male patients yet less likely to get a TZD prescription (Section 2.3.4.1, Figure 2.2). That could be partly explained by the weight loss effect of GLP1-RA, which was found to be greater among female patients *(Joung et al., 2020)*. In addition, it was reported that female patients had a better GLP1-RA tolerance than male patients, and the cardiovascular benefit of GLP1-RA was more prominent

among female patients *(Raparelli et al., 2020).* On the other hand, female patients are more likely to experience side effects from TZD, including weight gain, fracture, and oedema, and that could contribute to the observed lower prescription of TZD among female patients in this MA; Section 2.3.4.1, Figure 2.2 *(Campesi et al., 2017, Joung et al., 2020)*. However, sex had a non-significant association with prescribing choice of other antidiabetic groups (Section 2.3.4.1, Figure 2.2). This non-significant association could be linked partially to the lower variability in the cardiovascular benefits and rate of adverse drug reactions (ADR) reported with those antidiabetic groups between male and female patients *(Campesi et al., 2021).*

The other identified demographic factor was patient age. A significant difference was observed in the effect of age according to the investigated antidiabetic group (Section 2.3.4.1, Figure 2.3). Patient age had the highest impact on selecting SU, GLP1-RA, SGLT2-I, and metformin, respectively (Section 2.3.4.1, Figure 2.3). Despite the higher risk of SU-related hypoglycaemia among older people, the pooled estimate showed that older people were significantly more likely to get SU prescriptions. The low cost of SU and the current availability of short-acting second generation of SU (e.g., glipizide) with fewer side effects might be partially responsible for the previous observation *(Yakaryılmaz and Öztürk, 2017).* That could also reflect the legacy availability of SU for T2DM management as none of the newer ADDs has been available for ten years, and more than half (26/41, 63.41%) of included studies were conducted before 2014. Accordingly, patients starting on SU will stay on the same regimen unless they develop side effects or need additional drug therapy to maintain glycaemic control.

In contrast, patients at an older age were significantly less likely to be prescribed GLP1-RA, SGLT2-I, and metformin (Section 2.3.4.1, Figure 2.3). Older people with T2DM are more likely to have been diagnosed before the introduction of new antidiabetic classes (e.g., GLP1-RA and SGLT2-I); thus, they are more likely to be already treated with older antidiabetic groups. Additionally, the safety of newer ADDs in older adults was less studied; thus, clinicians might be less confident to prescribe newer ADDs for older patients because of the higher concern that elderly

patients are more susceptible to developing ADR *(Kim et al., 2012, Lublóy, 2014, Yakaryılmaz and Öztürk, 2017)*. That could also justify the higher likelihood of prescribing SU for older adults with T2DM. Furthermore, the higher cost of newer drugs, the cost of the required monitoring, and the familiarity of prescribers with the recent guidelines and updated literature could contribute to the lower prescription of GLP1-RA and SGLT2-I for older patients. Therefore, further studies investigating the prescribing quantity of newer ADDs compared to the older groups for older patients are still required since older patients are more likely to have cardiovascular and renal diseases, the conditions where newer ADDs are recommended. The negative association between metformin and age could be related to the fact that metformin is not recommended for patients with gastrointestinal complaints, functional impairment, or renal insufficiency, conditions that are increasingly present with increasing age *(Schlender et al., 2017, Kim et al., 2012, American Diabetes Association, 2021).* That might positively reflect clinical practice adherence to drug characteristics when prescribing metformin to older patients with T2DM.

Of the identified clinical factors, baseline BMI had the most significant influence on selecting GLP1-RA and SGLT2-I, followed by metformin and SU (Section 2.3.4.1, Figure 2.4). Obese patients or patients with higher BMI were more likely to be prescribed GLP1-RA, SGLT2-I, and metformin, yet less likely to receive a SU prescription (Section 2.3.4.1, Figure 2.4). The results were in line with the weight effect of ADDs, in which GLP1-RA and SGLT2-I are known to have weight loss effects, metformin has weight-neutral to slight weight loss effects, while SU is associated with weight gain *(Vilsboll et al., 2012, Wang et al., 2019, Apovian et al., 2019)*. All other antidiabetic groups had a non-significant association with the baseline BMI which was negative for insulin and TZD but weakly positive for DPP4-I (Section 2.3.4.1, Figure 2.4). Although these findings were not significant, the direction of association was also consistent with the effect of ADDs on body weight, in which insulin and TZD are known to cause weight gain, while DPP4-I has weight neutral effect *(Apovian et al., 2019).* The variability in the significance of the results among

antidiabetic groups could be related to the magnitude of their impact on body weight and the number of studies that assessed each class of ADDs. Overall, these findings might indirectly reflect a consistency of ADD selection in clinical practice considering patient weight against the features of ADDs. However, this conclusion could not be guaranteed based on the findings of this MA since the results might be confounded by other characteristics and because of the nature of observational studies where the causal relationship cannot be established.

Baseline HbA1c level had the strongest association with insulin prescription, in which patients with a higher baseline value/category of HbA1C were 2.41 times more likely to get an insulin prescription. In contrast, a higher baseline value/category of HbA1c had negative and weak significant associations with metformin, TZD, and DPP4-I prescriptions (Section 2.3.4.1, Figure 2.5). All associations mentioned above were consistent with the known effectiveness of the individual antidiabetic class in terms of HbA1c reduction, which partially indicate clinicians' consideration of disease control (indicated by HbA1c) for selecting the most appropriate ADDs for each patient. Insulin is known as the most effective ADD in terms of HbA1c reduction, and that might explain the greater likelihood of prescribing insulin for patients with higher baseline HbA1c values *(Chaudhury et al., 2017, Sherifali et al., 2010).*

Lastly, kidney-related problems had the most significant association with metformin prescription, followed by insulin and DPP4-I (Section 2.3.4.1, Figure 2.6). Patients with kidney problems were significantly more likely to get insulin and DPP4-I, yet significantly less likely to be treated with metformin (Section 2.3.4.1, Figure 2.6). Management of diabetes in patients with kidney-related problems is challenging as the impairment in kidney function might affect glucose metabolism and alter drug clearance *(Betônico et al., 2016).* That further complicates the selection of an appropriate ADD, considering the need for more frequent adjustment of doses and monitoring for the risk of hypo- or hyper-glycaemia *(Betônico et al., 2016)*. Insulin is considered the best choice for patients with T2DM and kidney problems, yet it still requires close monitoring and dose adjustment *(Betônico et al., 2016).* Also, DPP4-I is

one of the most acceptable options for patients with kidney problems considering dose adjustment based on the agent and degree of impairment *(Betônico et al., 2016)*. On the contrary, metformin is not recommended for patients with renal disease, and it is contraindicated when eGFR is < 30 ml/min/1.73m^2 because of the higher risk of lactic acidosis *(Betônico et al., 2016)*. Collectively, that could explain the observed associations of kidney-related problems with prescribing insulin, DPP4-I, and metformin.

Multiple clinical trials have shown favourable effects of SGLT2-I and GLP1-RA on reducing the progression of kidney disease, the need for renal replacement therapy, and death via several mechanisms beyond their glucose-lowering effects *(Górriz et al., 2020, Ninčević et al., 2019, Li et al., 2020).* As a result, the use of SGLT2-I and GLP1-RA is recently encouraged by several guidelines, especially for patients with established or high risk of cardiovascular or renal diseases *(National Institute of Health and Care Excellence, 2021, American Diabetes Association, 2021)*. The pooled estimates of studies investigating the use of SGLT2-I and GLP1-RA for patients with kidney-related problems were not in line with the previous recommendations (Section 2.3.4.1, Figure 2.6). Nevertheless, those recommendations were included and encouraged in clinical guidelines only recently, while the majority of included studies were conducted early after the introduction of GLP1-RA and SGLT2-I. Furthermore, the earliest SGLT2-I was approved only for patients with eGFR> 60 ml/min/1.73m^2 and GLP1-RA for patients with eGFR> 30 ml/min/1.73m^2. In addition, the observed associations in this MA included different types of kidney-related problems. All previous explanations might contribute to the conflicting observed associations of SGLT2-I and GLP1-RA prescriptions for patients with kidney-related problems. Therefore, more studies are still required to investigate further the prescribing choice of ADDs, especially newer classes, for patients with kidney problems in clinical practice considering different values of eGFR and types of kidney disease.

2.4.2 Factors summarised narratively

Demographic factors

Patient ethnicity was one of the identified demographic factors in which the results varied by the compared ethnic groups and investigated antidiabetic groups (Section 2.3.4.2, Appendix S.2.6). The majority of studies compared White and Black ethnic groups. Four studies reported that Black patients were significantly less likely to be treated with GLP1-RA compared to White patients *(Hirsch et al., 2011, Montvida et al., 2018, Whyte et al., 2019, Yu et al., 2017).* Likewise, three studies revealed a similar direction of association with SGLT2-I prescription, but only two showed statistically significant results, Section 2.3.4.2, Appendix S.2.6 *(Montvida et al., 2018, Whyte et al., 2019, Wilkinson et al., 2018b)*. The lower preference for using GLP1-RA and SGLT2-I for Black patients in clinical practice could be explained in part by the findings of a recent MA showing that GLP1-RA and SGLT2-I have reduced the cardiovascular events in White but not Black patients *(Qiu et al., 2020).*

The risk of hypoglycaemia has been reported in previous studies to occur more frequently among patients of Black ethnicity *(Malawana et al., 2018, Stuart et al., 2017).* However, it has been mentioned in three of the included studies that SU was more likely to be prescribed for Black patients compared to White patients *(Montvida et al., 2018, Whyte et al., 2019, Wilkinson et al., 2018b).* Only Brouwer et al. (2012) and Montvida et al. (2018) (at the stage of first intensification) reported a lower prescription of SU for Black patients, Appendix S.2.6 *(Montvida et al., 2018, Brouwer et al., 2012).* Similarly, conflicting results were observed concerning the prescriptions of metformin, insulin, and DPP4-I for Black patients relative to White patients *(Montvida et al., 2018, Whyte et al., 2019, Wilkinson et al., 2018b, Yu et al., 2017, Brouwer et al., 2012)*. Overall, the variability in the sample size of SU users in each study, the stage of treatment at which the outcome was observed, the comparison antidiabetic group, the quality of the study, and the type of effect measure could contribute to the observed inconsistent results. For example, the included studies varied by the type of effect measure, in which the outcome was presented in Brouwer et al. (2012) as probability ratio compared to the OR in all other studies

(Brouwer et al., 2012). Another example related to the quality of the study, some studies, such as Montvida et al. (2018), were rated as poor since they did not adjust for the possible confounders in the study method or analysis *(Montvida et al., 2018).* To conclude, the influence of ethnicity on the selection of ADDs in clinical practice was not thoroughly explored, so more studies are required to investigate that subject.

Only five studies examined the association of smoking status with ADP, in which all except one showed non-significant inconsistent results; section 2.3.4.2, Appendix S.2.6 *(Geier et al., 2014, Saine et al., 2015, Wilkinson et al., 2018c, Yu et al., 2017, Zoberi et al., 2017).* Smoking is linked with other factors such as obesity and CVD *(Powell-Wiley et al., 2021, Carbone et al., 2019, Dare et al., 2015, Sun et al., 2019),* which could confound smoking association with ADP as these factors were also associated with ADP. For instance, in the current SR and MA, insulin was positively associated with CVD and negatively associated with obesity. However, the impact of smoking status on the selection of ADDs was scarcely studied. Thereby, to reliably assess the effect of smoking status on the decision-making regarding ADD selection, more studies are required to investigate that under the control of all possible confounders, including obesity and CVD.

Lastly, only three studies examined the influence of educational level and diabetes FH on the choice of ADDs in clinical practice, section 2.3.4.2, Appendix S.2.6 *(Dhanaraj et al., 2013, Stargardt et al., 2009, Nicolucci et al., 2019).* These studies showed variable results; hence further research is required to investigate that.

Clinical-related factors

Long-term hyperglycaemia associated with T2DM can cause deleterious effects on the vascular system, affecting small vessels (microvascular complications) and large vessels (macrovascular complications), which increase the risk of mortality and morbidity among patients with T2DM *(Chawla et al., 2016).* The prevalence of those complications could be linked to several risk factors, particularly the severity of hyperglycaemia and the duration of the disease *(Fowler, 2011).* Multiple prospective

studies showed that achieving better glycaemic control by starting an appropriate antidiabetic therapy decreases the development and progression of diabetes-related complications, primarily microvascular ones *(Christensen et al., 2016, Holman et al., 2008, Ohkubo et al., 1995, Stratton et al., 2000).* Microvascular complications affect the eye, autonomic nervous system, and kidney leading to retinopathy, neuropathy, and nephropathy, respectively.

Four studies included in the current SR showed that insulin prescription for T2DM had a significant positive association with the presence of retinopathy (Section 2.3.4.2, Appendix S.2.6). This finding was in line with previous results of prospective studies showing the benefit of starting insulin for achieving glycaemic control on reducing the progression of retinopathy since the severity of hyperglycaemia is a vital risk factor of retinopathy *(Ohkubo et al., 1995, Stratton et al., 2000).* That could also be linked to the fact that with longer diabetes duration, both the risk of retinopathy and the need for starting insulin increase *(Home et al., 2014, Fong et al., 2004)*. On the other hand, two studies reported a lower likelihood of getting GLP1-RA prescriptions for patients diagnosed with retinopathy, yet only one showed a statistically significant result; section 2.3.4.2, Appendix S.2.6 *(Levin et al., 2014).* While pre-clinical studies have demonstrated a potential protective effect of GLP1-RA against retinopathy by modifying the neurodegeneration and blood-retinal barrier permeability through its anti-inflammatory and anti-apoptotic activity, the clinical benefits are still unclear. For instance, retinopathy was evaluated as a secondary outcome in previous controlled trials, showing a deterioration in retinopathy with liraglutide and semaglutide *(Marso et al., 2016a, Marso et al., 2016b).* That might partially contribute to the negative association of GLP1-RA prescription with retinopathy diagnosis.

For SU, two out of three studies showed a non-significant negative association with retinopathy (Section 2.3.4.2, Appendix S.2.6), which could be related to the un-proven influence of SU on retinopathy progression *(Chung et al., 2019, Saw et al., 2019).* The results of studies examining the other ADDs were diverse. For instance, three out of five and two out of three studies reported positive relations of DPP4-I

and SGLT2-I prescriptions with the presence of retinopathy, respectively (Section 2.3.4.2, Appendix S.2.6). This positive relation could be explained in part by the proposed protecting effects of DPP4-I and SGLT2-I against retinopathy via reducing neural inflammation and apoptosis in addition to their glucose-lowering effect. Nonetheless, that was mainly proposed based on experimental studies and few human studies; thus, more research is needed to draw robust evidence *(Chung et al., 2019, Avogaro and Fadini, 2014, Sha et al., 2020, Lahoti et al., 2020).* Although some studies showed a promising effect of metformin on reducing the progression of retinopathy *(Zhang et al., 2017, Li et al., 2018),* the included studies in this SR that investigated metformin showed conflicting results; two studies showed a positive association between metformin prescription and retinopathy diagnosis, and two showed opposite results (Section 2.3.4.2, Appendix S.2.6).

Overall, the variability in the direction and significance of the results relevant to retinopathy association with ADP in the included studies could be related to the current lack of data and robust evidence about the influence of ADDs on the progression of retinopathy. That could also be driven by the methodological differences among included studies in the sample size, comparison group, and adjustment for confounders. Therefore, more studies are required to explore the effect of ADDs on the progression of retinopathy, which may assist in determining how this factor could affect the decision-making about the optimal ADDs for T2DM management.

Moreover, for neuropathy, three of the included studies reported that insulin was significantly more likely to be prescribed for patients with neuropathy (Section 2.3.4.2, Appendix S.2.6), and this could be explained by the same reason that was mentioned with retinopathy about glycaemic control and duration of disease. In addition to hyperglycaemia, neuronal insulin signalling dysfunction has been suggested as a crucial mediator in the development of neuropathy; thus, giving insulin might support the reduction in the progression of neuropathy *(Grote and Wright, 2016).* That could also explain the positive association of insulin prescription with neuropathy. Likewise, two studies of SGLT2-I showed a higher likelihood of

prescribing this class for patients with neuropathy (Section 2.3.4.2, Appendix S.2.6). Thus far, there are no clinical studies that assessed the influence of SGLT2-I on neuropathy, so the higher prescription of SGLT2-I could not be explained based on the available data. However, pre-clinical studies have demonstrated a promising benefit of SGLT2-Is in reducing neuropathy progression via their glucose-lowering, antioxidant, and anti-inflammatory effects *(El Mouhayyar et al., 2020).*

On the other hand, the likelihood of receiving SU prescriptions was negatively associated with neuropathy diagnosis in two of the included studies, with only one showing a statistically significant result (Section 2.3.4.2, Appendix S.2.6). The influence of SU on neuropathy was not extensively studied; a retrospective cohort study showed that SU was associated with a significantly higher incidence of neuropathy compared to vildagliptin, which could contribute to the demonstrated lower prescription of SU for patients with neuropathy in this SR *(Kolaczynski et al., 2016).* Regarding the other antidiabetic groups (metformin, DPP4-I, and GLP1-RA), the findings were highly diverse (Section 2.3.4.2, Appendix S.2.6), and this could be related to the limited availability of clinical data about the effect of those groups on the progression of neuropathy *(El Mouhayyar et al., 2020, Won, 2020).* In summary, neuropathy and retinopathy are important factors that could influence decision-making regarding ADP. Still, their influence on the selection of the individual antidiabetic class was not comprehensively studied; hence more studies are required to assess the effect of neuropathy and retinopathy on the prescribing choice of ADDs in clinical practice.

Macrovascular complications of diabetes are the primary cause of death among patients with T2DM *(Buse et al., 2007).* Since the benefit of intensive glycaemic control alone in reducing the progression and development of macrovascular complications is still unclear and less established compared to microvascular ones *(Holman et al., 2008, Terry et al., 2012),* research is now focusing on assessing the benefit of different ADDs in improving macrovascular complications through mechanisms that are independent of their glucose-lowering effects *(Marso et al.,*

2016b, Zinman et al., 2015). Therefore, the presence of macrovascular complications is expected to be associated with the selection of the optimal ADDs.

Multiple studies supported the potential benefit of metformin in reducing cardiovascular outcomes in patients with diabetes *(Han et al., 2019, Zhang et al., 2020, Hong et al., 2013)*. However, this SR reported a lower likelihood of prescribing metformin for patients with CVD; Appendix S.2.6 *(Katakami et al., 2020, Montvida et al., 2018, Morita et al., 2019, Wang et al., 2013a, Zoberi et al., 2017).* CVDs usually develop with a longer duration of diabetes when most patients eventually require more ADDs to maintain glycaemic control, while metformin is mainly prescribed early after disease diagnosis *(Fox et al., 2004, McGurnaghan et al., 2019)*. Correspondingly, the observed negative association between diabetes duration and metformin prescription along with the positive association of diabetes duration with the incidence of CVD could explain the lower likelihood of prescribing metformin for patients with CVD. Nevertheless, since it is possible for patients with T2DM to have CVD at the time of diabetes diagnosis, the influence of the treatment stage on the likelihood of prescribing metformin for patients with CVD should be explored. Besides, the result of studies examining metformin prescribing for patients with CAD and cerebrovascular disease were diverse. This discrepancy in the findings could be related to the current lack of evidence about the direct cardiovascular endpoint of metformin in patients with T2DM in the real-world setting, as most of the available evidence was derived from clinical trials. In addition, only a few studies have been retrieved in this SR assessing the influence of CVD on prescribing metformin in clinical practice, hence limiting the proper assessment of CVD/CAD/cerebrovascular disease on the use of metformin for T2DM management.

Two studies have also shown a negative association of metformin prescription with HF diagnosis *(Arnold. et al., 2018, Abdelmoneim et al., 2013).* That could be linked to the concern about the risk of lactic acidosis associated with metformin in the presence of HF. However, more recent evidence has demonstrated a beneficial effect of metformin in reducing the incidence and hospitalisation of HF *(Pantalone et al., 2009,*

Eurich et al., 2013, Tseng, 2019, Inzucchi, 2005), and the risk of lactic acidosis is considered to be minimal for hemodynamically stable patients who do not complain of severe renal impairment *(Cosmi and Cosmi, 2011).* Accordingly, metformin is considered a viable option for patients with HF and T2DM *(Kinsara and Ismail, 2018).* Thereby, more studies are required to assess the influence of this update on prescribing metformin for patients with HF.

The reported negative association of TZD prescription with CVD diagnosis could be linked to the cardiovascular warning risk of rosiglitazone *(Loke et al., 2011, Lipscombe et al., 2007).* Although no cardiovascular risk other than HF was linked to pioglitazone *(Pantalone et al., 2009, Erdmann et al., 2009)*, the rosiglitazone-related cardiovascular risk could discourage healthcare providers from using TZD for patients with known CVD. However, the number of studies that evaluated the influence of CVD, CAD, HF, and PVD on the prescription of TZD are scarce, so their effect on the decision-making of TZD prescription in clinical practice is still inconclusive and needs to be more thoroughly investigated *(Singh et al., 2007).*

Multiple clinical trials and cohort studies reported an increase in cardiovascular risk and mortality with SU treatment *(Roumie et al., 2017, Azoulay and Suissa, 2017, Phung et al., 2013, Douros et al., 2018),* yet it is controversial if this should be considered a class effect since glimepiride showed positive cardiovascular safety in some studies *(Simpson et al., 2015, Rosenstock et al., 2019, Abdelmoneim et al., 2013).* However, this SR showed conflicting results regarding the association of CVD with SU prescription. For instance, four out of five studies including CVD/macrovascular complications *(Montvida et al., 2018, Nicolucci et al., 2019, Katakami et al., 2020, Wilkinson et al., 2018b)* and two out of three studies examining HF showed that SU was more likely to be prescribed for patients who were diagnosed with the aforementioned diseases. Contrastingly, two out of three studies investigating CAD/IHD *(Dhanaraj et al., 2013, Arnold et al., 2018)* and two studies including cerebrovascular disease/stroke *(Dhanaraj et al., 2013, Abdelmoneim et al., 2013)* reported negative associations with SU prescription. These contradictory findings could be related to the variability and the limited number of studies investigating each disease and to the controversial

evidence of SU effect on CVD risk and mortality. The variability across studies could be related to the differences in the studied sample size, the definition of the outcome, the study duration, and the utilised data source. For instance, the type of utilised data sources varied across studies, where some studies used primary care data *(Montvida et al., 2018, Wilkinson et al., 2018b)*, while others used insurance-based databases *(Abdelmoneim et al., 2013)* or secondary and primary data *(Katakami et al., 2020).* Furthermore, a discrepancy in the duration and time of data collection was observed across studies; for example, the time interval of data collection in Montvida et al. (2018) was between 2005 and 2016 *(Montvida et al., 2018)*, Wilkinson et al. (2018) between 2000 and 2017 *(Wilkinson et al., 2018b)*, and Abdelmoneim et al. (2013) between 1998 and 2010 *(Abdelmoneim et al., 2013).*

Despite that the cardiovascular safety of insulin has been questioned *(Herman et al., 2017, Triggle and Ding, 2014),* recent studies have shown a safety profile of basal insulin *(Gerstein et al., 2012, Marso et al., 2017)*. CVD usually develops with a longer diabetes duration, and insulin is a fundamental part of T2DM management, especially with a longer duration of the disease. Collectively, that could partially justify the higher prescription of insulin for patients with CVD/macrovascular complications *(Yu et al., 2017, Zoberi et al., 2017, Montvida et al., 2018, Hartmann et al., 2020)*, CAD/IHD *(Arnold et al., 2018, Dhanaraj et al., 2013, Levin et al., 2014),* HF *(Arnold. et al., 2018, Kostev et al., 2014, Levin et al., 2014),* PVD, and cerebrovascular disease/stroke *(Kostev et al., 2014, van den Boom et al., 2020, Zoberi et al., 2017)* which were identified in the majority of the relevant studies in the current SR.

Cardiovascular outcome studies on the newer ADDs have demonstrated that DPP4-I had a neutral effect on the risk of CVD and mortality with concern regarding HF hospitalisation risk associated with saxagliptin and alogliptin, while SGLT2-I and GLP1-RA showed cardioprotective effects *(Fei et al., 2019).* However, this SR showed that the prescribing choice of newer agents (DPP4-I, GLP1-RA, and SGLT2-I) for patients with CVD/macrovascular complications in clinical practice was not in agreement with the previous evidence. The majority of studies that investigated CVD/macrovascular complications showed a higher prescription of DPP4-I for

patients with CVD/macrovascular complications, but a lower prescription of SGLT2-I and GLP1-RA. That non-adherence to the recent evidence could be related to the fact that the time and duration of data collection of included studies were either before or early after the publication of evidence on the cardiovascular benefits of SGLT2-I and GLP1-RA. More than half of included studies (23/41, 56.10%) were conducted before 2013, and the most recent study interval included up to 2018, while cardiovascular outcome studies of the newer ADDs were conducted from 2012 onwards. In addition, the fear of side effects associated with GLP1-RA and SGLT2-I could contribute to the observed non-adherence since healthcare providers might not be confident about starting these medications for patients with CVD. The influence of other cardiovascular outcomes (e.g., CAD/IHD, PVD, HF, and cerebrovascular disease) on the selection of newer ADDs was much less frequently studied; hence further studies are required in that area.

The impact of ADDs on blood pressure (BP) was indirectly evaluated in clinical trials, which revealed that all groups, except SGLT2-I and GLP1-RA, had neutral to minimal reduction effects on BP. SGLT2-I has reduced both the systolic and diastolic BP, while GLP1-RA showed a moderate reduction in the systolic BP *(Ilias et al., 2020, Balfour et al., 2014, Liakos et al., 2021, Yaribeygi et al., 2021).* Due to the lack of direct comparison among antidiabetic groups, the effect of ADDs on BP is still uncertain. In line with this conflicting evidence, all studies included in this SR that assessed the impact of HTN on the choice of ADDs showed contradictory and non-significant results. Furthermore, consistent with the favourable effect of SGLT2-I and GLP1-RA on BP, two out of three relevant studies revealed that a diagnosis of HTN was associated with a higher likelihood of receiving GLP1-RA *(Levin et al., 2014, Longato et al., 2020)* and SGLT2-I for T2DM management *(Grabner et al., 2015, Kim et al., 2019a).*

The effect of ADDs on the lipid profile was more frequently studied. Overall, metformin, SGLT2-I, and GLP1-RA were reported in the literature to have beneficial effects on the lipid profile in terms of HDL, LDL, total cholesterol, and TG. In contrast, insulin, SU, DPP4-I, and TZD had a less favourable or neutral effect *(Chaudhuri and Dandona, 2011, Rigato et al., 2020, Rosenblit, 2016, Roumie et al., 2011).*

However, all mentioned effects could vary by the agents within each antidiabetic class *(Rigato et al., 2020).* Consistent with previous evidence, this SR showed that dyslipidaemia had a statistically significant association with ADP in all relevant studies. Dyslipidaemia was negatively associated with prescribing SU *(Kim et al., 2019a, Abdelmoneim et al., 2013)* and insulin *(Kostev et al., 2014, Levin et al., 2014, Yu et al., 2017)*, while positively associated with the use of DPP4-I *(Kim et al., 2019b, Ou et al., 2017, Saine et al., 2015),* SGLT2-I *(Grabner et al., 2015, Kim et al., 2019a, Longato et al., 2020)*, and GLP1-RA *(Levin et al., 2014, Yu et al., 2017)*. Nevertheless, a limited number of studies examined each antidiabetic group; hence further research is required to obtain more comprehensible results.

Furthermore, among studies examining the association between diabetes duration and ADP, it was observed that longer diabetes duration was associated with a significant rise in insulin prescription but a significant fall in metformin use. The increment in insulin prescription with longer diabetes duration could be related to the reduction in the secretory capacity of beta-cells in patients with T2DM over time and the increasing requirement to maintain glycaemic control *(American Diabetes Association, 2020, Home et al., 2014).*

Socioeconomic factors:

Socioeconomic factors were the least frequently reported factors in the included studies. Only one study examined the association of each socioeconomic measure with the individual antidiabetic group (Section 2.3.4.2, Appendix S.2.6). As a result, a reliable conclusion cannot be drawn based on one study, and further studies are needed to investigate the impact of different socioeconomic measures on the selection of ADDs in clinical practice.

Prescriber-related factors

This SR showed a difference in the prescribing choice of ADDs between specialists and non-specialists (section 2.3.4.2, Appendix S.2.6). The greater likelihood of prescribing metformin *(Liu et al., 2017, Winkelmayer et al., 2011b),* GLP1-RA *(Ackermann et al., 2017, Nicolucci et al., 2019, Yu et al., 2017)*, DPP4-I *(Ackermann et al., 2017, Grabner*

et al., 2015, Kim et al., 2019a, Nicolucci et al., 2019), and insulin *(Ackermann et al., 2017, Nicolucci et al., 2019, Kostev et al., 2014, van den Boom et al., 2020)* by Endocrinologists/Diabetologists and prescribers with Internal Medicine speciality compared to non-specialists (GP or FM) (section 2.3.4.2, Appendix S.2.6) could be related to the fact that patients who visit specialist tend to have more uncontrolled disease than patients who visit non-specialist, for whom these drugs are more likely to be prescribed. In addition, the degree of knowledge about the recent guidelines, new publications, and newer medications among specialists versus non-specialists might affect the confidence level in prescribing these medications, especially insulin and newer ADDs *(Rushforth et al., 2016)*. However, the higher prescription of SU *(Ackermann et al., 2017, Nicolucci et al., 2019)* and TZD *(Ackermann et al., 2017)* by FM/GP (section 2.3.4.2, Appendix S.2.6) could be explained by the observation that patients who visit non-specialists may have a lower socioeconomic status; thus, more likely to be treated with more affordable drugs like SU *(Dunlop et al., 2000, Zgibor and Songer, 2001)*. Additionally, non-specialists could be more confident working with older antidiabetic groups (e.g., SU and TZD) because more extensive studies are available on their safety and efficacy profiles.

Prescriber age, sex, and practice experience play an essential role in the decision-making regarding ADD selection (section 2.3.4.2, Appendix S.2.6). For example, female physicians are more likely to consider psychological factors and patients' expectations than male physicians for deciding regarding ADD selection *(Hajjaj et al., 2010).* Also, younger physicians tend to order more tests than older ones, which might influence the choice of ADDs *(Hajjaj et al., 2010).* However, the influence of these factors on the prescribing decision of ADDs was not frequently examined, where metformin was the only investigated ADD. According to the current SR, older prescribers were less likely to prescribe metformin than younger ones *(Liu et al., 2017, Winkelmayer et al., 2011b).* As treatment guidelines are constantly updated, a younger physician who has more recently graduated is more likely to be aware of newer guideline recommendations than older ones, and this might explain the previous findings that older physicians were less likely to prescribe metformin; the

recommended drug of choice for all newly diagnosed patients with T2DM *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021).* Besides, female prescribers were more likely to prescribe metformin compared to male prescribers *(Liu et al., 2017, Wang et al., 2013a, Winkelmayer et al., 2011b)*, yet only Liu et al. showed a statistically significant result *(Liu et al., 2017).* The greater likelihood of prescribing metformin by female prescribers compared to male prescribers could be partly explained by the suggestion that female clinicians are more likely to adhere to guideline recommendations than males *(Mishra et al., 2020).* Nevertheless, it is necessary to assess further the association of prescriber-related factors with the selection of ADDs in clinical practice.

2.4.3 Strength and limitations

To the best of our knowledge, this is the first SR/MA that integrated the results of observational studies assessing the association of specific factors with ADP to draw an overall estimate. The search strategy was reviewed for its accuracy and comprehensiveness and conducted on multiple databases. Moreover, this SR and MA provided a wide range of data by investigating each factor with seven antidiabetic groups. Additionally, applying a three-level MA approach to account for the presence of dependency among effect sizes allowed for answering the research question without losing valuable data and directly comparing different antidiabetic groups.

Nevertheless, all previous results should be interpreted cautiously because of several limitations of the study. Firstly, a limited number of studies examined certain classes of ADDs, especially the newer ones; thus, more studies are required to draw a more robust conclusion. Secondly, the possible presence of publication bias, especially for age, BMI, and kidney-related problems, may have affected the reliability of the findings; however, there is no agreed-upon method available to adjust for publication bias in the three-level MA model. Thirdly, bias could have been introduced by including all studies in the pooled estimate regardless of the type of data presentation (categorical vs. continuous) and categorization scheme; yet, subgroup analyses were done and showed no significant impact, and the

pooled estimate of each sub-group was reported separately. Lastly, other important factors, including socioeconomic and prescriber-related factors, were much less frequently studied, and further investigations are needed.

2.4.4 Conclusion

In conclusion, all the quantified five factors are crucial predictors of the prescribing decision of ADDs for patients with T2DM. The magnitude, direction, and significance of the influence of the identified factors on ADP varied according to the type of antidiabetic group. Age, baseline BMI, and baseline HbA1c had the greatest impact on the selection of ADDs, in which they had statistically significant associations with prescribing four out of the seven investigated antidiabetic classes (metformin, SU, SGLT2-I, and GLP1-RA for age and baseline BMI, while metformin, DPP4-I, insulin, and TZD for baseline HbA1c). On the other hand, sex had the least impact on ADDs selection, which had only a significant effect on prescribing GLP1-RA and TZD. The findings of this SR and MA could help determine the need for improving the prescribing practice of ADDs by reflecting the consistency of the prescribing decision of ADDs with guideline recommendations and specific drug features. Nevertheless, the number of studies examining each antidiabetic group, especially the newer ones, is minimal; thus, more studies are required to validate the results. Additionally, further studies are necessary to assess the impact of each factor on ADP under the adjustment of the other factors. Lastly, several other potential factors influencing ADP were much less frequently studied, including socioeconomic and prescriber-related factors, which need further investigation.

3 Chapter 3: Data sources and data management

3.1 Data sources

Each patient registered with the health care system in Scotland is allocated a unique identification number called the Community Health Index (CHI) number *(Information Service Division- Scotland, 2021a)*. The CHI number is a ten-digit number that is formed considering the individual's date of birth in the form of day/month/year (DDMMYY) with additional four digits; where two are randomly selected, one indicates the sex of patients, and the last one is a check digit *(Information Service Division- Scotland, 2021c)*. The use of the CHI number across all healthcare systems in Scotland facilitates patient tracking and supports the linkage of patient data from different electronic medical records *(Information Service Division- Scotland, 2021a)*. Thereby, the CHI number was used for linking patients' data across multiple datasets requested for this project. The data available for this project has been extracted from five datasets: Scottish Care Information-Diabetes (SCI-Diabetes), Prescribing Information System (PIS), Scottish Morbidity Records Outpatient Attendance dataset (SMR00), Scottish Morbidity Records General/Acute Inpatient and Day Case dataset (SMR01), and National Records of Scotland (NRS).

1.1.1 Scottish Care Information-Diabetes (SCI-Diabetes)

The Scottish Care Information-Diabetes Collaboration (SCI-DC) is a national register and database, launched in April 2002, which collates all relevant information on all patients diagnosed with diabetes within the primary and secondary care settings across Scotland *(Cunningham et al., 2011)*. This electronic health system is an update of the one developed by Diabetes Audit and Research in Tayside Study (DARTS), which expanded the care of diabetes from regional to national care delivery while maintaining the original system functions *(Morris et al., 1997).* The DARTS system was developed to support the Managed Clinical Network (MCN) for chronic diseases to ensure multidisciplinary teamwork and sharing of information between different healthcare settings and a variety of clinicians *(Cunningham et al., 2011)*. The completeness of this database has been increased since 2004, where all except five

of the 1076 general practices in Scotland were linked to the registry and contributed to the shared data; consequently, over 99.5% of people with diabetes across Scotland have been registered to this database *(Mair et al., 2019)*. The SCI-DC system was replaced in January 2014 with a single technical product called SCI-Diabetes which represents a fully integrated web-based diabetes record *(The Scottish Care Information Diabetes Collaboration, 2015).* Additionally, SCI-diabetes has the advantage of single-point data entry across all providers by supporting the functionality of "back-population", which transfers data that are present on SCI-Diabetes but absent from general practice systems on a nightly basis; hence decreasing the risk of duplication and errors related to manual data entry and transfer. The functionality of "back-population" also provides an earlier update of patients' records *(Emslie-Smith, 2010)*.

Moreover, SCI-Diabetes supports record linkage with other data sources like death registries, laboratory data, and morbidity records via CHI number. It is considered a main data source for many national programs and surveys, such as the Scottish Foot Framework support, the Scottish Diabetes Survey, the Diabetes Retinal Screening Programme, and SIGN clinical guideline support *(The Scottish Care Information-Diabetes Collaboration, 2015)*. Besides having been initially created to improve diabetes management across Scotland, it is increasingly used to assist diabetes research while securing patient confidentiality by providing anonymised data *(Walker et al., 2018).* Several studies have used SCI-Diabetes database linkage to examine the mortality, renal status, and cancer risk among people with diabetes *(Walker et al., 2013, Bell et al., 2015)*. The dataset provides a wide range of data relevant to patient demographic, type of diabetes, date of diagnosis, type of diabetes management, type of hypoglycemic medications, weight measurements (weight, height, and body mass index), as well as laboratory data including a lipid profile, glycemic control (HbA1c), renal function, and others.

3.1.1 Prescribing Information System (PIS)

The Prescribing Information System (PIS) gathers information on medicines and their costs that are prescribed and dispensed, and reimbursed within the community setting in Scotland *(Information Service Division- Scotland, 2021b)*. PIS has been established since 1993; however, data at the patient level became only available from 2009 onwards after incorporating CHI numbers which permits the linkage of PIS data with other datasets within Public Health Scotland (PHS) *(Information Service Division- Scotland, 2021b)*. PIS data is primarily provided by the Practitioner & Counter Fraud Services Division (P&CFS), which is responsible for processing and pricing all prescriptions dispensed in Scotland *(Information Service Division- Scotland, 2021b).* The collection of PIS data occurs on a monthly basis, with about 100 million data items being entered every year primarily by General Practitioners (GPs), in addition to other authorised prescribers, including nurses *(Information Service Division- Scotland, 2021b)*. Data provided within PIS can be grouped into four categories, as summarized in Table 3.1.

Table 3.1: Data items provided within Prescribing Information System (PIS)

Category	Items
Patient-data	CHI number, age, sex, area of residency, and geographical information, including the Scottish Index of Multiple deprivation (SIMD) score and urban-rural classification
Prescription-data	Medicine-approved name (the active ingredient), product name, strength, formulation, prescribed and dispensed dates, and prescribed and dispensed quantity (expressed either by the number of dosage forms or in defined daily doses (DDDs))
Prescriber data	Prescriber location, prescriber type, prescriber sex
Dispenser-data	The location where dispensing takes place

All prescribing information in PIS is presented based on the British National Formulary (BNF) classification system, developed by NHS England, with the first edition published in 1949. The BNF item code is a 15-digit code where the site of each digit shows the correspondent Chapter (first two digits), section (3rd and 4th digits), subsection (5th and 6th digits), paragraph (7th digit), chemical substance (8th and 9th digits), product (10th and 11th digits), strength and formulation (12th and 13th

digits); the 14th and 15th digits show the link of the item to the equivalent generic product (if the product is generic, then the 14th and 15th digits will be the same as the 12th and 13th digits) *(Information Service Division-Scotland, 2016)*. The following is an example of a BNF item code for metformin hydrochloride: 0601022B0, representing Chapter 6 (Endocrine System), section 1 (Drugs used in diabetes), subsection 2 (Antidiabetic drugs), paragraph 2 (Biguanides), and the unique code gives the information specific to metformin hydrochloride.

PIS data is considered of high quality as it is collected using electronic dispensing and prescribing messages; hence decreasing the possible errors that would arise from manual data entry. Plus, the data undergoes multiple steps of quality checking before and after being submitted to the PIS dataset *(Alvarez-Madrazo, 2016)*. The completeness level of PIS data is generally high because it was created initially for submitting prescriptions for payment. Nevertheless, the completeness of the individual-level data relies on the type of healthcare practitioner providing the data and/or the service delivery models *(Alvarez-Madrazo, 2016)*.

3.1.2 Scottish Morbidity Records (SMR)

The Scottish Morbidity Records (SMR) are a group of records that contain clinically coded and administrative data on an individual patient level from all Health Boards and hospitals across Scotland *(Information Service Division- Scotland, 2020d)*. Each type of record represents the type of healthcare provider or setting of each episode *(Information Service Division- Scotland, 2020d).* These records were created primarily for care planning and collected by the Information Services Division (ISD). ISD was a part of NHS Scotland, yet it is now integrated into Public Health Scotland (PHS). Data is usually provided to PHS 42 days after the end of the month of hospital discharge or clinic date *(Public Health Scotland, 2020c)*. Two SMR datasets were available for this project: outpatient attendance dataset SMR00 and general/acute inpatient and day case dataset SMR01 *(Information Service Division- Scotland, 2020d).*

SMR00 relates to patient-level data from all people on their attendances (new, return, and did not attend appointments) at outpatient clinics in all specialities of

Scottish NHS hospitals except for Accident & Emergency and Genito-Urinary Medicine *(Information Service Division- Scotland, 2020c)*. Outpatient data collection was started in the 1990s and was made available from 1997 onwards *(Information Service Division- Scotland, 2020c)*. It supplies around 4.4 million records annually, providing information about patient identification and demographics such as date of birth, postcode, CHI number, and ethnicity. Furthermore, SMR00 holds data about the referral reason, procedure, and geographical measures like the Scottish index of multiple deprivation (SIMD), urban/rural areas, and the NHS Board *(Information Service Division- Scotland, 2020c)*. On the other hand, SMR01 denotes the records of episode-level data on all inpatient and day case discharges from hospitals and general acute specialities in Scotland *(Information Service Division- Scotland, 2020a)*. Data collection of SMR01 was started in 1960 and submitted to PHS and its predecessors from 1996/1997 *onwards (Information Service Division- Scotland, 2020a)*. Similar to SMR00, in addition to the patient identifier, demographics, and geographic data, SMR01 contains data on episode management, admission type, diagnosis, procedure, and discharge location *(Information Service Division- Scotland, 2020a)*.

In both datasets, SMR00 and SMR01, all clinical and health-related data are recorded using a nationally agreed coding system such as the International Classification of Disease codes, 10th edition (ICD-10), for the recording of diagnoses, and the Office of Population Censuses and Surveys procedural codes, 4th revision (OPCS-4), for the recording of surgical procedures *(Public Health Scotland, 2021)*. The accuracy and consistency of SMR data are assessed by the Data Quality Assurance (DQA) team established in 1990. For instance, the data quality of SMR01 was evaluated over 20 years and remained almost sTable, with 88% accuracy for the primary condition and 94% accuracy for the main operation *(National Service Scotland, 2016)*. Moreover, the completeness of SMR01 is considered higher than SMR00, yet it is generally high for both datasets, but could vary by the NHS Board as well as the structure of the outpatient clinics and organisation *(Information Service Division- Scotland, 2018)*.

3.1.3 National Records of Scotland (NRS)

National Records of Scotland (NRS) is a non-ministerial department of the Scottish Government that was formed in April 2011 with the merger of two institutions: the National Archives of Scotland and the General Register Office for Scotland *(National Records of Scotland, 2016a)*. It is responsible for storing data relevant to the life events of the Scottish people, such as births, marriage, civil partnerships, adoption, divorce, and deaths, to preserve the information as well as prepare and publish demographic statistics *(National Records of Scotland, 2016b)*. Data about life events are provided to the register by one or more of the informants in addition to other sources like the Medical Certificate of the Cause of Death (MCCD) *(National Records of Scotland, 2016d)*. A quality assessment procedure of the NRS data is available to assess the correctness and completeness of the entered information. Data relevant to each event is scrutinised by one of the NRS examiners, who reported that NRS has an overall high quality and completeness *(National Records of Scotland, 2012).*

NRS-Death registry holds information about every death in Scotland since the start of 1974, with approximately 55,000 deaths registered annually *(Information Service Division- Scotland, 2020b).* In addition to the information on the CHI number, date of birth, date of death, age of death, and place of death, this database provides data about the cause(s) of death *(National Records of Scotland, 2016c)*. The primary source of information about the cause of death is the MCCD, which is completed by a registered medical practitioner *(National Records of Scotland, 2016d)*. The cause of death has been coded using the ICD-10 classification system since the start of 2000, in which one primary cause of death and up to ten underlying secondary causes of death are reported *(National Records of Scotland, 2017)*.

3.2 Study data overview

A broad range of data has been requested for this project, including socio-demographic information, prescription details, laboratory tests, comorbid conditions, surgical procedures, and death. NRS is the smallest dataset in this project, providing 15 variables and 86,320 death records over the study period (Jan/2010-Feb/2021). PIS is the largest dataset, consisting of 21 variables and

providing a total of 193,138,704 observations, followed by SCI-Diabetes containing 100,571,761 observations of 25 variables; both cover the period of Jan/2009 to Feb/2021. Lastly, the requested extracts of SMR00/SMR01 include 34 and 27 variables, respectively, and both contribute to a total of 9,540,245 observations between Jan/2007 and Feb/2021.

Nevertheless, the number of observations within each dataset has been reduced considerably after extracting only the observations relevant to the study cohort and removing duplicated records, as demonstrated in Figure 3.1, section 3.4. Furthermore, not all supplied variables were used in the analyses; variables with irrelevant (not useful for this project) or duplicated information (presented the same data a different way) or providing low-quality data mostly due to extensive missing information were not used for subsequent analyses. The following sections detail the main variables used for describing the study cohort and investigating the desired outcomes.

3.2.1 Sociodemographic data

Sociodemographic data consists of information related to the patient's date of birth (*DOB_YM*), sex (*SEX*), marital status (*M_S*), deprivation level (*SIMD_D, SIMD_Q*), and area of residence (*UR*), which stemmed from PIS, SMR00, and SMR01 datasets. Patient age at the time of drug prescribing (*PRESC_AGE*) and age at the time of disease diagnosis (*DISEASE_AGE*) were calculated by subtracting the date of prescription (derived from PIS) and date of diagnosis (derived from SMR00/SMR01 for comorbidities) from a patient's date of birth (derived from PIS), respectively. All other sociodemographic information, including patient age at the time of death (*DEATH_AGE* from NRS), is readily available within the relevant datasets.

Area of residence was described using an urban/rural categorisation scheme of the geographical location, which is defined by the Scottish Government based on the number of population and accessibility of the area; the latter was measured by the time required for driving to an urban location *(The Scottish Government, 2018)*. Data relevant to the area of residence was provided in this study based on the 2016

governmental classification, which classifies all urban and rural areas into eight levels, each given a one-digit code, as shown in Table 3.2. Data referring to the deprivation level in this study was measured based on the SIMD. SIMD is a tool that identifies areas in Scotland where people experience disadvantages in their lives compared to the other areas, considering a variety of aspects, including income, employment, housing, education, health, accessibility to services, and crime. Accordingly, this score reflects the deprived areas, not deprived people *(The Scottish Government, 2020)*. The SIMD score focuses on data zones below a certain rank, like 10% and 20% most deprived areas in Scotland, with decile and quantile representing 10% and 20% of the population of Scotland , respectively *(The Scottish Government, 2020)*. It is coded in descending order, with code one representing the highest level of deprivation, while code five and ten reflects the least deprived areas for quantile and decile, respectively *(The Scottish Government, 2020)*. SIMD is updated regularly, and in this study, the latest version, SIMD 2020 (decile and quantile), was provided within PIS, SMR00, and SMR01 datasets. Since both the SIMD decile (SIMD-D) and SIMD quintile (SIMD-Q) provide similar information, only SIMD-Q was used in the subsequent analyses because of the lower number of levels (five levels) to simplify the analyses compared to the ten levels of SIMD-D.

Table 3.2: Scottish Government classification of urban-rural areas 2016 (The Scottish Government, 2018)

Code	Area Name	Description
1	**Large Urban Areas**	>= 125,000 people.
2	**Other Urban Areas**	10,000 to 124,999 people.
3	**Accessible Small Towns**	3,000 to 9,999 people & within a 30-min drive to an urban area.
4	**Remote Small Towns**	3,000 to 9,999 people & 30-60 min drive time to an urban area.
5	**Very Remote Small Towns**	3,000 to 9,999 people & > 60 min drive time to an urban area.
6	**Accessible Rural Areas**	< 3,000 people & within 30 min drive time to an urban area.
7	**Remote Rural Areas**	< 3,000 people & 30-60 min drive time to an urban area.
8	**Very Remote Rural Areas**	< less than 3,000 people& > 60 min drive time to an urban area.

Marital status has been recorded within SMR00 and SMR01. However, for this study, there was a significant percentage of missing data in the marital status variable from both datasets (56%). In addition, the consistency of the marital status coding system is questionable, and there is a lack of regular updates on marital status data, resulting in limitations concerning the quality and reliability of marital status data. Therefore, that variable was not included in describing the study cohort or for subsequent analyses. Besides the patient's date of birth and patient age (at time of prescription, disease diagnosis, and death), which were date and numerical variables, respectively, all other sociodemographic variables were categorical, with only patient sex being binary (male: 1, female: 2).

3.2.2 Prescription details (antidiabetic drugs and concomitant medications)

All details about prescriptions were obtained from the PIS dataset. In addition to the BNF full code, PIS provides information regarding the approved name, which represents the chemical substance of a drug, and prescribed item name, which could be either the generic or brand name, along with information on the strength, unit, formulation, and quantities of prescribed items, as well as the dates at which a drug was prescribed and dispensed. All medications of interest (ADDs and concomitant medications) were identified based on the BNF code (*BNF_chapter and BNF_section*) and the approved item name (*approved_name);* the first was a combined text/numeric variable, while the latter was a text variable. The BNF codes of all medications of interest are presented in Appendix S.3.1.

The strength of the prescribed item (*item_strength*) and the corresponding unit of measurement (*item_strenth_uom*) were provided in separate variables. The strength of the prescribed drug represents the amount of drug contained in one unit of formulation (Tablet, capsule, or syringe). The item unit was a text variable, while item strength was numerical. Also, the prescribed and dispensed quantities (*presc_quantity, disp_quantity*) were numerical variables and readily available in the PIS dataset. Item strength and quantity were used for investigating the prescribing patterns of ADDs which supported stratifying the cohort into monotherapy and

combination therapy users (chapters 4 and 5). Information related to dose instructions was not available for this study.

Prescription (*presc_YMD*) and dispensing dates (*disp_YMD*) were also provided. Prescription dates were used in this study since they represent the time when ePrescribing messages were submitted by the prescriber, while dispensed dates denote the last day of each month. Therefore, prescription dates reflect more the prescribing patterns and behaviour compared to the dispensing dates, which are mostly default dates. Lastly, the type of individual prescriber (*prescriber_type*) was available for the entire cohort, and it was a factor variable with four possible levels (GP, nurses, pharmacist, hospital).

3.2.3 Clinical conditions and laboratory data

All information pertaining to patient health conditions was obtained from SMR01 and SMR00, covering three years prior to the starting date of the study to increase the probability of capturing all relevant comorbidities. The medical conditions of interest were identified based on their diagnostic code presented as ICD-10 code (Appendix S.3.2). Both datasets include one main condition as well as up to five other conditions for SMR01 (*main_con, other_con1, other_con2, other_con3, other_con4, other_con5*) and up to four referral reasons for SRM00 (*ref_reason1, ref_reason2, ref_reason3, ref_reason4*). Additionally, two main codes indicating the type of procedures that were undertaken in a hospital setting (*main_opA, main_opB*) were available in the two datasets. All variables related to the medical conditions or surgical procedure were character variables. Furthermore, data relevant to the cause of death was identified from the NRS dataset, which provides one main cause of death (*death_cause_main*) and up to ten additional causes of death (*death_cause0 to death_cause9*); all were character variables. Dates of the hospital admission (*adm_date*), outpatient clinic attendance (*clinic_date*), and death (*death_date*) were also provided within SMR01, SMR00, and NRS, respectively.

Multiple clinical measures and laboratory tests were also investigated in this project, which were obtained from the SCI-diabetes dataset, including measurement of glycated haemoglobin blood glucose (*HbA1c*) and lipid profile consisting of LDL (*LDL*), HDL (*HDL*), triglyceride (*TG*), and total cholesterol (*Tcholesterol*). Moreover, SCI-Diabetes provides information on a patient's weight, height, BMI (*BMI*), as well as kidney function, including serum creatinine (*Cr*), albumin to creatinine ratio (*Alb_Cr_ratio*), albumin concentration (*Alb_con*), and albumin excretion stage (*alb_exc_stage*). All laboratory variables were numerical, but albumin excretion stage (alb_exc_stage) was a character variable. Because of the considerable percentage of missing values, the following variables were not included in the analyses; albumin concentration, albumin to creatinine ratio, and albumin excretion stage (73.8%, 65.3%, and 97.2% missingness, respectively).

3.3 Data management

3.3.1 Health data and information governance

Health research can be conducted effectively utilising linked routinely collected data. In Scotland, the collection of individual health data by healthcare providers has been commenced since the start of the NHS. Health research data was managed by the ISD for over 50 years, which was a part of the NHS National Services Scotland (NHS NSS) *(Public Health Scotland, 2020b, Public Health Scotland, 2020a)*. However, in April 2020, PHS was developed and took over the services of certain health bodies, including ISD. PHS now holds the health and administrative data for over five million people in Scotland *(The Scottish Government, 2019, Public Health Scotland, 2020d)*. This wide range of health and health-related data can be summarized and linked to support research projects, including progressing the quality of healthcare services, planning, and decision-making *(Public Health Scotland, 2020a, Public Health Scotland, 2020d)*.

However, due to concerns regarding patient privacy or data misuse, a robust Information Governance (IG) framework was developed to ensure that accessing and sharing of clinical data are handled securely and legally, are used for the benefit

of the Public, and meet all appropriate ethical standards *(Information Service Division-Scotland, 2010).* In 1998, the Data Protection Act considered the presence of data controllers who are responsible for processing personal data fairly and lawfully a key requirement. This was initially controlled by the Privacy Advisory Committee (PAC), which advised NHS NSS and the General Register Office for Scotland (GROS) on the processing of personal data and assessed the applications requesting permission for data access held by ISD and other divisions of NHS NSS *(The Scottish Government, 2011)*. Nevertheless, from the 1st of May 2015, PAC, the Community Health Index Advisory Group (CHIAG), and the National Caldicott Guardians application were merged into a single panel; the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) *(Information Services Division, 2017)*.

In Scotland, data can be requested at the local/regional, or national level. For projects including only a single site, a local Caldicott approval is sufficient. In contrast, for large-scale complex research projects, which include multiple linked datasets from multiple sites, PBPP approval must be obtained, which is managed by the PHS electronic Data Research and Innovation Service (eDRIS). Approval for data access is granted only for projects showing an added benefit to the public and for those that adhere to all requirements of the data controller, such as data minimization, in which the request of personal data must be limited to only relevant data that is necessary to accomplish the aim of the study *(Public Health Scotland, 2020e)*. The HSC-PBPP approval for this project was granted in three separate phases. An initial PBPP application covering a study period of Jan/2010 to Dec/2019 was submitted in July/2020 (eDRIS application number: 1920-0280), and the approval was obtained in Feb/2021. Before the start of data linkage, an amendment was submitted in Feb/2021 to extend the study duration until Feb/2021, and the amendment was approved in April/2021. Lastly, a second amendment was submitted in Feb/2022 requesting additional variables from SCI-diabetes, approved in March/2022. Notifications of approvals are presented within Appendix S.3.3. Access to the data was made available on the 24th of September 2021 for SMR00, SMR01, and NRS, while access to the PIS dataset was granted on the 19th of January

2022. Lastly, access to the SCI-diabetes dataset became available on the 5th of May 2022. As a prerequisite for PBPP approval, an accredited course in IG was completed, and the certificate can be found in Appendix S.3.4.

3.3.2 Data access

As stated in the previous section (3.3.1), one of the main concerns in making health data available for research is that a patient's identity could be compromised. Therefore, multiple governance processes were put in place to ensure that data are used safely for clear purposes and to safeguard the identity and confidentiality of patients. As a result, a Safe Haven environment was developed to minimise the risk of identification by providing de-identified or 'pseudonymised' data *(The Scottish Government, 2015).*

The Safe Haven is a platform where researchers can securely access the data that was processed, collated, and linked with other data (health and/or non-health related data) by the PHS eDRIS and made available for research purposes while minimising the risk of patient disclosure *(The Scottish Government, 2015).* Access to data within the Safe Haven environment is under strict control, and only the approved researchers have permission to access and analyse the data *(The Scottish Government, 2015).* In addition, data can be accessed remotely via a Virtual Private Network (VPN) in a process that is password protected and using university-based computers with approved IP addresses. Otherwise, the data can be accessed at a secure point using only a dedicated computer at a secure location in a specific Safe Haven place *(Public Health Scotland, 2020f, The Scottish Government, 2015)*. Moreover, the Safe Haven offers a range of analytical software, including STATA, SAS, SPSS, and R, for data analyses, where the outputs are highly controlled and checked for any statistical disclosure before being released to reassure the integrity of data *(Public Health Scotland, 2020f, The Scottish Government, 2015)*.

Four regional and one National Safe Haven platforms are currently available in Scotland *(The Scottish Government, 2015)*. Data for this project was stored securely within the National Safe Haven environment operated by PHS, and remote access was granted via a VPN connection. Data was provided in the form of comma

delimited values (.csv) and stored in a secure read-only folder (*Linked data*) within the secure Safe haven environment, and copies of the files were placed in an editable research folder (*Research, Fatema*). All analytical outputs were saved in a separate folder (*Result*) and released upon request after undergoing statistical disclosure procedures by the National Safe Haven team (eDRIS team).

3.3.3 Ethical Consideration

The consideration of getting ethical approval from an appropriate research ethics committee (university/departmental or NHS ethics committee) is a part of the IG process aiming to protect the dignity, safety, rights, and well-being of included subjects. The requirement of ethical approval depends on the type and methodology of conducted research. Although there is minimal harm to the patients in studies where patients are not directly involved, patient safety and confidentiality remain vital aspects that should be protected and ensured in this type of research, as stated by several frameworks and codes of practice, including the University of Strathclyde code of practice *(University of Strathclyde, 2017)*. This project used data collected previously in routine care that was collated for this project and accessed in a 'pseudonymised' form to ensure that no patient identity can be disclosed. In addition, departmental ethical approval was sought from the Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS) at the University of Strathclyde and indicated that the nature of this project, the type of information collected, and the method of data collection do not require a university ethical approval; a notification of that is presented within Appendix S.3.5. Furthermore, the privacy risks that may potentially be posed by this project were assessed by evaluating the Privacy Impact Assessment (PIA) screening questions (Appendix S.3.6).

3.4 Data cleaning and preparation

Data stored in a database is exposed to errors that can occur at any stage of data measurement, entry, processing, and analysis. Therefore, it is essential to check the accuracy and consistency of data before starting data analyses, and this can be accomplished by implementing an appropriate process of data cleaning and

preparation. Data cleaning is a process of detecting, modifying, and fixing errors, inaccuracies, duplicates, outliers, miscoded data, incomplete data, and irrelevant data within a dataset to improve data quality before processing data for analyses *(Van den Broeck et al., 2005)*; while data preparation involves transforming and reformatting raw data into a consistent form that is appropriate and ready for statistical analyses. All efforts spent on data preparation are vital to improving the quality and reliability of statistical statements since multiple steps of this process (e.g., handling missing data and outliers) might extensively influence the results of statistical analyses.

In this project, multiple steps of data cleaning and preparation were carried out on the five included datasets (SMR00, SMR01, NRS, PIS, and SCI-Diabetes) before proceeding with the analyses. That generally included removing duplicated and irrelevant data, changing the name of variables into convenient ones to facilitate their use in the analyses and the linkage of different datasets, as well as transforming the type of variables into the correct format, such as converting numeric variables which should be factors or dates. Examples of variable format conversions are presented in Table 3.3. The automatic conversion of character or string variables into factors when importing files in .csv format into the R software was prevented by adding the command stringsAsFactors = FALSE to the import dataset function that forces the variable format to a character. Data cleaning also included correcting any inaccuracies that might have happened during data entry, such as zero values of some variables, decimal point shifting, or inappropriate letter inclusion that were observed with some of the continuous variables included in this project, such as BMI, body weight, serum creatinine, and HbA1c.

Table 3.3: Examples of variable format conversion

Before reformatting	After reformatting	Changed variables
Numeric	Factor	Sex, SIMD-D, SIMD-Q, UR
Numeric	Date	Clinic date, admission date, death date, date of birth, prescription date, dispensing date
Character	Date	Diabetes diagnosis date, laboratory test date
Character	Factor	Marital status, prescriber type, BNF chapter, BNF section, BNF subsection, diabetes type

SIMD-D: Scottish index of multiple deprivation-decile; SIMD-Q: Scottish index of multiple deprivation-quantile; BNF: British National Formulary; UR: urban/rural.

Furthermore, variable recoding was required in multiple situations; for instance, the patient's date of birth was provided in the form of month and year; thus, the 15th day of each month was used as an approximation of the patient's date of birth in the form of day/month/year (yyyy/mm/dd) to facilitate its use for further calculations (e.g., patient age at prescription and patient age at disease diagnosis). Likewise, multiple continuous variables were recoded into categorical ones using the categorization scheme or recommended goal of clinical guidelines, as illustrated in Table 3.4. Additionally, missing data was mainly presented in all datasets as '*NA*' (Not Available), a regular symbol indicating unavailable data in R. Therefore, to ensure the consistency of data, unavailable data presented as space was recoded into 'NA'. The percentage of missingness within each included variable is described in Table 3.4, with most of the missing data identified within the laboratory test variables.

Table 3.4: Percentage of missingness and recoding of the included variables from the five available datasets

Variable name	Type of variables	Measurement unit	% Of missingness (Out of 145,909)	Recoded categorical variable
Prescription year	Factor	Year	Complete	-
Patient age at prescription	Continuous	Years	Complete	Recoded into binary: >= 65 years and < 65 Years
Patient sex	Binary	-	Complete	-
Urban-Rural	Categorical (8 levels)	-	0.05%	-
Scottish index of multiple deprivation-quantile	Categorical (5 levels)	-	0.04%	-
Prescriber type	Categorical (4 levels)	-	Complete	Recoded into binary: GP and non-GP
Body mass index (BMI)	Continuous	Kg/m2	42.38%	Recoded into three levels: <= 24.9 (underweight/normal weight), 25.0-29.9 (overweight), >=30.0 (obese) (Nuttall, 2015)
Total cholesterol	Continuous	mmol/l mg/dl	26.67%	Recoded into three levels: < 200mg/dl (<5.17 mmol/l), 200-239 mg/dl (5.17-6.19 mmol/l), >=240 mg/dl (>=6.20 mmol/l) (Jacobson et al., 2014)
Triglyceride	Continuous	mmol/l mg/dl	43.48%	Recoded into three levels: < 150 mg/dl (<1.69 mmol/l), 150-499 mg/dl (1.69 -5.63 mmol/l), >=500 mg/dl (>=5.64 mmol/l) (Jacobson et al., 2014)
High-density lipoprotein (HDL)	Continuous	mmol/l mg/dl	37.51%	Recoded into three levels: < 40 mg/dl (< 1.03 mmol/l) for male or < 50 mg/dl (< 1.29 mmol/l) for female, 40-59 mg/dl for male (1.03-1.53 mmol/l) or 50-59 mg/dl (1.29-1.53 mmol/l) for female, >= 60 mg/dl (1.54 mmol/l) (Jacobson et al., 2014)

HbA1c	Continuous	mmol/mol %	18.33%	Recoded into three levels: < 7%(< 53 mmol/mol), 7-9%(53-75 mmol/mol), and >=9%(> 75 mmol/mol)
Creatinine	Continuous	mmol/l, mg/dl	15.77%	-

SIMD-D: Scottish index of multiple deprivation-decile

Whenever possible, the missingness in certain variables was reduced using the content of other observations or relevant variables within the same or different datasets. For example, the prescription date variable in the PIS was complete for all medications of interest for all study years (2011 until 2021) except the prescription dates of ADDs in 2010, where 0.6% (11,470/1,766,050) of observations were missing. In that situation, the missing values of the prescription date in 2010 were addressed using the dispensing dates as an approximation to the prescription date. Furthermore, missing data in the BNF chapter, section, and subsection relevant to the study outcome was manually added after being checked from the most recent online BNF handbook based on the approved drug name (a complete variable). Data relevant to the UR location and SIMD-Q score within SMR00/SMR01 datasets was used to cover some of the missing observations in the two variables, which were primarily extracted from the PIS dataset. Lastly, the missing values of the BMI variable were calculated using the available information of weight and height; BMI = Weight (kg)/(Height (m))^2 *(Weir and Jan, 2022).* There was significant missingness in the LDL variable (77.2%), but the missing values of LDL were not calculated using the Friedewald equation, a commonly used formula for LDL calculation in clinical practice from the known values of total cholesterol, TG, and HDL. This was based on concerns around the validity and reliability of using this equation among patients with diabetes mellitus since multiple studies reported that the Friedewald equation tends to underestimate LDL even if TG is < 200 mg/dl *(Kuthethur, 2015, Alpdemir and Alpdemir, 2021)*. Therefore, LDL was not included in the analyses. Other undertaken measures and statistical techniques for handling the missing data are described in chapters 4 and 5.

During data preparation, several new variables were created from the supplied variables within each dataset, as detailed in Table 3.5. For instance, an additional numerical variable representing the eGFR in ml/min/1.73m^2 was derived using the 2021 refit Chronic Kidney Disease Collaboration (CKD-EPI) equation for eGFR prediction from patient serum creatinine, age, and sex without the endorsement of race coefficient as explained in Table 3.6 *(Meeusen et al., 2022)*. The National Kidney Foundation has recommended using the CKD-EPI refit equation for eGFR calculation as it increased the accuracy of eGFR classification, especially for patients with lower values of eGFR *(Miller et al., 2022, Meeusen et al., 2022).* Then eGFR values were recoded into a binary variable (>= 60 Vs. < 60 ml/min/1.73m^2) *(Iino, 2008).* A simple calculation was made on some of the continuous variables to display them in a different unit of measurement, such as converting HbA1c values from mmol/mol to percentage, lipid profile values from mmol/l to mg/dl, and serum creatinine from mmol/l to mg/dl to facilitate their classification and subsequent calculation *(Arch et al., 2016, Rugge et al., 2011)*. All formulas used for converting between units of measurement are presented in Table 3.7.

Table 3.5: Summary of newly derived variables from the supplied variables of the original datasets

Newly derived variable	Variable names	The supplied variable name from the original dataset
Individual comorbid condition	ischemic heart disease (*IHD*), hypertension (*HTN)*, heart failure (*HF*), stroke (*stroke*), peripheral vascular disease (*PVD*), liver disease, cancer, retinal disease, neuropathy disease, diabetic retinopathy (*diab_retino*), diabetic neuropathy (*diab_neuro*)	Based on ICD-10 codes of main_condition, other_condition1, other_condition2, other_condition3, other_condition4, and other_condition5 from smr01 and smr00 Referal_reason0, Referal_reason1, Referal_reason2, Referal_reason3, and Referal_reason4 from smr00
Composite comorbidity measure	Quan Charlson comorbidity index (*CCI_score_quan*)	The same as the individual comorbid condition

Concomitant medications	Thiazide diuretics (*thiazide*), beta-blockers (beta_blocker), angiotensin inhibitors (angiotensin_inhibitor), calcium channel blocker (CCB), other antihypertensive medications (other_AntiHTN), loop diuretic (loop_diuretic), antiplatelet, lipid drugs, anti-psychotic.	Based on the BNF codes of the bnf item code variable from PIS datasets
Number of concomitant drugs	Number of concomitant drugs (*num_conc_med*)	Based on the BNF codes of the bnf item code variable from PIS

Table 3.6: Chronic Kidney Disease Collaboration (CKD-EPI) equation for eGFR prediction 2021 based on creatinine, sex, and age

Sex	Serum creatinine	eGFR equation
Male	<= 0.9 mg/dl	$eGFR = 142 * (S_{cr}/0.9)^{-0.302} * 0.9938^{Age}$
Male	> 0.9 mg/dl	$eGFR = 142 * (S_{cr}/0.9)^{-1.200} * 0.9938^{Age}$
Female	<= 0.7 mg/dl	$eGFR = 142 * (S_{cr}/0.7)^{-0.241} * 0.9938^{Age} * 1.012$
Female	> 0.7 mg/dl	$eGFR = 142 * (S_{cr}/0.7)^{-1.200} * 0.9938^{Age} * 1.012$

eGFR; estimated glomerular filtration rate. Scr; Serum creatinine.

Table 3.7: Unit measurement conversion formulas for HbA1C, lipid profile, and serum creatinine

Laboratory Variable	Unit measurement conversion formula
HbA1C	HbA1C (%) = (HbA1c (mmol/mol)/10.929)+2.15 (Arch et al., 2016)
Triglyceride (TG)	TG (mg/dl) = TG (mmol/l) * 88.57 (Rugge et al., 2011)
Total cholesterol (TC)	TC (mg/dl) = TC (mmol/l) * 38.67 (Rugge et al., 2011)
High-density lipoprotein (HDL)	HDL (mg/dl) = HDL (mmol/l) * 38.67 (Rugge et al., 2011)
Low-density lipoprotein (LDL)	LDL (mg/dl) = LDL (mmol/l) * 38.67 (Rugge et al., 2011)
Serum creatinine	Serum creatinine (mg/dl)= Serum creatinine (mmol/l) / 88.4

Furthermore, multiple binary variables indicating comorbid conditions of interest, which were presented at or prior to ADD prescribing (within three years), were created based on the ICD-10 codes (Appendix S.3.2) of the relevant variables within the SMR00 and SMR01 datasets (Table 3.6). A general summary measure of co-existing diseases was also generated using a weighted Quan Charlson comorbidity index (CCI) based on the ICD-10 classification system, estimating a patient's one-year mortality risk. The CCI is calculated by assigning each disease a specific weight

that ranges from 1 to 6 based on the severity of a disease and its potential effect on mortality, and then the sum of all weights yields a single score for the individual patient *(Quan et al., 2005)*. This score was categorized into four levels: 0, 1-2 (mild), 3-4 (moderate), and >=5 (severe) (Huang et al., 2014).

Lastly, for concomitant medications, a binary variable was initially created for the individual medication of interest, including angiotensin inhibitors, calcium channel blockers (CCB), beta-blockers, and thiazide diuretics. In addition, the total number of concomitant medications that were prescribed at or within six months prior to ADDs prescribing was calculated based on the BNF item names. This was calculated including all medications covered in the BNF (all chapters 1-15), but excluding all ADDs, vaccines, emollients, sunscreens, shampoos, skin cleansers, and antiperspirants. In this project, the number of concomitant medications was categorised into three levels: 0 medications, 1-4 medications, and >=5 medications. The categorisation of the number of concomitant medications was based on the definition of polypharmacy, in which the most common numerical cut-off for defining polypharmacy is five or more medications *(Masnoon et al., 2017)*. Therefore, it was used for describing patients who were not taking any medications along with ADDs (0 medications), those who used concomitant medications but were not classified as polypharmacy (1-4 medications), and those on polypharmacy (>= five medications).

Figure 3.1 summarises the entire data cleaning and preparation process applied to all datasets to define the study cohort included in the first-line study (Chapter 4) and used to define the intensification cohort (Chapter 5). All data preparation and cleaning steps were conducted using the following packages in R software version 3.5.0 within the National Safe Haven environment: readxl, R base, dplyr, tidyverse, lubridate, reshape, and comorbidity.

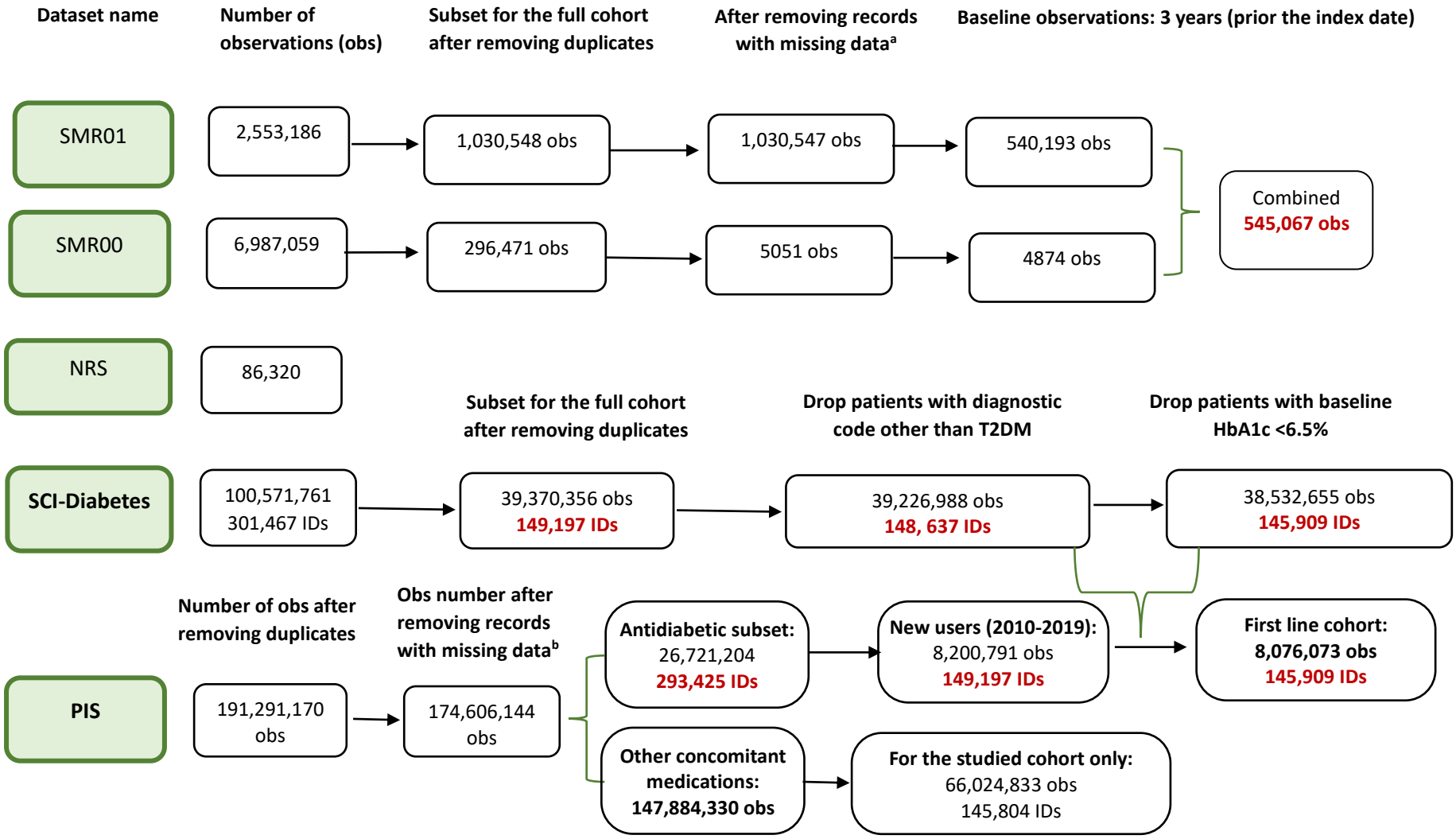

Figure 3.1: The process of data cleaning and preparation of the five included datasets, a; missing data was based on referral reason variables in SMR00 and condition (main and other) variables in SMR01, b; missing data was based on prescription variables (BNF code and approved name).

4 Chapter 4. Prescribing Pattern and Factors Influencing Prescribing of Initial Antidiabetic Drugs Among Patients with Type 2 Diabetes Mellitus Across Scotland Over the Period of 2010-2019

4.1 Introduction

Parallel with the constant increase in the prevalence and burden of T2DM globally *(Sun et al., 2021, International Diabetes Federation, 2021)*, there is a considerable development in the treatment options and management strategies of T2DM worldwide *(Williams et al., 2022)*. This is accompanied by changes in national and international guidelines for T2DM management, including the Scottish guideline, especially after the approval of newer classes of ADDs with proven cardiovascular and potential renal benefits; namely, SGLT2-I and GLP1-RA *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. The constant provision of updated guidelines is only the start towards improving disease management and patient care, which should be followed by ensuring the implementation of clinical guidelines and physicians' adherence to guideline recommendations. The availability of electronic administrative databases represents a robust and reliable tool for evaluating changes in treatment selection and prescription over time. That, in turn, might reflect the impact of updating guidelines and the availability of more classes of ADDs, where physicians can now select from wider options, on the prescribing pattern of ADDs.

Although all clinical guidelines recommended metformin as first-line therapy for newly diagnosed or drug naïve patients with T2DM *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*, there are a considerable number of patients who could be started on a different class of ADDs for multiple reasons potentially related to drug tolerability, presence of contraindication, and other co-existing diseases *(Montvida et al., 2018, Bouchi et al., 2022).* In addition, some patients might need to be initiated on more than one ADD, depending on the severity of the disease *(American Diabetes*

Association, 2021, Wilkinson et al., 2018a). However, there is no clear recommendation in the NICE and SIGN guidelines regarding the selection of the initial ADD alternative to metformin or the conditions where patients need to be treated with multiple ADDs and which to select among the available options *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. All clinical guidelines recommended following a patient-centred approach considering several factors such as patient age, baseline HbA1c value, comorbid conditions, and drug cost, amongst others, for choosing the most appropriate ADD for the individual patient without guiding the choice of specific therapies *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*; all of which create a large variability and complexity in the selection of the optimal ADDs for managing T2DM. Therefore, it is vital to understand how prescribing patterns of initial ADDs have changed over time, especially after the introduction of newer classes; and which factors may have been considered for making a decision regarding ADD selection for drug naïve patients with T2DM in clinical practice.

Furthermore, ADD prescribing patterns might vary by region or country, which could be related to the variability in the clinical guideline, available drugs, and other healthcare policies. That highlights the importance of measuring the prescribing patterns and drug selection strategies in each country to assess the discrepancies across countries. Despite the high prevalence and burden of T2DM, few studies have examined the prescribing patterns of ADDs over time in the UK, and no studies have been conducted in Scotland at a national level. Additionally, the most recent studies investigating the prescribing patterns were performed early after introducing newer drug classes; thus, they might not adequately capture how the newer classes affected the prescribing patterns of other groups. Investigating which factors are associated with the prescribing decision of ADDs is even more scarce and needs to be thoroughly investigated, as reflected from the results of the SR and MA (Chapter 2). Moreover, most studies examining the prescribing patterns and factors associated with the prescribing decision focused on using ADDs as

monotherapy with little discussion of the prescribing patterns and factors involved in selecting a combination regimen for drug naïve patients. Accordingly, it is crucial to understand, describe, and evaluate the prescribing process of ADDs for drug naïve patients to assess whether they are in line with recent evidence on the safety and effectiveness of ADDs as well as guideline recommendations.

Aims and objectives

This study aimed to describe the prescribing patterns of initial ADDs for patients diagnosed with T2DM in Scotland and to explore the association of patient characteristics with the type of regimen and antidiabetic class at the stage of drug initiation.

The objectives of this study were to: first examine the change in the prescribing patterns of initial ADDs for people with T2DM in Scotland over a ten-year period (Jan/2010 to Dec/2020), to observe any potential change in the prescribing patterns resulting from the introduction of newer antidiabetic classes. Second, investigate the association of several baseline demographic, clinical, prescriber-related, and socioeconomic factors with the regimen type and antidiabetic class at the initiation stage. That could potentially reflect the consistency of guideline recommendations and specific drug features with the choice of initial ADDs for patients diagnosed with T2DM in clinical practice in Scotland.

4.2 Method

4.2.1 Study design and study timeline

This retrospective cohort study used linked routinely collected administrative data of patients diagnosed with T2DM who were prescribed at least one ADD in primary care in Scotland. The study period spans from January 2010 until December 2020; Figure 4.1 demonstrates the timeline of this study. The earliest prescribed ADD is defined as the first event of ADD prescribing for each patient (the index prescription), even if it was prescribed only once. The corresponding prescription date represents the index date for each included patient.

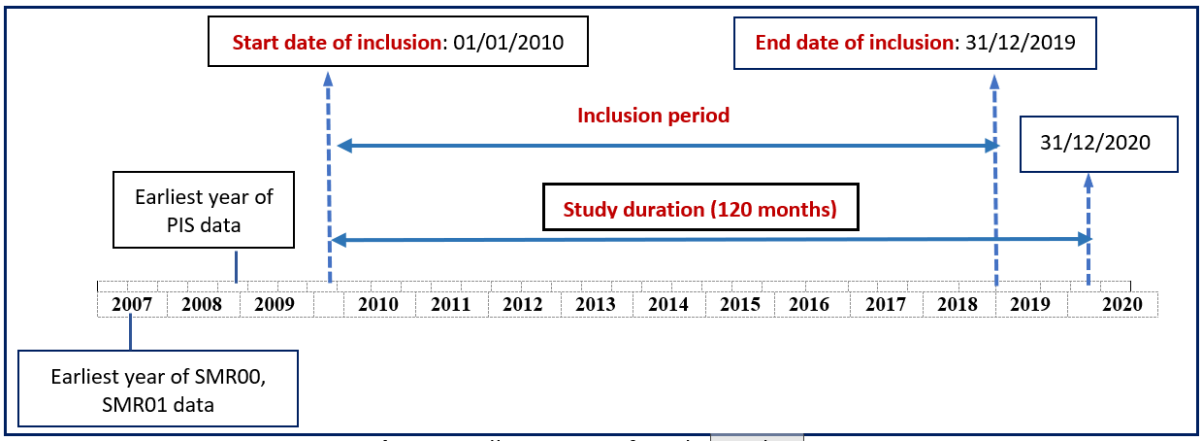

Figure 4.1: Illustration of the study timeline

4.2.2 Study cohort identification and selection

4.2.2.1 Inclusion/Exclusion criteria

The target population of this project comprised all patients identified within the SCI-Diabetes database (Chapter 3) in Scotland with a diagnostic code for T2DM (Read code: starting with C10F: mainly C10F.00 and C10F.11) between 1st January 2010 and 31st December 2019 who used at least one ADD over the study period (1st January 2010 – 31st December 2020). Each patient must have at least one year of follow-up for studying the change in T2DM management over time; therefore, the last date of patient inclusion was 31st December 2019. Patients were also required to be at least 18 years old at the date of T2DM diagnosis and the date of first identified ADD since different treatment guidelines are in place for children and adolescents with T2DM. Accordingly, ensuring that all included patients are subject to the same treatment recommendations is vital. In addition, patients were required to have at least one year of registration with a GP prior to the index date to define new users of ADDs and retrieve all required baseline data. Patients who had a diagnostic code for other types of diabetes (such as gestational diabetes or type 1 DM) or had a baseline HbA1c of < 6.5% were excluded. Table 4.1 summarises the inclusion/exclusion criteria.

Table 4.1: Cohort Identification: Inclusion/Exclusion criteria

Criteria	Definition	
	Inclusion	**Exclusion**
Diabetes diagnosis	Read codes for type 2 diabetes mellitus (starting with C10F: mainly C10F.00 and C10F.11)	Read codes for other types of diabetes (Type 1 diabetes, gestational diabetes, others)
Prescription	All antidiabetic drug codes (SCI-diabetes: ATC code A10, PIS: BNF code 6.1.2) during the study period to identify drug prescriptions	No codes for antidiabetic drugs or codes for antidiabetic drugs outside the study period
Study periods	Jan/2010-Dec/2020	Before Jan/2010 or after Dec/2021
Patient age	>= 18 years at the index date	< 18 years at the index date
Prior registration	At least one-year registration with a GP before the index date	Less than one-year registration with a GP before the index date
Follow-up	At least one year of follow-up post the index date	Less than one year of follow-up post the index date

4.2.2.2 Cohort identification and classification

The SCI-diabetes team identified the target population based on the presence of a Read code for T2DM diagnosis and records of pharmacological management with ADDs (both oral and injectable) within the SCI-diabetes database. The identified population by the SCI-Diabetes team was linked to the PIS dataset to retrieve the information relevant to the prescribed ADDs, the corresponding dates of prescription, and other baseline data such as the patient's date of birth, patient sex, geographical location, level of deprivation, and concomitant medications (Chapter 3). Additionally, the identified population was linked to the SMR00 and SMR01 datasets to extract all comorbid conditions data (Chapter 3). Of the target population, only new users (incident users) of ADDs were included in this project who were identified using the linked PIS records. As stated previously (section 4.2.1), the first prescription within the dataset for each patient was categorised as the index prescription. The 2009 PIS data was used to define the incident users who had no prescriptions of ADDs within the year preceding cohort entry; the earliest entry was on 1st January 2010.

Cohort-1 includes all patients with T2DM who were identified as new users of ADDs in Scotland over the study period. Each item of ADDs was assigned to the appropriate antidiabetic class, providing a total of 12 main classes, including biguanide (metformin), TZD, SU, DPP4-I, GLP1-RA, SGLT2-I, alpha-glucosidase inhibitors, meglitinide, short-acting insulin, intermediate-acting insulin, long-acting insulin, and biphasic insulin. The list of agents within each class of ADD is shown in Table 4.2. Short-acting insulin, intermediate-acting insulin, long-acting insulin, and biphasic insulin were grouped as insulin, and the less frequently prescribed antidiabetic groups (meglitinide and alpha-glucosidase inhibitors) were grouped as others, reducing the number of antidiabetic groups to a total of eight main classes.

Cohort-1 was then stratified into monotherapy or combination therapy users based on the number of different antidiabetic classes that were prescribed for the individual patient over a specific period called the initiation period. The initiation period was defined as the first three months following the earliest identified ADD in the PIS records. A three-month interval was selected since clinical guidelines of T2DM management recommended reassessing the glycaemic control after at least three months of starting an ADD. Accordingly, no change in drug therapy is expected to occur within three months of drug initiation based on the effectiveness of initiated treatment. The change in drug therapy within the first three months could occur for other reasons, such as drug tolerability. Generally, monotherapy users were defined as patients who were started on a single ADD over the initiation period, while combination therapy users comprised patients who started on two or more ADDs from different classes over the defined period.

Each patient was assigned to either a monotherapy group or a combination therapy group following specific criteria that were established based on three variables within PIS, including the type of prescribed ADDs, the corresponding prescription date, and prescribing quantity. Accordingly, all the following criteria were considered collectively to classify the patients into monotherapy versus combination therapy users: 1- the number of different antidiabetic classes prescribed for the individual patient, 2- the date of prescription of the individual

ADD, and 3- the prescribing coverage of the individual drug item over the initiation period, which was determined by looking for the presence of repeated/overlapping prescriptions and checking prescribing quantity when possible. Figure 4.2 explains all criteria for patient stratification into monotherapy or combination therapy groups. The clinical relevance of all applied criteria was discussed with a specialised pharmacist and a diabetologist.

First, patients were classified as monotherapy users if they were treated with a single ADD over the initiation period (Figure 4.2, case 1); or if they were on more than one drug over the initiation period, yet the drugs were prescribed on different not overlapped times during the initiation period. An illustration is displayed in Figure 4.2, case 2. The latter was further classified as monotherapy users with early change in drug therapy, where the earliest item was considered as the index drug. Accordingly, monotherapy users were sub-grouped into 1- monotherapy users without change in drug therapy over the initiation period (Figure 4.2, case 1) and 2- monotherapy users with early change in drug therapy (Figure 4.2, case 2). Second, patients were classified as combination therapy users in case of adopting any of the following conditions: 1- If they were prescribed more than one ADD on the same date (the earliest date) or very close dates (one-week interval) over the initiation period, Figure 4.2 (case 3). 2- If they had more than one ADD that were not prescribed on the same date or very close date, but prescriptions overlapped and were repeated over the initiation period, Figure 4.2 (case 4). 3- If they were prescribed a fixed-dose combination at the earliest date of drug prescription, Figure 4.2 (case 5). Combination therapy users were further stratified into dual-therapy (two drugs) users and triple or more ADD users based on the number of antidiabetic classes used in combination over the initiation period (Figure 4.2).

Table 4.2: List of agents within each class of antidiabetic drugs

Antidiabetic group	Approved chemical substance names
Biguanide	Metformin Hydrochloride
Sulfonylurea	Gliclazide, Glimepiride, Glipizide, Glibenclamide, Tolbutamide
DPP4-I	Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Alogliptin
GLP1-RA	Exenatide, Liraglutide, Lixisenatide
SGLT2-I	Dapagliflozin, Canagliflozin, Empagliflozin
TZD	Pioglitazone, Rosiglitazone
Meglitinide	Repaglinide, Nateglinide
Alpha-glucosidase inhibitor	Acarbose
Insulin	
Rapid/Short-acting insulin	Aspart, Lispro, Glulisine, Soluble insulin
Long-acting insulin	Glargine, Detemir, Degludec
Intermediate-acting insulin	Isophane
Biphasic insulin	Biphasic lispro, Biphasic isophane, Biphasic aspart

DPP4-I: Dipeptidyl peptidase-4 inhibitors, GLP1-RA: Glucagon-like peptide receptors agonist, SGLT2-I: Sodium glucose co-transporter-2 inhibitors.

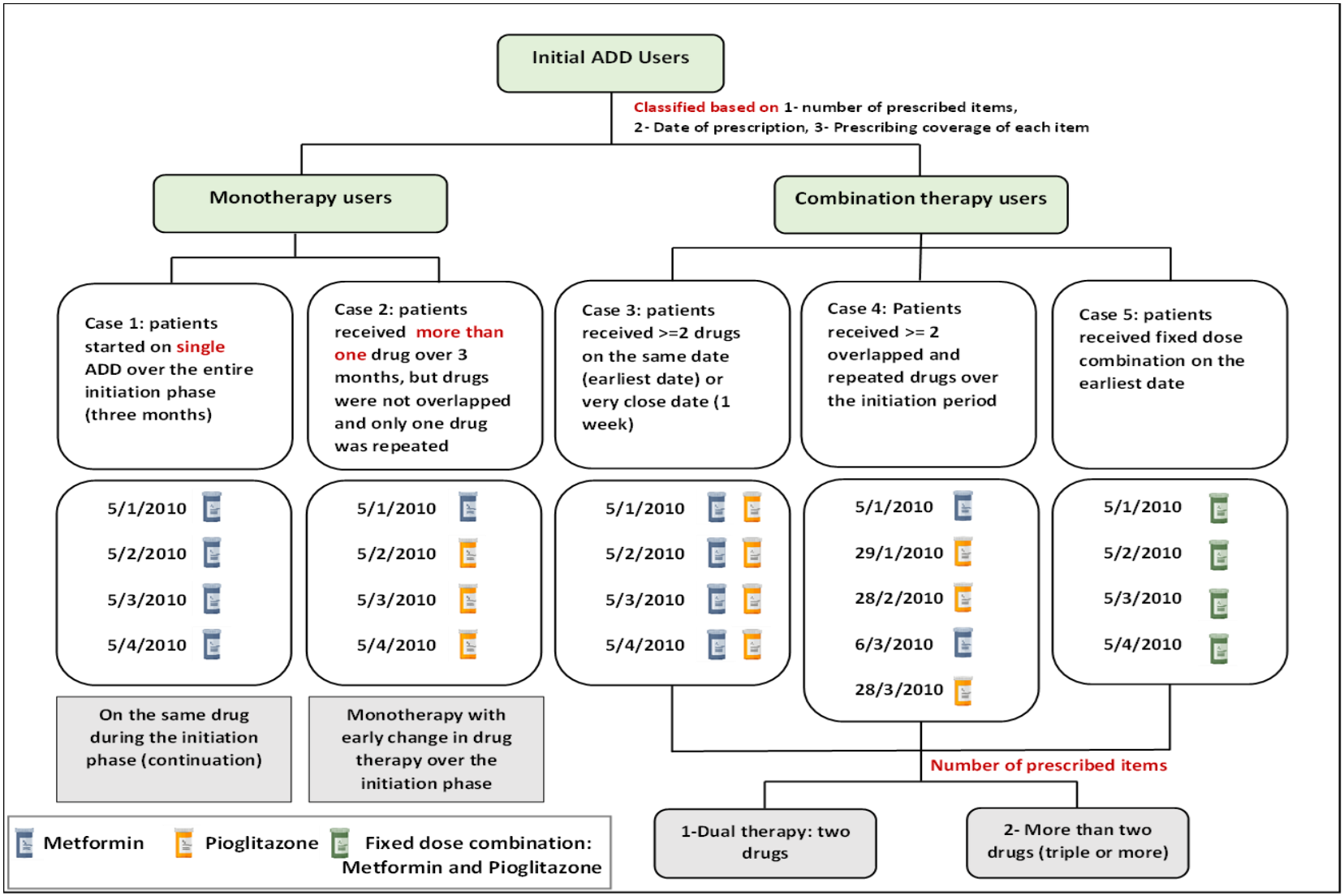

Figure 4.2: Categorization of antidiabetic drugs into monotherapy and combination therapy at stage of drug initiation. Dates represent the prescription date

4.2.3 Study outcomes

The primary outcomes of this study were: the changes in prescribing patterns of initial ADDs over the ten-year period; and factors potentially associated with the regimen type and class of ADDs prescribed at the stage of drug initiation.

4.2.3.1 Prescribing patterns of antidiabetic drugs over time

Prescribing frequency of the regimen type and individual class of ADDs was calculated per calendar year. The trend of the initial antidiabetic prescribing over ten years (Jan/2010- Dec/2019) was also investigated. This outcome was assessed from different perspectives; first, the change in the prescription of antidiabetic regimen (monotherapy and combination therapy) as initial drug therapy was described without specifying the individual class of ADD to reflect the variability in antidiabetic prescribing according to the type of prescribed regimen. Secondly, the change in prescribing patterns of the individual classes of ADD used as monotherapy was measured. And lastly, the pattern of different combination regimens use was evaluated by describing the type of combination regimens, including dual and triple or more combinations, and how frequently each class of ADDs was used in combination regimens.

Clinical guidelines recommended metformin monotherapy as a drug of choice for patients newly diagnosed with T2DM *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)* and the majority of patients (89%) in the UK were initiated on metformin monotherapy as reported by Wilkinson and colleagues *(Wilkinson et al., 2018a)*. The current study included all classes of ADDs to ensure the generalizability of included cohort and to assess whether the introduction of newer agents influenced the choice of the initial ADD.

4.2.3.2 Baseline characteristics and factors associated with the prescribing of antidiabetic class

Study covariates were determined based on the current knowledge of T2DM, the clinical guideline recommendations, and specific drug features (e.g., effectiveness, side effects, and extra-glycaemic benefits). These covariates were also informed from the results of the SR and MA about factors associated with ADDs prescribing (Chapter 2), in which the identified factors were mapped into four categories: demographic factors, clinical-related factors, socioeconomic factors, and prescriber-related factors. Hence, the baseline characteristics in this study comprised patient age and sex as demographic factors, BMI, comorbid conditions, concomitant medications, laboratory tests such as glycaemic status (HbA1c), lipid profile, BMI, and renal function as clinical factors, prescriber type as prescriber-related factors, as well as SIMD score and geographical areas (urban Vs. rural) as socioeconomic factors. Table 4.3 summarises the baseline characteristics and the definition of covariates. Details relevant to the process of cleaning, preparation, and classification of the study covariates are presented in Chapter 3, section 3.4.

Comorbid conditions of interest included HTN, IHD, HF, stroke, PVD, and liver disease. The co-existing conditions were also assessed using the Charlson Comorbidity Index (CCI), a summary measure of co-existing diseases. CCI has a total score that ranges from 0 to 24, and it was categorised into four levels: 0, 1-2 (mild), 3-4 (moderate), and >=5 (severe) (Chapter 3, section 3.4). Concomitant medications comprised thiazide diuretics, angiotensin inhibitors, beta-blockers, CCB, antihyperlipidemic, and antipsychotic drugs. The total number of medications used concurrently with ADDs was calculated and categorised into three levels: 0, 1-4, and >=5 (Chapter 3, section 3.4). All comorbid conditions, concomitant medications, and laboratory tests were selected since they are commonly presented along with T2DM, they act as surrogate indicators for important comorbid conditions associated with diabetes, and they may potentially affect the control of T2DM or the development of life-threatening complications.

Baseline characteristics were defined at the index date, or the closest ones recorded prior to the day of drug prescribing, within six months for concomitant medications and laboratory data (except HbA1c within three months) and three years for comorbid conditions. The baseline characteristics were initially described for the entire cohort of this study (cohort 1). Then the identified variables were stratified by the type of regimen (monotherapy versus combination therapy) and the individual antidiabetic class among monotherapy and combination therapy subgroups.

Table 4.3: The definition of covariates identified in the relevant datasets

Covariate	Definition	Dataset
Age at prescription	Age was calculated at the date of indexed drug prescription. It was assessed as a continuous variable and categorized into two categories (>= 65 and < 65 years).	PIS
Sex	It was assessed as a binary variable; Male or female.	PIS
Body mass index (BMI)	It was assessed as a continuous variable, and it was categorized into three categories: underweight-normal weight (<=24.9kg/m2), overweight (25.0-29.9kg/m2), and obese (>=30 kg/m2).	SCI-Diabetes
Glycaemic status (HbA1c)	It was assessed as a continuous variable, and it was categorized into three categories: < 7%, 7-9%, and > 9%	SCI-Diabetes
Renal function	Serum creatinine (Scr) was provided as a continuous variable. The estimated glomerular filtration rate (eGFR) was calculated from Scr, presented as a continuous variable, and then categorized into two categories: >=60 ml/min/1.73m^2 and < 60ml/min/1.73m^2.	SCI-Diabetes
Lipid profile	Total cholesterol, HDL, and TG were summarised as continuous variables and categorised as described in Chapter 3, section 3.4	SCI-Diabetes
Comorbidities	The individual co-existing disease of interest was defined as a binary indicating the presence of a disease (yes/no). Also, the CCI score as a general measure was calculated and categorized into four categories: 0, 1-2, 3-4, and >=5.	SMR00, SMR01
Concomitant medications	Each concomitant medication of interest was defined as a binary indicating the prescription of a concomitant drug for the individual patient (yes/no).	PIS
Number of concomitant medications	The total number of drugs was calculated and categorised into; 0, 1-4, >=5.	PIS
Deprivation level	The Scottish Index of Multiple Deprivation (SIMD)-quantile version 2020 was used as a measurement of deprivation and presented as five categories, coded in descending order. SIMD- quantile: 1 (the most deprived) to 5 (the least deprived).	PIS
Geographical area	following the urban/rural classification scheme developed by the Scottish Government (Scottish Government, 2018), it was presented as eight categories based on the number of inhabitants and distance to the nearest urban center.	PIS
Prescriber type	Readily available in the datasets, presented as four categories and recoded into binary: GP versus non-GP	PIS

4.2.4 Statistical analyses

4.2.4.1 Analysis of prescribing patterns of ADDs over time at the stage of drug initiation

Several analyses were conducted to describe the change in the prescribing pattern of ADDs. First, an initial descriptive analysis was conducted by measuring the frequency and percentage of patients started on a particular regimen or class of ADD per calendar year, where the percentage was measured as the total number of patients who used a specific regimen or class of ADD in a year (numerator) over the total number of new antidiabetic users in that year (denominator) multiplied by 100%. Likewise, the count and percentage of prescribing different agents within each class of ADD over the study period were calculated.

Second, the absolute and relative change in the use of the individual regimen and class of ADD was calculated to evaluate prescribing trends of each regimen and group of ADD over the ten-year study period *(King et al., 2012).* The absolute change in drug prescribing represents the difference between the number of patients who received a particular regimen (monotherapy or combination) or class of ADDs in the last year (2019) and the number of patients who were prescribed that regimen or class in the first year (2010). On the other hand, relative change is defined as the proportion of the absolute change in prescribing a specific regimen or class of ADD over the number of patients prescribed that regimen or class of ADD in the first year (2010). Third, a Cochran–Armitage test for trend analysis was conducted to assess the trend of the proportion of patients prescribed each regimen or class of ADDs annually; a p-value of less than 0.05 indicates a significant change in the prescribing patterns of a treatment regimen or antidiabetic class over the study period *(Kikuchi et al., 2022, Armitage, 1955, Cochran, 1954).*

4.2.4.2 Baseline characteristics and factors associated with the prescribing choice of the regimen type and antidiabetic class

Baseline characteristics were summarised as frequency/percentage for categorical variables and median± IQR or mean± SD for continuous variables as appropriate. The normality of the distribution of continuous variables was assessed based on the

histogram and Kolmogorov-Smirnov test, which showed that all continuous variables except patient age at the time of prescription of the entire cohort were not normally distributed (Appendix S.4.1). Baseline characteristics were described for the entire study cohort (cohort 1), and then stratified by the type of regimen and antidiabetic class.

Furthermore, univariable analyses were conducted to estimate the association of the individual covariate with the prescribing choice of combination regimen over monotherapy regimen (reference group) at the stage of drug initiation using binomial logistic regression. Multinomial logistic regression analyses were used to measure the odds of receiving each class of ADDs with metformin as the reference group since it is the initial drug of choice for T2DM management. This was followed by conducting multivariable analyses to calculate the adjusted odds ratio (OR) including all variables studied at the univariable stage. All classes of ADDs were included in the regression models except the other-monotherapy and the other-combination therapy groups. Two multinomial multivariable logistic regression models were performed; one for monotherapy groups and the other one for combination groups. That was done because of the complexity of conducting one multinomial multivariable regression analysis including all monotherapy and combination therapy groups, where a large number of covariates along with a large number of levels of the outcome variable (prescribed antidiabetic groups) need to be included in the regression model. In the two regression models, metformin was assigned as the reference group. The ORs for all explanatory variables denote the association between the study variable (independent variable) and the prescribing of the regimen type/antidiabetic class (dependent variable). The global p-value of non-binary categorical variables was measured using the likelihood ratio test. A p-value of <0.05 indicates a significant influence of the covariate on the prescribing choice of the regimen type or antidiabetic class.

The assumptions of collinearity and influential effects were tested for each regression model by conducting a variance inflation factor (VIF) test for multicollinearity, as well as outliers and Cook's distance for influential cases *(Park,*

2013, Stoltzfus, 2011). Since all continuous variables were inserted in the regression models in the categorical form, testing for the linearity assumption was not required. Model fitness was evaluated using several approaches, including the likelihood ratio test, pseudo-R^2, and Hosmer-Lemeshow test *(Hosmer et al., 1997, Stoltzfus, 2011).* Pseudo R^2 has a value that is greater than zero but less than one, with values closer to zero reflecting a low predictive power of the model, yet since the main purpose of the regression in this study is measuring the association, not for prediction, Hosmer-Lemeshow test was measured where a non-significant p-value (> 0.05) indicates a good fitness of the model. The results of the model assumption and fitness tests are summarised in Appendix S.4.2.

The completeness level of the variables included in the regression models has ranged from 0% (complete variable) to 43.4% of missingness in the triglyceride variable (Chapter 3, Table 3.4). Missing data can be one of three types depending on the mechanism or reason for missingness, reflecting the relation of missing data with other missing and observed data *(Dong and Peng, 2013, Kang, 2013):* missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). MCAR assumes that the missing data is randomly distributed across the variable and independent of the other observed variables. In contrast, MAR assumes that the missing data is independent of the other missing data within the same variable yet related to the observed variables. For MNAR, the missing data is dependent on both observed and unobserved data *(Dong and Peng, 2013, Kang, 2013).* Unfortunately, no definitive test can distinguish the exact type of missingness, and all available tests should not be used as definitive evidence for the type of missing data. One of the commonly used tests is the Little test which examines the plausibility of MCAR with a p-value of <0.05, rejecting the null hypothesis (no difference between the means of different missing patterns), providing evidence that the mechanism of missing data is not MCAR *(Little, 1988).* The Little test was conducted and showed a p-value of <0.001, indicating that the missing data in this study is not MCAR (Appendix S.4.2).

The regression analyses were done by initially including the original cohort, where missing data was added as a separate level in the model (NA was coded as unknown). However, as a sensitivity analysis, complete case regression analyses were conducted, including only patients without missingness in any of the covariates (complete records) in the regression model. Additionally, the regression analyses were then applied after handling and adjusting for missing data, in which the last observation carried forward (LOCF) method and multiple imputation approach were used to adjust for data missingness *(Blankers et al., 2010, Kang, 2013).* First, the LOCF method was carried out with the closest observation in the prior 12 months of a missing observation in a particular variable for an individual patient to fill in the missing value. This method was applied to all laboratory variables except the HbA1c since the time of HbA1c measurement in this study is very critical for cohort identification. The LOCF approach has reduced the percentage of missingness by approximately 10% for each variable (Table 4.4).

Secondly, the remaining missing data was handled using a multiple imputation approach, which creates multiple copies of a dataset after replacing the missing values with imputed ones, in which the imputed values are generated considering the distribution of the missing data across the observed variables. In this study, multiple imputations were performed by generating five imputed datasets with ten iterations for each dataset, in which the polynomial logistic regression was used to model the categorical variables (UR, SIMD_Q), and the predictive mean matching (PMM) was applied to the non-normally distributed numeric variables (BMI, HbA1c, eGFR, TG, total cholesterol, HDL). All variables included in the regression models were included in the imputation model. The missingness in the continuous variables (laboratory variables) was imputed on the numeric scale, which were then converted into a categorical form for regression analyses.

Data analyses were conducted in RStudio using the following packages: Base, dplyr, tidyverse, gtsummary, Table1, ggplot2, CochranArmitageTest, DescTools, stats, IRTest, Pscl, RColorBrewer, stringr, mcar_test, and broom. R script excerpts can be found in Appendix S.4.3.

Table 4.4: The reduction in the percentage of missingness of variables after applying the last observation carried forward (LOCF) method at the initiation stage

Variable name	% Of missingness before LOCF	% Of missingness after LOCF
Body mass index (BMI)	42.4%	32.2%
Triglyceride (TG)	43.4%	34.8%
Total cholesterol	26.7%	16.9%
High-density lipoprotein (HDL)	37.5%	27.9%
Estimated glomerular filtration rate (eGFR)	15.8%	9.9%

4.3 Results

A cohort of 149,197 patients was identified as new users of ADD out of the 293,425 patients aged 18 and older with a diagnosis code for T2DM who got at least one ADD throughout the study period (Jan/2010-December/2020) (incident users). The reasons for exclusion are shown in Figure 4.3. Of these, 3288 patients were excluded based on the exclusion criteria, leaving 145909 patients included in this study. Figure 4.4 shows the total number and percentage of ADD incident users by calendar year. The highest number of incident users was recorded in 2010 (15387/145909, or 10.5%), while the lowest number was recorded in 2014 (13220/145909, or 9.1%).

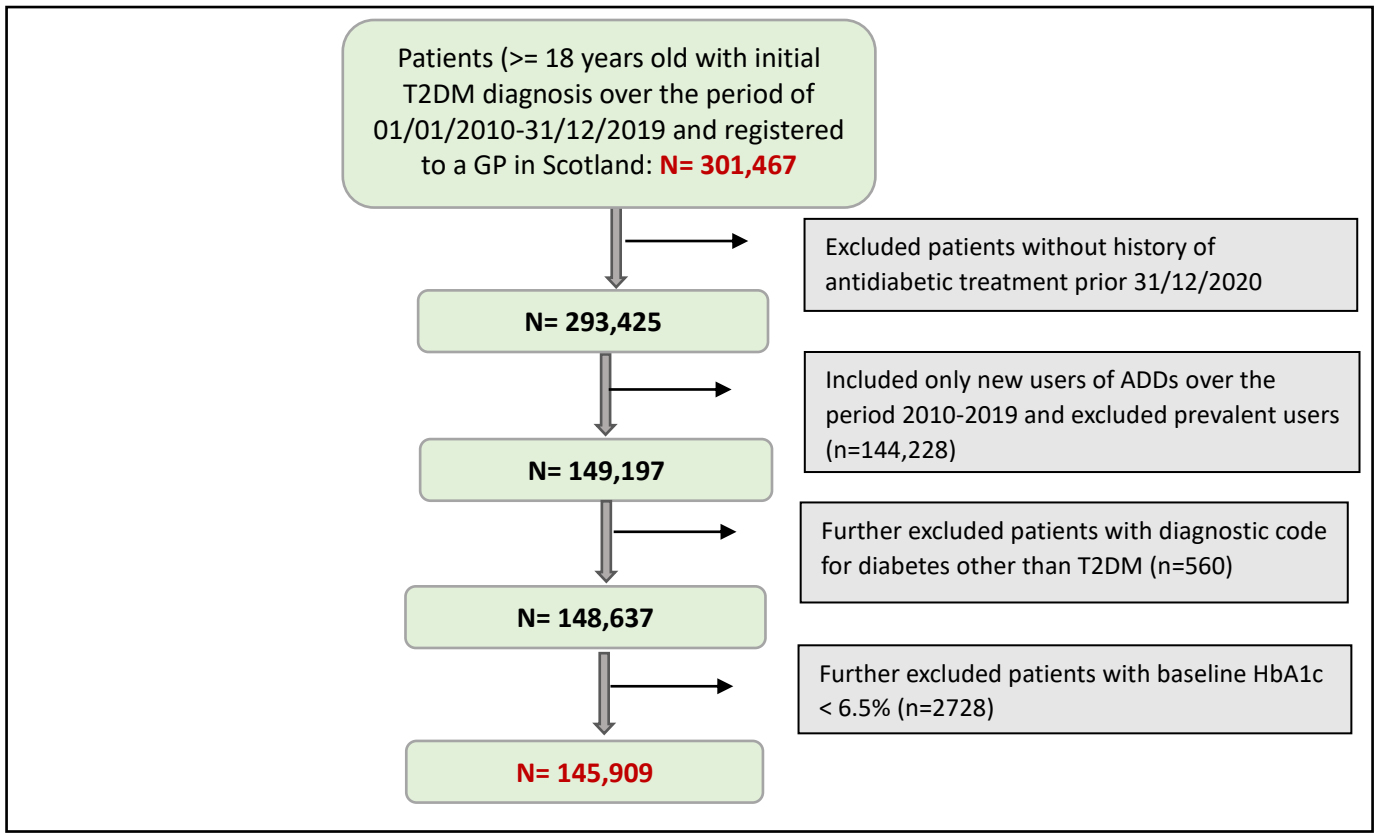

Figure 4.3: Flowchart of cohort identification process at the stage of drug initiation

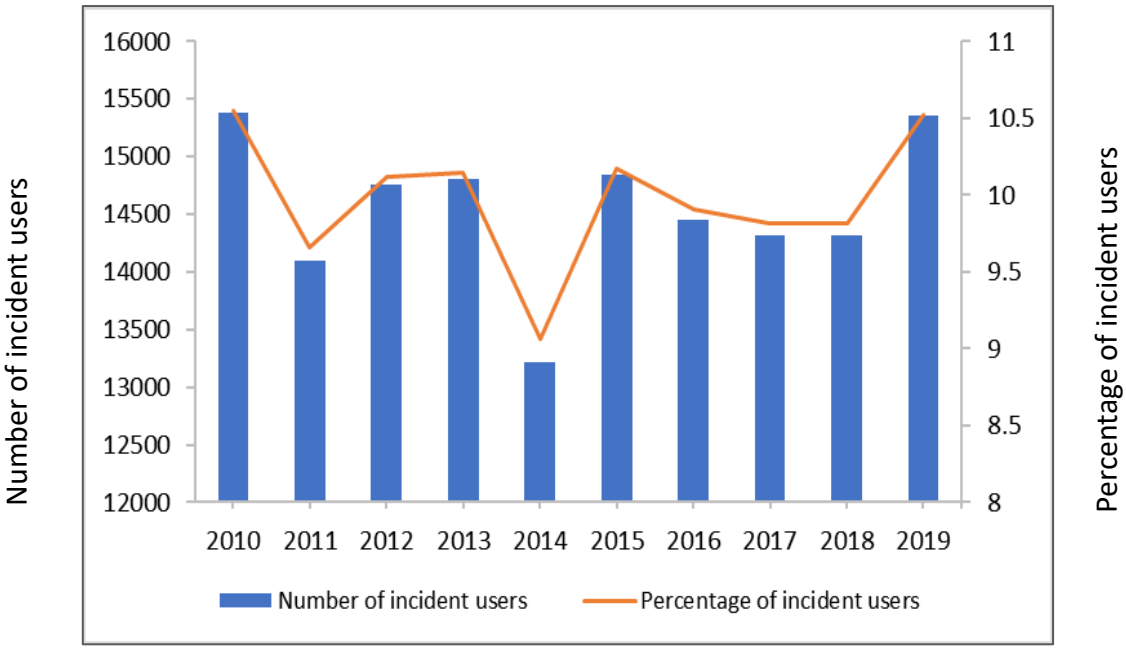

Figure 4.4: Number and percentage of incident users of antidiabetic drugs per calendar year. The denominator for the percentage is all patients in a given year

4.3.1 Baseline characteristics of included patients

4.3.1.1 Baseline characteristics of the overall cohort stratified by regimen type

Table 4.5 shows the baseline sociodemographic and clinical characteristics of the included cohort, overall and stratified by the type of prescribed regimen (monotherapy and combination). Of the 145909 patients, 84542 were male (57.9%) and the overall median age of the entire cohort was 61 years [IQR 52-70], with 60.6% (N=88414) of patients being younger than 65 years. The percentage of male patients among combination therapy users was higher than that among monotherapy users (60.3% Vs. 57.7%); the median age (IQR) of patients started on combination therapy was lower than that of patients started on monotherapy (58[49-67] Vs. 61[52-70], respectively). Prescriber type is the only prescriber-related characteristic provided in this study; 93.6% (N=136,563) of the included patients got their prescriptions from a GP, whereas the remaining patients (N=9346, 6.4%) received their prescriptions from non-GPs, including hospitals, nurses, or pharmacists.

Clinical features of the patients included pre-existing comorbid illnesses, concurrent medications, and laboratory testing. Just 2.3%(N=21,559) of the study cohort (N=115579) had a baseline CCI score of >= five, whereas the majority (N=115579) had a score of zero. Patients who started on combination medication had a higher CCI score than those who started on monotherapy. The most common disease among the studied individual comorbid conditions of interest was HTN (N=26061, 17.9%), followed by IHD (N=18232, 12.5%). HTN and IHD were also more common in patients who used monotherapy (HTN: 18%, IHD: 12.6%) than in patients who used combination therapy (HTN: 16.4%, IHD: 11.4%). Contrarily, HF, stroke, PVD, and liver disease were present in fewer than 5% of the entire cohort. In contrast to HTN and IHD, they were more common in patients who received combination therapy than in those who received monotherapy. Neuropathy and retinal disorders were assessed as baseline indicators of microvascular problems; it was discovered that these conditions were present in less than 1% and 3% of individuals, respectively. None of the patients had diabetic neuropathy or diabetic retinopathy at baseline. Regarding

the number of concomitant medications, more than half of the entire cohort (63.3%, 92418/145909) were on five or more concomitant medications at or prior to the index date. Patients who used five or more concomitant medications accounted for 63.95% of patients initiated on monotherapy compared to 57.40% of patients treated with combination therapy (Table 4.5). Among the included patients (N=145909), 57.9% (N=84422), 42.6% (N=62165), 24.6% (N=35837), 22.6% (N=33016), and 16.6% (N=24260) used lipid-lowering medications, angiotensin inhibitors, beta-blockers, CCB, and thiazide diuretics, respectively.

Furthermore, baseline BMI was available for 57.6% of the entire cohort, where the median baseline BMI (IQR) was 32[28-37] kg/m^2. More than one-third of the included patients were obese (BMI>=30 kg/m^2, N= 55560, 38.1%). Although the median BMI of patients receiving combination therapy was comparable to that of patients receiving monotherapy, the proportion of patients receiving monotherapy who were overweight or obese was higher (15.2% and 39.0% Vs. 13.5% and 28.8%, respectively). On the contrary, 84.2% of the included cohort had a known baseline eGFR value, with a median of 91[75-102] ml/min/1.73m^2; this was similar among combination and monotherapy groups (92 [73-105] Vs. 91[75-102], respectively).

The overall median HbA1c (IQR) where available (81.32%) was 8.6 [7.7-10.3]. Just 5.3% (N=7733) of the included patients had a baseline HbA1c value of 7. The median baseline HbA1c of patients starting combination therapy was substantially higher than that of patients starting monotherapy (11% Vs. 8.5%, respectively), with 47.7% of the combination group having a baseline HbA1c value of >= 9 compared to 33.7% in the monotherapy group.

Table 4.5: Baseline characteristics of the included cohort as overall and stratified by the type of prescribed regimen

Characteristic	Overall N=145,909	Combination N=13,527	Monotherapy N=132,382
Sex			
Male	57.94%(84,542)	60.26%(8,151)	57.70%(76,391)
Female	42.06%(61,367)	39.74%(5,376)	42.30%(55,991)
Age at prescription	61 (52, 70)	58 (49, 67)	61 (52, 70)
< 65 years	60.60%(88,414)	67.56%(9,139)	59.88%(79,275)
>= 65 years	39.40%(57,495)	32.44%(4,388)	40.12%(53,107)
Urban/rural			
1	32.40%(47,274)	33.26%(4,499)	32.31%(42,775)
2	37.90%(55,300)	35.67%(4,825)	38.13%(50,475)
3	8.61%(12,564)	8.53%(1,154)	8.62%(11,410)
4	2.40%(3,498)	2.52%(341)	2.38%(3,157)
5	1.27%(1,857)	1.31%(177)	1.27%(1,680)
6	10.98%(16,020)	10.99%(1,486)	10.98%(14,534)
7	3.41%(4,976)	4.24%(573)	3.33%(4,403)
8	2.98%(4,342)	3.39%(459)	2.93%(3,883)
Unknown	0.05%(78)	0.10%(13)	0.05%(65)
Scottish index of multiple deprivation-quantile			
1	26.30%(38,369)	27.09%(3,664)	26.22%(34,705)
2	23.62%(34,460)	23.69%(3,204)	23.61%(31,256)
3	20.31%(29,628)	20.38%(2,757)	20.30%(26,871)
4	16.70%(24,374)	16.59%(2,244)	16.72%(22,130)
5	13.04%(19,021)	12.21%(1,652)	13.12%(17,369)
Unknown	0.04%(57)	0.04%(6)	0.04%(51)
Prescriber type			
General Practitioner (GP)	93.59%(136,563)	96.24%(13,018)	93.32%(123,545)
Non-GP	6.41%(9,346)	3.76%(509)	6.68%(8,837)
Ischemic heart disease	12.50%(18,232)	11.37%(1,538)	12.61%(16,694)
Hypertension	17.86%(26,061)	16.40%(2,219)	18.01%(23,842)
Heart failure	3.48%(5,074)	4.08%(552)	3.42%(4,522)
Stroke	2.75%(4,018)	3.09%(418)	2.72%(3,600)
Peripheral vascular disease	2.50%(3,652)	2.74%(371)	2.48%(3,281)
Liver disease	2.41%(3,521)	3.23%(437)	2.33%(3,084)
Retinal disease	0.69%(1,011)	0.74%(100)	0.69%(911)
Neuropathy disease	2.14%(3,122)	1.77%(239)	2.18%(2,883)
Charlson comorbidity index-Quan *(Quan et al., 2005)*			
0	79.21%(115,579)	77.61%(10,498)	79.38%(105,081)
1-2	14.78%(21,559)	14.88%(2,013)	14.76%(19,546)
3-4	3.67%(5,353)	4.35%(588)	3.60%(4,765)
>=5	2.34%(3,418)	3.16%(428)	2.26%(2,990)

Lipid drugs	57.86%(84,422)	46.51%(6,291)	59.02%(78,131)
Antipsychotics	3.14%(4,581)	3.54%(479)	3.10%(4,102)
Thiazide diuretics	16.63%(24,260)	13.01%(1,760)	17.00%(22,500)
Beta-blockers	24.56%(35,837)	21.80%(2,949)	24.84%(32,888)
Angiotensin inhibitors	42.61%(62,165)	36.65%(4,957)	43.21%(57,208)
Calcium channel blocker	22.63%(33,016)	18.28%(2,473)	23.07%(30,543)
Polypharmacy			
0	4.26%(6,216)	6.46%(874)	4.04%(5,342)
1-4	32.40%(47,275)	36.14%(4,888)	32.02%(42,387)
>=5	63.34%(92,418)	57.40%(7,765)	63.95%(84,653)
Body mass index (kg/m^2)	32 (28, 37)	32 (28, 37)	32 (29, 37)
	4.49%(6,547)	4.95%(669)	4.44%(5,878)
<=24.9	15.03%(21,929)	13.48%(1,824)	15.19%(20,105)
25-29.9	38.08%(55,560)	28.82%(3,898)	39.02%(51,662)
>=30	42.41%(61,873)	52.75%(7,136)	41.35%(54,737)
Unknown			
HbA1c (%)	8.60 (7.70, 10.30)	11.00 (9.10, 12.60)	8.50 (7.60, 10.00)
mmol/mol	70 (61, 89)	97 (76, 114)	69 (60, 86)
<7	5.30%(7,733)	2.35%(318)	5.60%(7,415)
7- <9	41.01%(59,833)	11.90%(1,610)	43.98%(58,223)
>= 9	35.01%(51,089)	47.73%(6,456)	33.72%(44,633)
Unknown	18.68%(27,254)	38.02%(5,143)	16.70%(22,111)
Estimated glomerular filtration rate (ml/min/1.73m^2)	91 (75, 102)	92 (73, 105)	91 (75, 102)
>= 60	76.15%(111,103)	60.51%(8,185)	77.74%(102,918)
< 60	8.01%(11,688)	8.94%(1,209)	7.92%(10,479)
Unknown	15.84%(23,118)	30.55%(4,133)	14.34%(18,985)
High- density lipoprotein (mg/dl)	43 (35, 50)	39 (34, 48)	43 (35, 50)
<40 (M) or <50 (F)	35.28%(51,475)	27.62%(3,736)	36.06%(47,739)
40-59 (M) or 50-59 (F)	21.85%(31,876)	13.58%(1,837)	22.69%(30,039)
>=60	5.34%(7,793)	3.35%(453)	5.54%(7,340)
Unknown	37.53%(54,765)	55.45%(7,501)	35.70%(47,264)
Total cholesterol (mg/dl)	186 (155, 220)	193 (159, 236)	186 (155, 220)
<200			
200-239	44.46%(64,873)	28.91%(3,911)	46.05%(60,962)
>=240	16.51%(24,088)	12.20%(1,650)	16.95%(22,438)
Unknown	12.31%(17,956)	12.60%(1,704)	12.28%(16,252)
	26.72%(38,992)	46.29%(6,262)	24.72%(32,730)
Triglyceride (mg/dl)	195 (138, 283)	213 (146, 337)	194 (136, 275)
<150	16.74%(24,429)	10.22%(1,383)	17.41%(23,046)
150-499	35.96%(52,474)	24.68%(3,339)	37.12%(49,135)
>=500	3.76%(5,490)	5.15%(696)	3.62%(4,794)
Unknown	43.53%(63,516)	59.95%(8,109)	41.85%(55,407)

The results presented as % (frequency) or median (Interquartile range)

4.3.1.2 Baseline characteristics of monotherapy users stratified by class of antidiabetic drugs

Table 4.6 describes the baseline characteristics of patients with T2DM who were started on single ADD stratified by antidiabetic class. Among patients started on monotherapy, female patients accounted for more than 50% of patients who received DPP4-I, GLP1-RA, TZD, or other-monotherapy (54.9%, 57.1%, 55.9%, and 62.1%, respectively). More than half of patients who were treated with GLP1-RA (83.3%), SGLT2-I (73.9%), metformin (61.4%), or insulin (61.7%) were younger than 65 years, with a median (IQR) age of 54 (48-60), 57 (49-65), 61 (52-69), and 59 (46-71) years, respectively. On the contrary, the median age (IQR) of patients who were started on DPP4-I was 72 (62-79) years, with more than two-thirds of patients aged 65 years or older at the time of drug prescribing (68.8%).

Regarding the baseline comorbid conditions, the proportion of patients with a zero baseline CCI score ranged from 56.4% (532/944) to 81.6% (96,837/118,737) for patients starting on DPP4-I and metformin, respectively (Table 4.6). The most prevalent co-existing disease was HTN, followed by IHD for all antidiabetic classes, except the other group (alpha-glucosidase inhibitor and meglitinide), where none of the patients had HTN at baseline (Table 4.6). The highest prevalence of HTN and IHD was observed among patients treated with DPP4-I as initial therapy (33.3% and 24.4%, respectively). On the other hand, liver disease was most frequently found among patients who received insulin as initial therapy (9.4%). Moreover, the percentage of patients taking five or more concomitant medications ranged from 54.8% (23/42) to 81.7% (771/944) of patients starting on GLP1-RA and DPP4-I, respectively. Antihyperlipidemic drugs and angiotensin inhibitors were the most commonly used concomitant medications across all classes of ADDs, followed by beta-blockers, CCB, and thiazide diuretics, whereas antipsychotic drugs were the least frequently used medications (Table 4.6). The highest percentage of consumption of all concomitant medications was observed among patients starting on TZD and DPP4-I (Table 4.6).

Regarding the available baseline laboratory data, the median (IQR) BMI was the highest among patients receiving GLP1-RA (39[35-46] kg/m^2) or SGLT2-I (36[31- 41] kg/m^2). In contrast, it was the lowest among patients starting on SU (28[24-32] kg/m^2) or insulin (29[25-34] kg/m^2). However, the highest baseline HbA1c was observed among patients starting on insulin, followed by SU. Patients who received insulin or SU as initial therapy had a baseline median (IQR) HbA1c of 11.1 (8.70-13.00) and 9.6 (8.10-11.60), respectively. Additionally, the baseline median (IQR) eGFR of patients who were prescribed DPP4-I and TZD was 63 (43-88) and 65 (39-93) ml/min/1.73m^2, respectively, with more than one-third of patients having a low baseline eGFR of <60 ml/min/1.73m^2 in both groups (40.47% and 34.65%, respectively).

Table 4.6: Baseline characteristics of the patients started on monotherapy stratified by the class of antidiabetic drugs

Characteristics	Biguanide N=118,737	SU N=10,029	DPP4-I N=944	GLP1-RA N=42	insulin, N=2,171	SGLT2-I N=303	TZD N=127	Other N=29
Sex								
Male	57.96%(68,815)	56.90%(5,707)	45.13%(426)	42.86%(18)	55.27%(1,200)	52.15%(158)	44.09%(56)	37.93%(1)
Female	42.04%(49,922)	43.10%(4,322)	54.87%(518)	57.14%(24)	44.73%(971)	47.85%(145)	55.91%(71)	62.07%(18)
Age at prescription	61 (52, 69)	67 (56, 77)	72 (62, 79)	54 (48, 60)	59 (46, 71)	57 (49, 65)	65 (56, 76)	58 (45, 68)
< 65 years	61.37%(72,864)	44.28%(4,441)	31.25%(295)	83.33%(35)	61.68%(1,339)	73.93%(224)	47.24%(60)	58.62%(17)
>= 65 years	38.63%(45,873)	55.72%(5,588)	68.75%(649)	16.67%(7)	38.32%(832)	26.07%(79)	52.76%(67)	41.38%(12)
Urban-rural								
1	32.27%(38,322)	33.23%(3,333)	29.34%(277)	21.43%(9)	32.66%(709)	30.03%(91)	21.26%(27)	24.14%(7)
2	38.28%(45,456)	36.21%(3,632)	41.31%(390)	28.57%(12)	37.36%(811)	35.64%(108)	41.73%(53)	44.83%(13)
3	8.61%(10,221)	8.79%(882)	8.90%(84)	*	8.57%(186)	7.92%(24)	7.87%(10)	*
4	2.34%(2,783)	2.81%(282)	2.44%(23)	*	2.21%(48)	4.62%(14)	*	*
5	1.24%(1,477)	1.48%(148)	2.22%(21)	*	1.38%(30)	*	0.00%(0)	0.00%(0)
6	10.92%(12,970)	11.16%(1,119)	11.55%(109)	*	11.61%(252)	15.51%(47)	18.11%(23)	*
7	3.30%(3,921)	3.68%(369)	2.01%(19)	*	3.41%(74)	2.97%(9)	5.51%(7)	*
8	2.97%(3,531)	2.58%(259)	2.22%(21)	11.90%(5)	2.63%(57)	2.31%(7)	*	0.00%(0)
Unknown	0.05%(56)	0.05%(5)	0.00%(0)	*	*	0.00%(0)	0.00%(0)	0.00%(0)
Scottish index of multiple deprivation-quantile								
1	26.38%(31,328)	24.53%(2,460)	24.58%(232)	16.67%(7)	25.79%(560)	25.74%(78)	24.41%(31)	31.03%(9)
2	23.63%(28,059)	23.15%(2,322)	25.00%(236)	21.43%(9)	23.58%(512)	24.75%(75)	26.77%(34)	31.03%(9)
3	20.38%(24,198)	19.24%(1,930)	21.72%(205)	*	20.45%(444)	19.80%(60)	17.32%(22)	*
4	16.62%(19,732)	18.02%(1,807)	14.94%(141)	30.95%(13)	15.66%(340)	22.11%(67)	19.69%(25)	17.24%(5)

5	12.95%(15,375)	15.04%(1,508)	13.67%(129)	*	14.37%(312)	7.59%(23)	11.81%(15)	*
Unknown (total 51)								
Prescriber type								
General practitioner (GP)	93.18%(110,639)	93.99%(9,426)	93.01%(878)	> 90%	98.62%(2,141)	90.10%(273)	93.70%(119)	> 90%
Non-GP	6.82%(8,098)	6.01%(603)	6.99%(66)	< 10%	1.38%(30)	9.90%(30)	6.30%(8)	< 10%
Ischemic heart disease	12.03%(14,287)	17.96%(1,801)	24.36%(230)	< 10%	13.77%(299)	19.47%(59)	9.45%(12)	< 10%
Hypertension	17.23%(20,453)	25.17%(2,524)	33.26%(314)	16.67%(7)	21.00%(456)	21.12%(64)	18.90%(24/)	0.00%(0)
Hear failure	2.84%(3,378)	8.42%(844)	12.82%(121)	< 10%	6.86%(149)	7.59%(23)	< 10%	< 10%
Stroke	2.50%(2,973)	4.68%(469)	6.25%(59)	0.00%(0)	4.15%(90)	1.98%(6)	< 10%	0.00%(0)
Peripheral vascular disease	2.22%(2,636)	4.81%(482)	4.66%(44)	0.00%(0)	4.79%(104)	3.63%(11)	< 10%	< 10%
Liver disease	1.96%(2,326)	5.08%(509)	3.60%(34)	< 10%	9.44%(205)	< 10%	< 10%	0.00%(0)
Retinal disease	0.63%(751)	1.19%(119)	1.48%(14)	0.00%(0)	0.83%(18)	< 10%	< 10%	< 10%
Neuropathy disease	2.17%(2,574)	2.08%(209)	3.39%(32)	0.00%(0)	2.67%(58)	3.30%(10)	0.00%(0)	0.00%(0)
Charlson comorbidity score- Quan								
0	81.56%(96,837)	60.23%(6,040)	56.36%(532)	> 80%	59.93%(1,301)	73.60%(223)	72.44%(92)	> 60%
1-2	13.91%(16,515)	22.46%(2,253)	26.80%(253)	< 10%	19.99%(434)	19.47%(59)	19.69%(25)	< 15%
3-4	2.89%(3,430)	9.92%(995)	10.81%(102)	< 10%	9.67%(210)	4.95%(15)	*	< 15%
>=5	1.65%(1,955)	7.39%(741)	6.04%(57)	0.00%(0)	10.41%(226)	1.98%(6)	*	< 10%
Lipid drugs	59.99%(71,232)	52.68%(5,283)	64.41%(608)	30.95%(13)	33.72%(732)	51.16%(155)	74.80%(95)	44.83%(13)
Antipsychotics	3.02%(3,591)	3.64%(365)	3.28%(31)	0.00%(0)	4.51%(98)	3.63%(11)	3.94%(5)	< 10%
Thiazide diuretics	17.33%(20,576)	14.81%(1,485)	17.37%(164)	14.29%(6)	9.63%(209)	11.55%(35)	18.11%(23)	< 10%
Beta-blockers	24.44%(29,014)	28.45%(2,853)	40.89%(386)	26.19%(11)	22.11%(480)	30.69%(93)	33.86%(43)	27.59%(8)

Angiotensin inhibitors	43.79%(51,992)	38.80%(3,891)	53.18%(502)	30.95%(13)	27.27%(592)	46.53%(141)	52.76%(67)	34.48%(10)
Calcium channel blocker	23.31%(27,679)	21.84%(2,190)	26.17%(247)	19.05%(8)	14.42%(313)	17.82%(54)	36.22%(46)	20.69%(6)
Polypharmacy								
0	4.10%(4,866)	3.55%(356)	1.91%(18)	16.67%(7)	3.68%(80)	3.63%(11)	*	*
1-4	32.78%(38,921)	24.60%(2,467)	16.42%(155)	28.57%(12)	32.20%(699)	29.37%(89)	*	*
>=5	63.12%(74,950)	71.85%(7,206)	81.67%(771)	54.76%(23)	64.12%(1,392)	67.00%(203)	70.87%(90)	62.07%(18)
Body mass index (kg/m^2)	33 (29, 38)	28 (24, 32)	32 (28, 36)	39 (35, 46)	29 (25, 34)	36 (31, 41)	32 (29, 38)	32 (28, 35)
<= 24.9	3.47%(4,115)	14.52%(1,456)	7.42%(70)	0.00%(0)	10.18%(221)	2.97%(9)	3.94%(5)	6.90%(2)
25-29.9	15.14%(17,973)	16.73%(1,678)	15.78%(149)	< 5%	11.61%(252)	10.23%(31)	14.17%(18)	*
>= 30	41.17%(48,882)	18.21%(1,826)	36.55%(345)	> 50%	15.98%(347)	60.07%(182)	40.16%(51)	*
Unknown	40.23%(47,767)	50.54%(5,069)	40.25%(380)	45.24%(19)	62.23%(1,351)	26.73%(81)	41.73%(53)	58.62%(17)
HbA1c (%) **mmol/mol**	8.40 (7.60, 9.90) 68 (60, 85)	9.60 (8.10, 11.60) 81 (65, 103)	8.40 (7.70, 9.50) 68 (61, 80)	8.00 (6.95, 8.90) 64 (52, 74)	11.10 (8.70, 13.00) 98 (72, 119)	8.40 (7.60, 9.80) 68 (60, 84)	8.40 (7.60, 9.20) 68 (60, 77)	8.50 (7.60, 9.40) 69 (60, 79)
< 7	5.88%(6,983)	2.82%(283)	4.13%(39)	11.90%(5)	3.41%(74)	7.92%(24)	5.51%(7)	0.00%(0)
7- <9	46.10%(54,732)	25.70%(2,577)	50.85%(480)	21.43%(9)	10.13%(220)	46.53%(141)	46.46%(59)	*
>=9	33.03%(39,214)	41.99%(4,211)	30.30%(286)	11.90%(5)	35.88%(779)	34.98%(106)	22.05%(28)	*
Unknown	15.00%(17,808)	29.49%(2,958)	14.72%(139)	54.76%(23)	50.58%(1,098)	10.56%(32)	25.98%(33)	68.97%(20)
Estimated glomerular filtration rate (m/min/1.73m^2)	91 (77, 102)	82 (56, 99)	63 (43, 88)	94 (85, 105)	86 (57, 104)	98 (85, 105)	65 (39, 93)	77 (49, 94)
>= 60	80.20%(95,227)	58.73%(5,890)	46.19%(436)	> 40%	47.21%(1,025)	85.15%(258)	37.80%(48)	44.83%(13)
< 60	6.21%(7,376)	22.76%(2,283)	40.47%(382)	<20%	17.09%(371)	4.95%(15)	34.65%(44)	20.69%(6)

Unknown	13.59%(16,134)	18.51%(1,856)	13.35%(126)	45.24%(19)	35.70%(775)	9.90%(30)	27.56%(35)	34.48%(10)
High density lipoprotein (mg/dl)	43 (35, 50)	43 (35, 51)	43 (36, 50)	44 (38, 50)	41 (34, 50)	43 (35, 50)	42 (38, 50)	44 (35, 52)
<40 (M) or <50 (F)	37.04%(43,978)	28.71%(2,879)	34.00%(321)	19.05%(8)	18.06%(392)	35.64%(108)	37.01%(47)	20.69%(6)
40-59 (M) or 50-59 (F)	23.36%(27,737)	17.81%(1,786)	20.55%(194)	*	9.17%(199)	31.35%(95)	14.96%(19)	*
>=60	5.46%(6,481)	6.75%(677)	7.52%(71)	*	4.19%(91)	2.31%(7)	7.87%(10)	*
Unknown	34.14%(40,541)	46.73%(4,687)	37.92%(358)	61.90%(26)	68.59%(1,489)	30.69%(93)	40.16%(51)	65.52%(19)
Total cholesterol (mg/dl)	186 (155, 220)	182 (151, 220)	178 (147, 209)	193 (170, 211)	189 (155, 236)	186 (151, 220)	182 (143, 219)	209 (166, 234)
< 200	47.11%(55,935)	38.87%(3,898)	49.26%(465)	33.33%(14)	20.87%(453)	44.88%(136)	44.09%(56)	17.24%(5)
200-239	17.45%(20,724)	13.18%(1,322)	13.35%(126)	*	8.25%(179)	20.13%(61)	15.75%(20)	*
>=240	12.48%(14,821)	11.03%(1,106)	9.11%(86)	*	8.57%(186)	12.21%(37)	7.87%(10)	*
Unknown	22.96%(27,257)	36.92%(3,703)	28.28%(267)	52.38%(22)	62.32%(1,353)	22.77%(69)	32.28%(41)	62.07%(18)
Triglyceride (mg/dl)	195 (138, 275)	190 (129, 285)	186 (129, 266)	162 (120, 228)	188 (124, 342)	195 (133, 258)	195 (140, 293)	162 (119, 240)
< 150	17.67%(20,986)	15.79%(1,584)	18.54%(175)	11.90%(5)	10.00%(217)	20.46%(62)	>10%	<12%
150-499	38.31%(45,485)	28.35%(2,843)	34.96%(330)	23.81%(10)	14.28%(310)	39.60%(120)	25.98%(33)	>12%
>= 500	3.63%(4,314)	3.62%(363)	1.69%(16)	0.00%(0)	4.15%(90)	1.98%(6)	<5%	<5%
Unknown	40.39%(47,952)	52.24%(5,239)	44.81%(423)	64.29%(27)	71.58%(1,554)	37.95%(115)	59.84%(76)	72.41%(21)

The results presented as % (frequency) or median (Interquartile range). DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

4.3.1.3 Baseline characteristics of combination therapy users

Table 4.7 presents the baseline characteristics of patients started on combination therapy (both dual ADD and triple or more ADD) stratified by the antidiabetic class of combination regimens. For patients starting on dual therapy, a small difference was observed in the distribution of male and female patients across different dual combination regimens, with a slightly more presentation of male patients than females. However, the percentage of male patients in the metformin+SU group exceeded the percentage of female patients in that group by more than 1.5 times (M to F: 61.7% Vs. 38.3%, Table 4.7). Additionally, the median age of patients across all dual combination regimens was less than 65 years, except the median age of DPP4-I+SU users (70 years [IQR: 56-82]).

Baseline comorbidity was highest among patients started on SU+ insulin, followed by DPP4-I+SU, reflected by the lower percentage of patients with a zero baseline CCI score and the higher percentage of all studied co-existing diseases (Table 4.7). Likewise, the percentage of patients taking five or more concomitant medications ranged from 48.9% (metformin+TZD group) to 79.3% (SU+ insulin group). Similar to the monotherapy group, antihyperlipidemic and angiotensin inhibitors represented the most commonly used concomitant medications across all dual therapy regimens, which are mostly presented among patients who received metformin+TZD followed by metformin+DPP4-I (Table 4.7)

The highest median (IQR) BMI was present among patients who were prescribed metformin+GLP1-RA (38[33-43] kg/m^2), followed by metformin+SGLT2-I and metformin+TZD (34[30- 39] kg/m^2); patients started on SU+ insulin had the lowest median BMI (27[24-32] kg/m^2). Concerning the baseline HbA1c, the median value was greater than 9 for all dual therapy groups except metformin+TZD users, who had a median (IQR) HbA1c of 8.7 [7.8-11.2]. Additionally, the baseline median (IQR) eGFR for all dual therapy users was greater than 60 ml/min/1.73m^2, excluding the DPP4-I+SU group, where the median (IQR) eGFR was 57 (38-88) ml/min/1.73m^2.

Furthermore, male patients comprised more than 50% of patients who received triple or more ADDs as initial therapy. The median age of patients across all studied triple or more regimens was less than 65 years.

Furthermore, metformin+SU+ insulin shared the lowest percentage of a baseline zero CCI score (63.4%) and the highest percentage of using five or more concomitant medications (64.2%). Like monotherapy and dual therapy users, HTN and IHD were the most frequently presented diseases among triple therapy users, and they were most prevalent among patients starting on metformin+SU+ insulin (HTN: 19.9%, IHD: 13.8%). The prevalence and rate of consumption of the remaining co-existing diseases and concomitant medications among patients receiving triple or more ADDs as a first-line therapy are summarised in Table 4.7.

Furthermore, the baseline median BMI was >= 30 kg/m^2 across all groups of triple or more therapy users, where the highest median (IQR) BMI was observed among patients started on metformin+SU+GLP1-RA (37 [30-42]). Conversely, the highest baseline median (IQR) HbA1c was presented among metformin+SU+ insulin users (11.9 [9.7-13.8]), with half of the patients (50%) having a baseline HbA1c of >=9 compared to less than one-quarter of the remaining regimens (Table 4.7). Additionally, the percentage of patients with a baseline eGFR value of < $60ml/min/1.73m^2$ was highest among metformin+SU+ insulin users, yet it was lowest among metformin+SU+SGLT2-I users (11.8% Vs. 2.2%, respectively).

Table 4.7: Baseline characteristics of the patients started on combination therapy

Characteristic	biguanide+ DPP4-I N=1,042	biguanide+ GLP1-RA N=97	biguanide+ insulin N=1,332	biguanide+ SGLT2-I N=454	biguanide+ SU N=8,408	biguanide+ TZD N=233	DPP4-I+ SU N=158	SU+ insulin N=347
Sex								
Male	59.79%(623)	51.55%(50)	50.38%(671)	56.61%(257)	61.73%(5,190)	59.66%(139)	50.00%(79/158)	60.52%(210)
Female	40.21%(419)	48.45%(47)	49.62%(661)	43.39%(197)	38.27%(3,218)	40.34%(94)	50.00%(79/158)	39.48%(137)
Age at prescription	58 (50,67)	54 (45,61)	55 (40,65)	55 (49,63)	58 (49,68)	59 (50,67)	70 (56,82)	63 (54,74)
< 65 years	68.62%(715)	83.51%(81)	72.52%(966)	77.31%(351)	67.08%(5,640)	66.52%(155)	37.34%(59)	54.76%(190)
>= 65 years	31.38%(327)	16.49%(16)	27.48%(366)	22.69%(103)	32.92%(2,768)	33.48%(78)	62.66%(99)	45.24%(157)
Urban-rural								
1	30.81%(321)	27.84%(27)	34.98%(466)	35.02%(159)	34.12%(2,869)	21.89%(51)	29.75%(47)	31.41%(109)
2	38.58%(402)	19.59%(19)	36.04%(480)	33.70%(153)	36.42%(3,062)	37.77%(88)	29.75%(47)	40.92%(142)
3	7.87%(82)	10.31%(10	8.11%(108)	7.49%(34)	8.82%(742)	9.01%(21)	17.09%(27)	6.63%(23)
4	2.69%(28)	*	2.48%(33)	3.08%(14)	2.47%(208)	*	*	1.44%(5)
5	2.02%(21)	*	1.50%(20)	2.42%(11)	1.03%(87)	*	*	2.02%(7)
6	11.52%(120)	11.34%(11)	10.14%(135)	9.69%(44)	10.49%(882)	15.45%(36)	10.13%(16)	11.53%(40)
7	3.65%(38)	13.40%(13)	3.08%(41)	4.63%(21)	4.02%(338)	6.01%(14)	5.06%(8)	2.88%(10)
8	2.88%(30)	11.34%(11)	3.60%(48)	3.96%(18)	2.60%(219)	5.15%(12)	6.96%(11)	3.17%(11)
Unknown (total 3)								
Scottish index of multiple deprivation-quantile								
1	28.12%(293)	22.68%(22)	31.38%(418)	30.62%(139)	26.91%(2,263)	20.17%(47)	29.75%(47)	24.50%(85)
2	22.94%(239)	20.62%(20)	23.05%(307)	23.35%(106)	24.55%(2,064)	21.46%(50)	20.25%(32)	21.90%(76)
3	21.02%(219)	32.99%(32)	19.29%(257)	20.48%(93)	19.58%(1,646)	25.32%(59)	21.52%(34)	21.04%(73)
4	15.16%(158)	15.46%(15)	15.69%(209)	16.52%(75)	16.50%(1,387)	15.02%(35)	17.72%(28)	19.88%(69)

5	12.76%(133)	8.25%(8)	10.51%(140)	9.03%(41)	12.45%(1,047)	17.60%(41)	10.76%(17)	12.68%(44)
Unknown								
Prescriber type								
General practitioner (GP)	94.91%(989)	100.00%(97)	98.50%(1,312)	93.39%(424)	95.67%(8,044)	> 90%	> 90%	97.69%(339)
Non-GP	5.09%(53)	0.00%(0)	1.50%(20)	6.61%(30)	4.33%(364)	< 10%	< 10%	2.31%(8)
Ischemic heart disease	8.16%(85)	6.19%(6)	11.86%(158)	13.22%(60)	12.10%(1,017)	6.01%(14)	20.25%(32)	17.87%(62)
Hypertension	11.80%(123)	7.22%(7)	17.34%(231)	14.10%(64)	17.46%(1,468)	16.31%(38)	27.22%(43)	27.09%(94)
Hear failure	2.69%(28)	< 10%	4.20%(56)	2.86%(13)	4.19%(352)	< 10%	13.92%(22)	9.80%(34)
Stroke	2.59%(27)	< 10%	2.93%(39)	3.30%(15)	3.18%(267)	< 10%	10.13%(16)	6.05%(21)
Peripheral vascular disease	1.73%(18)	< 10%	2.40%(32)	1.76%(8)	2.87%(241)	< 10%	6.33%(10)	7.49%(26)
Liver disease	1.63%(17)	< 10%	3.90%(52)	1.54%(7)	3.20%(269)	< 10%	4.43%(7)	13.83%(48)
Retinal disease	0.48%(5)	< 10%	0.90%(12)	< 10%	0.73%(61)	0.00%(0)	< 10%	< 10%
Neuropathy disease	1.63%(17)	< 10%	1.35%(18)	2.42%(11)	1.87%(157)	< 10%	0.00%(0)	3.46%(12)
Charlson comorbidity score- Quan								
0	84.55%(881)	84.54%(82)	75.98%(1,012)	81.94%(372)	76.89%(6,465)	> 70%	60.13%(95)	42.07%(146)
1-2	10.46%(109)	10.31%(10)	15.77%(210)	12.78%(58)	15.77%(1,326)	> 10%	21.52%(34)	27.95%(97)
3-4	3.36%(35)	5.15%(5)	4.58%(61)	3.74%(17)	4.27%(359)	< 10%	10.76%(17)	13.83%(48)
>=5	1.63%(17)	0.00%(0)	3.68%(49)	1.54%(7)	3.07%(258)	< 10%	7.59%(12)	16.14%(56)
Lipid drugs	53.45%(557)	43.30%(42)	34.23%(456)	50.22%(228)	45.35%(3,813)	63.09%(147)	49.37%(78)	43.23%(150)
Antipsychotics	2.88%(30)	< 10%	3.98%(53)	3.30%(15)	3.51%(295)	4.72%(11)	< 10%	5.76%(20)
Thiazide diuretics	13.92%(145)	11.34%(11)	10.44%(139)	9.69%(44)	13.59%(1,143)	21.03%(49)	10.13%(16)	13.83%(48)
Beta-blockers	21.69%(226)	20.62%(20)	20.05%(267)	24.01%(109)	22.15%(1,862)	17.17%(40)	32.28%(51)	29.11%(101)
Angiotensin inhibitors	44.91%(468)	44.33%(43/97)	29.50%(393)	38.99%(177)	34.56%(2,906)	48.50%(113)	40.51%(64)	37.46%(130)
Calcium channel	21.40%(223)	22.68%(22)	15.17%(202)	15.86%(72)	17.79%(1,496)	24.46%(57)	24.05%(38)	20.46%(71)

blocker								
Polypharmacy								
0	7.58%(79)	12.37%(12)	4.88%(65)	7.93%(36)	6.34%(533)	6.01%(14)	3.80%(6)	3.17%(11)
1-4	38.68%(403)	28.87%(28)	37.61%(501)	36.78%(167)	34.69%(2,917)	45.06%(105)	29.11%(46)	17.58%(61)
>=5	53.74%(560)	58.76%(57)	57.51%(766)	55.29%(251)	58.97%(4,958)	48.93%(114)	67.09%(106)	79.25%(275)
Body mass index (kg/m^2)	32 (28,38)	38 (33,43)	32 (28,38)	34 (30,39)	31 (28,36)	34 (30,39)	31 (26,35)	27 (24,32)
<= 24.9	4.03%(42)	0.00%(0)	3.45%(46)	1.98%(9)	5.07%(426)	3.00%(7)	10.76%(17)	13.26%(46)
25-29.9	16.31%(170)	6.19%(6)	11.19%(149)	10.79%(49)	13.56%(1,140)	9.01%(21)	12.03%(19)	12.97%(45)
>= 30	31.48%(328)	50.52%(49)	28.53%(380)	43.61%(198)	27.71%(2,330)	41.63%(97)	26.58%(42)	15.27%(53)
Unknown	48.18%(502)	43.30%(42)	56.83%(757)	43.61%(198)	53.66%(4,512)	46.35%(108)	50.63%(80)	58.50%(203)
HbA1c (%) **mmol/mol**	9.70 (8.10,11.30) 83 (65,100)	10.30 (8.20,11.30) 89 (66,100)	10.80 (8.30,12.85) 95 (67,116)	10.20 (8.60,11.70) 88 (70,104)	11.40 (9.70,12.8) 101 (83,116)	8.70 (7.80,11.20) 72 (62,99)	10.00 (8.53,11.80) 86 (69,105)	11.50 (9.40,14.30) 102 (79,133)
< 7	4.32%(45)	3.09%(3)	4.13%(55)	3.30%(15)	1.49%(125)	3.86%(9)	3.16%(5)	1.15% (4)
7- <9	17.85%(186)	11.34%(11)	11.71%(156)	18.94%(86)	9.95%(837)	24.03%(56)	18.99%(30)	8.65%(30)
>=9	36.76%(383)	31.96%(31)	35.44%(472)	49.56%(225)	55.99%(4,708)	24.89%(58)	44.94%(71)	38.90%(135)
Unknown	41.07%(428)	53.61%(52)	48.72%(649)	28.19%(128)	32.56%(2,738)	47.21%(110)	32.91%(52)	51.30%(178)
Estimated glomerular filtration rate ($m/min/1.73m^2$)	93 (75,104)	101(87,110)	91 (67,108)	97 (84,108)	92 (74,104)	93 (75,106)	57 (38,88)	76 (51,96)
>= 60	54.32%(566)	> 40%	46.10%(614)	70.48%(320)	67.60%(5,684)	50.64%(118)	37.97%(60)	48.70%(169)
< 60	7.77%(81)	< 10%	9.91%(132)	1.54%(7)	8.58%(721)	8.15%(19)	39.24%(62)	26.51%(92)
Unknown	37.91%(395)	47.42%(46)	43.99%(586)	27.97%(127)	23.82%(2,003)	41.20%(96)	22.78%(36)	24.78%(86)
High density lipoprotein (mg/dl)	42 (35,50)	40 (35,50)	39 (31,46)	40 (34,48)	39 (34,48)	43 (35,50)	39 (32,48)	39 (32,51)
<40 (M) or <50 (F)	24.09%(251)	22.68%(22)	21.85%(291)	34.58%(157)	30.36%(2,553)	25.32%(59)	27.22%(43)	22.19%(77)

40-59 (M) or 50-59 (F)	14.49%(151)	*	9.01%(120)	14.98%(68)	14.85%(1,249)	17.60%(41)	12.03%(19)	8.65%(30)
>=60	3.93%(41)	*	1.95%(26)	3.96%(18)	3.47%(292)	4.29%(10)	3.16%(5)	5.48%(19)
Unknown	57.49%(599)	60.82%(59)	67.19%(895)	46.48%(211)	51.31%(4,314)	52.79%(123)	57.59%(91)	63.69%(221)
Total cholesterol (mg/dl)	189 (155,224)	196 (155,243)	184 (151,224)	186 (155,220)	197 (162,240)	182 (147,232)	178 (151,216)	199 (162,235)
< 200	30.71%(320)	24.74%(24)	23.57%(314)	36.12%(164)	29.72%(2,499)	32.62%(76)	34.18%(54)	21.04%(73)
200-239	10.94%(114)	9.28%(9)	6.61%(88)	14.54%(66)	14.07%(1,183)	10.30%(24)	12.03%(19)	10.66%(37)
>=240	9.79%(102)	13.40%(13)	7.66%(102/)	10.57%(48)	15.21%(1,279)	10.73%(25)	5.70%(9)	10.37%(36)
Unknown	48.56%(506)	52.58%(51)	62.16%(828)	38.77%(176)	41.00%(3,447)	46.35%(108)	48.10%(76)	57.93%(201)
Triglyceride (mg/dl)	195 (133,292)	216 (156,416)	220 (142,389)	220 (142,301)	221 (151,348)	206 (142,283)	204 (133,279)	214 (135,352)
< 150	12.19%(127)	5.15%(5)	7.96%(106)	14.32%(65)	10.31%(867)	10.73%(25)	10.76%(17)	8.93%(31)
150-499	24.18%(252)	20.62%(20)	15.32%(204)	33.92%(154)	27.60%(2,321)	22.32%(52)	21.52%(34)	18.16%(63)
>= 500	3.07%(32)	5.15%(5)	4.95%(66)	3.08%(14)	6.07%(510)	3.86%(9)	3.16%(5)	2.88%(10)
Unknown	60.56%(631)	69.07%(67)	71.77%(956)	48.68%(221)	56.02%(4,710)	63.09%(147)	64.56%(102)	70.03%(243)

Table 4.7: Baseline characteristics of the patients started on combination therapy (continued)

Characteristic	biguanide+ DPP4-I+ SU N=370	biguanide+ GLP1-RA+ SU N=81	biguanide+ SGLT2-I+ SU N= 93	biguanide+ SU+ insulin N=246	biguanide+ SU+ TZD N=132	Other combination N=534
Sex						
Male	63.78%(236)	55.56%(45)	68.82%(64)	68.70%(169)	65.15%(86)	62.17%(332)
Female	36.22%(134)	44.44%(36)	31.18%(29)	31.30%(77)	34.85%(46)	37.83%(202)
Age at prescription	61 (53,70)	58 (48,66)	57 (50,63)	58 (50,67)	63 (55,69)	58 (51,66)
< 65 years	61.35%(227)	70.37%(57)	80.65%(75)	68.29%(168)	55.30%(73)	71.54%(382)
>= 65 years	38.65%(143)	29.63%(24)	19.35%(18)	31.71%(78)	44.70%(59)	28.46%(152)
Urban-rural						
1	27.03%(100)	16.05%(13)	25.81%(24)	35.77%(88)	35.61%(47)	21.89%(51)
2	27.03%(100)	43.21%(35)	23.66%(22)	31.30%(77)	26.52%(35)	37.77%(88)
3	6.76%(25)	7.41%(6)	10.75%(10)	8.13%(20)	10.61%(14)	9.01%(21)
4	2.70%(10)	*	*	2.85%(7)	*	*
5	1.89%(7)	*	*	*	0.00%(0)	*
6	19.19%(71)	8.64%(7)	18.28%(17)	10.57%(26)	13.64%(18)	15.45%(36)
7	7.84%(29)	13.58%(11)	6.45%(6)	*	*	6.01%(14)
8	7.30%(27)	*	8.60%(8)	5.28%(13)	7.58%(10)	5.15%(12)
Unknown (total 8)						
Scottish index of multiple deprivation-quantile						
1	19.73%(73)	20.99%(17)	25.81%(24)	29.27%(72)	21.21%(28)	25.47%(136)
2	19.46%(72)	24.69%(20)	20.43%(19)	22.76%(56)	23.48%(31)	20.97%(112)
3	27.30%(101)	27.16%(22)	18.28%(17)	23.17%(57)	24.24%(32)	21.54%(115)
4	21.08%(78)	14.81%(12)	18.28%(17)	18.29%(45)	16.67%(22)	17.60%(94)
5	12.43%(46)	12.35%(10)	16.13%(15)	6.50%(16)	14.39%(19)	14.04%(75)
Unknown (total 3)						

Prescriber type						
General practitioner (GP)	98.11%(363)	> 90%	> 90%	> 90%	> 90%	97.94%(523)
Non-GP	1.89%(7)	< 10%	< 10%	< 10%	< 10%	2.06%(11)
Ischemic heart disease	6.22%(23)	6.17%(5)	< 10%	13.82%(34)	3.79%(5)	6.18%(33)
Hypertension	8.92%(33)	9.88%(8)	10.75%(10)	19.92%(49)	5.30%(7)	8.24%(44)
Hear failure	2.97%(11)	< 10%	< 10%	4.88%(12)	< 10%	2.62%(14)
Stroke	1.35%(5)	0.00%(0)	< 10%	6.10%(15)	< 10%	1.31%(7)
Peripheral vascular disease	< 10%	< 10%	< 10%	3.66%(9)	< 10%	2.43%(13)
Liver disease	< 10%	< 10%	< 10%	5.69%(14)	< 10%	1.31%(7)
Retinal disease	< 10%	< 10%	< 10%	< 10%	0.00%(0)	1.31%(7)
Neuropathy disease	< 10%	0.00%(0)	< 10%	2.44%(6)	< 10%	1.50%(8)
Charlson comorbidity score- Quan						
0	89.19%(330)	90.12%(73)	93.55%(87)	63.41%(156)	93.94%(124)	88.01%(470)
1-2	8.11%(30)	*	6.45%(6)	23.98%(59)	*	8.24%(44)
3-4	*	*	0.00%(0)	7.72%(19)	*	2.06%(11)
>=5	*	*	0.00%(0)	4.88%(12)	*	1.69%(9)
Lipid drugs	63.24%(234)	49.38%(40)	49.46%(46)	45.93%(113)	66.67%(88)	55.99%(299)
Antipsychotics	2.70%(10)	6.17%(5)	< 10%	4.88%(12)	< 10%	3.18%(17)
Thiazide diuretics	10.81%(40)	18.52%(15)	7.53%(7)	16.26%(40)	13.64%(18)	8.43%(45)
Beta-blockers	19.73%(73)	11.11%(9)	18.28%(17)	21.14%(52)	14.39%(19)	19.29%(103)
Angiotensin inhibitors	47.84%(177)	49.38%(40)	44.09%(41)	37.80%(93)	52.27%(69)	45.51%(243)
Calcium channel blocker	22.16%(82)	20.99%(17)	20.43%(19)	18.29%(45)	16.67%(22)	20.04%(107)
Polypharmacy						
0	7.57%(28)	6.17%(5)	11.83%(11)	5.69%(14)	8.33%(11)	9.18%(49)
1-4	49.19%(182)	38.27%(31)	46.24%(43)	30.08%(74)	56.82%(75)	47.75%(255)
>=5	43.24%(160)	55.56%(45)	41.94%(39)	64.23%(158)	34.85%(46)	43.07%(230)

Body mass index (kg/m^2)	30 (27,35)	37 (30,42)	32 (28,35)	30 (27,35)	31 (28,35)	32 (28,37)
<= 24.9	6.76%(25)	*	*	5.28%(13)	3.79%(5)	5.62%(30)
25-29.9	17.30%(64)	*	*	16.67%(41)	15.91%(21)	14.04%(75)
>= 30	27.30%(101)	37.04%(30)	27.96%(26)	24.39%(60)	28.79%(38)	31.09%(166)
Unknown	48.65%(180)	51.85%(42)	52.69%(49)	53.66%(132)	51.52%(68)	49.25%(263)
HbA1c (%)	8.75(7.40,10.90)	10.30(7.90,12.20)	9.80(8.30,12.00)	11.90	8.40(7.10,10.6	9.10
mmol/mol	72 (57,96)	89 (63,110)	84 (67,108)	(9.70,13.80) 107 (82,127)	0) 68 (54,92)	(7.60,11.07) 76 (60,98)
< 7	4.59%(17)	*	*	2.03%(5)	6.82%(9)	3.75%(20)
7- <9	16.22%(60)	*	*	10.98%(27)	16.67%(22)	15.92%(85)
>=9	17.03%(63)	28.40%(23)	31.18%(29)	50.00%(123)	16.67%(22)	21.16%(113)
Unknown	62.16%(230)	54.32%(44)	51.61%(48)	36.99%(91)	59.85%(79)	59.18%(316)
Estimated glomerular filtration rate (m/min/1.73m^2)	95 (71,105)	89 (66,104)	93 (78,103)	90 (69,103)	83 (65,104)	94 (77,105)
>= 60	35.95%(133)	39.51%(32)	49.46%(46)	57.32%(141)	37.12%(49)	38.39%(205)
< 60	6.22%(23)	4.94%(4)	2.15%(2)	11.79%(29)	6.06%(8)	4.87%(26)
Unknown	57.84%(214)	55.56%(45)	48.39%(45)	30.89%(76)	56.82%(75)	56.74%(303)
High density lipoprotein (mg/dl)	39 (35,46)	40 (33,47)	39 (31,45)	39 (31,45)	43 (37,48)	42 (35,50)
<40 (M) or <50 (F)	18.65%(69)	22.22%(18)	24.73%(23)	23.17%(57)	19.70%(26)	16.85%(90)
40-59 (M) or 50-59 (F)	11.08%(41)	*	*	9.35%(23)	*	10.11%(54)
>=60	1.89%(7)	*	*	3.25%(8)	*	3.00%(16)
Unknown	68.38%(253)	67.90%(55)	61.29%(57)	64.23%(158)	68.94%(91)	70.04%(374)
Total cholesterol (mg/dl)	170 (147,202)	174 (131,229)	186 (155,251)	193 (151,228)	178 (152,220)	170 (140,206)
< 200	28.65%(106)	23.46%(19)	26.88%(25)	25.20%(62)	28.79%(38)	25.66%(137)
200-239	5.68%(21)	8.64%(7)	6.45%(6)	10.98%(27)	10.61%(14)	6.55%(35)
>=240	4.59%(17)	7.41%(6)	15.05%(14)	9.76%(24)	4.55%(6)	4.31%(23)
Unknown	61.08%(226)	60.49%(49)	51.61%(48)	54.07%(133)	56.06%(74)	63.48%(339)
Triglyceride (mg/dl)	196 (133,310)	212 (142,358)	208 (124,341)	221 (164,341)	151 (120,233)	168 (120,248)

< 150	8.38%(31)	8.64%(7)	15.05%(14)	7.32%(18)	12.88%(17)	9.93%(53)
150-499	16.49%(61)	16.05%(13)	20.43%(19)	19.92%(49)	13.64%(18)	14.79%(79)
>= 500	3.51%(13)	4.94%(4)	7.53%(7)	4.88%(12)	0.00%(0)	1.69%(9)
Unknown	71.62%(265)	70.37%(57)	56.99%(53)	67.89%(167)	73.48%(97)	73.69%(393)

The results presented as % (frequency) or median (Interquartile range). DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

4.3.2 Prescribing pattern of antidiabetic drugs at the stage of drug initiation

Overall, about 91% (132382/145909) of the included cohort were started on single ADD (monotherapy), with only 9.3% (13527/145909) being treated with combination therapy. Although most of the patients with T2DM (>89%) in this study were initiated on monotherapy from 2010 until 2019, the proportion of patients starting on monotherapy decreased over the studied ten years (from 91.7% in 2010 to 89.4% in 2019, absolute change = -715, relative change = -0.050). On the contrary, the use of combination therapy as an initial ADD increased from 8.3% in 2010 to 10.6% in 2019 (absolute change= 329, relative change = 0.253). Results are presented in Table 4.3 and Figure 4.5. The trend test (Table 4.8) also showed a significant increase in the prescription of combination therapy compared to monotherapy for newly treated patients with T2DM over the study period (z= 13.56, p< 0.001).

Table 4.8: Prescribing pattern of antidiabetic regimen type at the stage of drug initiation presented as frequency, percentage, absolute change, relative change, and trend test

Prescription Year	Monotherapy	Combination therapy	Total per year
2010	14438 (91.74%)	1300 (8.26%)	(N=15738)
2011	12991 (92.13%)	1110 (7.87%)	(N=14101)
2012	13579 (91.98%)	1184 (8.02%)	(N=14763)
2013	13591 (91.82%)	1211 (8.18%)	(N=14802)
2014	11940 (90.32%)	1280 (9.68%)	(N=13220)
2015	13551 (91.29%)	1293 (8.71%)	(N=14844)
2016	12976 (89.76%)	1480 (10.24%)	(N=14456)
2017	12831 (89.62%)	1486 (10.38%)	(N=14317)
2018	12762 (89.15%)	1554 (10.85%)	(N=14316)
2019	13723 (89.39%)	1629 (10.61%)	(N=15352)
Total per regimen	132382 (90.73%)	13527 (9.27%)	(N=145909)
Absolute change	-715	329	
Relative change	-0.05	0.25	
Trend test*	Z = 13.56, p-value **< 0.001**		

*Using Cochran-Armitage test for trend comparing combination therapy to monotherapy

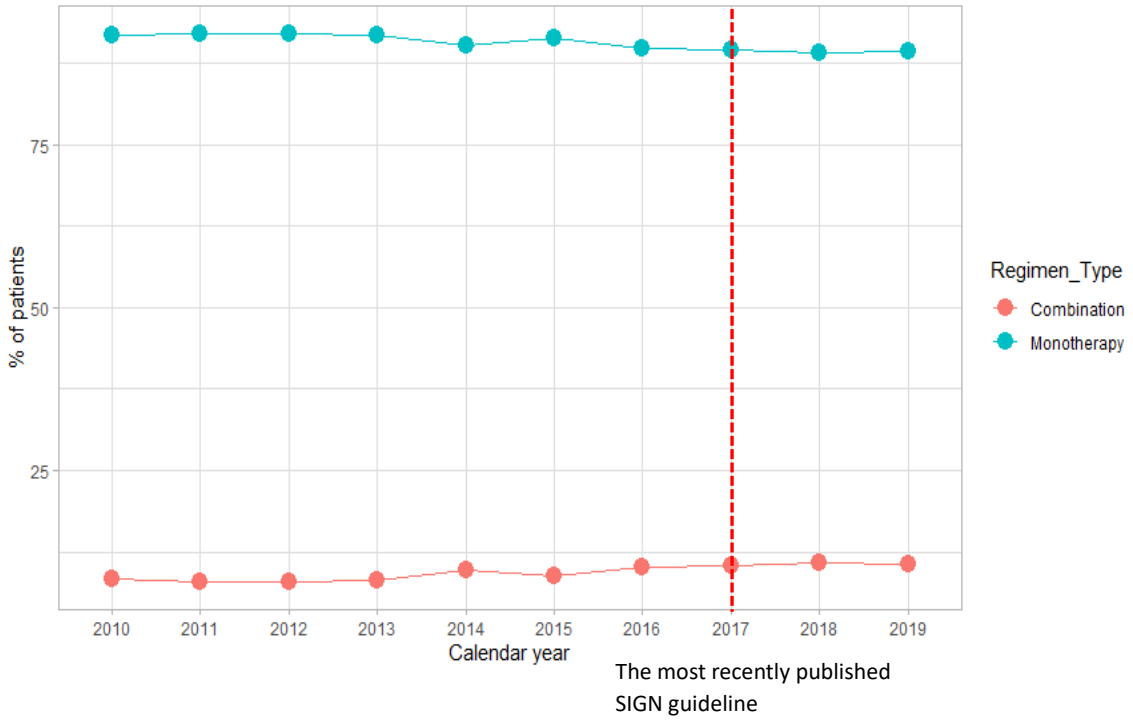

Figure 4.5: The change in the prescribing patterns of antidiabetic regimen type over the study period

Of the initial monotherapy users (N=138382), only 4%(N= 5322) of patients have experienced an early change in drug therapy over the initiation period (first three months following the index date), while around 96%(N= 127060) of patients used the same treatment over the first three months. Among monotherapy groups, metformin was the most frequently prescribed ADD (Figure 4.6), used by around 90%(118737/132382) of subjects over the entire study period. Its share of prescriptions amongst all new monotherapy users increased from 87.3% in 2010 to 91.0% in 2019 (trend test: z= 14.92, p< 0.001). Figure 4.7 demonstrates the change in the prescription of non-metformin antidiabetic groups over the study period. While SU was the second most commonly prescribed ADD after metformin (7.6%, 10029/132382), its use significantly decreased over time by approximately 50%, from 10.2% in 2010 to 5.5% in 2019 (trend test: z= -22.63, p< 0.001). Similar to SU, there was a progressive decrease in the proportion of patients treated with insulin

as initial monotherapy (from 1.9% in 2010 to 1.5% in 2019, trend test: z= -2.35, p =0.019). On the other hand, the use of newer ADDs like DPP4-I and SGLT2-I increased significantly over time; from 0% to 0.9%(2010 to 2019) for SGLT2-I (trend test: z= 19.87, p< 0.001) and from 0.2% to 1.1% for DPP4-I (trend test: z =12.94, p< 0.001).

The proportional prescription of GLP1-RA, TZD, and other ADD (alpha-glucosidase inhibitor and meglitinide) for newly treated patients with T2DM was very low (0.03%, 0.1%, and 0.02%, respectively). Although the trend tests showed no significant change in the prescription of GLP1-RA over the study period (trend test: z = 0.53, p-value = 0.60), they did show a significant drop in the prescription of TZD (trend test: z = -8.52, p< 0.001) and other ADDs (trend test: z = -2.19, p-value = 0.03). It was also noted that no patient received a prescription for GLP1-RA in 2013, the year SGLT2-I was first introduced into the market (Table 4.9). The change in the prescribing patterns of the individual class of ADD used as an initial monotherapy is summarised in Table 4.9 as frequency (percentage) and Table 4.10 in terms of the absolute/relative change and trend test.

Moreover, a difference in the prescriptions of the individual agents within each class of ADDs was observed over the study period. For instance, gliclazide was the most frequently prescribed agent within the SU group, which was used by 87.6%(8781/10029) of patients who received SU as initial monotherapy. On the other hand, sitagliptin (49.3%, 465/944) and linagliptin (30.5%, 288/944) comprised the highest share of prescriptions compared to the other agents of the DPP4-I group. Liraglutide and empagliflozin were the most commonly prescribed agents within GLP1-RA (64.3%, 27/42) and SGLT2-I (50.5%, 153/303) groups, respectively. Lastly, more than 50% of the initial insulin users were treated with multiple insulin regimens (more than one insulin type), including biphasic insulin aspart (13.8%, 294/2171), biphasic isophane insulin (26.4%, 574/2171), insulin aspart with insulin glargine (13.7%, 298/2171), and insulin aspart with isophane insulin (6.0%, 131/2171). The change in prescribing the individual agents within each class of ADDs over the study period is presented in Appendix S.4.4.

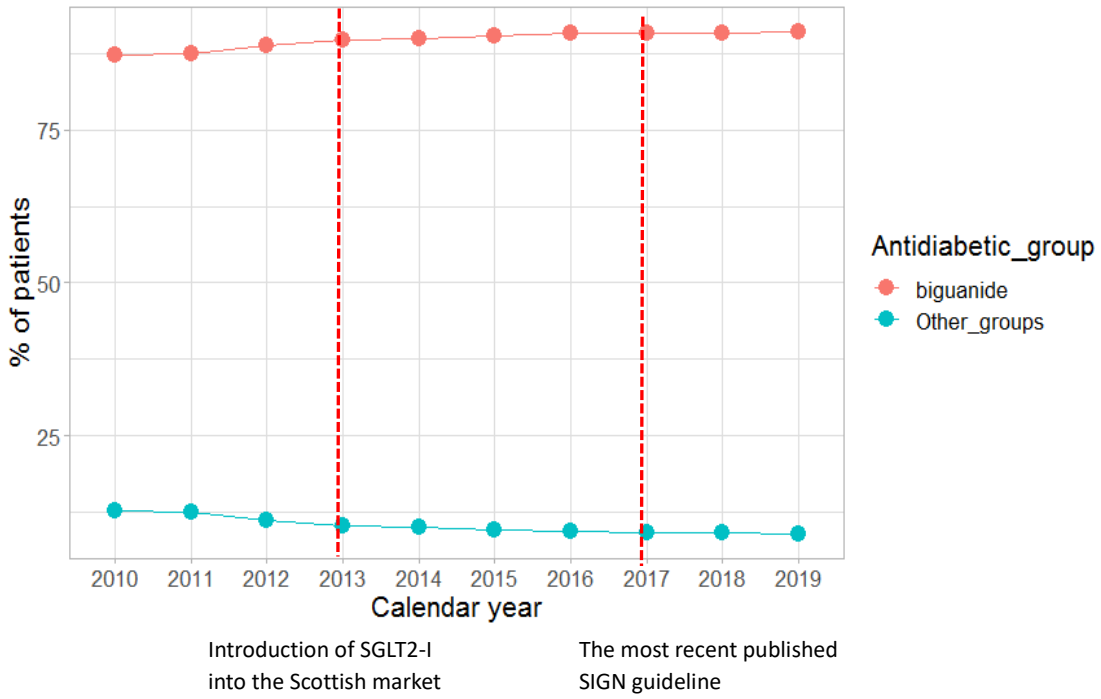

Figure 4.6: The change in the prescribing patterns of biguanide compared to the other antidiabetic groups over the study period amongst all new patients initiated on monotherapy

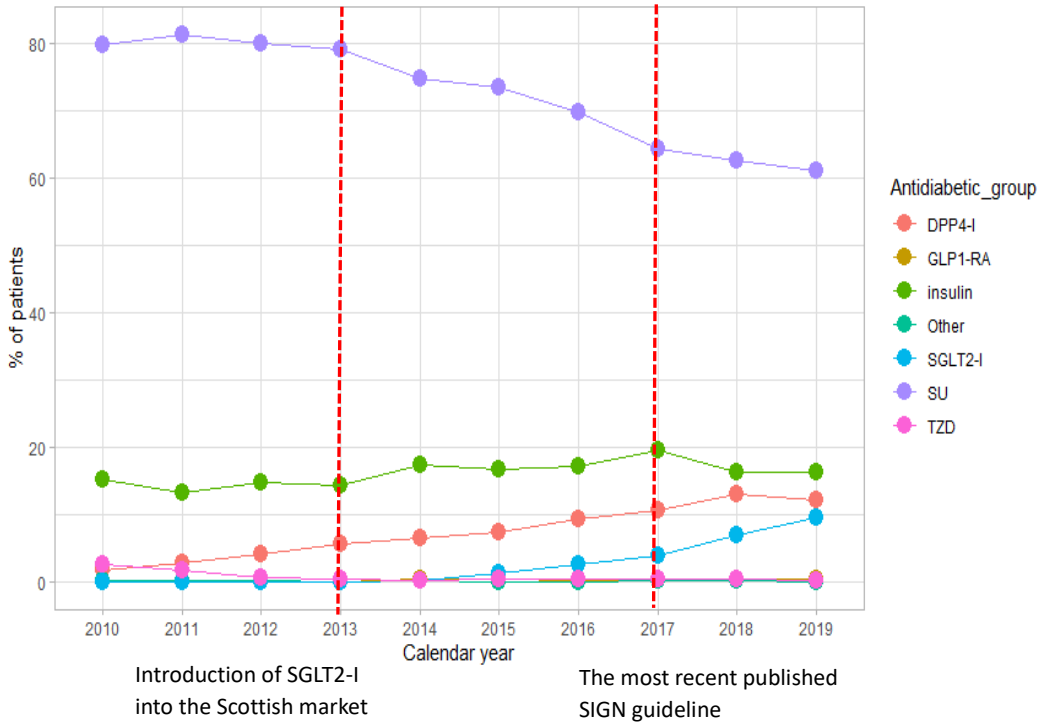

Figure 4.7: The change in the prescribing patterns of non-metformin antidiabetic groups over the study period amongst all new patients initiated on monotherapy. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

Table 4.9: Frequency and percentage of the individual class of antidiabetic drugs prescribed as monotherapy over the study period

Antidiabetic group	2010 (N=14438)	2011 (N=12991)	2012 (N=13579)	2013 (N=13591)	2014 (N=11940)	2015 (N=13551)	2016 (N=12976)	2017 (N=12831)	2018 (N=12762)	2019 (N=13723)	Total (N=132382)
Biguanide	12600 (87.27%)	11372 (87.54%)	12070 (88.89%)	12190 (89.69%)	10732 (89.88%)	12249 (90.39%)	11775 (90.74%)	11666 (90.92%)	11591 (90.82%)	12492 (91.03%)	118737 (89.69%)
DPP4-I	34 (0.24%)	48 (0.37%)	64 (0.47%)	80 (0.59%)	79 (0.66%)	96 (0.71%)	113(0.87%)	125(0.97%)	154(1.21%)	151(1.10%)	944 (0.71%)
GLP1-RA	*	5 (0.00%)	*	0 (0.00%)	7 (0.06%)	*	*	*	*	5 (0.03%)	42 (0.03%)
Insulin	280 (1.94%)	214 (1.65%)	223 (1.64%)	200 (1.47%)	210 (1.76%)	218 (1.61%)	207 (1.60%)	229 (1.78%)	190 (1.49%)	200 (1.45%)	2171 (1.64%)
Other	*	6 (0.00%)	*	*	*	*	*	*	*	*	29 (0.02%)
SU	1467 (10.16%)	1317 (10.14%)	1206 (8.88%)	1109 (8.16%)	903 (7.56%)	955 (7.05%)	837 (6.45%)	750 (5.85%)	733 (5.74%)	752 (5.48%)	10029 (7.58%)
TZD	47 (0.33%)	29 (0.22%)	10 (0.07%)	8 (0.06%)	*	6 (0.04%)	7 (0.05%)	6 (0.04%)	6 (0.05%)	*	127 (0.09%)
SGLT2-I	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	19 (0.14%)	32 (0.25%)	46 (0.35%)	83 (0.65%)	118(0.86%)	303 (0.23%)

*; values were removed either because they are very small (<5) or to not disclose a very small value because of the high risk of patient identification. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

Table 4.10: The change in prescribing patterns of the individual class of antidiabetic drug prescribed as monotherapy: absolute change, relative change, and trend test

Antidiabetic group	Absolute change	Relative change	Trend-test*
biguanide	-108	-0.01	Z = 14.92, p-value **< 0.001**
DPP4-I	117	3.44	Z = 12.94, p-value **< 0.001**
GLP1-RA	1	0.25	Z = 0.53, p-value = 0.599
insulin	-80	-0.29	Z = -2.35, p-value = **0.019**
Other	-5	-0.83	Z = -2.19, p-value = **0.029**
SGLT2-I	118	58.00	Z = 19.87, p-value **< 0.001**
SU	-715	-0.49	Z = -22.63, p-value **< 0.001**
TZD	-43	- 0.92	Z = -8.52, p-value **< 0.001**

*Using Cochran-Armitage test for trend (each group was compared to all other groups). DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

A total of 13527 patients (9.3%) were treated with combination ADDs as initial therapy for T2DM between January 2010 and December 2019. Of those, 90.5% were started on dual therapy (two drugs), while the remaining 9.5% were treated with triple or more ADDs over the initiation period. It was observed that the use of dual therapy significantly decreased over time, yet using triple or more ADDs increased (94.5% in 2010 to 85.9% in 2019 Vs. 5.5% in 2010 to 14.1% in 2019, Figure 4.8 and Table 4.11). Tables 4.12 and 4.13 describe the contribution of the individual class of ADDs in combination regimens. Overall, metformin and SU were the most frequently used antidiabetic classes, which were included in 95.1% and 74.9% of combination regimens, respectively. However, insulin, DPP4-I, and SGLT2-I accounted for 16.1%, 13.5%, and 5.6% of the initial combination regimens, respectively. The use of the remaining classes of ADDs in combination regimens was minimal (TZD: 3.5%, GLP1-RA: 2.1%, and other ADDs: 0.5%). Nevertheless, the use of older ADDs (SU, insulin, and TZD) in combination regimens decreased over the study period, while prescribing of newer classes (GLP1-RA, DPP4-I, and SGLT2-I) increased, where the most significant increase was identified with SGLT2-I, showing around 17% increment over the studied ten years (from 0% to 17.4%).

Furthermore, the results of the prescribing patterns of the exact combination regimens among the subgroups of dual therapy users and triple or more therapy

users are summarised in Tables 4.14 and 4.15 and displayed in Figures 4.9 and 4.10. For dual therapy users, the majority of patients were prescribed metformin-based regimens, with more than two third (68.7%, 8408/12241) of patients receiving metformin+SU, yet its use has significantly declined over time (Z= -10.33, p< 0.001). On the other hand, the use of metformin+DPP4-I and metformin+SGLT2-I has significantly increased despite their low overall consumption during the studied ten years (z = 9.22, p< 0.001 and Z = 21.91, p< 0.001, respectively). A small percentage of patients who received dual therapy was initiated on non-metformin regimens; for instance, 2.8% (347/ 12241) of patients were prescribed SU+ insulin, and 1.3% (158/12241) were treated with DPP4-I+SU.

Of the remaining 1286 patients (triple-therapy users), more than two third (71.7%) were treated with a metformin-SU-based triple regimen. A triple combination of metformin, SU, and DPP4-I was the most commonly used combination regimen (28.8%), with no significant change in its prescription throughout the studied ten years (z = 1.35, p = 0.18). It was followed by metformin+SU+ insulin and metformin+SU+ TZD, which were used by about 19% and 10% of patients who were receiving triple or more therapies, respectively. However, between January 2019 and December 2019 (z = -3.41, p = 0.001 and z = -10.94, p 0.001, respectively), the use of these medications as an initial combination therapy significantly decreased. Similar to the prescribing pattern findings pertinent to the SGLT2-I prescribing among monotherapy and dual therapy groups, its use in triple combination with metformin and SU significantly increased over time compared to the other combination regimens including three or more ADDs (z = 8.12, p< 0.001). Regarding the proportional prescriptions of the individual agents within each class of ADDs used in combination regimens, the results were consistent with the findings of the monotherapy subgroup (Appendix S.4.5). For instance, gliclazide was the most commonly used agent in combination regimens (both dual therapy and triple or more therapy) compared to the other agents of the SU group. Additionally, sitagliptin was the most frequently used DPP4-I in combination regimens, followed by linagliptin.

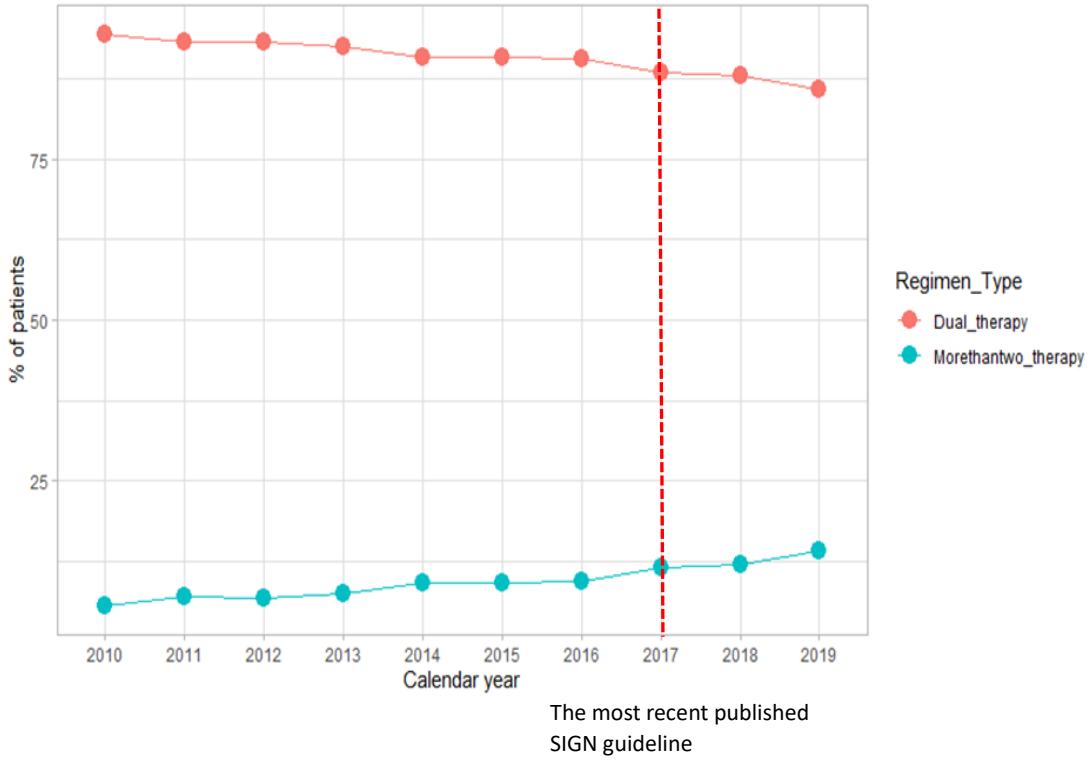

Figure 4.8: The change in the prescribing patterns of regimen type of combination therapy over the study period

Table 4.11: Prescribing pattern of the regimen type of combination therapy at the stage of drug initiation: frequency (percentage), absolute change, relative change, and trend test

Prescription Year	Dual therapy	Triple or more therapy	Total per year
2010	1228 (94.46%)	72 (5.54%)	(N=1300)
2011	1033 (93.06%)	77 (6.94%)	(N=1110)
2012	1104 (93.24%)	80 (6.76%)	(N=1184)
2013	1119 (92.41%)	92 (7.59%)	(N=1211)
2014	1163 (90.86%)	117 (9.14%)	(N=1280)
2015	1175 (90.87%)	118 (9.13%)	(N=1293)
2016	1340 (90.54%)	140 (9.46%)	(N=1480)
2017	1313 (88.36%)	173 (11.64%)	(N=1486)
2018	1367 (87.97%)	187 (12.03%)	(N=1554)
2019	1399 (85.88%)	230 (14.12%)	(N=1629)
Total per regimen	12241 (90.49%)	1286 (9.51%)	(N=13527)
Absolute change	171	158	
Relative change	0.14	2.19	
Trend test*	Z = -10.11, p< **0.001**		

*Using Cochran-Armitage test for trend comparing dual therapy to more than two drugs.

Table 4.12: Frequency and percentage of antidiabetic classes used in combination regimens at the stage of drug initiation over the study period

Antidiabetic group	2010 (N=1300)	2011 (N=1110)	2012 (N=1184)	2013 (N=1211)	2014 (N=1280)	2015 (N=1293)	2016 (N=1480)	2017 (N=1486)	2018 (N=1554)	2019 (N=1629)	Total (N=13527)
Biguanide	1241 (95.46%)	1057 (95.23%)	1129 (95.35%)	1157 (95.54%)	1220 (95.31%)	1224 (94.66%)	1407 (95.07%)	1398 (94.08%)	1468 (94.47%)	1556 (95.52%)	12857 (95.05%)
Dpp4-i	80 (6.15%)	96 (8.65%)	103 (8.7%)	104 (8.59%)	174 (13.59%)	198 (15.31%)	241 (16.28%)	282 (18.98%)	268 (17.25%)	279 (17.13%)	1825 (13.49%)
Glp1-ra	23 (1.77%)	30 (2.70%)	23 (1.94%)	28 (2.31%)	25 (1.95%)	22 (1.70%)	24 (1.62%)	32 (2.15%)	33 (2.12%)	48 (2.95%)	288(2.13%)
Insulin	193 (14.85%)	173 (15.59%)	198 (16.72%)	184 (15.19%)	235 (18.36%)	252 (19.49%)	241 (16.28%)	218 (14.67%)	236 (15.19%)	241 (14.79%)	2171 (16.05%)
Su	1017 (78.23%)	849 (76.49%)	945 (79.81%)	1004 (82.91%)	970 (75.78%)	937 (72.47%)	1084 (73.24%)	1038 (69.85%)	1089 (70.08%)	1063 (65.25%)	9996 (73.90%)
Tzd	116 (8.92%)	84 (7.57%)	46 (3.89%)	35 (2.89%)	34 (2.66%)	39 (3.02%)	25 (1.69%)	34 (2.29%)	28 (1.80%)	27 (1.66%)	468 (3.46%)
Sglt2-i	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	14 (1.09%)	*	86 (5.81%)	152 (10.23%)	185 (11.9%)	284 (17.43%)	762 (5.63%)
Other (alpha glucosidase+ meglitinide)	5 (0.38%)	8 (0.72%)	10 (0.84%)	*	8 (0.63%)	*	8 (0.53%)	5 (0.34%)	6 (0.39%)	8 (0.49%)	66 (0.49%)

DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

Table 4.13: The change in the prescribing patterns of the individual class of antidiabetic drug used in combination regimen: absolute change, relative change, and trend test

Antidiabetic group	Absolut change	Relative change
Biguanide	315	0.25
DPP4-I	199	2.49
GLP1-RA	25	1.09
Other	3	0.60
Insulin	48	0.25
SU	46	0.05
TZD	-89	-0.77
SGLT2-I	284	70.00

DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

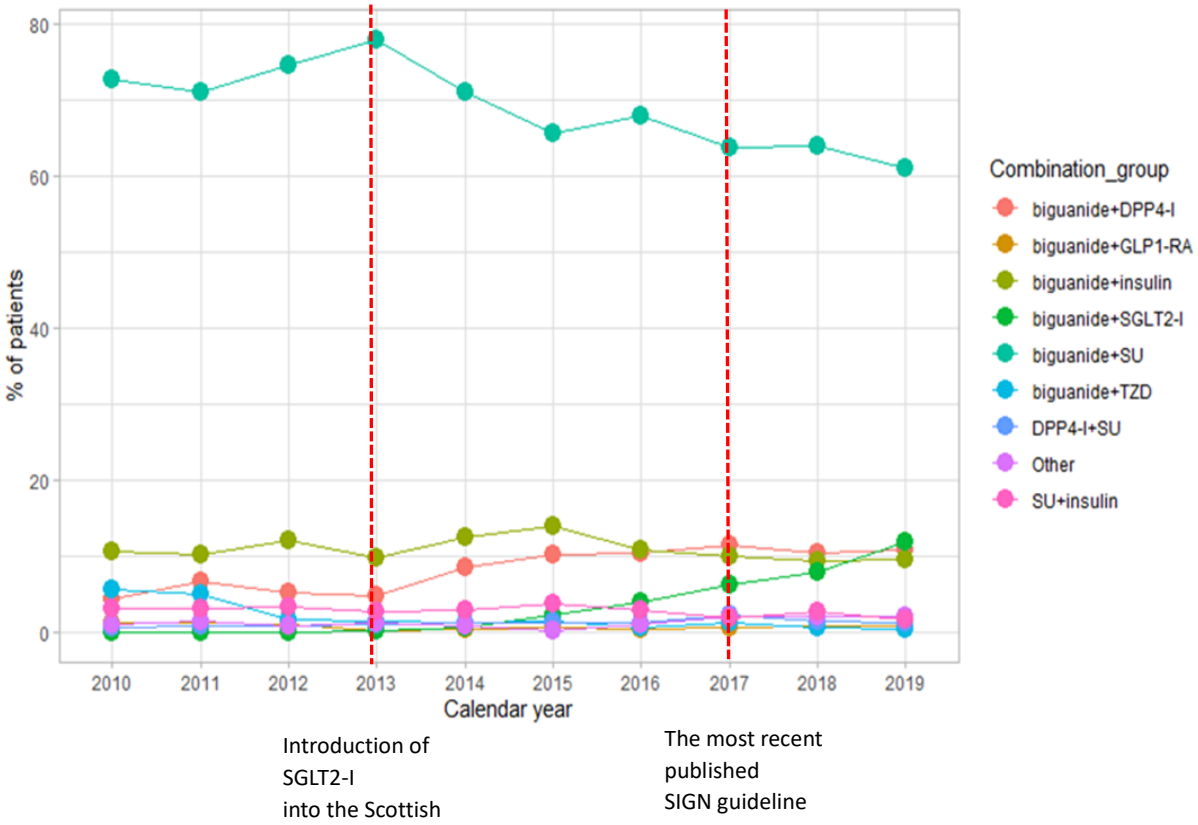

Figure 4.9: The change in the prescribing patterns of dual combination regimens over the study period. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium-glucose co-transporter-2 inhibitors

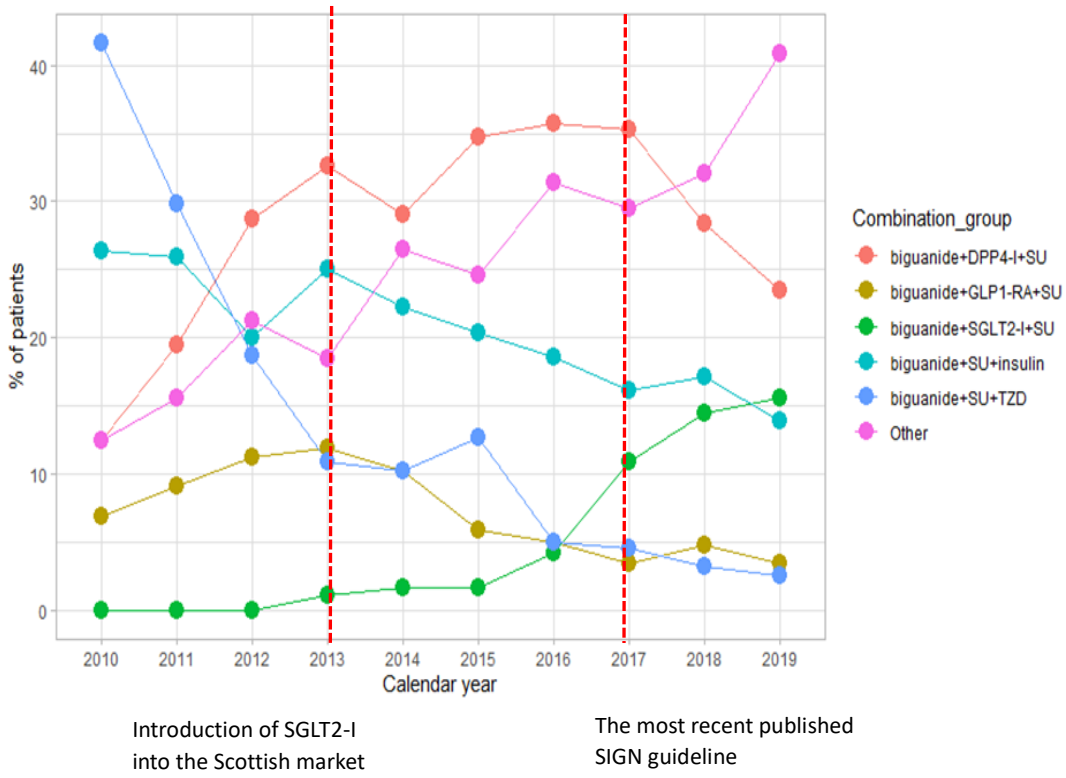

Figure 4.10: The change in the prescribing pattern of triple or more therapy regimens over the study period. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium-glucose co-transporter-2 inhibitor

Table 4.14: The change in the prescribing patterns of the exact combination regimens: absolute change, relative change, and trend test

Combination group	Absolute change	Relative change	Trend test
Dual therapy			
Biguanide+DPP4-I	96	1.75	Z = 9.22, p-value **< 0.001**
Biguanide+GLP1-RA	-4	-0.24	Z = -1.85, p-value = 0.064
Biguanide+ insulin	4	0.03	Z = -1.50, p-value = 0.132
Biguanide+SGLT2-I	167	82.50	Z = 21.91, p-value **< 0.001**
Biguanide + SU	-38	-0.04	Z = -10.33, p-value **< 0.001**
Biguanide+ TZD	-64	-0.90	Z = -11.61, p-value **< 0.001**
Dpp4-i+su	10	1.11	Z = 3.03, p-value = **0.002**
SU+ insulin	-15	-0.39	Z = -2.51, p-value = **0.012**
Other	15	1.07	Z = 3.14, p-value = **0.002**
More than two drugs			
Biguanide+DPP4-I+SU	45	5.00	Z = 1.35, p-value = 0.178
Biguanide+GLP1-RA+SU	3	0.60	Z = -3.45, p-value = **0.001**
Biguanide+SGLT2-I+SU	36	35.00	Z = 8.12, p-value **<0.001**
Biguanide+ SU+ insulin	13	-0.68	Z = -3.41, p-value = **0.001**
Biguanide+ SU+ TZD	-24	-0.80	Z = -10.94, p-value **< 0.001**
Other	85	9.44	Z = 6.19, p-value **<0.001**

DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors

Table 4.15: Frequency and percentage of exact combination regimens prescribed at the stage of drug initiation over the study period

Dual Therapy	2010 (N=1228)	2011 (N=1033)	2012 (N=1104)	2013 (N=1119)	2014 (N=1163)	2015 (N=1175)	2016 (N=1340)	2017 (N=1313)	2018 (N=1367)	2019 (N=1399)	Total (N=12241)
Biguanide+ DPP4-I	55 (4.48%)	69 (6.68%)	58 (5.25%)	54 (4.83%)	99 (8.51%)	121 (10.30%)	141 (10.52%)	151 (11.50%)	143 (10.46%)	151 (10.79%)	1042 (8.51%)
Biguanide+ GLP1-RA	17(1.38%)	14(1.36%)	11(0.99%)	*	6 (0.52%)	*	5 (0.37%)	8 (0.61%)	12(0.88%)	13(0.93%)	97 (0.79%)
Biguanide+ insulin	130 (10.59%)	107 (10.36%)	133 (12.05%)	110 (9.83%)	147 (12.64%)	164 (13.96%)	147 (10.97%)	131 (9.98%)	129 (9.44%)	134 (9.58%)	1332 (10.88%)
Biguanide + SU	893 (72.72%)	735 (71.15%)	825 (74.73%)	874 (78.11%)	828 (71.20%)	772 (65.70%)	912 (68.06%)	838 (63.82%)	876 (64.08%)	855 (61.11%)	8408 (68.68%)
Biguanide+ TZD	71(5.78%)	52(5.03%)	20(1.81%)	17(1.52%)	14(1.20%)	18(1.53%)	8 (0.60%)	16 (1.22%)	10 (0.73%)	7 (0.50%)	233 (1.90%)
Biguanide+ SGLT2-I	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	28(2.38%)	54(4.03%)	84(6.40%)	110(8.05 %)	167(11.94 %)	454 (3.71%)
DPP4-I+SU	9 (0.73%)	9 (0.87%)	10(0.91%)	12(1.07%)	14(1.20%)	16(1.36%)	18(1.34%)	31 (2.36%)	20 (1.46%)	19 (1.36%)	158 (1.29%)
SU+ insulin	39(3.18%)	32(3.10%)	37(3.35%)	31(2.77%)	35(3.01%)	45(3.83%)	40(2.99%)	25 (1.90%)	39 (2.85%)	24 (1.72%)	347 (2.83%)
Other	14(1.14%)	15(1.45%)	10(0.91%)	15(1.34%)	*	*	15(1.11%)	29(2.21%)	28 (2.05%)	29 (2.07%)	170 (1.39%)
More than two drugs	**2010 (N=72)**	**2011 (N=77)**	**2012 (N=80)**	**2013 (N=92)**	**2014 (N=117)**	**2015 (N=118)**	**2016 (N=140)**	**2017 (N=173)**	**2018 (N=187)**	**2019 (N=230)**	**Total (N=1286)**
Biguanide+DPP4-I +SU	9 (12.50%)	15 (19.48%)	23 (28.75%)	30 (32.61%)	34 (29.06%)	41 (34.75%)	50 (35.71%)	61 (35.26%)	53 (28.34%)	54 (23.48%)	370 (28.77%)
Biguanide+GLP1-RA+SU	5 (6.94%)	7 (9.09%)	9(11.25%)	*	*	*	7 (5.00%)	6 (3.47%)	9 (4.81%)	8 (3.48%)	81 (6.30%)
Biguanide+ SU+ insulin	19 (26.39%)	20 (25.97%)	16 (20.00%)	23 (25.00%)	26 (22.22%)	24 (20.34%)	26 (18.57%)	28 (16.18%)	32 (17.11%)	32 (13.91%)	246 (19.13%)
Biguanide+ SU+TZD	30 (41.67%)	23 (29.87%)	15 (18.75%)	10 (10.87%)	12 (10.26%)	15 (12.71%)	7 (5.00%)	8 (4.62%)	6 (3.21%)	6 (2.61%)	132 (10.26%)

Biguanide+ SGLT2-I+SU	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	*	6 (4.29%)	19(10.98 %)	27(14.44 %)	36 (15.65%)	93 (7.23%)
Other	9 (12.50%)	12 (15.58%)	17 (21.25%)	17 (18.48%)	31 (26.50%)	29 (24.58%)	44 (31.43%)	51 (29.48%)	60 (32.09%)	94 (40.87%)	364 (28.30%)

DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-I; Sodium glucose co-transporter-2 inhibitor.

4.3.3 Factors associated with antidiabetic prescribing

I. Factors influencing the prescribing choice of the regimen type (combination therapy Vs. monotherapy)

Table 4.16 presents the results of the univariable and multivariable binomial logistic regression analyses of factors associated with the prescribing choice of the regimen type at the stage of drug initiation. According to the univariable analysis, female and elderly patients were 10% and 28% significantly less likely to be treated with combination therapy at the stage of drug initiation, respectively (unadjusted OR[95%CI]: 0.9[0.87-0.93] and 0.72[0.69-0.74], respectively). The results of the multivariable analysis were in line with the univariable one for patient sex and age (adjusted OR[95%CI]: 0.95[0.91-0.98] and 0.77[0.74-0.81]). Of the studied socioeconomic factors, only SIMD-Q (rank 3) and UR (rank 7 and 8) show significant associations with the prescribing choice of the regimen type at the stage of drug initiation in the univariable and multivariable analyses (Table 4.16). In addition, the univariable and multivariable analyses revealed that combination therapy was 45% and 28% significantly less likely than monotherapy to be prescribed as a first-line by non-GP prescribers (e.g., Pharmacists, nurses, and hospitals) compared to GP prescribers, respectively (OR[95%CI]: unadjusted: 0.55[0.50-0.60], adjusted: 0.72[0.65-0.79]).

The choice of the regimen type was significantly influenced by a number of clinical features (Table 4.16). For instance, a baseline CCI score of >=5, a low baseline eGFR (<60ml/min/1.73m2), a baseline HbA1c of >=9, and a baseline TG of >= 500 mg/dl were associated with greater odds of prescribing combination therapy than monotherapy for drug-naïve patients (Table 4.16). Opposite results were found with the number of concomitant medications (>= 5 vs. 0), antihyperlipidemic or CCB, a baseline BMI of >= 30kg/m^2, a baseline HbA1c level of >=9, a medium baseline level of HDL (40-59 (M) or 50-59 (F), and a baseline total cholesterol in a range of 200-239 mg/dl (Table 4.16).

Table 4.16: Univariable and multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type (combination versus monotherapy) for new ADD users (N=145,909)

Studied factor	Combination regimen	
	Univariate	Multivariate
1- Demographic factors		
Age at prescription	<0.001	<0.001
>= 65 vs. < 65 years	**0.72[0.69, 0.74]**	**0.77[0.74, 0.81]**
Sex	<0.001	0.005
Female vs. Male	**0.9[0.87, 0.93]**	**0.95[0.91, 0.98]**
2- Socioeconomic factors		
Urban-rural	<0.001	<0.001
1	1	1
2	**0.91[0.87, 0.95]**	**0.93[0.89, 0.98]**
3	0.96[0.90, 1.03]	0.98[0.91, 1.05]
4	1.03[0.91, 1.15]	1[0.88, 1.13]
5	1[0.85, 1.17]	1.08[0.91, 1.27]
6	0.97[0.91, 1.03]	1.01[0.94, 1.08]
7	**1.24[1.13, 1.36]**	**1.3[1.18, 1.44]**
8	**1.12[1.01, 1.24]**	**1.17[1.05, 1.31]**
Unknown	1.9[1.00, 3.33]	1.34[0.59, 2.86]
Scottish index of multiple deprivation-quantile	0.039	0.1
1	1	1
2	0.97[0.92, 1.02]	0.98[0.93, 1.03]
3	0.97[0.92, 1.02]	**0.94[0.88, 0.99]**
4	0.96[0.91, 1.01]	0.96[0.90, 1.02]
5	**0.9[0.85, 0.96]**	**0.93[0.87, 0.99]**
Unknown	1.11[0.43, 2.40]	0.55[0.17, 1.53]
3- Prescriber-related factor		
Prescriber type	<0.001	<0.001
Non-general practitioner (GP) vs. GP	**0.55[0.50, 0.60]**	**0.72[0.65, 0.79]**
4- Clinical-related factors		
Ischemic heart disease	<0.001	0.8
Yes vs. No	**0.89[0.84, 0.94]**	0.99[0.93, 1.06]
Hypertension	<0.001	0.7
Yes vs. No	**0.89[0.85, 0.94]**	1.01[0.95, 1.07]
Heart failure	<0.001	0.2
Yes vs. No	**1.2[1.10, 1.32]**	1.08[0.97, 1.21]
Stroke	0.014	0.2
Yes vs. No	**1.14[1.03, 1.26]**	1.08[0.96, 1.20]
Peripheral vascular disease	0.064	0.046

Yes vs. No	1.11[0.99, 1.24]	1.13[1.00, 1.26]
Liver disease	<0.001	0.069
Yes vs. No	**1.4[1.26, 1.55]**	1.12[0.99, 1.25]
Charlson comorbidity index score	<0.001	0.2
0	1	1
1-2	1.03[0.98, 1.08]	1.04[0.98, 1.10]
3-4	**1.24[1.13, 1.35]**	1.03[0.92, 1.15]
>= 5	**1.43[1.29, 1.59]**	**1.13[1.01, 1.27]**
Antihyperlipidemic drugs	<0.001	<0.001
Yes vs. No	**0.6[0.58, 0.63]**	**0.86[0.83, 0.90]**
Antipsychotic	0.006	0.6
Yes vs. No	**1.15[1.04, 1.26]**	0.97[0.88, 1.07]
Thiazide diuretics	<0.001	0.4
Yes vs. No	**0.73[0.69, 0.77]**	0.97[0.92, 1.03]
Beta-blockers	<0.001	0.8
Yes vs. No	**0.84[0.81, 0.88]**	0.99[0.95, 1.05]
Angiotensin inhibitors	<0.001	0.1
Yes vs. No	**0.76[0.73, 0.79]**	1.04[0.99, 1.09]
Calcium channel blocker	<0.001	0.022
Yes vs. No	**0.75[0.71, 0.78]**	**0.94[0.90, 0.99]**
Number of concomitant medications	<0.001	0.051
0	1	1
1-4	**0.7[0.65, 0.76]**	0.95[0.87, 1.03]
>= 5	**0.56[0.52, 0.60]**	**0.91[0.83, 0.99]**
Body mass index (kg/m^2)	<0.001	<0.001
<=24.9	1	1
25-29.9	**0.8[0.73, 0.88]**	0.91[0.83, 1.01]
>= 30	**0.66[0.61, 0.72]**	**0.76[0.70, 0.84]**
Unknown	**1.15[1.05, 1.25]**	**0.9[0.83, 0.99]**
HbA1c (%)	<0.001	<0.001
< 7	1	1
7- < 9	**0.64[0.57, 0.73]**	**0.7[0.62, 0.79]**
>=9	**3.37[3.01, 3.79]**	**3.25[2.90, 3.66]**
Unknown	**5.42[4.84, 6.10]**	**3.94[3.50, 4.45]**
Estimated glomerular filtration rate (ml/min/1.73m^2)	<0.001	<0.001
< 60 vs. >= 60	**1.45[1.36, 1.55]**	**1.6[1.49, 1.72]**
Unknown vs. < 60	**2.74[2.63, 2.85]**	**1.36[1.29, 1.44]**
High density lipoprotein (mg/dl)	<0.001	<0.001
<40 (M) or <50 (F)	1	1

40-59 (M) or 50-59 (F)	**0.78[0.74, 0.83]**	**0.86[0.81, 0.91]**
>= 60	**0.79[0.71, 0.87]**	0.94[0.85, 1.05]
Unknown	**2.03[1.95, 2.11]**	1.05[0.98, 1.13]
Triglyceride (mg/dl)	<0.001	<0.001
< 150	1	1
150-499	**1.13[1.06, 1.21]**	0.97[0.90, 1.04]
>= 500	**2.42[2.20, 2.66]**	**1.45[1.30, 1.62]**
Unknown	**2.44[2.30, 2.59]**	**1.13[1.04, 1.22]**
Total cholesterol (mg/dl)	<0.001	<0.001
< 200	1	1
200-239	**1.15[1.08, 1.22]**	**0.91[0.85, 0.97]**
>=240	**1.63[1.54, 1.73]**	1.06[0.99, 1.14]
Unknown	**2.98[2.86, 3.11]**	**1.22[1.13, 1.32]**

The results are presented as OR[95%CI] and the global p-value.

II. Factors influencing the prescribing choice of antidiabetic class

Table 4.17 summarises the results of the multivariable multinomial logistic regression analyses of factors associated with prescribing antidiabetic classes at the stage of drug initiation. The results of the univariable regression analysis are presented in Appendix S.4.6. All monotherapy and combination therapy regimens described in section 4.4.2 for newly treated patients were included in the regression model except the other-monotherapy (N=29) and the other-combination therapy (N=534) groups, leaving a total of 145346 out of 145909 patients included in the regression models. The exclusion of the other-monotherapy and other-combination therapy groups is related to the presence of a wide variety of regimens with small sample sizes, making it difficult to understand the analysis results and rendering no clinical value. Several factors were significantly associated with the prescribing choice of each investigated antidiabetic class compared to metformin.

- Non-clinical factors: demographic, socioeconomic, and prescriber-related factors

It was found that elderly patients (65 years or older) were significantly more likely to be treated with DPP4-I, SU, and DPP4-I+SU as a first-line therapy than metformin alone compared to younger individuals but less likely to be initiated on SGLT2-I, metformin+DPP4-I, metformin+ insulin, metformin+SGLT2-I, metformin+SU, and SU+ insulin (Tables 4.17 and 4.18). Additionally, the results of the multivariable

regression analyses demonstrated greater odds of prescribing DPP4-I, GLP1-RA, TZD, metformin+DPP4-I, metformin+ insulin, metformin+SGLT2-I, and DPP4-I+SU as a first-line therapy than metformin monotherapy for female patients with T2DM compared to male patients (Adjusted OR[95%CI]: 1.55[1.33-1.81], 17[1.22-236], 2.01[1.46-2.77], 1.19[1.03-1.36], 1.51[1.33-1.71], 1.73[1.43-2.10], and 9.6[5.90-15.6], respectively). However, lower odds of starting SU, metformin+SU, metformin+TZD, and SU+ insulin than metformin monotherapy was observed for female compared to male patients (Adjusted OR[95%CI]: 0.89[0.85-0.93], 0.87[0.82-0.91], 0.55[0.39-0.76], and 0.72[0.55-0.93], respectively).

In terms of the studied socioeconomic factors, the impact of UR and SIMD-Q on the prescribing choice was complex and highly variable by the class of ADDs and the variable levels (Tables 4.17). For example, compared to initial metformin, the multivariable analyses showed that patients living in more rural areas were significantly more likely to be treated with DPP4-I (UR rank 5), GLP1-RA (UR rank 6 and 8), SGLT2-I (UR rank 4), insulin (UR rank 7), TZD (UR rank 6), and multiple combination groups. However, they are significantly less likely to be treated with SU (UR rank 2, 3, and 8), metformin+ insulin (UR rank 2), metformin+SU (UR rank 2 and 6), DPP4-I+SU (UR rank 2 and 6), and metformin+SU+ TZD (UR rank 6) compared to patients living in a large urban area with UR rank 1 (Table 4.17). Regarding prescriber type, metformin+SU+ insulin, metformin+SU, metformin+TZD, and insulin monotherapy were significantly less likely to be prescribed by non-GP prescribers than by GP prescribers (Adjusted OR[95%CI]: 0.3[0.20-0.45], 0.26[0.15-0.44], 0.82[0.74-0.92], 0.23[0.08-0.67], 0.31[0.12-0.79], and 0.01[0.00-0.97], respectively).

- Clinical-related factors

First, several baseline comorbid conditions had a significant association with the prescribing choice of multiple antidiabetic classes prescribed as initial therapy for patients diagnosed with T2DM (Table 4.17). Amongst the studied initial monotherapy groups, baseline comorbid conditions had the most significant association with the prescribing choice of SU and insulin, followed by DPP4-I, while the least association was with GLP1-RA prescription. The multivariable analyses

showed significant associations of the baseline CCI score, HTN, and PVD with insulin and SU prescriptions. A significant association was also observed between IHD and SU prescription as well as between liver disease and insulin prescription (Table 4.17). For instance, patients with HTN or PVD had 36% and 83% greater odds of receiving insulin over metformin as a first-line therapy for T2DM management (adjusted OR[95%CI]: 1.36[1.20-1.55] and1.83[1.46, 2.29], while they were 18% and 27% significantly more likely to be started on SU (adjusted OR[95%CI]: 1.18[1.11, 1.25] and 1.27[1.14, 1.42]). Furthermore, the baseline CCI score, stroke, and HF had significant associations with the prescribing choice of DPP4-I over metformin as a first-line therapy for drug naïve patients with T2DM, which was positive significant with CCI-score and stroke, yet negative significant with HF (Table 4.17). In contrast, none of the studied comorbid conditions was significantly associated with prescribing GLP1-RA versus metformin as initial therapy (Table 4.17). Only the baseline CCI score had a significant association with the choice of SGLT2-I and TZD at the stage of drug initiation. Patients with a higher baseline CCI score had greater odds of being treated with SGLT2-I (CCI score 1-2 and 3-4) or TZD (CCI score 1-2) over metformin as initial therapy compared to patients with a zero baseline CCI score (Table 4.17).

Among the studied combination dual regimens, baseline comorbid conditions were mainly associated with the prescribing choice of metformin+SU, metformin+ insulin, and DPP4-I+SU, followed by metformin+DPP4-I and SU+ insulin for drug naïve patients with T2DM. Patients with higher baseline CCI scores were significantly more likely to be treated with metformin+ insulin, metformin+SU, DPP4-I+SU, or SU+ insulin as first-line therapy, yet significantly less likely to be started on metformin+DPP4-I (Table 4.17). HTN was also positively associated with using metformin+ insulin, metformin+SU, and metformin+TZD, while negatively associated with metformin+DPP4-I prescription as first-line therapy over metformin alone (Table 4.17).

Additionally, metformin+ insulin for the management of T2DM was more likely to be started in patients with IHD by 53%(adjusted OR[95%CI]: 1.53[1.24, 1.90]), but metformin+SU and metformin+DPP4-I were less likely to be used as first-line treatments by 21% and 36%, respectively (adjusted OR[95%CI]: 0.79[0.73-0.87]) and 0.64[0.47-0.87], respectively). The likelihood of prescribing metformin+ insulin, DPP4-I+SU, and SU+ insulin was also positively correlated with the presence of liver disease. A positive association was also observed between metformin+SU, metformin+SGLT2-I, DPP4-I+SU, and SU+ insulin prescriptions and the presence of PVD (Table 4.17). Last but not least, having stoke increased the likelihood that patients diagnosed with T2DM to be initiated on SU+ insulin or DPP4-I+SU rather than metformin (Table 4.17). Of the examined triple therapy regimens, only the prescribing choice of metformin+SU+ insulin and metformin+DPP4-I+SU had significant associations with multiple studied comorbid conditions according to the multivariable analysis. For example, patients with HTN, stroke, liver disease, and a CCI score of 1-2, 3-4, and >=5 were significantly more likely to be treated with metformin+SU+ insulin than metformin monotherapy (Table 4.17). Only HTN had a significant impact on the use of metformin+DPP4-I+SU as an initial therapy, in which patients with HTN were 3.2 times more likely to be initiated on metformin+DPP4-I+SU than metformin monotherapy compared to patients without HTN (Adjusted OR[95%CI]: 3.2[2.39-4.30]).

Second, the association of concomitant medications with the prescribing choice of first-line antidiabetic monotherapy and combination therapy was diverse. According to the multivariable analysis, individuals receiving CCB, thiazide diuretics, angiotensin-inhibitors, and antihyperlipidemic medications were less likely to get prescriptions for insulin or SU than metformin as first-line therapy (Tables 4.17). On the other hand, choosing to prescribe SU and insulin was positively related to the use of 1-4 or >=5 concurrent drugs (Table 4.17). Additionally, the likelihood of prescribing SGLT2-I or DPP4-I rather than metformin for drug naïve patients with T2DM was significantly influenced by taking antihyperlipidemic drugs, CCB, and beta-blockers (Table 4.17). It was also found that patients taking antihyperlipidemic

or CCB were significantly less likely to be initiated on SGLT2-I or DPP4-I over metformin (Adjusted OR[95%CI]: DPP4-I and SGLT2-I: antihyperlipidemic drugs: 0.79[0.67-0.94] and 0.75[0.59-0.96], CCB: 0.73[0.61-0.87] and 0.67[0.49-0.93], respectively). However, the use of beta-blockers had a 39% and a 44% greater likelihood of prescribing SGLT2-I and DPP4-I prescriptions, respectively (Adjusted OR[95%CI]: 1.39[1.17-1.63] and 1.44[1.07-1.94]).

Furthermore, taking concomitant medications had significant associations with the prescribing choice of a variety of combination regimens, including metformin+DPP4-I, metformin+ insulin, metformin+SU, DPP4-I+SU, metformin+SU+ TZD, and metformin+DPP4-I+SU (Table 4.17). Prescribing metformin+DPP4-I, metformin+ insulin, metformin+ SU, metformin+ TZD, and DPP4-I+SU over metformin for drug-naive patients was negatively correlated with the use of antihyperlipidemic medications. Further, patients using CCB or angiotensin inhibitors were less likely to receive metformin+SU and more likely to receive metformin+DPP4-I, metformin+TZD, or DPP4-I+SU. Thiazide diuretics were positively linked with prescribing metformin+TZD but negatively and significantly associated with metformin+ insulin and DPP4-I+SU prescriptions. Whereas beta-blockers had only a significant association with prescribing of DPP4-I+SU and metformin+TZD (Adjusted OR[95%CI]: 2.52[1.64-3.88] and 0.58[0.35-0.97]). Nevertheless, due to the small number of patients who started on triple or more therapy as their initial treatment for T2DM, the majority of effect sizes pertinent to the triple therapy regimens were either too wide or too narrow (Table 4.17).

Third, in terms of the impact of the baseline laboratory values, the baseline BMI had a significant association with the choice of DPP4-I, insulin, SU, SGLT2-I, and multiple combination regimens over metformin. Overweight (BMI 25-29.9 kg/m^2) patients were significantly less likely to be initiated on DPP4-I, insulin, SU, SGLT2-I, and combination regimens of DPP4-I+SU, SU+ insulin, than metformin compared to patients with a low/normal BMI (<= 24.9 kg/m^2) (Table 4.17). In contrast, overweight patients had a significantly greater likelihood of receiving metformin+DPP4-I, metformin+ insulin, metformin+SGLT2-I, and metformin+SU+

TZD (Table 4.17). Furthermore, obese patients (BMI >= 30 kg/m^2) had lower odds of receiving DPP4-I, insulin, SU, metformin+SU, metformin+DPP4-I+SU, and metformin+SU+ insulin as initial therapy for drug naïve patients, and a lower likelihood of starting metformin+SGLT2-I, metformin+TZD, and metformin+SU+ TZD (Table 4.17).

Patients with a low eGFR of < 60 ml/min/1.73m^2 had a greater likelihood of receiving DPP4-I, insulin, SU, TZD, and combination regimens of metformin+DPP4-I, metformin+ insulin, metformin+SU, metformin+TZD, DPP4-I+SU, SU+ insulin, and metformin+DPP4-I+SU than metformin monotherapy compared to patients with a baseline eGFR of >= 60 ml/min/1.73m^2 (Table 4.17). The results relevant to the association of the baseline HbA1c level with prescribing ADDs as initial therapy showed that patients with a baseline HbA1c of >= 9 were significantly more likely to be treated with insulin, SU, and metformin-based combinations (metformin+DPP4-I, metformin+insulin, metformin+SGLT2-I, metformin+SU, metformin+DPP4-I+SU, metformin+SGLT2-I+SU, and metformin+SU+insulin) than metformin monotherapy compared to patients with a baseline HbA1c of < 7 (Table 4.17). However, they were significantly less likely to be initiated on SGLT2-I and DPP4-I+SU (0.62[0.43-0.90] and 0.2[0.11-0.36], respectively). On the contrary, a baseline HbA1c of 7-9 was negatively associated with the prescribing choice of insulin, SGLT2-I, and combination regimens of metformin+DPP4-I, metformin+ insulin, metformin+SU, DPP4-I+SU, and SU+ insulin over metformin (adjusted OR[95%CI]: 0.56[0.41, 0.76], 0.58[0.41, 0.84], 0.56[0.36, 0.86], 0.54[0.37, 0.78], 0.4[0.34, 0.47], 0.02[0.01, 0.05], and 0.04[0.02, 0.10], respectively).

The association of the baseline lipid profile with the prescribing decision of ADDs was highly variable. As an example, patients with a very high baseline TG level of >= 500 mg/dl were significantly more likely to receive initial therapy of SU, metformin+GLP1-RA, metformin+ insulin, metformin+TZD, metformin+DPP4-I+SU, and metformin+SU+ insulin (Adjusted OR[95%CI]: 1.19[1.04-1.37), 3705[15.5-inf], 3.01[2.04-4.43], 2.68[1.11-6.43], 2.95[1.23-7.04], and 2.52[1.38-4.62], respectively), but less likely to start on metformin+SGLT2-I than metformin alone compared to a

normal TG level of < 150 mg/dl (Adjusted OR[95%CI]: 0.12[0.04, 0.38]). In addition, patients with a baseline TG level of 150-499 mg/dl had a greater likelihood of receiving metformin+DPP4-I rather than metformin alone as initial therapy (adjusted OR[95%CI]: 1.66[1.24-2.22]). However, they were less likely to receive insulin, SU, metformin+SGLT2-I, metformin+SU, DPP4-I+SU, SU+ insulin, and metformin+SU+ insulin than metformin monotherapy compared to patients with normal TG level (adjusted OR[95%CI]: 0.59[0.48-0.72], 0.92[0.85-0.98], 0.69[0.51-0.94], 0.73[0.67-0.79], 0.13[0.03-0.65], 0.43[0.20-0.89], and 0.36[0.21-0.64], respectively). The associations of baseline HDL and total cholesterol levels with the prescribing choice of ADDs (monotherapy and combination) are shown in Table 4.17.

Table 4.17: Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to metformin monotherapy) at the stage of drug initiation (N=145346): Monotherapy groups

Studied factor	DPP4-I	GLP1-RA	insulin	SGLT2-I	SU	TZD	P-value
1- Demographic factors							
Age at prescription	<0.001	0.004	<0.001	<0.001	<0.001	0.6	<0.001
>= 65 vs. < 65 years	**1.76[1.46, 2.11]**	**0[0.00, 0.00]**	**0.67[0.59, 0.74]**	**0.52[0.39, 0.70]**	**1.36[1.29, 1.42]**	1.05[0.74, 1.49]	
SEX	<0.001	0.015	0.11	0.11	<0.001	0.053	>0.9
Female vs. Male	**1.55[1.33, 1.81]**	**17[1.22, 236]**	0.92[0.83, 1.01]	1.09[0.86, 1.38]	**0.89[0.85, 0.93]**	**2.01[1.46, 2.77]**	
2- Socioeconomic factors							
Urban-rural	0.006	0.081	0.5	0.2	<0.001	0.079	>0.9
2 vs. 1	1.1[0.92, 1.32]	0.01[0.00, inf]	1.05[0.94, 1.17]	1.18[0.91, 1.54]	**0.92[0.88, 0.97]**	1.42[0.96, 2.11]	
3 vs. 1	0.96[0.72, 1.28]	0[0.00, 0.00]	0.99[0.83, 1.18]	1.05[0.67, 1.64]	**0.88[0.81, 0.96]**	1.12[0.59, 2.14]	
4 vs. 1	1.07[0.67, 1.71]	182[0.26, inf]	1.07[0.79, 1.45]	**2.21[1.25, 3.93]**	1.13[0.99, 1.29]	1.56[0.59, 4.12]	
5 vs. 1	**2.07[1.29, 3.34]**	4.74[0.00, 7,246]	1.37[0.92, 2.04]	0.79[0.24, 2.66]	1.18[0.98, 1.41]	0.28[0.02, 4.94]	
6 vs. 1	0.99[0.75, 1.30]	**137[2.17, 8,629]**	1.11[0.94, 1.31]	1.25[0.84, 1.84]	1.04[0.96, 1.12]	**2.67[1.64, 4.35]**	
7 vs. 1	0.64[0.38, 1.06]	0.04[0.00, inf]	**1.29[1.01, 1.66]**	0.95[0.46, 1.94]	1.02[0.90, 1.15]	2.04[0.95, 4.39]	
8 vs. 1	0.72[0.44, 1.19]	**2173[8.52, inf]**	1.16[0.89, 1.53]	0.67[0.26, 1.68]	**0.85[0.75, 0.98]**	1.02[0.34, 3.07]	
Unknown vs. 1	0.21[0.00, 20.8]	0.89[0.00, inf]	3.8[0.84, 17.2]	0.66[0.00, 417]	2.9[0.94, 9.00]	1.29[0.00, 4,167]	
Scottish index of multiple deprivation-quantile	0.2	0.2	0.026	0.11	<0.001	0.7	>0.9
2 vs. 1	0.98[0.80, 1.21]	0.41[0.00, 46.0]	0.95[0.83, 1.09]	1.02[0.75, 1.37]	1.06[1.00, 1.13]	1.08[0.71, 1.63]	
3 vs. 1	1[0.80, 1.26]	0.02[0.00, 7.10]	1.15[1.00, 1.32]	0.84[0.59, 1.19]	1.03[0.96, 1.10]	0.61[0.37, 1.02]	
4 vs. 1	0.89[0.69, 1.13]	9.97[0.21, 467]	1[0.86, 1.17]	1.11[0.79, 1.56]	**1.14[1.06, 1.22]**	1.04[0.65, 1.67]	
5 vs. 1	1.06[0.83, 1.36]	4.69[0.02, 965]	**1.3[1.12, 1.52]**	0.82[0.55, 1.21]	**1.18[1.10, 1.27]**	0.76[0.43, 1.34]	
Unknown vs. 1	13.3[0.94, 189]	0.6[0.56, 0.65]	1.94[0.34, 11.0]	0.82[0.00, 7,208]	0.36[0.07, 1.83]	1.33[0.00, 4,981]	
3- Prescriber-related factors							
Prescriber type	0.7	0.3	<0.001	0.4	0.006	0.9	<0.001
Non-general practitioner (GP) vs. GP	1.13[0.86, 1.50]	0[0.00, 10,231]	**0.3[0.20, 0.45]**	1.17[0.81, 1.70]	1.06[0.96, 1.16]	0.88[0.44, 1.75]	
4- Clinical-related factors							
Ischemic heart disease	0.5	0.2	0.2	0.044	0.5	0.032	>0.9
Yes vs. No	0.84[0.69, 1.04]	**0[0.00, 0.00]**	0.96[0.82, 1.13]	1.4[0.95, 2.05]	**0.9[0.84, 0.96]**	0.77[0.47, 1.25]	
Hypertension	0.4	0.4	0.003	0.8	<0.001	0.4	>0.9

Yes vs. No	1.13[0.95, 1.35]	13.4[0.27, 660]	**1.36[1.20, 1.55]**	0.99[0.70, 1.39]	**1.18[1.11, 1.25]**	0.67[0.43, 1.04]	
Heart failure	0.022	0.4	0.5	0.044	0.5	0.4	<0.001
Yes vs. No	**0.69[0.51, 0.93]**	59.2[0.00, inf]	1.09[0.88, 1.35]	1.02[0.53, 1.98]	1.05[0.95, 1.17]	1.03[0.46, 2.34]	
Stroke	0.07	0.2	0.2	0.3	<0.001	0.8	<0.001
Yes vs. No	**1.36[1.01, 1.84]**	**0.01[0.01, 0.01]**	1.19[0.94, 1.51]	0.64[0.26, 1.58]	1.09[0.98, 1.22]	0.8[0.31, 2.03]	
Peripheral vascular disease	>0.9	0.3	<0.001	0.2	<0.001	0.8	<0.001
Yes vs. No	0.98[0.68, 1.41]	**0.02[0.02, 0.02]**	**1.83[1.46, 2.29]**	1.22[0.57, 2.62]	**1.27[1.14, 1.42]**	0.86[0.33, 2.24]	
Liver disease	>0.9	0.9	<0.001	0.11	0.002	0.4	<0.001
Yes vs. No	0[0.00, 52,740]	1.02[0.00, 7,376]	**1.51[1.23, 1.84]**	0.45[0.17, 1.15]	1.05[0.94, 1.18]	2.36[0.98, 5.67]	
Charlson comorbidity index score	<0.001	0.3	<0.001	0.6	<0.001	0.11	<0.001
1-2 vs. 0	**1.79[1.48, 2.15]**	0.01[0.00, 240,309]	**1.82[1.59, 2.07]**	**1.5[1.08, 2.09]**	**1.73[1.63, 1.83]**	**1.85[1.23, 2.79]**	
3-4 vs. 0	**3.07[2.29, 4.11]**	611[0.17, 2,164,637]	**2.38[1.93, 2.93]**	**2.11[1.07, 4.14]**	**2.56[2.32, 2.82]**	1.25[0.53, 2.94]	
>= 5 vs. 0	**4.47[3.31, 6.02]**	0.02[0.00, 201,811]	**4.2[3.45, 5.11]**	0.83[0.26, 2.70]	**3.43[3.09, 3.80]**	0.56[0.13, 2.42]	
Antihyperlipidemic drugs	0.064	0.05	<0.001	0.035	<0.001	0.005	>0.9
Yes vs. No	**0.79[0.67, 0.94]**	**0[0.00, 0.00]**	**0.48[0.43, 0.54]**	**0.75[0.59, 0.96]**	**0.72[0.69, 0.76]**	**2.69[1.77, 4.09]**	
Antipsychotic	0.8	0.075	0.5	>0.9	0.4	0.5	<0.001
Yes vs. No	0.63[0.39, 1.02]	**0.01[0.01, 0.01]**	0.9[0.71, 1.15]	1.07[0.59, 1.96]	0.99[0.88, 1.11]	1.45[0.68, 3.12]	
Thiazide diuretics	0.07	>0.9	0.004	0.5	<0.001	0.058	<0.001
Yes vs. No	0.83[0.68, 1.01]	2.02[0.00, 19,615]	**0.8[0.68, 0.95]**	1.02[0.70, 1.49]	**0.88[0.82, 0.93]**	0.78[0.53, 1.15]	
Beta-blockers	0.001	0.14	0.7	0.091	0.039	0.2	<0.001
Yes vs. No	**1.39[1.17, 1.63]**	**143[2.35, 8,637]**	0.91[0.80, 1.03]	**1.44[1.07, 1.94]**	**1.1[1.04, 1.16]**	1.24[0.88, 1.75]	
Angiotensin inhibitors	0.2	0.5	<0.001	0.2	<0.001	0.8	>0.9
Yes vs. No	1.06[0.91, 1.25]	0[0.00, 29,118]	**0.82[0.73, 0.92]**	1[0.78, 1.30]	**0.82[0.78, 0.86]**	1.14[0.82, 1.59]	
Calcium channel blocker	0.3	0.7	<0.001	0.036	0.025	0.005	>0.9
Yes vs. No	**0.73[0.61, 0.87]**	0.75[0.01, 59.9]	**0.77[0.67, 0.88]**	**0.67[0.49, 0.93]**	**0.89[0.84, 0.94]**	**1.95[1.41, 2.71]**	
Number of concomitant medications	0.004	0.094	<0.001	0.5	<0.001	0.4	>0.9
1-4 vs. 0	1.12[0.62, 2.04]	**0.01[0.00, 0.48]**	**1.95[1.55, 2.47]**	1.37[0.81, 2.32]	**1.14[1.01, 1.27]**	0.66[0.24, 1.86]	
>= 5 vs. 0	1.65[0.92, 2.99]	0.09[0.00, 2.22]	**1.58[1.24, 2.02]**	0.85[0.48, 1.49]	**1.29[1.14, 1.44]**	0.47[0.16, 1.36]	
Body mass index (kg/m^2)	0.005	0.029	<0.001	0.001	<0.001	0.8	<0.001
25-29.9 vs. <=24.9	**0.42[0.31, 0.57]**	0[0.00, 0.00]	**0.27[0.22, 0.33]**	**0.47[0.26, 0.85]**	**0.3[0.28, 0.33]**	1.04[0.37, 2.92]	
>= 30 vs. <=24.9	**0.39[0.29, 0.51]**	27[0.00, 2,921,439]	**0.13[0.11, 0.16]**	0.73[0.43, 1.23]	**0.16[0.15, 0.17]**	1.25[0.47, 3.29]	

Unknown vs. <= 24.9	0.47[0.36, 0.62]	5.32[0.00, 523,674]	0.36[0.31, 0.43]	0.71[0.41, 1.20]	0.29[0.27, 0.32]	1.11[0.43, 2.91]	
HbA1c (%)	<0.001	0.001	<0.001	>0.9	<0.001	0.7	<0.001
7- <9 vs. < 7	1.33[0.96, 1.84]	0[NA]	0.56[0.41, 0.76]	**0.58[0.41, 0.84]**	1.08[0.96, 1.22]	0.67[0.31, 1.44]	
>=9 vs. < 7	1.3[0.93, 1.81]	0[NA]	**2.32[1.75, 3.07]**	**0.62[0.43, 0.90]**	**2.31[2.05, 2.61]**	0.43[0.18, 1.01]	
Unknown vs. < 7	1.01[0.69, 1.48]	>1000[>1000, inf]	3.62[2.72, 4.81]	0.65[0.37, 1.12]	2.49[2.20, 2.83]	2.78[1.28, 6.01]	
Estimated glomerular filtration rate (ml/min/1.73m^2)	<0.001	0.079	<0.001	>0.9	<0.001	<0.001	<0.001
< 60 vs. >= 60	**7.64[6.41, 9.10]**	0.03[0.00, >1000]	**6.61[5.74, 7.62]**	0.78[0.41, 1.48]	**3.47[3.26, 3.69]**	**8.52[5.60, 13.0]**	
Unknown vs. < 60	2.13[1.63, 2.77]	48[0.10, 23,160]	1.27[1.12, 1.44]	0.96[0.53, 1.73]	1.14[1.07, 1.22]	3.21[1.95, 5.30]	
High-density lipoprtein (mg/dl)	0.6	0.7	0.004	0.001	<0.001	0.05	<0.001
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.16[0.95, 1.43]	0[0.00, inf]	**0.75[0.62, 0.92]**	**1.62[1.27, 2.07]**	1.02[0.95, 1.08]	1.15[0.71, 1.87]	
>= 60 vs. <40 (M) or <50 (F)	1.08[0.79, 1.49]	1.74[0.00, inf]	**1.68[1.31, 2.16]**	**0.51[0.26, 0.97]**	**1.43[1.30, 1.57]**	1.11[0.54, 2.30]	
Unknown vs. <40 (M) or <50 (F)	0.91[0.68, 1.21]	1.06[0.00, inf]	0.9[0.71, 1.13]	0.43[0.22, 0.83]	1.11[1.03, 1.21]	0.4[0.20, 0.80]	
Troglyceride (mg/dl)	0.3	0.7	<0.001	0.14	<0.001	0.027	<0.001
150-499 vs. < 150	1.02[0.82, 1.28]	0[0.00, 0.00]	**0.59[0.48, 0.72]**	1.13[0.85, 1.50]	**0.92[0.85, 0.98]**	1.15[0.63, 2.11]	
>= 500 vs. < 150	0.57[0.28, 1.15]	0[0.00, 0.00]	1.17[0.85, 1.62]	0.83[0.46, 1.50]	**1.19[1.04, 1.37]**	1.08[0.24, 4.89]	
Unknown vs. < 150	1.09[0.83, 1.42]	0.01[0.00, 736]	0.77[0.61, 0.96]	0.38[0.23, 0.63]	0.92[0.85, 1.00]	2.16[1.18, 3.98]	
Total cholesterol (mg/dl)	0.6	0.4	<0.001	0.8	<0.001	0.5	>0.9
200-239 vs. < 200	0.99[0.79, 1.25]	0[0.00, 0.00]	**0.76[0.62, 0.94]**	**1.7[1.30, 2.22]**	0.93[0.87, 1.00]	0.61[0.33, 1.14]	
>=240 vs. < 200	0.97[0.72, 1.29]	0[0.00, 79,515]	1.12[0.91, 1.38]	1.32[0.94, 1.84]	0.99[0.92, 1.07]	0.66[0.32, 1.34]	
Unknown vs. < 200	1.16[0.86, 1.58]	0.57[0.00, 762]	3[2.40, 3.76]	0.96[0.41, 2.28]	1.52[1.40, 1.66]	1.45[0.71, 2.95]	

Table 4.17: continued: dual therapy regimens (compared to metformin monotherapy)

Studied factor	biguanide+DPP4-I	biguanide+GLP1-RA	biguanide+ insulin	biguanide+SGLT2-I	biguanide+ SU	biguanide+ TZD	DPP4-I+SU	SU+ insulin
1- Demographic factors								
Age at prescription	<0.001	<0.001	<0.001	<0.001	<0.001	0.2	0.038	<0.001
>= 65 vs. < 65 years	**0.62[0.52, 0.72]**	**0[0.00, 0.00]**	**0.5[0.42, 0.58]**	**0.69[0.55, 0.88]**	**0.8[0.76, 0.85]**	**0.47[0.32, 0.71]**	**48.1[15.8, 147]**	**0.45[0.33, 0.61]**
Sex	0.8	0.09	<0.001	0.1	<0.001	>0.9	0.3	<0.001
Female vs. Male	**1.19[1.03, 1.36]**	1.25[0.22, 7.01]	**1.51[1.33, 1.71]**	**1.73[1.43, 2.10]**	**0.87[0.82, 0.91]**	**0.55[0.39, 0.76]**	**9.6[5.90, 15.6]**	**0.72[0.55, 0.93]**
2- Socioeconomic factors								
Urban-rural	0.3	<0.001	0.7	0.054	<0.001	0.013	0.003	0.5
2 vs. 1	1.08[0.92, 1.27]	0[0.00, 0.00]	**0.69[0.59, 0.80]**	1.01[0.81, 1.27]	**0.72[0.68, 0.77]**	0.69[0.46, 1.04]	**0.06[0.03, 0.14]**	0.92[0.67, 1.26]
3 vs. 1	1.08[0.84, 1.40]	36.9[0.56, 2,437]	0.95[0.75, 1.19]	0.85[0.57, 1.26]	**1.12[1.04, 1.22]**	1.41[0.83, 2.38]	**2.83[1.73, 4.63]**	0.98[0.59, 1.64]
4 vs. 1	1.16[0.75, 1.79]	78.3[0.11, 54,289]	1.01[0.69, 1.49]	1.32[0.75, 2.31]	1.1[0.96, 1.27]	1.09[0.40, 2.97]	0.59[0.19, 1.87]	0.66[0.23, 1.92]
5 vs. 1	**1.72[1.03, 2.88]**	3.12[0.00, inf]	1.41[0.86, 2.30]	**2.24[1.19, 4.20]**	0.84[0.68, 1.05]	**8.06[3.92, 16.6]**	0.01[0.00, 1.01]	**5.13[2.65, 9.92]**
6 vs. 1	1.19[0.94, 1.52]	9.27[0.03, 2,853]	1.15[0.94, 1.42]	0.88[0.61, 1.25]	**0.71[0.65, 0.77]**	**3[1.92, 4.68]**	**0.22[0.09, 0.51]**	0.9[0.56, 1.46]
7 vs. 1	1.21[0.82, 1.79]	**448[5.99, >1000]**	0.95[0.66, 1.37]	1.57[0.99, 2.49]	0.97[0.86, 1.10]	1.79[0.83, 3.84]	0.9[0.39, 2.07]	1.3[0.65, 2.61]
8 vs. 1	1.06[0.68, 1.66]	**406[4.49, >1000]**	1.24[0.87, 1.78]	1.46[0.84, 2.53]	**1.2[1.06, 1.36]**	**2.54[1.24, 5.20]**	0.96[0.45, 2.06]	1.12[0.54, 2.34]
Unknown vs. 1	0.02[0.00, 92,816]	1.25[1.17, 1.33]	0.49[0.01, 18.1]	0.12[0.00, 36.9]	0.24[0.02, 2.32]	2.5[0.00, 145,863]	1.05[0.00, inf]	0.56[0.00, inf]
Scottish index of multiple deprivation-quantile	0.4	0.9	0.2	0.4	0.2	0.2	0.5	0.2
2 vs. 1	0.98[0.81, 1.17]	0.15[0.01, 3.44]	1.14[0.97, 1.33]	0.95[0.74, 1.21]	**0.87[0.82, 0.93]**	**0.56[0.35, 0.92]**	**0.23[0.12, 0.45]**	1.08[0.75, 1.56]
3 vs. 1	**0.76[0.61, 0.94]**	0.72[0.07, 7.18]	**0.68[0.55, 0.83]**	**0.66[0.49, 0.89]**	**1.18[1.11, 1.27]**	0.83[0.53, 1.31]	1.34[0.81, 2.23]	1.14[0.76, 1.70]

4 vs. 1	**0.72[0.58, 0.91]**	0.25[0.01, 4.93]	0.9[0.74, 1.10]	0.95[0.71, 1.26]	**1.21[1.13, 1.30]**	**0.38[0.21, 0.67]**	**0.34[0.18, 0.68]**	**1.67[1.11, 2.50]**
5 vs. 1	1.03[0.83, 1.28]	0.03[0.00, inf]	**0.76[0.60, 0.95]**	**0.64[0.45, 0.91]**	0.94[0.87, 1.02]	**1.93[1.27, 2.94]**	**0.1[0.04, 0.27]**	1.21[0.76, 1.94]
Unknown vs. 1	0.08[0.00, 9,884]	0.12[0.12, 0.12]	1.4[0.04, 47.4]	0.78[0.01, 58.6]	0.82[0.09, 7.17]	2.2[0.00, 107,157]	0.21[0.00, inf]	0.65[0.00, inf]
3- Prescriber-related factors								
Prescriber type	0.6	0.002	<0.001	>0.9	<0.001	<0.001	0.2	0.059
Non-general practitioner (GP) vs. GP	0.97[0.70, 1.35]	**0[0.00, 0.00]**	**0.26[0.15, 0.44]**	0.95[0.65, 1.39]	**0.82[0.74, 0.92]**	**0.23[0.08, 0.67]**	0.01[0.00, 3.41]	0.48[0.17, 1.33]
4- Clinical-related factors								
Ischemic heart disease	0.01	0.4	0.01	0.2	0.11	0.087	>0.9	0.5
Yes vs. No	**0.64[0.47, 0.87]**	**0[0.00, 0.00]**	**1.53[1.24, 1.90]**	1.18[0.82, 1.72]	**0.79[0.73, 0.87]**	0.42[0.16, 1.13]	1.29[0.75, 2.20]	1.24[0.87, 1.77]
Hypertension	0.001	0.018	0.007	0.2	<0.001	0.14	0.9	0.8
Yes vs. No	**0.59[0.46, 0.75]**	**0[0.00, 0.00]**	**1.41[1.17, 1.70]**	0.79[0.57, 1.09]	**1.56[1.46, 1.68]**	**2.2[1.41, 3.45]**	**0.16[0.09, 0.27]**	1.23[0.90, 1.67]
Heart failure	>0.9	0.8	0.6	0.5	0.2	0.7	0.072	0.2
Yes vs. No	0.95[0.55, 1.62]	0.15[0.00, >1000]	1.01[0.71, 1.43]	0.47[0.21, 1.06]	0.98[0.85, 1.14]	0.98[0.13, 7.43]	1.25[0.59, 2.69]	0.9[0.60, 1.37]
Stroke	>0.9	0.6	0.6	0.4	0.13	0.3	0.005	0.3
Yes vs. No	1.03[0.66, 1.60]	0.01[0.00, inf]	1.18[0.82, 1.70]	1.37[0.78, 2.39]	1.07[0.93, 1.23]	0.29[0.03, 2.53]	**33.3[19.3, 57.5]**	**1.84[1.14, 2.98]**
Peripheral vascular disease	0.8	0.13	0.6	0.7	0.009	0.7	0.3	0.011
Yes vs. No	0.93[0.53, 1.66]	**526[1.07, >1000]**	1.15[0.77, 1.71]	0.92[0.42, 2.01]	**1.25[1.08, 1.44]**	0.81[0.14, 4.61]	**8.35[4.22, 16.5]**	**2.73[1.75, 4.26]**
Liver disease	0.4	0.3	0.068	0.076	0.044	0.7	0.5	<0.001
Yes vs. No	0.85[0.47, 1.54]	43.8[0.19, 10,139]	**1.7[1.24, 2.33]**	**0.25[0.09, 0.72]**	1.13[0.97, 1.32]	1.14[0.24, 5.32]	**3.55[1.54, 8.22]**	**3.15[2.16, 4.61]**
Charlson comorbidity index	0.3	0.2	0.024	0.4	<0.001	0.6	0.4	<0.001

score								
1-2 vs. 0	**0.69[0.53, 0.90]**	0.3[0.01, 14.9]	1.12[0.93, 1.35]	1.04[0.76, 1.44]	0.93[0.87, 1.00]	0.76[0.42, 1.40]	**2.58[1.59, 4.18]**	**3.28[2.29, 4.71]**
3-4 vs. 0	1.22[0.76, 1.98]	17.9[0.06, 4,984]	1.28[0.92, 1.79]	**2.71[1.56, 4.73]**	0.97[0.84, 1.13]	0.21[0.02, 2.72]	0[0.00, 2.14]	**6.33[4.02, 9.97]**
>= 5 vs. 0	1.14[0.65, 1.99]	0[0.00, 0.00]	**1.79[1.25, 2.57]**	**2.37[1.26, 4.47]**	**1.79[1.55, 2.06]**	0.6[0.09, 3.85]	**9.74[4.61, 20.6]**	**16.3[10.5, 25.3]**
Antihyperlipidemic drugs	0.053	0.4	<0.001	0.4	<0.001	<0.001	0.031	<0.001
Yes vs. No	**0.81[0.69, 0.94]**	0.19[0.01, 3.54]	**0.53[0.46, 0.61]**	1.2[0.96, 1.48]	**0.72[0.68, 0.76]**	**0.54[0.39, 0.74]**	**0.43[0.28, 0.67]**	**0.38[0.28, 0.52]**
Antipsychotic	0.6	0.7	0.4	0.6	0.4	0.052	0.5	0.7
Yes vs. No	0.81[0.52, 1.25]	0.98[0.01, 67.6]	0.87[0.64, 1.19]	0.9[0.52, 1.55]	1.09[0.97, 1.23]	1.56[0.70, 3.49]	1.52[0.44, 5.25]	1.17[0.69, 1.98]
Thiazide diuretics	0.4	0.2	0.079	0.4	0.7	0.3	0.028	>0.9
Yes vs. No	1.05[0.87, 1.27]	0[0.00, inf]	**0.68[0.53, 0.86]**	0.98[0.71, 1.36]	0.98[0.91, 1.05]	**1.98[1.33, 2.94]**	**0.3[0.16, 0.55]**	1.09[0.74, 1.59]
Beta-blockers	0.6	0.7	0.5	0.14	0.6	0.076	0.6	0.5
Yes vs. No	1[0.84, 1.20]	3.23[0.40, 26.2]	1.05[0.89, 1.25]	0.92[0.70, 1.22]	1.02[0.96, 1.09]	**0.58[0.35, 0.97]**	**2.52[1.64, 3.88]**	0.98[0.73, 1.33]
Angiotensin inhibitors	<0.001	0.025	0.005	0.2	<0.001	0.038	0.6	0.6
Yes vs. No	**2.43[2.07, 2.84]**	1.01[0.04, 28.5]	**0.71[0.60, 0.83]**	1.14[0.91, 1.42]	**0.87[0.83, 0.92]**	0.75[0.53, 1.07]	**2.76[1.81, 4.21]**	1.12[0.83, 1.51]
Calcium channel blocker	0.6	0.3	0.12	0.045	0.006	0.4	0.4	0.8
Yes vs. No	**1.23[1.04, 1.45]**	0.28[0.00, 91.5]	**0.63[0.51, 0.76]**	0.9[0.69, 1.16]	**0.8[0.75, 0.86]**	**1.59[1.08, 2.33]**	**6.8[4.46, 10.4]**	0.88[0.63, 1.23]
Number of concomitant medications	0.001	0.028	<0.001	0.3	0.008	<0.001	0.5	<0.001
1-4 vs. 0	**0.72[0.55, 0.94]**	**0.02[0.00, 0.43]**	**3.14[2.18, 4.51]**	**0.71[0.51, 0.99]**	**1.24[1.11, 1.37]**	1.65[0.94, 2.91]	14.4[0.10, inf]	1.42[0.37, 5.51]
>= 5 vs. 0	**0.66[0.49, 0.88]**	0.2[0.02, 2.19]	**2.81[1.93,**	**0.4[0.28, 0.59]**	**1.35[1.21,**	0.56[0.29, 1.07]	2.11[0.01,	**5.6[1.52, 20.6]**

			4.07]		**1.51]**		325]	
Body mass index (kg/m²)	0.004	0.001	0.3	0.079	<0.001	0.026	0.006	<0.001
25-29.9 vs. <=24.9	**3.04[1.69, 5.49]**	0[0.00, 0.00]	**1.71[1.12, 2.59]**	**2.85[1.19, 6.82]**	**0.63[0.56, 0.72]**	0.08[0.01, 1.25]	**0.23[0.09, 0.58]**	**0.06[0.01, 0.34]**
>= 30 vs. <=24.9	1.32[0.73, 2.38]	18.6[0.00, inf]	1.16[0.78, 1.74]	**4.81[2.07, 11.2]**	**0.56[0.50, 0.63]**	**5.27[1.27, 21.9]**	0.66[0.31, 1.39]	0.79[0.37, 1.67]
Unknown vs. <= 24.9	2.78[1.56, 4.94]	5.58[0.00, inf]	1.18[0.79, 1.75]	2.37[1.01, 5.52]	0.71[0.64, 0.79]	2.44[0.59, 10.2]	0.4[0.20, 0.81]	1.4[0.69, 2.83]
HbA1c (%)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
7- <9 vs. < 7	**0.56[0.36, 0.86]**	0[0.00, 0.00]	**0.54[0.37, 0.78]**	1.14[0.45, 2.88]	**0.4[0.34, 0.47]**	0.76[0.28, 2.04]	**0.02[0.01, 0.05]**	**0.04[0.02, 0.10]**
>=9 vs. < 7	**2.47[1.65, 3.71]**	>1000 [inf, inf]	**1.99[1.40, 2.82]**	**12.2[5.08, 29.1]**	**3.62[3.16, 4.15]**	1.54[0.58, 4.06]	**0.2[0.11, 0.36]**	0.81[0.50, 1.31]
Unknown vs. < 7	4.51[2.98, 6.81]	>1000 [inf, inf]	3.58[2.51, 5.10]	20.7[8.54, 50.3]	4.44[3.85, 5.12]	2.87[1.08, 7.64]	0.26[0.14, 0.49]	0.86[0.52, 1.41]
Estimated glomerular filtration rate (ml/min/1.73m²)	<0.001	0.024	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
< 60 vs. >= 60	**2.05[1.51, 2.78]**	0[0.00, 0.00]	**3.92[3.13, 4.91]**	0.52[0.25, 1.11]	**1.98[1.81, 2.17]**	**3.35[1.79, 6.26]**	**16.4[9.81, 27.6]**	**15.4[10.8, 21.7]**
Unknown vs. < 60	2.54[2.08, 3.10]	211[4.31, 10,309]	1.75[1.48, 2.07]	2.31[1.74, 3.08]	0.95[0.89, 1.02]	1.83[1.18, 2.84]	3.82[2.10, 6.96]	1.66[1.15, 2.40]
High-density lipoprotein (mg/dl)	0.2	0.8	0.1	0.2	<0.001	0.2	0.8	0.018
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	**1.55[1.22, 1.95]**	0[0.00, 0.00]	**0.65[0.50, 0.85]**	**0.65[0.48, 0.88]**	**0.85[0.79, 0.91]**	1.35[0.88, 2.06]	**11.9[5.21, 27.4]**	**0.34[0.14, 0.83]**
>= 60 vs. <40 (M) or <50 (F)	1.48[0.97, 2.25]	0.02[0.00, inf]	0.91[0.59, 1.38]	0.7[0.41, 1.19]	**0.69[0.60, 0.80]**	**2.18[1.08, 4.43**]	0.95[0.22, 4.06]	**2.39[1.17, 4.89]**
Unknown vs. <40 (M) or <50 (F)	1.77[1.30, 2.42]	0.05[0.00, 3.52]	0.72[0.53, 0.98]	0.96[0.62, 1.48]	1.36[1.25, 1.48]	0.28[0.14, 0.57]	1.21[0.52, 2.81]	0.73[0.37, 1.46]
Triglyceride (mg/dl)	0.6	0.2	<0.001	0.1	<0.001	0.3	0.4	0.3

150-499 vs. < 150	**1.66[1.24, 2.22]**	0[0.00, 0.00]	1.08[0.82, 1.42]	**0.69[0.51, 0.94]**	**0.73[0.67, 0.79]**	1.32[0.69, 2.52]	**0.13[0.03, 0.65]**	**0.43[0.20, 0.89]**
>= 500 vs. < 150	0.95[0.53, 1.71]	**3705[15.5, inf]**	**3.01[2.04, 4.43]**	**0.12[0.04, 0.38]**	1.11[0.97, 1.26]	**2.68[1.11, 6.43]**	2.99[0.09, 100]	0.64[0.18, 2.29]
Unknown vs. < 150	0.99[0.69, 1.41]	14813[87.5, inf]	1.14[0.83, 1.58]	0.44[0.29, 0.67]	0.74[0.67, 0.81]	3.24[1.71, 6.12]	26.3[11.0, 62.4]	1.43[0.71, 2.90]
Total cholesterol (mg/dl)	0.3	0.7	<0.001	0.7	<0.001	0.2	0.4	<0.001
200-239 vs. < 200	0.99[0.78, 1.26]	0[0.00, 0.00]	**0.61[0.48, 0.79]**	0.9[0.66, 1.21]	0.93[0.86, 1.00]	0.63[0.38, 1.07]	0.5[0.22, 1.13]	1.45[0.77, 2.70]
>=240 vs. < 200	0.92[0.70, 1.21]	793[0.01, inf]	**0.52[0.39, 0.70]**	0.83[0.58, 1.19]	1.07[0.99, 1.16]	1.49[0.95, 2.36]	**0.23[0.06, 0.82]**	1.87[0.96, 3.66]
Unknown vs. < 200	1.26[0.92, 1.74]	11.6[0.00, inf]	2.12[1.55, 2.90]	1.15[0.71, 1.86]	1.14[1.04, 1.25]	2.14[1.03, 4.45]	0.66[0.34, 1.28]	4.03[2.13, 7.60]

Table 4.17: continued: triple therapy regimens (compared to metformin monotherapy)

Studied factor	biguanide+DPP4-I+SU	biguanide+GLP1-RA+SU	biguanide+SGLT2-I+SU	biguanide+ SU +insulin	biguanide+ SU+TZD
1- Demographic factors					
Age at prescription	0.9	0.4	0.003	<0.001	0.009
>= 65 vs. < 65 years	**2.84[2.24, 3.62]**	0[0.00, inf]	0[NA]	1.24[0.96, 1.60]	1.8[0.91, 3.55]
Sex	>0.9	0.6	0.4	<0.001	0.4
Female vs. Male	0.9[0.71, 1.14]	0.27[0.06, 1.16]	0[0.00, 0.09]	1[0.79, 1.26]	0.79[0.36, 1.74]
2- Socioeconomic factors					
Urban-rural	<0.001	0.002	0.001	0.051	0.2
2 vs. 1	1.17[0.86, 1.58]	0.95[0.14, 6.42]	0[0.00, 0.00]	**2.01[1.50, 2.68]**	**0.09[0.03, 0.30]**
3 vs. 1	1.16[0.74, 1.82]	0.02[0.00, 659]	90.7[0.40, 20,769]	0.98[0.59, 1.62]	0.6[0.22, 1.65]
4 vs. 1	1.59[0.85, 2.97]	**726[38.6, 13,646]**	61.2[0.35, 10,788]	0.9[0.37, 2.19]	0.13[0.01, 3.05]
5 vs. 1	**2.88[1.39, 5.98]**	9.13[0.08, 1,022]	58.3[0.07, 51,114]	1.36[0.50, 3.71]	0.05[0.00, 4,075]
6 vs. 1	1.01[0.66, 1.55]	0.01[0.00, inf]	**>1000[85.8, inf]**	1.25[0.82, 1.90]	0.27[0.08, 0.90]
7 vs. 1	**4.36[2.91, 6.54]**	**5264[246, inf]**	**>1000[134, inf]**	1.2[0.61, 2.38]	0.2[0.03, 1.26]
8 vs. 1	**3.8[2.46, 5.88]**	**28.7[1.80, 457]**	**>1000[5,547, in]**	**2.86[1.66, 4.91]**	**7.24[2.50, 20.9]**
Unknown vs. 1	1.89[0.14, 25.0]	1[0.98, 1.03]	48.8[0.25, 9,661]	78.3[15.9, 385]	0.32[0.00, inf]
Scottish index of multiple deprivation-quantile	0.7	>0.9	0.2	0.041	>0.9
2 vs. 1	**1.69[1.17, 2.43]**	0.43[0.05, 3.58]	0.01[0.00, 0.33]	1.34[0.97, 1.85]	10.6[2.48, 45.1]
3 vs. 1	**1.91[1.32, 2.76]**	0.28[0.03, 2.62]	0[0.00, 0.01]	1.05[0.73, 1.51]	2.5[0.49, 12.6]
4 vs. 1	1.15[0.76, 1.74]	**0.02[0.00, 0.24]**	0[0.00, 0.02]	**2.02[1.44, 2.82]**	6.08[1.29, 28.7]
5 vs. 1	1.38[0.90, 2.12]	2.57[0.21, 31.9]	0.38[0.03, 4.66]	0.42[0.24, 0.73]	10.8[2.48, 47.3]
Unknown vs. 1	0.08[0.00, 155]	0.88[0.88, 0.88]	109[0.00, inf]	0.07[0.00, 2.79]	0.18[0.00, inf]
3- Prescriber-related factors					
Prescriber type	0.009	0.047	0.2	0.002	0.043
Non-general practitioner (GP) vs. GP	0.31[0.12, 0.79]	0[0.00, 0.00]	0[0.00, 0.00]	0.01[0.00, 0.97]	0[0.00, 0.00]
4- Clinical-related factors					
Ischemic heart disease	0.012	0.8	0.087	0.8	0.2
Yes vs. No	0.72[0.47, 1.12]	0[0.00, 0.00]	0[0.00, 0.00]	1.44[0.99, 2.10]	0[0.00, 0.00]
Hypertension	0.021	0.4	0.8	0.9	0.047

Yes vs. No	0.58[0.38, 0.87]	0[0.00, 0.00]	0[0.00, 0.00]	3.2[2.39, 4.30]	0[0.00, 0.00]
Heart failure	0.05	0.6	0.5	0.3	0.7
Yes vs. No	3.14[1.64, 6.02]	0.51[0.00, inf]	0[NA]	0.82[0.45, 1.50]	0[0.00, 0.00]
Stroke	0.12	0.054	0.3	0.049	0.2
Yes vs. No	0.47[0.20, 1.11]	0[0.00, 0.00]	0.01[0.00, 244]	2.67[1.77, 4.04]	0.07[0.00, 758]
Peripheral vascular disease	0.4	>0.9	>0.9	0.6	0.7
Yes vs. No	0.67[0.28, 1.60]	0.04[0.00, inf]	0.02[0.00, 699]	1.34[0.73, 2.47]	0.2[0.00, inf]
Liver disease	>0.9	0.4	0.12	0.6	>0.9
Yes vs. No	1.17[0.40, 3.46]	3.41[0.01, 987]	12[NA]	2.09[1.28, 3.43]	0.14[0.00, inf]
Charlson comorbidity index score	0.2	0.073	0.032	<0.001	0.3
1-2 vs. 0	0.71[0.46, 1.08]	0[0.00, 0.00]	0[0.00, 0.00]	2.95[2.19, 3.96]	0[0.00, 0.00]
3-4 vs. 0	0.61[0.28, 1.32]	16.8[0.44, 634]	0[0.00, 0.00]	2.17[1.19, 3.95]	1.88[0.00, 1,319]
>= 5 vs. 0	0.23[0.05, 1.08]	26[0.30, 2,271]	0[0.00, 0.00]	3.63[2.07, 6.39]	0.31[0.01, 13.9]
Antihyperlipidemic drugs	<0.001	>0.9	0.4	0.073	<0.001
Yes vs. No	**2.42[1.86, 3.16]**	0[0.00, 0.00]	2.14[0.09, 51.7]	**0.48[0.37, 0.62]**	**4.79[2.10, 10.9]**
Antipsychotic	0.7	0.2	>0.9	0.6	0.3
Yes vs. No	0.74[0.31, 1.77]	**660[16.0, 27,145]**	18.3[0.44, 766]	1.68[0.97, 2.91]	0.16[0.00, 333]
Thiazide diuretics	0.029	0.5	0.2	0.069	0.3
Yes vs. No	**0.56[0.38, 0.84]**	**18.7[2.01, 174]**	0[0.00, 0.00]	1.18[0.84, 1.67]	**0.12[0.02, 0.81]**
Beta-blockers	0.8	0.006	0.6	0.3	0.15
Yes vs. No	1.17[0.87, 1.57]	0[0.00, 0.00]	0.02[0.00, 98.1]	**0.69[0.49, 0.98]**	0.31[0.06, 1.55]

Angiotensin inhibitors	<0.001	0.014	0.041	0.8	<0.001
Yes vs. No	1.15[0.90, 1.47]	**15886[146, inf]**	**32512[52.5, inf]**	1.23[0.95, 1.59]	**36[13.2, 98.1]**
Calcium channel blocker	0.6	0.8	>0.9	0.3	0.2
Yes vs. No	**0.53[0.39, 0.74]**	2.08[0.32, 13.6]	0.6[0.01, 30.7]	1.32[0.99, 1.78]	**0.2[0.06, 0.66]**
Number of concomitant medications	<0.001	>0.9	0.2	0.5	<0.001
1-4 vs. 0	0.93[0.58, 1.49]	0[0.00, inf]	0[0.00, 0.00]	**8.37[3.37, 20.8]**	0.28[0.05, 1.60]
>= 5 vs. 0	**0.36[0.21, 0.62]**	0[0.00, 0.10]	0[0.00, 0.00]	1.43[0.56, 3.70]	0.01[0.00, 0.06]
Body mass index (kg/m^2)	0.001	0.7	0.2	0.005	0.9
25-29.9 vs. <=24.9	0.79[0.47, 1.33]	0[0.00, 0.00]	0[0.00, 0.01]	0.9[0.48, 1.67]	786591[3,495, inf]
>= 30 vs. <=24.9	0.45[0.27, 0.76]	0[0.00, 0.01]	0[0.00, 0.00]	0.3[0.16, 0.57]	565864[2,520, inf]
Unknown vs. <= 24.9	0.83[0.52, 1.33]	0.04[0.00, 1.49]	0[0.00, 0.03]	1.15[0.65, 2.02]	236531[1,056, inf]
HbA1c (%)	<0.001	<0.001	<0.001	<0.001	<0.001
7- <9 vs. < 7	0.75[0.33, 1.72]	0[0.00, 0.00]	0[NA]	0[0.00, 0.00]	0[0.00, 0.00]
>=9 vs. < 7	2.77[1.26, 6.11]	0[0.00, 0.00]	4564[15.7, inf]	5.99[2.42, 14.8]	0[0.00, 0.00]
Unknown vs. < 7	7.75[3.53, 17.0]	>1000 [inf, inf]	>1000[inf, inf]	4.52[1.80, 11.4]	3.58[0.09, 136]
Estimated glomerular filtration rate (ml/min/1.73m^2)	<0.001	<0.001	0.004	<0.001	<0.001
< 60 vs. >= 60	4.31[2.87, 6.46]	0.04[NA]	0[0.00, 0.00]	0.96[0.59, 1.57]	111[0.98, 12,577]
Unknown vs. < 60	4.78[3.35, 6.83]	>1000[inf, inf]	>1000 [inf, inf]	1.09[0.80, 1.48]	45.1[0.74, 2,756]
High-density lipoprotein (mg/dl)	0.4	0.6	0.057	0.2	0.11
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.36[0.87, 2.11]	0[0.00, 0.00]	0[0.00, 0.00]	0.17[0.09, 0.34]	0[0.00, 0.00]

>= 60 vs. <40 (M) or <50 (F)	0.64[0.23, 1.74]	0[NA]	0[0.00, 0.00]	1.32[0.74, 2.37]	3.2[0.00, inf]
Unknown vs. <40 (M) or <50 (F)	1.46[0.82, 2.59]	>1000[inf, inf]	836[0.00, inf]	2.08[1.41, 3.07]	1.34[0.00, 3,065]
Triglyceride (mg/dl)	0.045	0.4	0.004	0.3	0.019
150-499 vs. < 150	0.86[0.51, 1.44]	0[NA]	0[0.00, 0.00]	0.36[0.21, 0.64]	0[NA]
>= 500 vs. < 150	2.95[1.23, 7.04]	570[570, 570]	123[0.00, inf]	2.52[1.38, 4.62]	0[0.00, 0.00]
Unknown vs. < 150	1.13[0.65, 1.96]	0.23[0.13, 0.43]	0[0.00, 0.00]	1.3[0.78, 2.18]	4.9[0.00, inf]
Total cholesterol (mg/dl)	<0.001	0.9	0.2	0.5	0.5
200-239 vs. < 200	0.25[0.12, 0.53]	0[NA]	0[0.00, 0.00]	0.81[0.50, 1.30]	0.22[0.00, inf]
>=240 vs. < 200	0.42[0.22, 0.78]	0[NA]	2399[0.12, inf]	2.74[1.86, 4.03]	0[0.00, 0.00]
Unknown vs. < 200	0.67[0.39, 1.14]	>1000 [inf, inf]	12.9[0.00, inf]	0.7[0.46, 1.05]	6.48[0.10, 424]

The results are presented as OR[95%CI] and the global p-value. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

III. Sensitivity analysis: factors influencing prescribing choice after addressing missing data

As mentioned previously, the substantial missingness in laboratory variables was addressed using the LOCF and multiple imputation methods and then applying the regression analyses on the imputed cohort in a sensitivity analysis. Tables 4.18 and 4.19 include the results of multivariable logistic regression applied to the imputed cohort for the regimen type and antidiabetic class, respectively. As presented in Table 4.18, the results of multivariate binomial logistic regression of the imputed cohort were consistent with the results of the regression of the original cohort for the majority of studied factors (Tables 4.16 and 4.18). Nevertheless, an increment in the extent of association was observed with prescriber type (from 0.72[95%CI: 0.65-0.79] to 0.57[95%CI: 0.52-0.63]) and stroke (from 1.08 [95%CI: 0.96-1.20] to 1.21[95%CI: 1.08-1.35]). On the other hand, multiple factors showed either a change in the direction or extent of association with different antidiabetic classes (Tables 4.17 and 4.19). Despite the change in the direction of association in some variables (e.g., age with TZD, IHD with DPP4-I, HTN with GLP1-RA, and others) before and after imputation, the results were statistically non-significant in both situations (Tables 4.17 and 4.19).

Furthermore, a sensitivity analysis was done by conducting a multivariable regression analysis including only patients with complete records (complete case analysis), and the results of factors influencing the choice of the regimen type and antidiabetic class are described in Appendix S.4.7. As described in the analyses of the imputed cohort, a change in the extent and direction of association of multiple factors with the prescribing choice of the regimen type and antidiabetic class was observed after including only the complete cases in the regression analyses (Table 4.16 and Appendix S.4.7). For instance, a change in the extent and significance of association was identified with PVD association with the regimen type (from 1.13[95%CI: 1.00-1.26 to 1.35[95%CI: 1.03-1.73]). Additionally, a change in the direction of the association of antipsychotic drugs, angiotensin inhibitors, and the number of concomitant medications with the regimen type was observed in

complete case analyses, yet the results were non-significant in both the original and complete case cohorts.

Table 4.18: Multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type (combination therapy versus monotherapy) for new ADD users after imputation (N=145,909)

Studied factor	OR[95%CI]	Overall p-value
Age at prescription		
>= 65 vs. < 65 years	0.76[0.73,0.8]	<0.001
Sex		
Female vs. Male	0.95[0.92,0.99]	0.019
Urban-rural		<0.001
1	1	
2	0.93[0.89,0.98]	
3	0.99[0.93,1.07]	
4	1.04[0.92,1.17]	
5	1.14[0.97,1.34]	
6	1.02[0.96,1.09]	
7	1.34[1.22,1.48]	
8	1.25[1.12,1.39]	
Scottish index of multiple deprivation-quantile		0.011
1	1	
2	0.98[0.93,1.03]	
3	0.95[0.9,1]	
4	0.95[0.9,1.01]	
5	0.92[0.87,0.98]	
Prescriber type		
Non-general practitioner (GP) vs. GP	0.57[0.52,0.63]	<0.001
Ischemic heart disease		
Yes vs. No	0.99[0.92,1.05]	0.675
Hypertension		
Yes vs. No	0.97[0.92,1.03]	0.356
Heart failure		
Yes vs. No	1.09[0.98,1.22]	0.107
Stroke		
Yes vs. No	1.21[1.08,1.35]	0.001
Peripheral vascular disease		
Yes vs. No	1.17[1.04,1.31]	0.008
Liver disease		
Yes vs. No	1.11[0.99,1.25]	0.070
Charlson comorbidity index-score		<0.001
1-2 vs. 0	1.05[0.99,1.11]	

3-4 vs. 0	1.09[0.98,1.22]	
>= 5 vs. 0	1.28[1.14,1.43]	
Antihyperlipidemic drugs		<0.001
Yes vs. No	0.74[0.71,0.77]	
Antipsychotic		0.769
Yes vs. No	1.02[0.92,1.12]	
Thiazide diuretics		0.022
Yes vs. No	0.94[0.88,0.99]	
Beta blocker		0.778
Yes vs. No	0.99[0.94,1.04]	
Angiotensin inhibitors		0.959
Yes vs. No	1[0.96,1.04]	
Calcium channel blocker		0.007
Yes vs. No	0.93[0.89,0.98]	
Number of concomitant medications		<0.001
0	1	
1-4	0.9[0.86,0.95]	
>= 5	1[0.95,1.06]	
Body mass index (kg/m^2)		<0.001
<=24.9	1	
25-29.9	0.92[0.85,0.99]	
>= 30	0.83[0.76,0.9]	
HbA1c (%)		<0.001
<7	1	
7- < 9	0.87[0.78,0.96]	
>= 9	2.15[1.95,2.37]	
Estimated glomerular filtration rate (ml/min/1.73m^2)		
< 60 vs. >= 60	1.5[1.4,1.6]	<0.001
High density lipoprotein (mg/dl)		<0.001
<40 (M) or <50 (F)	1	
40-59 (M) or 50-59 (F) vs.	0.91[0.87,0.95]	
>= 60	0.96[0.88,1.04]	
Triglyceride (mg/dl)		<0.001
< 150	1	
150-499	0.99[0.94,1.05]	
>= 500	1.28[1.16,1.42]	
Total cholesterol (mg/dl)		0.001
< 200	1	
200-239	0.9[0.85,0.94]	
>=240	0.99[0.93,1.05]	

The results are presented as OR[95%CI] and the global p-value

Table 4.19: Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to metformin) at stage of drug initiation after imputation (N=145346): Monotherapy groups

Studied factor	DPP4-I	GLP1-RA	insulin	SGLT2-I	SU	TZD
Age at prescription	0.199		<0.001	0.030	<0.001	0.489
>= 65 vs. < 65 years	1.39[0.89,2.15]	NA	**0.66[0.56,0.78]**	**0.44[0.25,0.78]**	**1.21[1.13,1.29]**	0.75[0.34,1.65]
Sex	0.228	0.098	0.431	0.177	0.003	0.441
Female vs. Male	1.16[0.92,1.47]	40.97[0.56, inf]	0.94[0.82,1.09]	1.28[0.91,1.79]	**0.91[0.86,0.96]**	1.46[0.59,3.62]
Urban-rural	0.034	0.007	0.602	0.160	0.013	0.006
2 vs. 1	1.05[0.74,1.5]	0[0,0]	1.02[0.85,1.22]	1.04[0.64,1.68]	0.93[0.86,1]	1.93[0.67,5.56]
3 vs. 1	1.04[0.74,1.45]	0[0, 393.94]	1.05[0.8,1.38]	0.91[0.57,1.47]	1.02[0.91,1.16]	2.02[0.57,7.19]
4 vs. 1	0.99[0.61,1.59]	113.44[0.38, inf]	0.98[0.65,1.48]	1.86[0.99,3.49]	1.16[0.97,1.39]	3.25[0.88,12.01]
5 vs. 1	**1.87[1.12, 3.14]**	12.35[0, inf]	1.49[0.84,2.65]	0.76[0.25,2.38]	1.18[0.97,1.44]	0.07[0,29183.23]
6 vs. 1	1.14[0.8,1.61]	**153.56[1.52, inf]**	1.14[0.95,1.37]	1.3[0.84,2.02]	1.01[0.87,1.16]	**3.19[1.06, 9.63]**
7 vs. 1	0.54[0.29,1]	0.19[0, inf]	1.09[0.83,1.44]	0.85[0.44,1.65]	1.04[0.89,1.22]	3.29[0.53,20.42]
8 vs. 1	0.71[0.4,1.24]	**>1000[15.57, inf]**	0.89[0.51,1.56]	0.84[0.39,1.82]	0.86[0.72,1.02]	1.5[0.28,8.13]
Scottish index of multiple deprivation-quantile	0.743	0.430	0.054	0.191	<0.001	0.795
2 vs. 1	1[0.76,1.31]	0.18[0, 9.37]	1.02[0.86,1.21]	1.15[0.79,1.67]	1.01[0.93,1.09]	1.16[0.59,2.25]
3 vs. 1	1.1[0.85,1.43]	0[0, 0.89]	1.07[0.92,1.26]	1.03[0.67,1.59]	0.95[0.84,1.07]	0.81[0.33,1.95]
4 vs. 1	0.93[0.69,1.25]	0.29[0, 243.34]	1.03[0.84,1.26]	1.43[0.84,2.42]	**1.15[1.04,1.27]**	1.04[0.45,2.43]
5 vs. 1	1.06[0.83,1.35]	5.76[0.09 ,368.61]	1.16[0.91,1.48]	0.7[0.31,1.57]	**1.21[1.05,1.39]**	1.03[0.41,2.6]
Prescriber type	0.818	<0.001	<0.001	0.155	0.892	0.951
Non-general practitioner (GP) vs. GP	1.04[0.77,1.39]	0[0,0]	**0.19[0.12,0.32]**	1.31[0.9, 1.9]	1.02[0.81, 1.28]	0.97[0.32, 2.95]
Ischemic heart disease	0.157	<0.001	0.546	0.118	0.548	0.312
Yes vs. No	1.19[0.94,1.5]	0[0,0]	1.07[0.87,1.32]	1.54[0.93,2.53]	0.95[0.82,1.1]	0.47[0.12,1.88]
Hypertension	0.434	0.946	0.363	0.441	0.303	0.615
Yes vs. No	1.09[0.88,1.36]	0.64[0, inf]	1.12[0.89,1.42]	1.19[0.77,1.83]	1.06[0.95,1.18]	0.82[0.39,1.75]
Heart failure	0.133	0.694	0.684	0.368	0.778	0.324
Yes vs. No	1.41[0.93,2.12]	36.16[0, inf]	0.93[0.68,1.29]	1.41[0.68,2.89]	0.97[0.79,1.19]	0.49[0.12,2.02]
Stroke	0.081	0.669	0.004	0.341	0.028	0.627
Yes vs. No	1.3[0.97,1.76]	0.01[0, inf]	**1.44[1.12,1.84]**	0.64[0.26,1.59]	**1.26[1.06, 1.51]**	0.64[0.11, 3.86]

Peripheral vascular disease	0.934	0.111	<0.001	0.218	<0.001	0.943
Yes vs. No	0.99[0.72,1.36]	0.01[0.01,0.01]	**1.84[1.4,2.41]**	1.49[0.8,2.78]	**1.31[1.14,1.49]**	0.95[0.24,3.79]
Liver disease	0.595	0.969	0.005	0.257	<0.001	0.488
Yes vs. No	1.14[0.71,1.85]	0.8[0, inf]	**2.01[1.42,2.87]**	0.48[0.14,1.62]	**1.26[1.11, 1.42]**	1.75[0.37,8.33]
Charlson comorbidity index score	<0.001	0.610	<0.001	0.733	<0.001	0.032
1-2 vs. 0	**1.43[1.06,1.93]**	0[0, inf]	**1.45[1.13,1.86]**	1.19[0.71,1.97]	**1.66[1.44,1.92]**	1.83[0.41,8.13]
3-4 vs. 0	**1.55[1.12,2.16]**	1357.22[0.03, inf]	**2.76[2.06,3.7]**	1.31[0.49,3.53]	**2.37[1.93,2.92]**	3.47[0.82,14.68]
>= 5 vs. 0	**1.92[1.02,3.63]**	0.01[0, 3.6]	**5.58[4.08,7.63]**	1.41[0.35,5.62]	**3.84[3.16,4.67]**	2.33[0.55, 9.88]
Antihyperlipidemic drugs	0.211		<0.001	0.524	<0.001	0.246
Yes vs. No	0.83[0.64,1.09]	NA	**0.37[0.29, 0.48]**	0.8[0.42,1.52]	**0.59[0.54,0.65]**	2.3[0.65, 8.19]
Antipsychotic	0.912	0.771	0.764	0.969	0.900	0.273
Yes vs. No	0.98[0.64,1.48]	0[0, inf]	1.04[0.81,1.34]	1.01[0.57,1.78]	0.99[0.87,1.13]	1.82[0.63,5.29]
Thiazide diuretics	0.077	0.857	0.033	0.284	0.038	0.428
Yes vs. No	0.8[0.63,1.01]	0.1[0, inf]	**0.78[0.63,0.97]**	0.81[0.55,1.19]	**0.85[0.75,0.97]**	0.73[0.35,1.55]
Beta blocker	0.251	0.007	0.849	0.367	0.050	0.154
Yes vs. No	1.2[0.9,1.6]	**179.62[4.12, inf]**	0.98[0.77,1.23]	1.27[0.78,2.07]	1.06[1, 1.13]	1.46[0.87, 2.45]
Angiotensin inhibitors	0.401	<0.001	<0.001	0.241	<0.001	0.472
Yes vs. No	1.08[0.9, 1.3]	0[0,0]	**0.64[0.54, 0.77]**	1.28[0.87, 1.89]	**0.81[0.75, 0.88]**	1.27[0.67, 2.39]
Calcium channel blocker	0.365	0.308	0.118	0.028	0.168	0.284
Yes vs. No	0.9[0.71, 1.13]	0.01[0, 55.09]	0.73[0.52, 1.02]	**0.67[0.47, 0.95]**	0.91[0.81, 1.03]	1.67[0.7, 3.97]
Number of concomitant medications	<0.001	0.980	<0.001	0.147	<0.001	0.189
1-4 vs. 0	**1.36[1.04, 1.79]**	0.03[0, 2.12]	1.18[0.92, 1.51]	1.19[0.5, 2.81]	1.16[1, 1.34]	0.7[0.2, 2.45]
>= 5 vs. 0	**1.7[1.31, 2.21]**	0[0, 1.82]	**1.52[1.24, 1.87]**	1.37[0.76, 2.45]	**1.79[1.51, 2.13]**	0.55[0.11, 2.64]
Body mass index (kg/m^2)	<0.001	0.737	<0.001	0.555	<0.001	0.811
25-29.9 vs. <=24.9	0.74[0.55, 1.01]	NA	**0.41[0.32, 0.53]**	0.72[0.21, 2.5]	**0.41[0.36, 0.47]**	2.4[0.12, 46.8]
>= 30 vs. <=24.9	**0.51[0.4, 0.64]**	>1000[0.02, inf]	**0.34[0.28, 0.41]**	1[0.29, 3.4]	**0.26[0.22, 0.29]**	2.02[0.08, 48.92]
HbA1c (%)	0.001	0.286	<0.001	0.993	<0.001	0.904
7-9 vs. < 7	**1.78[1.08, 2.95]**	0[0, 1.04]	0.68[0.45,1.01]	0.71[0.45,1.12]	1.12[0.98, 1.29]	0.6[0.06, 6.39]
>=9 vs. < 7	1.72[0.95, 3.1]	0[0, 2.84]	**1.56[1.23,1.98]**	0.82[0.35,1.88]	**2.05[1.81, 2.32]**	0.67[0.13, 3.55]
Estimated glomerular filtration rate	<0.001	0.133	0.001	0.958	<0.001	<0.001

(ml/min/1.73m^2)						
< 60 vs. >= 60	**6.79[4.87, 9.46]**	0[0, 9.75]	**4.34[2.96,6.35]**	0.98[0.42, 2.28]	**3.22[2.8, 3.69]**	**7.94[4.36, 14.47]**
High density lipoprotein (mg/dl)	0.306	0.756	0.129	0.041	0.028	0.924
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.2[0.95, 1.51]	1.07[0, 902.05]	0.87[0.74, 1.02]	1.47[0.71, 3.04]	0.96[0.83, 1.09]	1.2[0.36, 3.96]
>= 60 vs. <40 (M) or <50 (F)	1.32[0.91, 1.9]	0.03[0, inf]	1.17[0.9, 1.52]	0.58[0.32, 1.06]	1.16[0.99, 1.36]	0.43[0.01, 18.44]
Triglyceride (mg/dl)	0.325	0.715	0.009	0.255	0.020	0.874
150-499 vs. < 150	0.88[0.72, 1.09]	0.45[0, inf]	0.87[0.7, 1.09]	1.03[0.64, 1.65]	**0.92[0.85, 0.99]**	1.38[0.31, 6.03]
>= 500 vs. < 150	0.6[0.35, 1.05]	0[0, inf]	1.25[0.97, 1.61]	0.44[0.09, 2.18]	1.02[0.87, 1.2]	1.45[0.34, 6.24]
Total cholesterol (mg/dl)	0.965	0.422	0.354	0.678	0.125	0.659
200-239 vs. < 200	1.05[0.81,1.36]	0[0, inf]	0.93[0.75, 1.16]	1.06[0.72, 1.57]	**0.9[0.83, 0.98]**	1.51[0.53, 4.28]
>=240 vs. < 200	1.13[0.84,1.5]	0.82[0, inf]	1.14[0.91, 1.45]	1.03[0.73, 1.46]	1.06[0.97, 1.15]	0.83[0.11, 6.3]

Table 4.19: continued: dual therapy regimens

Studied factor	biguanide+DPP4-I	biguanide+GLP1-RA	biguanide+ insulin	biguanide+SGLT2-I	biguanide+ SU	biguanide+ TZD	DPP4-I+SU	SU+ insulin
Age at prescription	0.226	NA	0.302	0.364	0.270	0.206	0.530	0.233
>= 65 vs. < 65 years	0.64[0.34, 1.2]	NA	0.7[0.38, 1.28]	0.57[0.19, 1.72]	0.82[0.6, 1.12]	0.63[0.33, 1.22]	2.57[0.17, 38.64]	0.4[0.11, 1.47]
Sex	0.766	0.583	0.393	0.193	0.607	>0.9	0.483	0.251
Female vs. Male	0.87[0.36, 2.09]	11.77[0, inf]	1.26[0.78, 2.04]	1.25[0.9, 1.72]	0.93[0.72, 1.21]	0.98[0.49, 1.99]	1.79[0.4, 8.09]	0.59[0.26, 1.31]
Urban-rural	0.037	<0.001	0.416	0.060	0.001	<0.001	0.006	0.501
2 vs. 1	1.02[0.61, 1.69]	NA	0.93[0.54, 1.58]	**0.69[0.48, 0.98]**	0.82[0.52, 1.3]	2.11[0.83, 5.35]	4.71[0.19, 116.16]	1.29[0.81, 2.05]
3 vs. 1	0.8[0.37, 1.73]	550.03[1.32, >1000]	0.95[0.59, 1.54]	0.95[0.42, 2.17]	0.9[0.41, 1.95]	1.28[0.32, 5.12]	6.98[0.73, 66.28]	0.55[0.15, 1.97]
4 vs. 1	1.16[0.67, 2.01]	505.59[0.1, >1000]	0.95[0.57, 1.58]	1.21[0.56, 2.63]	0.85[0.54, 1.35]	0.64[0.06, 6.94]	0.04[0, inf]	0.13[0, >1000]
5 vs. 1	0.31[0, >1000]	25.62[0.02, >1000]	1.16[0.42, 3.2]	1.82[0.79, 4.21]	0.85[0.64, 1.13]	1.31[0.02, 95.7]	0[0, >1000]	1.24[0.13, 11.5]
6 vs. 1	1.11[0.79, 1.54]	60.48[0.08, >1000]	0.86[0.59, 1.24]	0.85[0.5, 1.44]	1.07[0.54, 2.09]	3.43[0.97, 12.15]	1.82[0.02, 150.63]	1.28[0.64, 2.57]
7 vs. 1	1.29[0.7, 2.37]	**>1000[2.33, >1000]**	0.95[0.61, 1.49]	1.03[0.21, 5.03]	1.06[0.69, 1.63]	3.13[0.83, 11.82]	5.13[0.16, 162.84]	0.87[0.38, 1.98]
8 vs. 1	1.01[0.41, 2.48]	**>1000[14.85, >1000]**	1.33[0.76, 2.33]	1.4[0.61, 3.23]	0.84[0.63, 1.11]	2.99[0.72, 12.39]	8.72[0.72, 105.98]	0.92[0.23, 3.65]
Scottish index of multiple deprivation-quantile	0.032	0.925	0.001	0.068	0.653	0.233	0.076	0.101
2 vs. 1	0.8[0.46, 1.38]	0.08[0, 6.44]	0.93[0.71, 1.21]	0.81[0.55, 1.19]	1.01[0.62, 1.66]	1.18[0.39, 3.54]	0.58[0.16, 2.05]	1.02[0.45, 2.31]
3 vs. 1	0.92[0.52, 1.64]	0.91[0, inf]	1[0.56, 1.81]	0.97[0.64, 1.48]	0.91[0.62, 1.33]	1.81[0.39, 8.3]	0.37[0.08, 1.62]	1.17[0.65, 2.08]
4 vs. 1	0.81[0.51, 1.31]	0[0, 7.09]	0.78[0.4, 1.52]	0.97[0.61, 1.54]	0.92[0.62, 1.36]	1.19[0.19, 7.67]	0.41[0.07, 2.36]	1.51[0.94, 2.41]
5 vs. 1	0.96[0.56, 1.62]	0[0, 185.79]	0.71[0.32, 1.6]	0.63[0.36, 1.1]	0.88[0.51,	2.7[0.57, 12.75]	0.07[0,	1.28[0.68,

					1.51]		>1000]	2.43]
Prescriber type	0.234	NA	0.082	0.821	0.008	0.502	0.398	0.509
Non-general practitioner (GP) vs. GP	0.74[0.46, 1.19]	NA	0.13[0.02, 0.87]	0.93[0.5, 1.74]	0.66[0.52, 0.82]	0[0, >1000]	0[0, >1000]	0.03[0, 495.19]
Ischemic heart disease	0.095	>0.9	0.441	0.179	0.773	0.356	0.675	0.675
Yes vs. No	0.72[0.5, 1.05]	0[0, 0]	1.24[0.74, 2.08]	1.41[0.86, 2.31]	0.88[0.4, 1.96]	0.18[0.01, 5.3]	0.45[0.01, 15.16]	0.86[0.43, 1.72]
Hypertension	0.007	NA	0.292	0.821	0.845	0.717	0.564	0.682
Yes vs. No	0.64[0.47, 0.87]	NA	1.22[0.87, 1.71]	0.9[0.38, 2.12]	1.04[0.73, 1.48]	1.46[0.21, 10.08]	0.61[0.12, 2.99]	1.1[0.69, 1.76]
Heart failure	0.873	0.720	0.824	0.632	0.904	0.935	0.806	0.770
Yes vs. No	0.94[0.45, 1.96]	0.03[0, 3308979.84]	1.08[0.56, 2.1]	0.73[0.21, 2.56]	0.96[0.53, 1.76]	1.14[0.05, 27.7]	0.34[0, 1559.39]	0.78[0.16, 3.75]
Stroke	0.393	0.017	0.688	0.252	0.686	0.408	0.676	0.823
Yes vs. No	1.26[0.74, 2.14]	0[0, 0]	1.12[0.65, 1.92]	1.55[0.74, 3.25]	1.17[0.57, 2.39]	0.53[0.12, 2.39]	2.94[0.03, 334.88]	1.11[0.45, 2.71]
Peripheral vascular disease	0.883	0.131	0.916	0.752	0.531	0.753	0.867	0.393
Yes vs. No	0.96[0.52, 1.76]	311.46[0.18, >1000]	0.97[0.6, 1.57]	0.87[0.35, 2.11]	1.19[0.72, 1.96]	0.79[0.19, 3.34]	0.65[0, 93.47]	1.88[0.5, 7.15]
Liver disease	0.337	0.077	0.474	0.432	0.263	0.803	0.952	0.101
Yes vs. No	0.51[0.14, 1.89]	419.23[0.56, >1000]	1.28[0.67, 2.42]	0.4[0.05, 3.53]	1.27[0.87, 1.84]	1.24[0.23, 6.58]	1.06[0.14, 8.02]	1.92[0.95, 3.86]
Charlson comorbidity index score	0.273	0.683	<0.001	0.356	<0.001	0.796	0.310	<0.001
1-2 vs. 0	0.84[0.55, 1.27]	0[0, inf]	1.04[0.66, 1.65]	0.97[0.55, 1.71]	1.13[0.74, 1.72]	0.73[0.23, 2.33]	0.92[0.43, 2]	**3.95[1.62, 9.64]**
3-4 vs. 0	1.48[0.76, 2.87]	>1000[1.3, inf]	1.4[0.83, 2.38]	1.88[0.83, 4.22]	1.06[0.58, 1.94]	0.34[0.04, 2.63]	0.04[0, >1000]	4.67[0.83, 26.26]
>= 5 vs. 0	0.19[0, >1000]	0[0, 400.61]	**1.96[1.15, 3.35]**	0.98[0.24, 3.89]	1.71[0.79, 3.72]	1.08[0.27, 4.38]	2.5[0.3, 20.59]	**9.86[2.03, 47.96]**

Antihyperlipidemic drugs	0.059	NA	0.053	0.628	0.028	0.176	0.887	0.214
Yes vs. No	**0.77[0.6, 0.98]**	NA	**0.48[0.27, 0.83]**	0.89[0.55, 1.42]	**0.62[0.46, 0.83]**	1.75[0.85, 3.6]	0.84[0.09, 7.94]	0.47[0.17, 1.32]
Antipsychotic	0.998	0.689	0.631	0.924	0.430	0.017	0.467	0.867
Yes vs. No	1[0.59, 1.7]	0.31[0, 97.05]	1.1[0.74, 1.64]	0.96[0.46, 2.01]	0.88[0.66, 1.18]	**2.84[1.25, 6.46]**	0.05[0, 158]	1.11[0.34, 3.57]
Thiazide diuretics	0.363	0.409	0.066	0.249	0.612	0.425	0.354	0.864
Yes vs. No	0.87[0.64, 1.17]	0[0, >1000]	0.75[0.56, 1]	0.69[0.38, 1.27]	0.84[0.45, 1.58]	1.64[0.54, 5]	0.07[0, 16.25]	1.05[0.61, 1.8]
Beta blocker	0.343	0.446	0.220	0.405	0.961	0.677	0.786	0.451
Yes vs. No	1.22[0.83, 1.81]	0.24[0.01, 9.23]	0.84[0.65, 1.09]	1.23[0.77, 1.97]	1.01[0.62, 1.66]	0.06[0, >1000]	0.82[0.21, 3.26]	1.23[0.73, 2.07]
Angiotensin inhibitors	0.154	0.135	0.080	0.832	0.381	0.587	0.875	0.987
Yes vs. No	1.34[0.94, 1.91]	513.26[0.39, >1000]	**0.7[0.5, 0.98]**	1.08[0.55, 2.12]	0.78[0.48, 1.27]	1.32[0.51, 3.39]	0.93[0.39, 2.2]	0.99[0.35, 2.8]
Calcium channel blocker	0.805	0.192	0.691	0.459	0.524	0.240	0.922	0.877
Yes vs. No	0.95[0.64, 1.42]	41.92[0.25, >!000]	0.93[0.68, 1.29]	0.83[0.51, 1.34]	0.89[0.64, 1.24]	1.41[0.82, 2.45]	0.92[0.21, 4.14]	1.05[0.56, 2]
Number of concomitant medications	<0.001	0.693	0.914	0.151	<0.001	<0.001	0.249	<0.001
1-4 vs. 0	0.82[0.53, 1.26]	2.93[0.17, 51.76]	0.98[0.32, 3.02]	0.83[0.56, 1.25]	0.89[0.68, 1.17]	0.55[0.19, 1.56]	1.31[0.05, 33.69]	1.77[0.41, 7.69]
>= 5 vs. 0	**0.67[0.48, 0.93]**	3.76[0.07, 213.57]	0.99[0.68, 1.45]	0.7[0.46, 1.07]	1.36[0.93, 1.97]	0.29[0.05, 1.73]	0.39[0.03, 4.51]	3.57[0.6, 21.3]
Body mass index (kg/m^2)	0.271	0.375	0.537	0.616	<0.001	0.696	0.002	<0.001
25-29.9 vs. <=24.9	1[0.66, 1.5]	NA	1.08[0.62, 1.89]	1.1[0.2, 5.93]	0.82[0.51, 1.3]	1.19[0.16, 8.78]	0.27[0, 493.71]	**0.31[0.13, 0.76]**
>= 30 vs. <=24.9	0.93[0.4, 2.15]	**>1000[2.19, inf]**	0.97[0.55, 1.7]	1.26[0.35, 4.58]	**0.51[0.3, 0.88]**	1.2[0.14, 10.41]	1.81[0, 3642.08]	**0.3[0.11, 0.81]**

HbA1c (%)	0.037	0.724	0.050	0.009	<0.001	0.584	0.085	0.043
7-9 vs. < 7	0.69[0.42, 1.12]	NA	0.57[0.23, 1.4]	0.83[0.42, 1.65]	0.81[0.44, 1.49]	1.83[0.3, 11.01]	115.87[0, inf]	11.25[0.04, >1000]
>=9 vs. < 7	1.19[0.42, 3.36]	0.04[0, 2.05]	1.06[0.5, 2.23]	2.16[0.39, 12.01]	**2.63[1.14, 6.1]**	1.75[0.13, 23.56]	431.65[0, inf]	19.7[0.23, >1000]
Estimated glomerular filtration rate (ml/min/1.73m^2)	<0.001	0.871	0.072	0.152	0.166	0.674	0.031	0.001
< 60 vs. >= 60	**2.17[1.57, 2.99]**	0.12[0, inf]	**2.43[1.15, 5.13]**	0.13[0.01, 1.73]	1.38[0.94, 2.03]	1.74[0.15, 19.85]	**4.35[1.43, 13.23]**	**5.64[3, 10.62]**
High density lipoprotein (mg/dl)	0.709	0.841	0.100	0.911	0.004	0.772	0.798	0.391
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.09[0.46, 2.56]	22.99[0.01, >!000]	0.78[0.28, 2.18]	1.09[0.51, 2.34]	0.96[0.77, 1.2]	0.81[0.43, 1.54]	1.78[0.43, 7.33]	0.77[0.36, 1.61]
>= 60 vs. <40 (M) or <50 (F)	1.01[0.54, 1.87]	0[0, inf]	0.82[0.47, 1.44]	1.12[0.53, 2.39]	0.89[0.56, 1.42]	1.43[0.53, 3.9]	0[0, >!000]	1.23[0.52, 2.92]
Triglyceride (mg/dl)	0.420	0.781	0.008	0.623	<0.001	0.810	0.709	0.934
150-499 vs. < 150	0.84[0.49, 1.45]	0.77[0, 190.45]	0.99[0.36, 2.77]	0.88[0.49, 1.57]	1.08[0.8, 1.46]	1.27[0.55, 2.93]	2.35[0.22, 24.71]	0.94[0.58, 1.54]
>= 500 vs. < 150	0.88[0.52, 1.49]	0.03[0, >1000]	1.43[0.82, 2.48]	0.69[0.11, 4.43]	1.64[0.73, 3.67]	1.15[0.14, 9.75]	2.75[0.03, 262.15]	0.92[0.43, 1.95]
Total cholesterol (mg/dl)	0.401	0.542	0.077	0.121	0.021	0.434	0.686	0.972
200-239 vs. < 200	1.12[0.69, 1.81]	0.02[0, 2660.13]	0.91[0.5, 1.64]	0.75[0.53, 1.06]	1.01[0.74, 1.39]	0.34[0, 23.29]	0.38[0, 162.95]	0.85[0.53, 1.38]
>=240 vs. < 200	0.81[0.56, 1.17]	1.11[0, >1000]	0.87[0.49, 1.57]	0.86[0.54, 1.39]	1.23[0.86, 1.77]	1.24[0.16, 9.4]	0.54[0, 131.15]	1.12[0.4, 3.08]

Table 4.19: continued: triple therapy regimens

Studied factor	biguanide+DPP4-I+SU	biguanide+GLP1-RA+SU	biguanide+SGLT2-I+SU	biguanide+ SU +insulin	biguanide+ SU+TZD
Age at prescription	0.470	>0.9	NA	0.524	0.589
>= 65 vs. < 65 years	0.85[0.56, 1.3]	0[0, 0]	NA	0.71[0.26, 1.91]	1.96[0.2, 19.05]
Sex	0.924	0.954	0.002	0.761	0.973
Female vs. Male	1.07[0.28, 4.12]	0.7[0, >1000]	0[0, 0]	0.8[0.21, 3.09]	1.07[0.03, 34.35]
Urban-rural	<0.001	<0.001	<0.001	0.561	0.367
2 vs. 1	0.87[0.47, 1.6]	>!000[0, inf]	NA	1.13[0.33, 3.85]	0.54[0.13, 2.19]
3 vs. 1	0.81[0.26, 2.53]	0[0, inf]	121.18[0.03, >1000]	1.11[0.51, 2.42]	1[0.21, 4.69]
4 vs. 1	1.11[0.38, 3.21]	>!000[0.86, inf]	57.27[0, inf]	0.77[0.21, 2.83]	0.61[0.08, 4.96]
5 vs. 1	0.99[0.12, 8.08]	145.3[0, inf]	174.77[0, inf]	1.07[0.11, 10.69]	0[0, inf]
6 vs. 1	**1.83[1.17, 2.86]**	0[0, inf]	>!000[0.18, inf]	0.7[0.17, 2.9]	0.44[0.02, 8.94]
7 vs. 1	**3.21[1.29, 7.95]**	>1000[0, inf]	>1000[0.06, inf]	1.05[0.37, 3.03]	0.4[0.02, 9.55]
8 vs. 1	**2.88[1.34, 6.17]**	3.09[0, inf]	>1000[6.79, inf]	0.93[0.1, 9.12]	1.04[0.12, 8.74]
Scottish index of multiple deprivation-quantile	0.965	0.932	0.090	0.151	0.979
2 vs. 1	0.94[0.4, 2.24]	1.02[0, inf]	0[0, 10.25]	1.05[0.36, 3.05]	0.92[0.04, 19.52]
3 vs. 1	1.24[0.65, 2.35]	8.91[0, inf]	0[0, 12.23]	0.83[0.34, 2]	0.67[0.14, 3.11]
4 vs. 1	1.28[0.66, 2.49]	0[0, inf]	0[0, 1.13]	0.95[0.2, 4.41]	0.83[0.18, 3.79]
5 vs. 1	1.06[0.62, 1.81]	0.03[0, 1789.8]	0.41[0, >1000]	0.36[0.1, 1.36]	1.09[0.39, 3.08]
Prescriber type	0.098	<0.001	0.938	0.443	>0.9
Non-general practitioner (GP) vs. GP	0.14[0.02, 1.21]	0[0, 0]	0[0, 0]	0[0, inf]	0[0, 0]
Ischemic heart disease	0.575	NA	NA	0.786	NA
Yes vs. No	0.3[0.01, 15.59]	NA	NA	1.14[0.46, 2.83]	NA
Hypertension	0.595	>0.9	0.028	0.951	NA
Yes vs. No	0.69[0.19, 2.49]	0[0, 0]	**0[0, 0.08]**	0.92[0.08, 11.12]	NA
Heart failure	0.202	NA	NA	0.621	<0.001
Yes vs. No	4.53[0.56, 36.45]	NA	NA	0.04[0, >1000]	0[0, 0]
Stroke	0.289	<0.001	<0.001	0.110	0.805
Yes vs. No	0.53[0.16, 1.71]	0[0, 0]	0[0, 0]	1.93[0.88, 4.25]	0[0, inf]
Peripheral vascular disease	0.463	0.295	0.148	0.477	0.935
Yes vs. No	0.63[0.18, 2.17]	0.01[0, 86.69]	**0[0, 0.01]**	1.59[0.46, 5.47]	1.16[0.03, 41.65]

Liver disease	0.892	0.669	0.555	0.950	0.867
Yes vs. No	0.9[0.19, 4.34]	4.34[0.01, >1000]	4.15[2.09, 8.26]	1.04[0.28, 3.94]	0.01[0, inf]
Charlson comorbidity index score	0.131	0.219	0.456	<0.001	0.465
1-2 vs. 0	0.66[0.25, 1.72]	NA	0[0, 0]	0.67[0.02, 19.22]	NA
3-4 vs. 0	0.55[0.12, 2.47]	15.2[0, inf]	0[0, 0]	1.79[0.06, 51.15]	0.03[0, inf]
>= 5 vs. 0	0.16[0.02, 1.63]	16.81[0, >1000]	0[0, 0]	1.06[0, 1298.56]	0.09[0, >1000]
Antihyperlipidemic drugs	0.356	NA	0.048	0.613	0.656
Yes vs. No	1.57[0.66, 3.72]	NA	**0[0, 0.85]**	0.6[0.1, 3.75]	2.28[0.08, 66.47]
Antipsychotic	0.602	0.299	0.863	0.810	0.815
Yes vs. No	1.35[0.45, 4.08]	>1000[0, inf]	1.31[0.07, 24.54]	0.86[0.24, 3]	0[0, inf]
Thiazide diuretics	0.547	0.699	NA	0.874	0.700
Yes vs. No	0.62[0.15, 2.6]	15.86[0, inf]	NA	1.09[0.4, 2.99]	0.33[0, 72.76]
Beta blocker	0.663	NA	0.001	0.850	0.273
Yes vs. No	0.51[0.03, 8.49]	NA	0[0, 0]	0.93[0.44, 1.95]	0.01[0, 24.22]
Angiotensin inhibitors	0.581	0.128	0.086	0.888	0.338
Yes vs. No	1.39[0.47, 4.18]	>!000[0.01, inf]	>1000[0.2, inf]	0.94[0.4, 2.2]	3.41[0.36, 32.18]
Calcium channel blocker	0.684	0.356	0.469	0.718	0.893
Yes vs. No	1.09[0.73, 1.62]	0[0, >1000]	0.07[0, 94.05]	0.87[0.42, 1.8]	0.73[0.01, 53.94]
Number of concomitant medications	<0.001	0.401	0.015	0.245	<0.001
1-4 vs. 0	0.37[0.11, 1.3]	228.47[0, inf]	5.92[0, inf]	1.24[0.11, 13.71]	0.15[0, 32.21]
>= 5 vs. 0	0.38[0.08, 1.75]	NA	NA	1.45[0.43, 4.87]	NA
Body mass index (kg/m^2)	0.001	0.613	0.910	0.073	>0.9
25-29.9 vs. <=24.9	0.71[0.24, 2.07]	0[0, 172.48]	0[0, >1000]	14.47[0, inf]	11.54[0, inf]
>= 30 vs. <=24.9	0.52[0.2, 1.33]	0.08[0, inf]	0[0, 0.68]	7.72[0, inf]	25.09[0, inf]
HbA1c (%)	0.820	0.822	0.634	0.017	0.114
7-9 vs. < 7	1.45[0.26, 7.99]	0[0, 1.13]	0[0, 0]	52.93[0, inf]	0.79[0.09, 6.9]
>=9 vs. < 7	0.96[0.06, 15.58]	1.69[0, inf]	0[0, 520.01]	146.75[0, inf]	1.15[0.04, 36.47]
Estimated glomerular filtration rate (ml/min/1.73m^2)	0.002	0.852	NA	0.185	0.923
< 60 vs. >= 60	**2.96[1.69, 5.22]**	12.88[0, inf]	NA	2.62[0.76, 9.08]	1.3[0.01, 216.92]
High density lipoprotein	0.758	0.646	0.798	0.301	>0.9

(mg/dl)					
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.73[0.37, 1.43]	0[0, 0]	0[0, inf]	0.4[0.13, 1.29]	0.46[0.06, 3.7]
>= 60 vs. <40 (M) or <50 (F)	1.01[0.51, 2.04]	0[0, inf]	0.03[0, inf]	0.38[0, 337.09]	0.16[0, inf]
Triglyceride (mg/dl)	0.632	0.688	0.730	0.748	0.346
150-499 vs. < 150	1.04[0.36, 3.01]	0[0, inf]	0[0, >1000]	0.84[0.17, 4.26]	0.98[0.29, 3.31]
>= 500 vs. < 150	0.93[0.09, 9.7]	12.97[0, inf]	0[0, 6.46]	0.14[0, >1000]	0[0, inf]
Total cholesterol (mg/dl)	<0.001	0.621	0.139	0.927	0.196
200-239 vs. < 200	0.54[0.29, 1]	0.04[0, >1000]	0[0, 0]	1.05[0.34, 3.31]	**0.52[0.03, 9.98]**
>=240 vs. < 200	**0.52[0.33, 0.84]**	0[0, >1000]	0[0, >1000]	1.18[0.41, 3.38]	0.14[0, >1000]

The results presented as OR[95%CI] along with the global p value. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

4.4 Discussion

This study aimed to comprehensively summarise the prescribing patterns of the first-line ADDs and identify a variety of clinical and non-clinical factors affecting the prescribing decision of ADDs at the stage of drug initiation in Scotland between January 2010 and December 2019. That, in turn, could potentially reflect the impact of the currently available new antidiabetic classes on the prescription of the older ones, as well as the agreement of the prescribing choice with clinical guidelines recommendations and specific drug features.

4.4.1 Key findings

According to this study, 90.7% of the 145909 new ADD users were started on monotherapy. Metformin was the most commonly prescribed initial antidiabetic monotherapy, followed by SU. Between 2010 and 2019, the use of metformin, DPP4-I, and SGLLT2-I as a first-line treatment for T2DM significantly increased, whereas SU, TZD, and insulin prescribing significantly decreased. The remaining 9.3% of new ADD users were started on combination therapy, where the majority of patients used dual ADDs, and only 9.5% were treated with triple or more therapy. Metformin+SU was the most frequently used dual therapy over the entire study period, yet its prescription has significantly fallen over the study period. In contrast, the use of metformin+DPP4-I, metformin+SGLT2-I, and DPP4-I+SU has considerably increased. Additionally, most triple therapy users were treated with a metformin-SU-based combination, in which metformin+SU+DPP4-I was the most often prescribed triple combination regimen; nevertheless, only the use of metformin+SU+SGLT2-I showed a significant increment over the course of the study.

Moreover, several factors were identified to be associated with the prescribing choice of the regimen type and the antidiabetic class at the stage of drug initiation for newly treated patients with T2DM. Living in more urban areas, having a baseline CCI score of >= 5, having a baseline HbA1c of >=9, having a low eGFR of <60, and having a TG level of >=500 were factors associated with combination regimen use. On the other hand, older age, female sex, living in a more deprived area, using lipid-lowering drugs, being obese, having a medium level of HDL (40-59 (M) or 50-59 (F)),

and having a total cholesterol level of 200-239 mg/dl were negatively associated with prescribing combination therapy. Nevertheless, factors influencing the prescribing choice of ADDs varied by the class of ADDs, with the most significant associations being seen with prescribing SU, insulin, and DPP4-I.

4.4.2 Baseline characteristics of the study cohort

Of the overall study cohort (N= 145909), 57.9% of patients were male, and about 61% were younger than 65 years at the time of drug initiation (median overall age = 61 [IQR: 52-70]). The baseline demographic characteristics of this study cohort were close to what have been reported by Read et al. (2016), which was conducted in Scotland and showed that the incidence of T2DM was higher among males compared to females (57.2 % vs. 42.8% in 2013), and the mean age of newly diagnosed patients with T2DM was 59.2 and 63.1 years in the most and least deprived deciles, respectively *(Read et al., 2016).* Consistent findings were found in McGurnaghan et al. (2022), in which the percentage of male patients with T2DM and the median age at diagnosis between 2006 and 2020 were 55.5% and 60.0 [IQR: 50.6-69.0] years, respectively *(McGurnaghan et al., 2022).* The Scottish diabetes survey also reported a greater proportion of males among patients with incident type 2 diabetes (56.4%) *(Scottish Diabetes Data Group, 2020).* Likewise, the proportion of male patients in this study was close to the ones conducted in the UK (55%), Denmark (57%), and Campania (54.8%) *(Filion et al., 2009, Grimes et al., 2015, Mor et al., 2015, Moreno Juste et al., 2019).* However, it was higher than multiple studies conducted in the USA *(Montvida et al., 2018, Brouwer et al., 2012, Desai et al., 2012)*, Germany *(Geier et al., 2014)*, Canada *(Wang et al., 2013a),* and Austria *(Winkelmayer et al., 2011a),* yet lower than a study conducted in Japan *(Morita et al., 2019)*.

The median age of the study cohort (61 years) was in the range of the baseline age of newly treated patients with T2DM reported in several studies from different countries (range: from 54 to 65.6 years). Some studies conducted in the USA reported a lower baseline age than the one identified in the current study *(Montvida et al., 2018, Brouwer et al., 2012, Desai et al., 2012)*, while other studies based in the UK

(Filion et al., 2009), Japan *(Morita et al., 2019)*, Campania *(Moreno Juste et al., 2019)*, Austria *(Winkelmayer et al., 2011a),* and Germany *(Geier et al., 2014)* showed a higher baseline age at drug initiation. The differences in the baseline demographics of the incident ADD users across studies may be attributed to the variability in the sample size, utilised data source, the characteristics of studied populations, and the prevalence of diabetes risk factors, such as the prevalence of obesity in each country. In terms of socioeconomic characteristics, the majority of patients in this study lived in urban areas (70.3%), and about one-quarter (26%) were based in the most deprived areas, with only 13.04% residing in the least deprived areas. The results were in agreement with what have been reported by McGurnaghan et al. (2022), where 23.9% and 13.6% of patients with T2DM in Scotland between 2006 and 2020 lived in the most and least deprived areas, respectively. The higher proportion of new ADD users living in the most deprived areas could be explained by the previous findings that the incidence and prevalence of T2DM were higher in the more deprived locations. That could be driven by the strong relation between deprivation and several diabetes-related risk factors, including obesity, smoking, and physical inactivity *(Connolly et al., 2000, Jacobs et al., 2019).*

Obesity is an important and well-known modifiable risk factor for T2DM *(Malone and Hansen, 2019)*, and the Scottish diabetes survey reported that a total of 87.3% of patients with T2DM with a known BMI data in 2020 were either overweight (31.2%) or obese (56.2%) *(Scottish Diabetes Data Group, 2020).* In accordance with that, the baseline median BMI of the available data (57.59%, 84036/145909) in this study was 32 [28-37] kg/m^2, in which more than one-half of the entire cohort (53.13%) were either overweight (15.03%) or obese (38.1%) at the time of drug initiation, representing a total of 92.2% of the included subjects with known BMI values (overweight: 26.1%(21929/84036), obese: 66.1%(55560/84036)). The higher percentage of overweight/obese patients in this study could be related to the difference in the time interval of data collection, in which data covered the period between 2010 and 2019 in this study, while in the Scottish diabetes survey, data covered only the year 2020. Additionally, there was variability in the percentage of

the available BMI data (57.59% in this study vs. 66.6% in the Scottish diabetes survey) and the type of included patients, as only new ADDs users were included in this study compared to all patients diagnosed with T2DM in the Scottish diabetes survey. Likewise, the baseline median BMI in this study was slightly higher than the one stated by McGurnaghan and colleagues (32 [28-37] vs. 30 [26-34]) *(McGurnaghan et al., 2022).* Additionally, the proportion of obese patients in this study was greater than the ones observed in Europe (45%) *(Heintjes et al., 2017)*. In contrast, it was lower than studies conducted in the USA, where 75.5% and 68% of patients were obese, as reported by Brouwer et al. (2012) and Montvida et al. (2018), respectively *(Brouwer et al., 2012, Montvida et al., 2018)*. In addition to the differences in the methodological aspects across studies (e.g., study duration, utilised data source, sample size, completeness level of data), the variability in the baseline BMI could be linked to the differences in obesity prevalence across countries. The rate of obesity in Scotland is higher than in European countries but lower than in the USA *(Scottish Government, 2020).*

Of the available baseline HbA1c values at drug initiation (81.3%, 118655/145909), the median HbA1c found in this study was higher than one reported by McGurnaghan and colleagues (8.6 [7.70-10.30] vs. 7.18 [6.45-8.37], and the proportion of patients with a very high baseline HbA1c value of >= 9% was more than two folds of the one reported in the Scottish diabetes survey (43.1% vs. 19.5%). This large difference could potentially be explained by the difference in the time interval of data collection and the fact that this study included only incident users of ADDs, while other studies examined all patients diagnosed (not only newly diagnosed) with T2DM over a specific period. Newly diagnosed patients with T2DM are expected to have a higher baseline HbA1c value, especially those who were assigned to receive pharmacological management for T2DM. Similarly, the percentage of patients with a baseline HbA1C of >= 9% in this study was greater than the ones identified in the USA (43.1% vs. 23.3%) and Europe (43.1% with HbA1c >= 9% vs. 12% with HbA1c of >= 8.5%) *(Brouwer et al., 2012, Heintjes et al.,*

2017). The differences in the sample size and the percentage of available data could contribute to the variability in the baseline HbA1c among studies.

Regarding the baseline lipid profile of the included patients in this study, the baseline median HDL was close to the one reported by McGurnaghan and colleagues (43 [IQR: 35-50] vs. 42.5[IQR: 39-54] mg/dl). However, the baseline total cholesterol was higher in this study compared to the latter one (185 [IQR: 155-220] vs. 158 [IQR: 131-189] mg/dl) *(McGurnaghan et al., 2022)*. The baseline TG level was not reported in previous studies as the median [IQR] for comparison. T2DM is a metabolic disease affecting the lipid profile as a result of insulin resistance and obesity, which is mainly manifested by decreasing HDL level and increasing TG level. Accordingly, the findings of the abnormal baseline HDL and TG levels in this study were expected. As mentioned above, the baseline lipid profile in this study was more abnormal than the one reported by McGurnaghan et al. (2022), and this could be linked to the fact that this study included only incident users of ADDs, while the latter included prevalent users as well. Newly diagnosed patients with T2DM tend to have more abnormal levels of lipid profile because they have not started yet on the treatment plan, including glycaemic control, weight loss, and starting antihyperlipidemic drugs, which would assist in improving the lipid profile *(Vijayaraghavan, 2010).*

On the other hand, a higher baseline median eGFR level was identified in this study compared to McGurnaghan et al. (2022) (91 [75-102] vs. 75 [54-91]). This could be related to the previous findings that the reduction in kidney function usually develops with the progression of T2DM *(Alicic et al., 2017);* thus, patients early in the disease are less likely to have reduced kidney function; the situation mostly related to the newly treated patients for T2DM. For the other clinical-related characteristics, the majority of patients had a zero baseline CCI score (79.2%), with HTN (17.9%), followed by IHD (12.5%) representing the most prevalent comorbid conditions. Additionally, around 63% of patients were on five or more concomitant medications, in which antihyperlipidemic drugs and angiotensin inhibitors were the most

frequently utilised comedications (57.9% and 42.6%, respectively). HTN and IHD were the most prevalent diseases among the included cohort, and this could be due to the reason that HTN and T2DM are common comorbid conditions that occur concurrently as the risk of T2DM among hypertensive patients is higher than normotensive ones; both HTN and T2DM are main risk factors for CVDs *(Long and Dagogo-Jack, 2011, Petrie et al., 2018).* However, the prevalence of HTN and IHD in this study was significantly lower than the prevalence of HTN and coronary heart disease among patients with T2DM in Japan (17.9% vs. 62.1% and 12.5% vs. 30.9%, respectively) *(Morita et al., 2019).*

4.4.3 Prescribing pattern of first-line ADDs for newly treated patients

Although more than 90% of patients in this study were started on single ADDs, a significant decline was observed in prescribing antidiabetic monotherapy for newly treated patients, with a significant rise in the initiation of combination therapy. The increasing use of combination therapy as initial management for T2DM could be related to the current availability of newer ADDs with different pathophysiologic effects and extra-glycaemic benefits (e.g., weight loss, renal/cardioprotective effects), providing prescribers with more options not only to achieve glycaemic control but also to decrease the progression of diabetes-related complications. For instance, clinical guidelines have recommended using ADDs with proven cardiovascular benefits (e.g., SGLT2-I) in addition to metformin as initial treatment for patients with established CVDs or with risk factors for CVDs *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. Besides, some clinical guidelines (e.g., ADA) recommended starting patients with a baseline HbA1c value that is different from the target by >=1.5% on a combination regimen; nevertheless, this recommendation is not clearly stated in the SIGN and NICE guidelines *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. Furthermore, patients presenting with very high HbA1c levels (>=9%) need to be started on insulin *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021)*. However, because of the several

barriers associated with using insulin injection as initial therapy for patients with T2DM, one would prefer to use combination therapy of oral drugs as initial treatment for T2DM over insulin *(Alidrisi et al., 2021, Haque et al., 2005).* Consistent with this study finding, Wang et al. (2013) reported that 92% of included subjects were started on single ADDs *(Wang et al., 2013a).* The result was also in keeping with Lee et al. (2021) showing a significant increase in combination therapy prescribing for T2DM management in Korea between 2000 and 2019, yet it was not mentioned at which stage of treatment the prescribing pattern was observed *(Lee et al., 2021).*

National and international guidelines have recommended metformin as a drug of choice for patients newly diagnosed with T2DM because of its pleiotropic effects, including glycaemic control, weight neutral to weight loss effects, cardiovascular risk improvement, as well as its low cost and low hypoglycaemic *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021)*. Consistently, this study showed that metformin was by far the most commonly used first-line ADDs for newly treated patients in each studied calendar year, with more than 85% of the included cohort using metformin as initial therapy. Furthermore, the proportional use of metformin increased to 91% in 2019.

Despite the favourable effects of metformin, there are certain conditions where metformin could be an inappropriate option, such as in the case of drug intolerance (mainly severe gastrointestinal side effects) or having relative/absolute contraindications, including significant renal impairment and advanced stage of HF *(Gu et al., 2022, Irons and Minze, 2014)*. In that situation, several treatment options are currently available, yet no definite guidance is available regarding the selection of the most appropriate alternative first-line therapy. As a result, variability in the prescribing decision, in that case, is expected. Of non-metformin monotherapy users in this study, SU represented the highest proportional share of prescribed ADDs at the stage of drug initiation between 2010 and 2019; however, its use almost halved by the end of the study period. Despite the low use of the remaining classes as initial therapy, a significant rise in prescribing DPP4-I and SGLT2-I was observed

between 2010 and 2019, accompanied by a significant decline in the use of TZD and insulin. The availability of more pharmacological options with multiple extra-glycaemic benefits for T2DM management and possibly increasing familiarity of prescribers with the safety and effectiveness of newer ADDs might partially explain the observed reduction in the use of older groups (SU, insulin, and TZD) and increment in prescribing of newer classes (SGLT2-I and DPP4-I) over the study period.

Additionally, the reduction in TZD prescribing might occur in response to the cardiovascular safety warning alert associated with rosiglitazone use issued in May 2007 *(Lipscombe et al., 2007, Loke et al., 2011)*. Similar to the SGLT2-I, GLP1-RA has a favourable effect on body weight and renal/cardiovascular risk *(Górriz et al., 2020, Ninčević et al., 2019, Li et al., 2020)*. Still, no significant increase in the use of GLP1-RA was noted between 2010 and 2019. The previous finding might be related to the availability of only the injecTable form of GLP1-RA since the oral formulation of GLP1-RA (semaglutide) was introduced into the Scottish market in 2020 and only accepted for restricted uses *(NHS Scotland, 2020)*. The injecTable form can be a barrier to GLP1-RA prescribing because it might negatively influence patient adherence *(Giorgino et al., 2018)*. Furthermore, the assignment of GLP1-RA as a third or fourth-line agent in the SIGN guideline might also contribute to the observed non-significant change in prescribing GLP1-RA as a first-line therapy in this study *(The Scottish Intercollegiate Guidelines Network, 2017)*.

The study findings relevant to the change in the prescribing patterns of ADDs for newly treated patients were in line with previous studies conducted in the UK *(Filion et al., 2009, Grimes et al., 2015, Leal et al., 2013, Sharma et al., 2016, Wilkinson et al., 2018a)*, Europe *(Christensen et al., 2016, Mata-Cases et al., 2016, Overbeek et al., 2017)*, the USA *(Brouwer et al., 2012, Desai et al., 2012, Montvida et al., 2018)*, and Taiwan *(Chu et al., 2017)*. These studies also reported a statistically significant reduction in prescribing old antidiabetic groups (SU, insulin, and TZD) as initial therapy, with a significant increase in the prescription of newer classes. Of the newer antidiabetic

classes, DPP4-I was the most commonly investigated one, while the prescribing trends of SGLT2-I were only examined in one study at drug initiation since most studies were conducted before or early after the introduction of SGLT2-I *(Montvida et al., 2018)*. In addition, inconsistent with this study finding, a study conducted in Europe showed a significant increase in the use of GLP1-RA as initial therapy over the study period. Nevertheless, the difference in the time interval of data collection between this study and Overbeek et al.(2017) could attribute to the abovementioned inconsistent result, in which the data was collected from 2007 and up to 2012 in Overbeek study *(Overbeek et al., 2017)* compared to a time interval of 2010 to 2019 in this study. That was supported by the finding of another study conducted in Europe which reported a rapid increase in GLP1-RA prescribing after their introduction and then stabilised in the last two years of the study interval (2013 and 2014) *(Christensen et al., 2016).*

Generally, the findings relevant to the proportional share or utilisation of antidiabetics classes imply a better adherence of prescribing practice in Scotland to the guideline recommendation of using metformin as initial therapy for newly treated patients with T2DM compared to previous studies. That was reflected by the greater proportion of patients receiving metformin as initial therapy in this study relative to the earlier ones conducted in different countries, including the UK, the USA, Europe, and Taiwan *(Christensen et al., 2016, Chu et al., 2017, Mata-Cases et al., 2016, Montvida et al., 2018, Overbeek et al., 2017).* For instance, in 2016, 77% of patients received metformin as initial therapy in a study conducted in the USA *(Montvida et al., 2018)* compared to 90.7% of patients starting on metformin in this study. Furthermore, a study conducted in Colombia reported that in 2013, 68% of patients were initiated on metformin *(Mata-Cases et al., 2016)* compared to 89.7% (in 2013) in this study. The discrepancy could be related to the differences in the utilised data sources, study sample size, and the baseline characteristics of the studied population.

The economic and clinical consequences of starting patients on more than one ADD rather than following the sequential or stepwise approach are still uncertain *(Cersosimo et al., 2018a, Bianchi et al., 2017)*. It has been suggested that combination therapy with complementary mechanisms of action would be beneficial in delaying disease progression *(Bianchi et al., 2017).* Nevertheless, as documented in this study, combination therapy was prescribed to a much lesser extent compared to monotherapy for patients newly diagnosed with T2DM. The majority of patients received a metformin-based combination, where metformin+SU was the most frequently prescribed combination regimen, followed by metformin+DPP4-I. However, the use of metformin+SU has significantly fallen over time, which was accompanied by the rise in the use of metformin+SGLT2-I and metformin+DPP4-I. As stated previously, metformin is the only drug recommended by all clinical guidelines as a first-line therapy for newly diagnosed patients with T2DM; thereby, it is not surprising to have metformin as a core treatment in the majority of combination regimens. The change in the prescribing trends of combination regimens is quite similar to the monotherapy regimens, in which the prescribing patterns of combination regimens that included SU or TZD showed significant fall over time, while regimens including DPP4-I or SGLT2-I were increasingly used over the study period. That is likely due to the same reasons mentioned above with monotherapy regimens relevant to the update in guidelines recommendation and the availability of wider options for T2DM management with different safety and extra-glycaemic benefits. In addition, it has been reported that early initiation of metformin+DPP4-I increases the durability of glycaemic control compared to the stepwise approach *(Ji et al., 2021).* Similar to monotherapy regimens, the prescribing trends of combination regimens that included GLP1-RA showed no significant change over the study period. That observation could be related to the potential barrier of the injectable route of administration of GLP1-RA and to the fact that GLP1-RA is recommended as third or fourth-line therapy in the SGIN guideline as described earlier.

Compared to the initial antidiabetic monotherapy prescribing, the prescribing patterns of combination regimens were much less frequently investigated. The

majority of studies either studied the use of combination therapy in general without specifying the class of combination regimen *(Brouwer et al., 2012, Chu et al., 2017)* and the stage of treatment *(Christensen et al., 2016, Engler et al., 2020, Ko et al., 2016, Lee et al., 2021)*, or examined the outcome at drug intensification (Aguadé et al., 2021, Overbeek et al., 2017, Sultana et al., 2010). Very few studies assessed the prescribing patterns of combination regimens at the stage of drug initiation. Wilkinson and colleagues reported that metformin+SU was the most commonly used combination regimen, followed by metformin+ insulin *(Wilkinson et al., 2018a)*, yet in this study, metformin+SU and metformin+DPP4-I represented the highest proportional share of combination regimens. As stated previously, the difference could be due to the variability in the study time interval as the current study included more recent years (from 2010 to 2019) compared to Wilkinson and colleagues (from 2000 to 2017) *(Wilkinson et al., 2018a)*. The difference in the utilised data source, the characteristics of the study population, and the study sample size might also have contributed to the abovementioned variability.

4.4.4 Factors influencing the prescribing choice of the regimen type and antidiabetic class at drug initiation

For factors influencing the prescribing choice of the regimen type, the decreasing odds of prescribing combination therapy compared to monotherapy for elderly patients (>= 65 years old) could reflect clinical practice adherence to guidelines recommendations regarding personalising treatment goals and considering less strict goals for elderly patients, especially in the presence of comorbid conditions and limited life expectancy because of the high risk of hypoglycaemia and mortality *(American Diabetes Association, 2020, National Institute of Health and Care Excellence, 2021).* Likewise, the lower likelihood of prescribing combination ADDs as initial therapy for female patients compared to male patients could be related to the observation that female patients tend to visit the GPs and get a consultation more than male patients, hence more likely to get diagnosed at an earlier less severe stage *(Wang et al., 2013b).* That could also be related to the findings that female patients were less adherent to their medications than male patients; thus, starting a

female patient on combination therapy may increase the risk of non-adherence *(Demoz et al., 2020, Manteuffel et al., 2014).* In addition, the lower odds of prescribing combination therapy for obese patients could be linked to the fear of non-adherence, particularly if the two drugs have weight gain effects. However, the current availability of ADDs with weight loss effects should be considered for selecting the most appropriate drugs for obese patients since achieving weight loss among patients with T2DM has positively influenced patient adherence *(Grandy et al., 2013).*

Combination regimens were more likely to be prescribed for patients with an HbA1c value of >= 9% at drug initiation, and this could be related to the fact that non-insulin ADDs can reduce HbA1c level by 1.5% at maximum when used as monotherapy. However, since the goal of HbA1c for the majority of patients with T2DM is less than 7%, patients who are away from the goal by more than 1.5%(e.g., HbA1c value >=9%) need to be started either on insulin or combination therapy to achieve the glycaemic target *(American Diabetes Association, 2021, Hirst et al., 2013, National Institute of Health and Care Excellence, 2021)*. Because of the barriers associated with insulin injection, a patient may prefer to start a combination regimen rather than insulin *(Alidrisi et al., 2021, Haque et al., 2005).* The greater likelihood of starting combination therapy for patients who had a low baseline eGFR (< 60 ml/min/1.73m^2) could be related to the required lower doses of antidiabetic medications for patients with reduced kidney function *(Betônico et al., 2016).* Therefore, multiple ADDs might be needed to achieve adequate glycaemic control. Factors influencing the prescribing choice of the regimen type as initial therapy for newly diagnosed type 2 diabetes were not substantially studied in the literature. Mor and colleagues examined predictors of receiving combination therapy over monotherapy for patients newly diagnosed with T2DM. The results were consistent with the findings of this study for age, CCI score, and HbA1c level, yet the result was non-significant for patient sex *(Mor et al., 2015).*

Regarding factors associated with the prescribing choice of antidiabetic class, of the studied demographic factors, patient age at prescription showed a significant association with prescribing most monotherapy and combination therapy regimens. Elderly patients were significantly more likely to be initiated on DPP4-I, SU, and DPP4-I+SU than metformin compared to younger individuals, yet less likely to receive insulin, SGLT2-I, GLP1-RA, metformin-based dual regimens, and SU+ insulin. The selection of ADDs for older patients is more challenging than for younger individuals since they tend to have more comorbid conditions or complicating factors, are more susceptible to ADR, and experience more adherence problems. Accordingly, treatment regimens should be kept as simple as possible for elderly patients *(Bajwa et al., 2014, Yakaryılmaz and Öztürk, 2017).* Consequently, that might be the reasons behind the significantly lower prescription of insulin, new ADDs (SGLT2-I and GLP1-RA), and most combination regimens (e.g., metformin-based dual therapy and SU+ insulin) for elderly patients who were newly diagnosed with T2DM. Besides, the lower prescription of insulin as initial therapy for elderly patients could be attributed to several other reasons, including the high risk of hypoglycaemia associated with insulin increasing risk of falls, fractures, and mortality; the difficulty in achieving a balance between insulin dose and food intake; and the adherence barriers associated with injectable medications *(Khunti and Millar-Jones, 2017, Yakaryılmaz and Öztürk, 2017)*. Regarding the newer classes of ADDs, patient information and prescriber confidence to prescribe newer agents with limited studies on the long-term safety and effectiveness, especially among older patients, may lie behind their lower prescriptions than metformin for elderly patients compared to younger individuals *(Kim et al., 2012, Lublóy, 2014, Yakaryılmaz and Öztürk, 2017).*

On the other hand, DPP4-I is considered a preferable option for older adults with T2DM because of its lower risk of hypoglycaemia, less frequent doses, and weight-neutral effect, given providing an appropriate renal adjusted dose *(Bajwa et al., 2014, Kim et al., 2012, Yakaryılmaz and Öztürk, 2017)*. Furthermore, the low cost of SU, the availability of more long-term studies on the safety and effectiveness of SU, and the

current availability of short-acting agents (e.g., glipizide) with a lower risk of hypoglycaemia may also make SU an attractive option for treating older patients with T2DM. Accordingly, this study showed a significantly higher prescription of DPP4-I and SU than metformin for older adults (>=65 years) compared to their counterparts. Since newly diagnosed elderly patients with T2DM could be presented with a very high HbA1c level, starting newly treated elderly patients on combination regimens could be justified. Following that, this study showed a considerably higher prescription of DPP4-I+SU *(Bajwa et al., 2014, Kim et al., 2012, Yakaryılmaz and Öztürk, 2017)* yet a lower metformin-based dual therapy prescription. The greater likelihood of prescribing DPP4-I+SU over metformin for elderly patients could be due to the advantages of DPP4-I and SU that were mentioned earlier. On the contrary, the lower use of metformin-based combination regimens could be related to the fact that metformin should be used with caution for elderly patients, and it is not recommended if a patient complains of gastrointestinal problems, renal insufficiency, or functional impairment, conditions that are commonly associated with advancing age *(American Diabetes Association, 2021, Kim et al., 2012, Schlender et al., 2017)*. All previously mentioned associations reflect a potential good consideration of patient age for selecting an appropriate ADD for patients newly treated for T2DM in clinical practice in Scotland, considering the variability in drug features.

Studies exploring the association of patient age with the prescribing choice of ADDs at the stage of drug initiation included only older ADDs (metformin, SU, insulin, TZD) and DPP4-I. The use of GLP1-RA, SGLT2-I, and combination regimens as initial therapy was not previously investigated since the majority of these studies were conducted early after the introduction of newer agents (primarily SGLT2-I), and only a small proportion of newly diagnosed patients would receive combination regimens or non-metformin antidiabetic monotherapy as initial treatment for T2DM. The results of previous studies were in keeping with the findings of this study, which showed a lower prescription of metformin and insulin with increasing patient age and a higher prescription of SU and DPP4-*I (Abdelmoneim et al., 2013,*

Brouwer et al., 2012, Fujihara et al., 2017, Geier et al., 2014, Heintjes et al., 2017, Morita et al., 2019, Wang et al., 2019).

For patient sex, female patients were significantly more likely to be initiated on DPP4-I, GLP1-RA, TZD, metformin+DPP4-I, metformin+ insulin, metformin+SGLT2-I, and DPP4-I+SU than metformin alone compared to male patients, but less likely to receive SU, metformin+SU, metformin+TZD, or SU+insulin. The greater use of the abovementioned regimens for female patients instead of metformin alone as initial therapy could be explained by previous studies showing that female patients with T2DM reported more metformin-induced ADR *(De Vries et al., 2020)*. Additionally, metformin effects on lipid and glucose metabolism are more evident among male than female patients with T2DM. The rate of early treatment failure and metformin non-adherence is also greater among women *(Walker et al., 2006, Mamza et al., 2016, Quan et al., 2016).* That would contribute to the observed lower initiation of metformin for newly diagnosed female patients with T2DM compared to male patients in this study (42.04% vs. 57.96%). Using metformin in combination with other ADDs would reduce the risk of treatment failure and allow providing a lower dose of metformin, thus, reducing the rate of ADRs. That could partially explain the greater prescription of metformin in combination regimens compared to metformin monotherapy as initial therapy for female patients with T2DM *(De Vries et al., 2020).* Moreover, the greater use of GLP1-RA, DPP4-I, and SGLT2-I as monotherapy or in combination among female patients could also be related to the better cardiovascular outcome observed with newer ADDs among females than males, particularly with GLP1-RA *(De Vries et al., 2020).*

Despite the previous identification that female patients have experienced more side effects from TZD compared to male patients *(Campesi et al., 2017, Joung et al., 2020),* this study showed a greater likelihood of using TZD monotherapy than metformin for female patients, yet a lower likelihood of using TZD in combination with metformin compared to metformin alone. The difference between the sample size of initial TZD users and the sample size of metformin+TZD users (N= 127 vs. 233)

could partly explain the inconsistency in the results. In contrast, the lower initiation of SU and metformin+SU for female patients could be referred to the findings that male patients with T2DM respond better to SU, while female patients are more susceptible to developing SU-associated coronary heart disease *(Li et al., 2014, Dennis et al., 2018)*. Some studies reported similar results for sex associated with the prescribing choice of metformin and SU *(Winkelmayer et al., 2010, Desai et al., 2012, Heintjes et al., 2017)*. However, other studies showed a non-significant difference in the choice of SU, TZD, and DPP4-I by patient sex *(Abdelmoneim et al., 2013, Brouwer et al., 2012, Fujihara et al., 2017, Geier et al., 2014, Heintjes et al., 2017, Wang et al., 2019).* The discrepancy in the findings across studies could be attributed to the differences in the characteristics of the study population or to the methodological differences across studies, including the duration of data collection, the quality and representativeness of the utilised data source, and the study sample size. The impact of sex on the remaining classes of ADDs at the stage of drug initiation was much less extensively studied. Therefore, more studies investigating sex differences in the prescribing choice of ADDs at the stage of drug initiation, especially for newer ADDs, are still required.

Clinical-related factors mainly influenced the prescribing choice of SU, insulin, and DPP4-I. It was found that patients with baseline IHD and those who were on antihyperlipidemic drugs, thiazide diuretics, angiotensin inhibitors, and CCB were significantly less likely to receive SU (Table 4.17). On the contrary, a baseline diagnosis of HTN or PVD, higher CCI score (1-2, 3-4, and >= 5 vs. 0), using beta-blockers, and being on 1-4 or >=5 comedications were positively associated with starting SU over metformin for newly treated patients with T2DM (Table 4.17). Some studies have raised the concern about all-cause mortality and CV risk associated with SU *(Azoulay and Suissa, 2017, Douros et al., 2018, Phung et al., 2013, Roumie et al., 2017),* and that could be responsible for the previous finding of a lower likelihood of initiating SU for patients with IHD. A contradictory result was found regarding the association of PVD with SU prescribing, where SU was more commonly prescribed for patients with PVD than metformin. Nevertheless, it is still controversial whether

to consider the mortality and cardiovascular risk of SU a class effect since glimepiride and gliclazide showed lower cardiovascular-related mortality and all-cause mortality compared to glibenclamide *(Simpson et al., 2015, John et al., 2020)*. That might justify the contradictory results of different types of CVD on SU prescribing. As a result, further studies are still required to investigate the cardiovascular safety of SU and its impact on the prescribing process of ADDs for patients with T2DM. Since the impact of SU on BP is still conflicting *(Ilias et al., 2020, Balfour et al., 2014, Liakos et al., 2021, Yaribeygi et al., 2021)*, inconsistent results were also observed relevant to the association of HTN and antihypertensive drugs (beta blocker, thiazide diuretics, CCB, and angiotensin inhibitors) with SU prescribing (Table 4.17). It has been reported that SU has a modest effect on lipid profiles, manifested by increasing TG and total cholesterol but decreasing LDL and HDL levels, while metformin, GLP1-RA, and SGLT2-I showed more favourable effects on lipid profiles *(Chaudhuri and Dandona, 2011, Rådholm et al., 2020, Rigato et al., 2020, Rosenblit, 2016).* Consistent with that, this study revealed a lower prescription rate of SU for patients who were using antihyperlipidemic drugs or had abnormal levels of HDL, TG, or total cholesterol (Table 4.17).

For patients starting on insulin, HTN, PVD, liver disease, CCI score (1-2, 3-4, and >= 5 vs. 0), and the number of concomitant medications (1-4 and >= 5 vs. 0) were positively and significantly associated with insulin selection over metformin as first-line therapy, while the use of antihyperlipidemic, thiazide diuretics, angiotensin inhibitors, or CCB showed negative statistically significant results (Table 4.17). Similar to SU, the impact of insulin on BP is still unclear *(Ilias et al., 2020)*, hence this study showed inconsistent results relevant to the association of HTN and antihypertensive medications (thiazide diuretics, angiotensin inhibitors, and CCB) with insulin use as initial therapy over metformin. Although the cardiovascular safety of insulin has been questioned *(Herman et al., 2017, Triggle and Ding, 2014)*, recent studies have shown no significant effects of insulin on the risk of cardiovascular events and all-cause mortality *(Mannucci et al., 2022, Rados et al., 2021)*. Furthermore, the presence of CVD, using a larger number of concomitant

medications, and having a higher baseline CCI score at drug initiation may indicate a more severe disease state where insulin becomes a fundamental part of T2DM management. All could partially explain the greater likelihood of prescribing insulin for patients with PVD, higher CCI scores, and more concomitant medications. Similar to SU, insulin has a modest effect on lipid profiles; thus, the association of using antihyperlipidemic drugs and having abnormal lipid profile levels with the likelihood of prescribing insulin over metformin as initial therapy was comparable to what has been discussed with SU.

The majority of drugs are metabolised in the liver; thus, patients with liver disease are at higher risk of developing side effects of medications such as lactic acidosis, fluid retention, and hypoglycaemia from metformin, TZD, and SU, respectively. Therefore, it is challenging to select the most appropriate ADD for patients with T2DM who have compelling liver disease, in which the treatment strategy should be tailored to the severity of both liver disease and T2DM. Insulin is considered a frequent treatment option for patients with T2DM and liver disease, given close monitoring of glucose levels and frequent adjustment of insulin doses(Chung et al., 2020, Yen et al., 2021). Following that, this study showed that insulin was more likely to be prescribed over metformin for patients with liver disease. Nonetheless, insulin should be used with extreme caution because it could have deleterious effects on patients with severe liver disease, including hypoglycaemia, high cardiovascular risk and mortality, and hepatocellular carcinoma *(Chung et al., 2020, Yen et al., 2021)*.

Furthermore, HF showed only a significant association with DPP4-I prescription, in which patients with a baseline HF were 31% less likely to receive DPP4-I than metformin as a first-line therapy; this may be due to the concern regarding HF hospitalisation risk associated with saxagliptin and aloglipitin use *(Fei et al., 2019)*. Similar to insulin and SU, DPP4-I has a less favourable to neutral effect on lipid profiles compared to metformin, GLP1-RA, and SGLT2-I, which could contribute to the lower initiation of DPP4-I than metformin for patients who were using

antihyperlipidemic drugs (Table 4.17). However, no significant difference was observed in the prescription of DPP4-I versus metformin according to the baseline TG, HDL, and total cholesterol *(Chaudhuri and Dandona, 2011, Rigato et al., 2020, Rosenblit, 2016, Roumie et al., 2011)*. Additionally, It has been reported that DPP4-Is have shown a good antihypertensive and blood pressure modulating effect, suggesting DPP4-I as a good treatment option for patients with HTN. Nevertheless, the sympathetic effect (increasing vasoconstriction) of DPP4-I when combined with other antihypertensive medications cannot be ignored *(Zhang et al., 2019).* That could partly explain the negative association between CCB use and DPP4-I prescription. On the other hand, a significant positive association was observed between beta-blockers and DPP4-I use, and this could be related to the antisympathetic effect of beta-blockers which might diminish the sympathetic effect of DPP4-I *(Zhang et al., 2019)*.

Cardiovascular outcome studies investigating GLP1-RA have proved a reduction in cardiovascular events, non-fatal stroke, and mortality, with no significant impact on HF hospitalisation *(Fei et al., 2019)*. Likewise, SGLT2-Is have decreased major cardiovascular events, HF hospitalisation, stroke, and death *(Fei et al., 2019)*. Consequently, recent guidelines recommended using GLP1-RA and SGLT2-I in addition to metformin as a first-line for patients with CVD or at high risk for CVD(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021). However, this study showed low utilisation of newer antidiabetic classes (GLP1-RA and SGLT2-I) as a monotherapy or combination for patients with IHD, PVD, HF, and stroke in clinical practice in Scotland. Accordingly, the result was not in agreement with the previous evidence and guideline recommendations. That observation could be related to patient knowledge and preference, as well as healthcare provider knowledge and experience with newer ADDs. Prescribers with limited knowledge about the advantage of newer ADDs might not be confident starting these medications for patients with CVD for several reasons, including fear of side effects. CVD is a major cause of death among patients with T2DM *(Buse et al., 2007),* and the benefit of intensive glycaemic control alone on reducing the

progression and development of cardiovascular complications is still unclear and less established *(Holman et al., 2008, Terry et al., 2012)*. As a result, research is now focusing on understanding the benefit of different ADDs in preventing or reducing the risk of CVD through mechanisms independent of the glucose-lowering effects of ADDs *(Marso et al., 2016b, Zinman et al., 2015)*. It is vital to take advantage of the cardioprotective effects of GLP1-RA and SGLT2-I and use them as recommended; therefore, more efforts should be spent on improving the knowledge of prescribers in this regard to encourage applying guideline recommendations in clinical practice.

Moreover, baseline BMI, HbA1c, and eGFR are essential factors that should be considered when a decision is to be made for selecting the most appropriate ADDs for each patient. GLP1-RA and SGLT2-I are known to have weight loss effects, and metformin was accepted to have weight-neutral or slight weight loss effects, while SU, insulin, and TZD are known to cause weight gain *(Apovian et al., 2019, Vilsboll et al., 2012, Wang et al., 2019)*. The results of this study were in keeping with the antidiabetic weight change effect of SU, insulin, and DPP4-I, in which overweight and obese patients were significantly less likely to be initiated on medications with weigh neutral or weight gain effect, including SU, insulin, and DPP4-I compared to metformin. Nevertheless, there was no significant difference in the prescription of SGLT2-I and GLP1-RA as monotherapy, medications that are well-known to reduce patient weight, for overweight and obese patients compared to patients with normal/low BMI. However, overweight/obese patients had greater odds of receiving metformin+SGLT2-I than metformin alone. Accordingly, the association of the baseline BMI on the prescribing choice of ADDs in clinical practice in Scotland was in partial agreement with the known differences among antidiabetic classes in terms of the weight-changing effect. Comparably, it was found that the association of the baseline HbA1c with the prescribing choice of ADDs at the stage of drug initiation in clinical practice in Scotland was consistent with the known HbA1c reduction effects of ADDs. That was reflected by the greater likelihood of prescribing SU and insulin than metformin for patients who were presented with a very high baseline HbA1c level (>= 9%) *(Chaudhury et al., 2017, Sherifali et al., 2010).*

Lastly, patients with a low eGFR of < 60 ml/min/1.73m^2 were significantly more likely to be initiated on insulin, DPP4-I, SU, and TZD than metformin compared to patients with eGFR of >= 60. Since the impairment in kidney function might affect glucose metabolism and alter drug clearance, selecting an appropriate ADD should be done carefully, considering the need for more frequent adjustment of doses and monitoring for the risk of hypo- and hyper-glycaemia *(Betônico et al., 2016)*. Insulin has been considered the best choice for patients with T2DM and kidney problems, given close monitoring and dose adjustment, while the use of metformin is not recommended because of the associated risk of lactic acidosis *(Betônico et al., 2016)*. In addition, DPP4-I, TZD, and SU are considered among the accepTable options for patients with kidney problems, given providing an adjusted dose based on the agent and degree of impairment *(Betônico et al., 2016)*. Collectively, that could explain the observed associations of reduced eGFR with prescribing insulin, DPP4-I, TZD, and SU as first-line therapy (Table 4.17). SGLT2-I and GLP1-RA have been recently recommended by several guidelines to be prescribed for patients with renal disease because of their favourable effects on the progression of kidney disease, the need for renal replacement therapy, and death *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021)*. However, this study showed no significant difference in the prescription of SGLT2-I and GLP1-RA for patients with low eGFR of < 60 ml/min/1.73m^2 compared to patients with eGFR of > 60 ml/min/1.73m^2. That observation could be linked to the fact that the earliest SGLT2-I was approved only for patients with an eGFR value of > 60 ml/min/1.73m^2, and GLP1-RA for patients with eGFR > 30ml/min/1.73m^2. Nonetheless, more emphasis should be placed on providing prescribers with an updated continuous educational program and encouraging the use of SGLT2-I and GLP1-RA as appropriate, considering the degree of renal impairment.

Compared to the demographic factors, the impact of clinical, socioeconomic, and prescriber-related factors on the prescribing choice of first-line ADDs was much less frequently studied in the literature, particularly for the newer antidiabetic classes. For instance, a study conducted across Europe investigating the association of

several clinical characteristics, including BMI, HbA1c, renal disease, and lipid profile, with prescribing SU as first-line therapy reported consistent results with this study *(Heintjes et al., 2017).* On the other hand, the results of Abdelmoneim et al. (2013) were inconsistent with this study, in which the earlier study showed greater odds of prescribing SU than metformin for patients with HF or liver disease but lower odds for patients with HTN, with no significant difference in the use of SU versus metformin by the presence of IHD and PVD. Whereas this study showed a significant positive association of SU prescribing with the presence of HTN or PVD at the time of drug initiation, and a significant negative result was observed with IHD, with no significant difference identified with HF or liver disease *(Abdelmoneim et al., 2013).*

Additionally, Fujihara et al. (2017) investigated the impact of HTN, HbA1c, and BMI on the choice of metformin versus SU as a first-line therapy, and the results were in keeping with this study *(Fujihara et al., 2017)*. It also examined the impact of those factors on the likelihood of prescribing DPP4-I and showed a significant negative association with HbA1c level but non-significant results with BMI and HTN. Nevertheless, DPP4-I was compared to SU in the latter study *(Fujihara et al., 2017),* while in this study, metformin was assigned as the reference group. Moreover, the results of a study conducted in Japan between October 2012 and September 2016 were partially in line with the findings of this study relevant to DPP4-I prescribing compared to metformin as a first-line therapy. It showed similar direction and significance of associations in terms of the BMI and liver disease effects to the ones observed in this study. However, while the baseline HbA1c level showed a negative significant result in Morita et al. (2019), the result was non-significant in this study *(Morita et al., 2019).* Collectively, the variability in the association of the clinical characteristics with the prescribing choice of ADDs across studies could be related to the differences in the study sample size, time and duration of data collection, characteristics of the study population, the quality and coverage of the utilised data sources, the percentage of missingness in the studied variables, and the definition of the covariates.

Overall, the results of this study relevant to patient age, sex, HbA1c, BMI, and kidney problems partially agreed with the findings of the conducted MA (Chapter 2). For example, consistent with this study, older age was significantly associated with higher SU prescriptions but lower metformin, SGLT2-I, and GLP1-RA prescribing. However, inconsistent with this study, the MA showed an overall non-significant association of patient age with DPP4-I and insulin prescribing. Only GLP1-RA and TZD showed significant associations with patient sex according to the MA (Chapter 2), while this study identified significant results with GLP1-RA, TZD, DPP4-I, and SU. Furthermore, this study observed greater odds of receiving TZD for female patients compared to male patients, but the MA showed the opposite result.

Regarding the baseline BMI, the result was comparable to the finding of this study for SU only. While the pooled estimate of studies included in the MA of SGLT2-I and GLP1-RA showed significant positive results, the associations were non-significant for both groups in this study. Although HbA1c in the MA showed only a positive significant association with insulin prescription, this study showed that both SU and insulin were significantly more likely to be initiated for patients with high baseline HbA1c values. Similarly, the results of the MA showed that patients with kidney problems were more likely to receive DPP4-I or insulin; in addition to that, this study showed a higher SU and TZD prescribing for patients with a low baseline eGFR level (< 60 ml/min/1.73m^2). It is important to mention that the meta-analyses of all factors (Chapter 2) included all studies that investigated the outcome at any stage of treatment (initiation, intensification, and not specified stage). Additionally, these studies might have assigned different reference groups and included both unadjusted and adjusted effect sizes in the pooled estimate. All of the abovementioned points might contribute to the discrepancy in the results between this study and MA.

4.4.5 Strength and limitations

To our knowledge, this study is the first analysis of prescribing patterns and factors associated with the prescribing choice of ADDs at the stage of drug initiation in Scotland. The study was conducted over a 10-year period (2010-2019) using national-level, record-linked data from five different datasets, which capture all patients with T2DM who are registered with a GP in Scotland and provide a wide range of information about patient demographic, comorbid conditions, and laboratory data. It also included all ADDs prescribed as monotherapy or in combination, while most previously conducted studies focused on the most commonly prescribed drugs with very limited focus on the newer ADDs and combination regimens as initial treatment for T2DM. Furthermore, the risk of time-lag bias that could arise from comparing treatments at different stages of the disease was minimised by including only new users of ADDs *(O'Brien, 2018, Raschi, 2018).*

Nevertheless, this study has some limitations. First, data on ethnicity, prescriber characteristics other than prescriber type, patient's opinion, and experienced side effects were not available for this study; thus, prescribing variations that could be driven by these factors were not investigated. Furthermore, the severity state of the disease is an important factor that could influence the prescribing choice of ADDs along with the clinical outcome. One proxy measure of disease severity is the time from diagnosis until treatment initiation, which was not measured in this study since the validation process of SCI-Diabetes suggests that the date of diabetes diagnosis could be unreliable *(Wild et al., 2016).* Nonetheless, other proxy measures for disease severity were included in this study, such as the baseline HbA1c, comorbid conditions, and renal function. Accordingly, further studies are required to examine the impact of the unmeasured factors on the prescribing decision of ADDs and whether the impact of the currently studied factors would change under the adjustment of the unmeasured ones.

Second, certain antidiabetic classes were grouped into 'other' in the prescribing trend analysis due to a limited number of patients using these classes. The 'other'

group was excluded from factor analyses. However, those patients accounted for only a small percentage of the study cohort; accordingly, the analysis of these classes would provide unreliable results that are not clinically relevant. Third, since there are no standard rules for classifying patients into monotherapy and combination therapy users using real-world data, the approach followed in this study was made based on rules that were decided by the study authors. Nevertheless, the clinical relevance of these rules was discussed and agreed upon with a diabetologist and a diabetes specialist pharmacist. Last, some investigated variables, particularly TG and BMI, had a substantial percentage of missingness which would introduce an information bias. However, the LOCF method and multiple imputations were performed to reduce the possible risk of information bias. Furthermore, a complete case analysis was conducted as a sensitivity analysis.

4.4.6 Implications for practice and recommendation

The study findings describe the change in the prescribing patterns of ADDs over ten years, indirectly reflecting the impact of the introduction of newer ADDs on T2DM management in clinical practice. By exploring factors influencing the prescribing decision, the findings may reflect the agreement of prescribing decision with guideline recommendations and specific drug features, through which the need for improving the clinical practice to meet the recent update in T2DM management and the new evidence on the safety and extra-glycaemic benefits of ADDs can be determined. As a result, an appropriate action (such as starting a continuous educational program) can be implemented. The dissemination of the results can inform prescribers about the available treatment options for T2DM management and which factors should be considered to make a more patient-oriented treatment choice decision.

4.4.7 Conclusion

In conclusion, the majority of type 2 diabetes patients were started on a single antidiabetic; of those, metformin was by far the most commonly prescribed ADD over the entire study period. Although SU was the second most frequently prescribed first-line therapy, its use has significantly decreased. On the contrary, the

use of newer ADDs (SGLT2-I and DPP4-I) has significantly increased, with no significant change observed in the prescribing patterns of GLP1-RA. Furthermore, several factors were identified to be associated with the prescribing choice of the regimen type and the antidiabetic class at the stage of drug initiation. For instance, having a baseline CCI score of >= 5, an HbA1c value of >=9, a low eGFR of <60, and a TG level of >=500 were associated with a higher likelihood of starting a combination regimen. In contrast, older age, female sex, using lipid-lowering drugs, being obese, having a medium level of HDL (40-59 (M) or 50-59 (F)), as well as having a total cholesterol level of 200-239 mg/dl were associated with lower odds of prescribing a combination regimen over monotherapy as initial treatment for T2DM.

On the other hand, factors influencing the prescribing choice of ADDs varied by antidiabetic class. The findings relevant to the demographic factors (patient age and sex) were more consistent with the safety and effectiveness characteristics of drugs. However, the association results of the clinical factors were partially in line with guideline recommendations and the current evidence about the safety and extra-glycaemic benefits of ADDs, particularly the newer ones. The most profound gap was observed in the association of the baseline IHD, PVD, HF, eGFR, and BMI with the newer ADDs (GLP1-RA and SGLT2-I). Inconsistent with guideline recommendations regarding using SGLT2-I and GLP1-RA with cardio and reno-protective effects for patients with established or high-risk CVD or renal disease, this study showed no significant difference in the utilisation of those medications by IHD, PVD, HF, and BMI. Furthermore, this study showed a significantly low utilisation of GLP1-RA and SGLT2-I for patients with low eGFR (< 60 ml/min/1.73m^2). Therefore, more efforts should be spent to ensure providing prescribers with continuous educational programs to update their knowledge regarding guideline recommendations for T2DM management and the current evidence on the safety and effectiveness of the currently available ADDs. That, in turn, would encourage using newer classes (SGLT2-I and GLP1-RA) as appropriate and recommended by clinical guidelines.

5 Chapter 5. Prescribing Patterns and Factors Influencing Prescribing of First Intensifying Antidiabetic Drugs Among Patients with Type 2 Diabetes Mellitus Across Scotland between 2010 and 2020

5.1 Introduction

Currently, most clinical guidelines recommend a glycaemic HbA1c target of < 7% for the majority of patients with T2DM, which can be attained using appropriate pharmacological therapy along with lifestyle modifications *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. However, given the progressive nature of T2DM and the limited durable effectiveness of ADDs, patients often fail to keep the targeted glycaemic control over time after the initial therapy, thus, warranting starting one or more additional ADDs to maintain the glycaemic target. Still, there are no definite recommendations regarding the selection of the second-line therapy, where clinicians can select from a wide range of the currently available options for T2DM management with variable safety and extra-glycaemic benefits *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*. In response to the introduction of new antidiabetic classes, clinical guidelines have been updated; the SIGN guideline lastly added SGLT2-I as a second-line therapy and beyond among the other available treatment options, including SU, DPP4-I, and pioglitazone. As a result, a change in the prescribing patterns of ADDs over time in response to the change in the clinical guideline is expected.

Despite the absence of agreement among clinical guidelines regarding the selection of intensifying therapy after failing the first-line ADDs, these guidelines, including the SIGN guideline, recommended following a patient-centred approach for selecting the most appropriate second-line therapy taking into account the characteristics of both patients and drugs *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017).* That, in turn, resulted in difficulty and variability in

selecting the most appropriate intensifying therapy among clinicians; hence it is expected that the prescribing decision will be influenced by several clinical and non-clinical factors *(Ackermann et al., 2017, Heintjes et al., 2017, Katakami et al., 2020, Nicolucci et al., 2019, Wilkinson et al., 2018c)*. As discussed in Chapter 1 (section), multiple previous studies investigated the change in the prescribing patterns of second-line ADDs with less emphasis on exploring factors influencing the prescribing choice at the stage of drug intensification *(Ackermann et al., 2017, Heintjes et al., 2017, Katakami et al., 2020, Montvida et al., 2018, Nicolucci et al., 2019, Wilkinson et al., 2018c).* The most recent study in the UK was conducted between 2000 and 2017, including only three antidiabetic classes (SU, DPP4-I, and SGLT2-I) and using the CPRD database. CPRD covers around 7% of the UK population but captures a few GPs from Scotland *(Herrett et al., 2015, Wilkinson et al., 2018a).* Given that data on the prescribing trend of ADDs and factors influencing prescribing in Scotland are scarce, and a different treatment guideline is available in Scotland (SIGN guideline) compared to England, research examining the prescribing practice of ADDs in Scotland is still required. In addition, limited data is available globally on prescribing SGLT2-I (the newest antidiabetic class) and combination regimens as the first intensifying therapy. Most previous studies focused on the older antidiabetic classes in addition to DPP4-I and mostly examined the use of ADDs as monotherapy *(Ackermann et al., 2017, Katakami et al., 2020, Montvida et al., 2018, Nicolucci et al., 2019, Wilkinson et al., 2018c, Heintjes et al., 2017)*. Besides, most studies investigated the change in the prescribing patterns or predictors of prescribing at the stage of first drug intensification either without standardising the first-line treatment *(Chu et al., 2017, Christensen et al., 2016, Engler et al., 2020, Ko et al., 2016)* or including only patients who received metformin as first-line therapy *(Curtis et al., 2018, Dennis et al., 2019, Kim et al., 2019a, Montvida et al., 2018, Sharma et al., 2016, Wilkinson et al., 2018a)*. Additionally, studies including patients starting on SU (the second most commonly prescribed initial ADDs) are rare, even globally *(Geier et al., 2014, Grimes et al., 2015, Moreno Juste et al., 2019).* Examining the prescribing trend and factors influencing prescribing decisions is crucial since the differences in the prescribing practice are linked with health outcomes and the utilisation of resources. Therefore, it is

important to study the prescribing patterns and factors influencing prescribing to evaluate the extent and rationale use of drugs, as well as the agreement of prescribing practice with guideline recommendations and the recent evidence on the safety and effectiveness profiles of ADDs.

Aims and objectives

This study aimed to: first describe the prescribing patterns of ADDs at the stage of first intensification for people diagnosed with T2DM, using Scottish national data over the period of January/2010 and December/2020; and secondly, identify factors associated with the selection of the type of regimen and antidabetic class at the time of first drug intensification.

Accordingly, the study objectives were first to examine the trend in the prescribing of the first intensifying ADDs for patients with T2DM in Scotland over the 11-year study period, to understand the prescribing patterns of ADDs at the first intensification stage, with a particular focus on the utilisation of the newer antidiabetic classes as a first intensifying therapy in comparison to the older ones. And secondly, to investigate the association of several baseline demographic factors, clinical factors, prescriber-related factors, and socioeconomic factors with the class of ADDs at the first intensification stage to reflect (indirectly) the concordance of clinical practice with the characteristics of ADDs in terms of the safety and extra-glycaemic benefits, including weight loss, cardioprotective, and renal protective effects.

5.2 Method

5.2.1 Study design and study timeline

A retrospective cohort study was conducted using linked collected national Scottish data of patients diagnosed with T2DM who were previously newly initiated on their first single ADD between January/2010 and December/2019, and then intensified with one or more ADD after at least three months of starting their first initial therapy. The earliest prescribed date for the second ADDs after at least three months of the initial therapy is defined as the first event of intensifying ADD

prescribing for the individual patient (the indexed intensifying ADD), and the corresponding prescription date is defined as the index intensification date.

5.2.2 Study cohort identification and selection

5.2.2.1 Inclusion/Exclusion criteria

The participants of this study represent adult patients (>= 18 years old) who were diagnosed with T2DM, identified as new users of ADD, and treated with single ADD as initial therapy between 1st January 2010 and 31st December 2019 in Scotland. Patients to be included must have at least one year of follow-up to examine if any change in the treatment has happened over the study period. Additionally, they were required to have at least one year of registration to a GP prior to the index intensification date to retrieve all required baseline data. In addition, patients were required to be treated with an additional one or more new antidiabetic class(es) after at least three months of the initial therapy. To ensure that the change in the treatment was an addition rather than a switching, the patients were required to have at least one further prescription of the initial therapy within 60 days after the start of a new drug class (first intensifying therapy) as defined in previous literature *(Wilkinson et al., 2018a)*.

Metformin is the recommended treatment of choice for newly diagnosed patients with T2DM *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*, and the findings of Chapter 4 showed that metformin was the most frequently prescribed ADD (118737/145909, 81.38%) as a first-line therapy for newly treated patients with T2DM in Scotland followed by SU (10029/145909, 6.87%), while the use of the other classes of ADD was very limited (17173/145909, 11.75%). Therefore, only patients who started on either metformin or SU in the first-line study (128766/145909, 88.25%, Chapter 4) were included in the intensification study. Accordingly, patients were excluded if they were previously treated with combination therapy or monotherapy other than metformin or SU, used the same class of the initial ADD over the entire study period, or switched from one antidiabetic class to another (indicated by the start of a different class of ADDs after at least three months of

initial therapy) without additional prescription of the initial therapy within the 60-day interval. Table 5.1 summarises the inclusion/exclusion criteria.

Table 5.1: Cohort Identification: Inclusion/Exclusion criteria at the stage of first drug intensification

Criteria	Definition	
	Inclusion	**Exclusion**
Diabetes diagnosis	Read codes for type 2 diabetes mellitus	Read codes for other types of diabetes (Type 1 diabetes, gestational diabetes, others)
Prescription	Patients previously identified as new users of ADD and started on either metformin or SU	Patients not previously identified as new ADD users or not started on metformin or SU
	Patients treated with new one or more antidiabetic class after at least three months of the initial therapy	Patients used the same initial antidiabetic class without any change in drug therapy or the change in treatment happened within less than three months of the initial therapy
	Patients had a further prescription of the initial therapy within 60 days interval of the new antidiabetic class (Addition)	Patients had no further prescription of the initial therapy within 60 days interval of the new antidiabetic class (switching)
Study periods	Jan/2010-Dec/2020	Before Jan/2010 or after Dec/2020
Patient age	>= 18 years at the index date	< 18 years at the index date
Patient sex	Female, Male	-
Prior registration	At least one-year of registration with a GP before the index intensification date	Less than one-year registration with a GP before the index intensification date
Follow-up	At least one year of follow-up post the start of the initial therapy	Less than one year of a follow-up post the beginning of the initial therapy

5.2.2.2 Cohort identification and classification

The cohort of this study (cohort-2) was derived from the cohort of the first-line study (cohort-1), in which the identified new users of ADDs at the stage of drug initiation who were started on either metformin or SU were followed from the date of first ADD prescribing until December 2020 to observe if there was any change in ADD prescribing after at least three months of the initial therapy. Patients might have experienced no change in drug therapy (stayed on the same initial antidiabetic class-continuation), switched to a different class of ADD (switchers), or added another class(es) of ADD (intensification). Of those, only the latest group was included in this study; defined as patients with newly added one or more antidiabetic class(es) after at least three months of the initial therapy and who had a further prescription of the initial antidiabetic class within 60 days after the index intensification date. Then the identified cohort was linked with the PIS, SMR00, and SMR01 datasets to retrieve all other patient demographic, socioeconomic, and clinical information as described in chapters 3 and 4 (section 4.2.2.2). Since patients treated with different ADDs could have different characteristics (e.g., age, comorbid conditions, and laboratory tests values) as manifested from the baseline analyses of the first-line study (section 4.4.2, Chapter 4), it is crucial to ensure that all included patients were initially treated with the same class of ADDs to have a reliable and valid comparison. Therefore, patients starting on metformin and those who started on SU were studied separately as two cohorts (Cohort 2a: initial-metformin users, cohort 2b: initial-SU users).

The process of assignment of the individual prescribed item to the appropriate class of ADDs in this study is similar to the one described in Chapter 4 (section 4.2.2.2), in which each of the prescribed items of ADDs was assigned to the appropriate antidiabetic class, providing a total of eight main classes; where short-acting insulin, intermediate-acting insulin, long-acting insulin, and biphasic insulin were grouped as insulin, and meglitinide and alpha-glucosidase inhibitors were grouped as others. The remaining six classes were biguanide, TZD, SU, DPP4-I, GLP1-RA, and SGLT2-I. Furthermore, patients within each of the two studied cohorts (initial-metformin

users and initial-SU users) were further stratified based on the number of different antidiabetic classes added to the initial therapy into patients who received one additional antidiabetic class (addition of monotherapy), and those who received two or more additional antidiabetic classes (addition of combination therapy). Treatment stratification into first intensifying monotherapy or combination therapy was done following the criteria and decision rules explained in the first-line study (section 4.2.2.2, Chapter 4). These criteria mainly relied on the number of different antidiabetic classes that were prescribed over a three-month interval, the date of prescription of the individual antidiabetic class, and prescribing quantity or the presence of overlapped prescriptions. Please refer to Chapter 4 (section 4.2.2.2) for more details about the applied criteria, the reason behind adopting a three-month interval, and the clinical relevance of all applied criteria. In summary, an intensifying treatment was classified as a monotherapy addition if patients were treated with a single antidiabetic class over a three-month interval or if they had more than one antidiabetic class over the defined interval, but the drugs did not overlap. The earliest antidiabetic class was considered the first intensifying therapy. On the other hand, intensifying treatments were classified as a combination therapy addition if the patients were prescribed more than one antidiabetic class at the same date (the earliest date) or very close dates (one-week interval), If they had more than one overlapping and repeated antidiabetic classes in a three-month interval, or if they were prescribed a fixed-dose combination at the index intensification date.

5.2.3 Study outcomes

The primary outcomes of this study were the change in the prescribing patterns of intensifying ADDs over an 11-year interval and the association of factors with the class of ADD that was prescribed at the stage of drug intensification.

Firstly, the prescribing patterns of the regimen type and the individual class of ADDs were described by calculating the prescribing frequency of the individual regimen (monotherapy vs. combination therapy addition) per calendar year and investigating the change in the prescribing trend over the 11-year period (Jan/2010-Dec/2020). The prescribing patterns of the individual class of ADD used as

monotherapy were calculated, in addition to the pattern of prescribing combination regimens. Secondly, baseline characteristics at the stage of drug intensification were defined as the characteristics of patients recorded at the index intensification date or the closest ones prior to the index intensification date; within six months for concomitant medications and laboratory data (including HbA1c) and three years for comorbid conditions. Similar to the first-line study (Chapter 4), baseline characteristics were initially described for the entire cohort and then stratified by the type of regimen (monotherapy versus combination therapy) and the individual antidiabetic class among monotherapy and combination therapy subgroups. Lastly, all described variables were tested for their association with the type of the added regimen and class of ADDs at the stage of first drug intensification. The definition and classification of all included variables were previously explained in Chapter 4, section 4.3.2. The outcomes in the current study were investigated for cohort-2a (initial-metformin users) and cohort-2b (initial-SU users).

5.2.4 Statistical analysis

The change in the prescribing patterns of the first intensifying ADDs over 11 years was initially described as frequency and percentage, representing the number of patients who were intensified with a particular regimen or class of ADD per calendar year and displayed in line plots. Consistent with the first-line study, the absolute and relative change in the use of the individual regimen and class of ADD were also computed, along with conducting a Cochran–Armitage test for trend analysis with a p-value of less than 0.05, indicating a significant change in the prescribing patterns of the added regimen or antidiabetic class over the study period *(Armitage, 1955, Cochran, 1954, Kikuchi et al., 2022, King et al., 2012)*. The calculation of the absolute and relative change was illustrated in Chapter 4, section 4.3.3.

Moreover, baseline characteristics were presented as frequency/percentage for categorical variables and median± IQR or mean± SD for continuous variables as appropriate. All continuous variables were tested for normality of distribution using histograms and Kolmogorov-Smirnov test, where only the patient age at

prescription of the entire cohort showed a normal distribution, while the remaining continuous variables were not normally distributed (Appendix S.5.1). Baseline descriptive statistics were presented for the entire study cohort and stratified by the type of regimen and antidiabetic class. The prescribing trend and baseline statistics were conducted for cohort 2a (patients started on metformin) and cohort 2b (patients initiated on SU).

For evaluating the association of the study covariates with the prescribing choice of the individual regimen and class of ADDs at the stage of drug intensification for each of the two studied cohorts (initial-metformin users and initial SU users), univariable analyses were conducted using binomial logistic regression for the regimen type, where the combination regimen was compared to the monotherapy regimen (the reference group). Furthermore, multinomial logistic regression analyses were performed to investigate the outcome by the class of ADDs. For the first studied cohort (cohort 2a; initial-metformin users), SU was assigned as the reference group since it is the most commonly added first intensifying therapy as reflected from previous literature and the prescribing patterns analyses of the current study, while for the second studied cohort (cohort 2b; initial SU users), metformin was assigned as the reference group since it is the most likely to be added to an initial SU monotherapy. This was followed by conducting multivariable analyses to calculate the adjusted OR and 95%CI, including all variables studied at the univariable stage. As illustrated in Chapter 4, the global p-value of the non-binary categorical variables was generated using the likelihood ratio test. A p-value of <0.05 indicates a significant influence of the studied variable on the prescribing choice of the treatment regimen type or class of ADDs. The assumptions and model fitness of the multivariable logistic regression model were tested using the same statistical analysis tests used in the first-line study (section 4.3.3, Chapter 4). The results of the assumptions and model fitness tests are presented in Appendix S.5.2.

Generally, the percentage of missingness in the variables of the intensification study (Tables 5.2 and 5.3) was lower compared to the first-line study (Table 4.4). Nonetheless, both studies observed the highest percentage of missingness in the

triglyceride variable. A total of 36.29% and 36.49% of triglyceride data were missing in cohort-2a and cohort-2b, respectively. All details related to the missing data and possible types of missingness were described in Chapter 4 (section 4.3.3). A Little test was conducted and showed a p-value of <0.001 for the two studied cohorts, indicating that the missing data is not MCAR in both cohorts (cohort-2a and cohort-2b). Consistent with the first-line study, a regression model was primarily applied to the original cohort, where missing data was inserted as a separate level in the model (NA was coded as unknown). As a sensitivity analysis, complete case regression analyses were conducted; only patients with complete records were included in the regression model.

Moreover, regression analyses were performed after handling and adjusting for missing data using first the LOCF method and then multiple imputations, following the same approach explained in the first-line study (Section 4.3.3, Chapter 4). The reduction in the percentage of missingness after applying the LOCF method is presented in Tables 5.2 for the initial-metformin users (cohort-2a) and 5.3 for the initial-SU users (cohort-2b). Baseline characteristics of cohort 2a and cohort 2b were also calculated and described after handling the missing data using the same statistical tests applied to the original cohort. All analysis tests were conducted in RStudio using the same packages reported in Chapter 4 (section 4.3.3). The same codes that described in Appendix S.4.3. were applied in this Chapter but on the intensification cohort (cohort 2-a and cohort 2-b).

Table 5.2: The reduction in the percentage of missingness of variables after applying the last observation carried forward (LOCF) method for the study cohort 2a (initial metformin users)

Variable name	% Of missingness before	% Of missingness after
Urban/rural (UR)	0.03%	0.03%
Scottish index of multiple deprivation-quantile	0.02%	0.02%
HbA1c	3.11%	1.46%
Body mass index (BMI)	31.74%	20.63%
Triglyceride (TG)	36.29%	24.26%
Total cholesterol	18.72%	6.00%
High-density lipoprotein (HDL)	29.56%	16.48%
Estimated glomerular filtration rate (eGFR)	8.21%	2.10%

SIMD-Q; Scottish index of multiple deprivation-Quantile

Table 5.3: The reduction in the percentage of missingness of variables after applying the last observation carried forward (LOCF) method for the study cohort 2b (initial SU users)

Variable name	% Of missingness before	% Of missingness after
Urban/rural (UR)	0.02%	0.02%
HbA1c	4.62%	2.57%
Body mass index (BMI)	34.37%	23.59%
Triglyceride (TG)	36.49%	24.94%
Total cholesterol	20.34%	7.90%
High-density lipoprotein (HDL)	30.74%	18.20%
Estimated glomerular filtration rate (eGFR)	8.12%	2.90%

5.3 Results

Out of 145909 patients who were identified as incident users of ADDs between Jan/2010 and Dec/2019 in the first-line study (Chapter 4), a total of 132382 patients were started on monotherapy (section 4.3, Chapter 4). Of those, a cohort of 52,206 (39.4%) patients were intensified with one or more antidiabetic class(es) after at least three months of initial therapy between Jan/2010 and Dec/2020. The remaining 80176 (60.6%) patients were not included in this study because either the patients have either experienced no change in drug therapy over the entire study

period; or switched to a different class of ADD (no further prescription of the initial therapy), as illustrated in Figure 5.1. Of the intensification cohort (N=52206), only patients who started on metformin (N= 46730, 89.51%) or SU (N=4001, 7.66%) were included in this study since they accounted for 97.17%(50731/52206) of the entire intensification cohort (Figure 5.1).

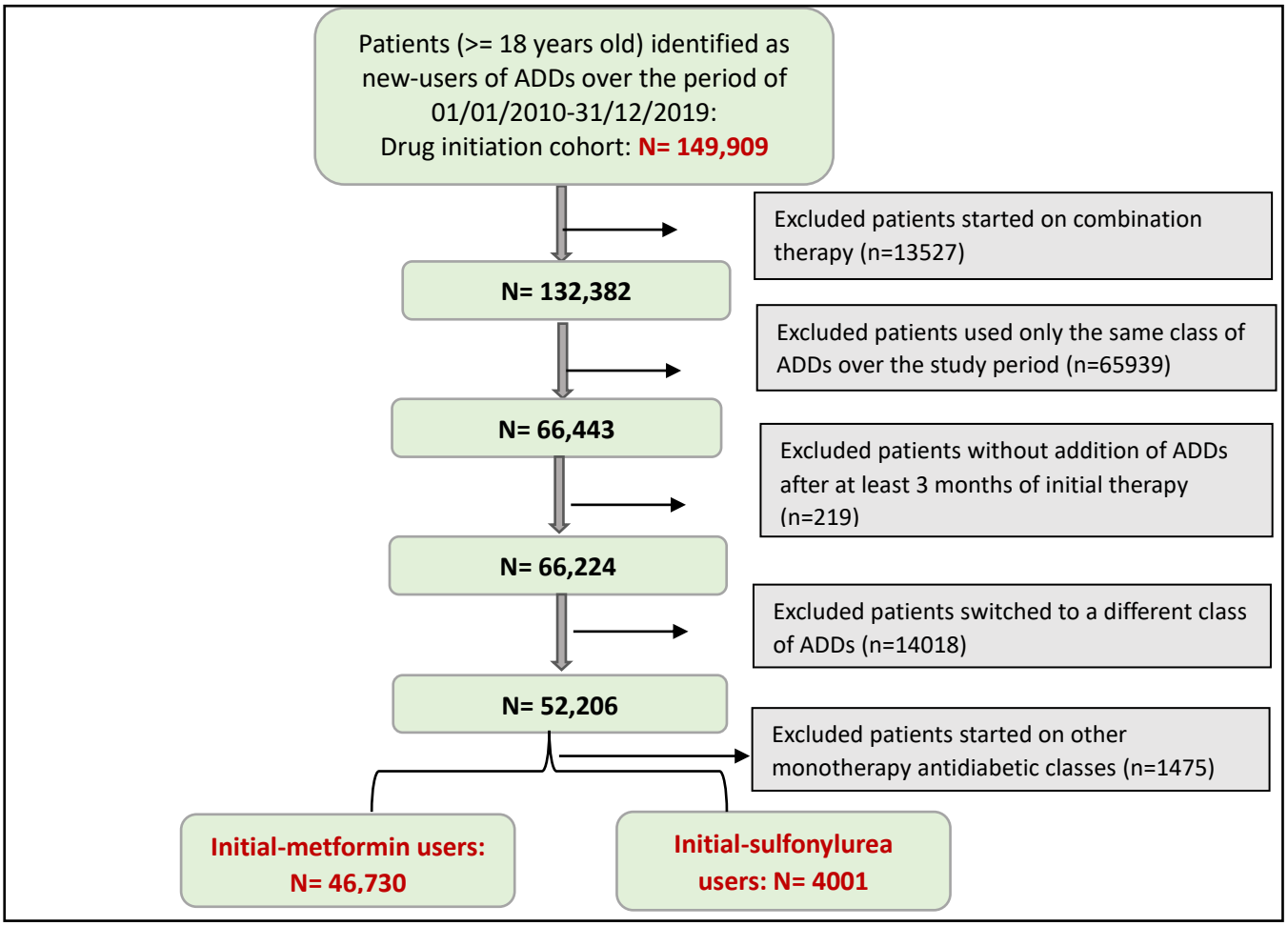

Figure 5.1: Flowchart of cohort identification at the stage of first drug intensification. ADDs, antidiabetic drugs

5.3.1 Baseline characteristics of included patients

5.3.1.1 Baseline characteristics of patients using metformin as an initial therapy

A. Baseline characteristics of the overall cohort stratified by regimen type

Table 5.4 summarises the baseline characteristics of the initial-metformin cohort overall and their distribution by the type of prescribed regimen (monotherapy and combination). Around 60% of patients who used metformin as initial therapy were male (28060/46730). In addition, the median age of the overall cohort was 59 years [IQR: 51-68], with more than two-thirds of patients being non-elderly (< 65 years old) at the date of drug intensification. Patients who were intensified with combination regimens included more women compared to patients intensified with monotherapy ADD (46.2% (354/767) vs. 39.9%(18,316/45,963)), and they had a lower median age (57[IQR: 49-67] vs. 59[IQR: 51-68]), with 29.6%(227/767) of patients in the combination group aged 65 years or over at the time of drug intensification compared to 33.7% (15,475/45,963) in the monotherapy group.

Overall, more than three-quarters of the initial-metformin cohort (N=38133, 81.6%) had a zero baseline CCI score. Among the studied individual comorbid conditions, the most prevalent co-existing disease was HTN (19.9%, 9315/46730) followed by IHD (13.2%, 6167/46730). All studied comorbid conditions of interest were more prevalent among patients who were intensified with combination therapy than those treated with monotherapy (Table 5.4). As an assessment of microvascular complications at baseline, neuropathy disease and retinal disease were investigated. They were presented in less than 1% and 3% of the initial-metformin cohort, respectively; none of the patients had diabetic neuropathy or diabetic retinopathy.

Despite the majority of patients having a zero CCI score, around two-thirds of the initial-metformin cohort used five or more concomitant medications (60.1%, 30881/46730). Antihyperlipidemic drugs were the most frequently used medications, which were utilised by 69.6%(32501/46730) of the initial-metformin cohort.

Furthermore, patient obesity was evaluated based on the value of the baseline BMI which was available for 68.26% of the initial-metformin cohort. The baseline median BMI of the initial-metformin cohort was 33[IQR: 29-38] kg/m^2. More than one-third of patients had a baseline BMI of >=30 kg/m^2 (N= 21922, 46.9%). For the baseline eGFR, data was available for 91.8% of the initial-metformin cohort in which the baseline median eGFR was 95[IQR: 81-105] ml/min/1.73m^2, and it was similar for monotherapy and combination therapy groups (Table 5.4).

Moreover, the baseline HbA1c was available for 96.9% of the initial-metformin cohort, where the overall median HbA1c (IQR) was 8.9(8.1-10.20), with 47.1%(22022/46730) of patients having a baseline HbA1c value of >= 9%. A large difference was observed in the median baseline HbA1c of patients intensified with combination therapy compared to those receiving a monotherapy (10.0% vs. 8.9%, respectively); 61.3%(470/767) of the combination group had a baseline HbA1c value of >= 9% compared to 46.8%(21552/45963) in the monotherapy group.

Table 5.4: Baseline characteristics of the initial-metformin cohort as overall and stratified by the type of prescribed regimen

Characteristics	Overall N=46,730	Combination N=767	Monotherapy N=45,963
Sex			
Male	60.05%(28,060)	53.85%(413)	60.15%(27,647)
Female	39.95%(18,670)	46.15%(354)	39.85%(18,316)
Age at prescription	59 (51, 68)	57(49, 67)	59(51, 68)
< 65 years	66.40%(31,028)	70.40%(540)	66.33%(30,488)
>= 65 years	33.60%(15,702)	29.60%(227)	33.67%(15,475)
Urban-rural			
1	32.21%(15,052)	32.86%(252)	32.20%(14,800)
2	38.60%(18,039)	37.55%(288)	38.62%(17,751)
3	8.48%(3,961)	8.21%(63)	8.48%(3,898)
4	2.31%(1,078)	2.22%(17)	2.31%(1,061)
5	1.28%(597)	0.78%(6)	1.29%(591)
6	10.89%(5,087)	10.82%(83)	10.89%(5,004)
7	3.33%(1,554)	4.04%(31)	3.31%(1,523)
8	2.88%(1,347)	3.52%(27)	2.87%(1,320)
Unknown	0.03%(15)	0.00%(0)	0.03%(15)
Scottish index of multiple deprivation-quantile			

1	27.67%(12,928)	28.94%(222)	27.64%(12,706)
2	24.10%(11,264)	24.12%(185)	24.10%(11,079)
3	20.15%(9,415)	22.03%(169)	20.12%(9,246)
4	16.23%(7,583)	14.21%(109)	16.26%(7,474)
5	11.84%(5,532)	10.69%(82)	11.86%(5,450)
Unknown	0.02%(8)	0.00%(0)	0.02%(8)
Prescriber type			
General practitioner (GP)	92.79%(43,361)	93.48%(717)	92.78%(42,644)
Non-GP	7.21%(3,369)	6.52%(50)	7.22%(3,319)
Ischemic heart disease	13.20%(6,167)	16.04%(123)	13.15%(6,044)
Hypertension	19.93%(9,315)	25.42%(195)	19.84%(9,120)
Hear failure	3.24%(1,512)	5.61%(43)	3.20%(1,469)
Stroke	2.48%(1,161)	3.26%(25)	2.47%(1,136)
Peripheral vascular disease	2.45%(1,146)	3.00%(23)	2.44%(1,123)
Liver disease	2.79%(1,302)	5.48%(42)	2.74%(1,260)
Retinal disease	0.61%(287)	0.91%(7)	0.61%(280)
Neuropathy disease	2.66%(1,243)	3.13%(24)	2.65%(1,219)
Charlson comorbidity score-Quan			
0	81.60%(38,133)	73.40%(563)	81.74%(37,570)
1-2	14.15%(6,613)	19.04%(146)	14.07%(6,467)
3-4	2.84%(1,329)	5.48%(42)	2.80%(1,287)
>=5	1.40%(655)	2.09%(16)	1.39%(639)
Lipid drugs	69.55%(32,501)	64.41%(494)	69.64%(32,007)
Antipsychotics	3.13%(1,464)	5.22%(40)	3.10%(1,424)
Thiazide diuretics	6.90%(3,223)	5.35%(41)	6.92%(3,182)
Beta-blockers	15.26%(7,132)	14.60%(112)	15.27%(7,020)
Angiotensin inhibitors	20.14%(9,411)	21.12%(162)	20.12%(9,249)
Calcium channel blocker	17.65%(8,249)	13.82%(106)	17.72%(8,143)
Polypharmacy			
0	2.12%(990)	1.56%(12)	2.13%(978)
1-4	31.80%(14,859)	21.77%(167)	31.96%(14,692)
>=5	66.08%(30,881)	76.66%(588)	65.91%(30,293)
Body mass index (kg/m^2)	33 (29, 38)	33 (29, 39)	33 (29, 38)
<= 24.9	4.39%(2,050)	5.74%(44)	4.36%(2,006)
25-29.9	16.96%(7,926)	13.82%(106)	17.01%(7,820)
>= 30	46.91%(21,922)	41.46%(318)	47.00%(21,604)
Unknown	31.74%(14,832)	38.98%(299)	31.62%(14,533)
HbA1c (%)	8.90(8.10, 10.20)	10.00(8.60, 11.80)	8.90(8.10, 10.20)
mmol/mol	74(65, 88)	86(70, 106)	74(65, 88)

< 7	2.23%(1,042)	2.74%(21)	2.22%(1,021)
7- <9	47.53%(22,212)	28.03%(215)	47.86%(21,997)
>=9	47.13%(22,022)	61.28%(470)	46.89%(21,552)
Unknown	3.11%(1,454)	7.95%(61)	3.03%(1,393)
Estimated glomerular filtration rate (m/min/1.73m^2)	95(81, 105)	95(77, 107)	95(81, 105)
>= 60	85.50%(39,955)	79.40%(609)	85.60%(39,346)
< 60	6.29%(2,938)	9.65%(74)	6.23%(2,864)
Unknown	8.21%(3,837)	10.95%(84)	8.17%(3,753)
High density lipoprotein (mg/dl)	41(35, 49)	39(35, 46)	41(35, 49)
<40 (M) or <50 (F)	41.85%(19,556)	40.03%(307)	41.88%(19,249)
40-59 (M) or 50-59 (F)	23.59%(11,025)	17.73%(136)	23.69%(10,889)
>=60	4.99%(2,334)	4.04%(31)	5.01%(2,303)
Unknown	29.56%(13,815)	38.20%(293)	29.42%(13,522)
Total cholesterol (mg/dl)	166(143, 197)	174(147, 209)	166(143, 197)
< 200	61.07%(28,537)	48.50%(372)	61.28%(28,165)
200-239	12.79%(5,976)	13.56%(104)	12.78%(5,872)
>=240	7.42%(3,467)	9.00%(69)	7.39%(3,398)
Unknown	18.72%(8,750)	28.94%(222)	18.55%(8,528)
Triglyceride (mg/dl)	195(142, 283)	213(151, 328)	195(142, 283)
< 150	18.37%(8,585)	13.04%(100)	18.46%(8,485)
150-499	41.44%(19,366)	37.16%(285)	41.51%(19,081)
>= 500	3.89%(1,819)	5.74%(44)	3.86%(1,775)
Unknown	36.29%(16,960)	44.07%(338)	36.16%(16,622)

The results presented as % (frequency) or median (Interquartile range)

B. Baseline characteristics stratified by the class of intensifying monotherapy

Table 5.5 describes the baseline characteristics of the initial-metformin users who were intensified with single ADD stratified by the antidiabetic class. Of the initial-metformin users who were intensified with monotherapy ADD, male patients accounted for more than 50% of patients who received TZD, DPP4-I, SGLT2-I, or SU (66.9%, 60.8%, 60.7%, and 60.2%, respectively), yet more than half of GLP1-RA, insulin, and other-monotherapy users were female patients (53.2%, 60.8%, and 53.3%, respectively). The median age of patients who were intensified with any of the investigated monotherapy antidiabetic classes was less than 65 years, with a

range of 51 years for patients treated with GLP1-RA to 60 years for patients receiving DPP4-I, SU, and other-monotherapy groups (Table 5.5).

Regarding the baseline comorbid conditions, more than three-quarters of patients who were intensified with any of the studied monotherapy groups had a zero baseline CCI score except the insulin group, where around 72%(595/826) of patients had zero baseline CCI score. HTN followed by IHD were the most commonly presented comorbid conditions across all monotherapy antidiabetic classes (Table 5.5). The highest prevalence of HTN, HF, PVD, liver disease, and neuropathy disease was observed among patients intensified with insulin (23.2%, 4.8%, 3.2%, 3.6%, and 3.1%, respectively). On the contrary, IHD and stroke most commonly occurred among SU users (14.3% and 2.4%, respectively). In addition, more than half of patients who were treated with DPP4-I, GLP1-RA, insulin, SGLT2-I, SU, or TZD used five or more concomitant medications at or prior to the date of drug intensification (Table 5.5). Of the investigated concomitant medications of interest, antihyperlipidemic medications were the most frequently prescribed ones, while antipsychotic drugs were the least prescribed ones across all monotherapy groups (Table 5.5).

Moreover, based on the available data on the baseline BMI, the median BMI was higher than 30kg/m^2 for all monotherapy groups, where the highest median BMI was observed among GLP1-RA users (median BMI = 41 kg/m^2), with 73.66%(411/558) of patients were obese (BMI >= 30 kg/m^2). The lowest median BMI was presented among patients started on insulin (31 kg/m^2), with around one-third (33.17%, 274/826) of patients having a high baseline BMI of >= 30 kg/m^2. Regarding the baseline eGFR, the median eGFR levels of the available data were higher than 60 ml/min/1.73m^2 for all monotherapy groups; nonetheless, the percentage of patients with a low baseline eGFR (< 60ml/min/1.73m^2) ranged from 0%(0/15) for the other-monotherapy users to 12.0%(99/826) for insulin users. Patients who were intensified with SU had the highest median HbA1c (9.1 [IQR: 8.20-10.50]), with 51.16%(11356/22197) of patients having a baseline HbA1c value of >=9%.

Table 5.5: Baseline characteristics of the initial-metformin cohort who received monotherapy groups stratified by antidiabetic class

Characteristics	DPP4-I N=12,986	GLP1-RA N=558	Insulin N=826	SGLT2-I N=7,850	SU N=22,197	TZD N=1,531	Other N=15
Sex							
Male	60.81%(7,897)	46.77%(261)	39.23%(324)	60.74%(4,768)	60.22%(13,366)	66.88%(1,024)	46.67%(7)
Female	39.19%(5,089)	53.23%(297)	60.77%(502)	39.26%(3,082)	39.78%(8,831)	33.12%(507)	53.33%(8)
Age at prescription	60(52, 69)	51(40, 59)	50(37, 66)	57(50, 64)	60(52, 69)	58(51, 66)	60(51, 69)
< 65 years	63.24%(8,212)	89.25%(498)	72.28%(597)	77.54%(6,087)	63.14%(14,016)	69.82%(1,069)	60.00%(9)
>= 65 years	36.76%(4,774)	10.75%(60)	27.72%(229)	22.46%(1,763)	36.86%(8,181)	30.18%(462)	40.00%(6)
Urban-rural							
1	29.34%(3,810)	37.99%(212)	34.26%(283)	35.53%(2,789)	33.72%(7,485)	14.24%(218)	*
2	41.95%(5,447)	34.41%(192)	38.38%(317)	37.72%(2,961)	36.05%(8,002)	54.21%(830)	*
3	8.72%(1,133)	6.09%(34)	7.63%(63)	6.90%(542)	8.83%(1,959)	10.78%(165)	*
4	1.96%(255)	3.23%(18)	2.54%(21)	2.08%(163)	2.58%(573)	2.02%(31)	0.00%(0)
5	1.34%(174)	1.79%(10)	*	*	1.23%(272)	0.20%(3)	0.00%(0)
6	10.59%(1,375)	8.42%(47)	9.56%(79)	10.01%(786)	11.25%(2,498)	14.11%(216)	*
7	3.12%(405)	3.23%(18)	3.87%(32)	3.17%(249)	3.56%(791)	1.76%(27)	*
8	2.93%(381)	4.84%(27)	3.03%(25)	2.94%(231)	2.75%(611)	2.68%(41)	>20%
Unknown	0.05%(6)	0.00%(0)	*	*	0.03%(6)	0.00%(0)	0.00%(0)
Scottish index of multiple deprivation-quantile							
1	28.62%(3,716)	32.26%(180)	31.48%(260)	29.40%(2,308)	26.52%(5,887)	23.12%(354)	*
2	23.71%(3,079)	27.06%(151)	25.54%(211)	23.20%(1,821)	24.51%(5,440)	24.49%(375)	*
3	20.29%(2,635)	19.53%(109)	18.28%(151)	19.21%(1,508)	20.27%(4,500)	22.01%(337)	40.00%(6)
4	16.04%(2,083)	12.19%(68)	15.25%(126)	16.03%(1,258)	16.61%(3,686)	16.26%(249)	*
5	*	8.96%(50)	9.44%(78)	*	12.07%(2,679)	14.11%(216)	*

Unknown	*	0.00%(0)	0.00%(0)	*	0.02%(5)	0.00%(0)	0.00%(0)
Prescriber type							
General practitioner (GP)	91.58%(11,892)	94.62%(528)	98.18%(811)	90.00%(7,065)	94.09%(20,886)	94.58%(1,448)	>90%
Non-GP	8.42%(1,094)	5.38%(30)	1.82%(15)	10.00%(785)	5.91%(1,311)	5.42%(83)	<10%
Ischemic heart disease	12.81%(1,664)	7.71%(43)	12.71%(105)	12.05%(946)	14.32%(3,178)	7.05%(108)	0.00%(0)
Hypertension	19.86%(2,579)	17.56%(98)	23.24%(192)	17.45%(1,370)	20.92%(4,644)	15.35%(235)	<20%
Hear failure	2.90%(377)	3.05%(17)	4.84%(40)	2.51%(197)	3.74%(831)	0.46%(7)	0.00%(0)
Stroke	2.51%(326)	1.08%(6)	1.94%(16)	1.99%(156)	2.74%(609)	1.50%(23)	0.00%(0)
Peripheral vascular disease	2.26%(294)	1.61%(9)	3.15%(26)	1.77%(139)	2.85%(633)	1.44%(22)	0.00%(0)
Liver disease	2.29%(298)	2.33%(13)	5.57%(46)	2.73%(214)	2.98%(661)	1.76%(27)	<10%
Retinal disease	0.78%(101)	0.18%(1)	0.48%(4)	0.42%(33)	0.61%(136)	0.33%(5)	0.00%(0)
Neuropathy disease	2.71%(352)	3.41%(19)	1.94%(16)	3.03%(238)	2.53%(561)	2.16%(33)	0.00%(0)
Charlson comorbidity score-Quan							
0	82.73%(10,743)	83.51%(466)	72.03%(595)	84.57%(6,639)	79.88%(17,730)	90.46%(1,385)	80.00%(12)
1-2	13.82%(1,795)	12.54%(70)	18.04%(149)	12.11%(951)	15.20%(3,374)	8.23%(126)	*
3-4	2.43%(316)	2.69%(15)	4.60%(38)	2.37%(186)	3.24%(719)	0.78%(12)	*
>=5	1.02%(132)	1.25%(7)	5.33%(44)	0.94%(74)	1.68%(374)	0.52%(8)	*
Lipid drugs	72.48%(9,412)	55.02%(307)	40.07%(331)	61.66%(4,840)	71.98%(15,978)	73.81%(1,130)	60.00%(9)
Antipsychotics	2.95%(383)	4.84%(27)	4.36%(36)	2.45%(192)	3.40%(754)	2.09%(32)	0.00%(0)
Thiazide diuretics	7.68%(997)	6.09%(34)	3.87%(32)	4.69%(368)	7.26%(1,611)	9.01%(138)	<20%
Beta-blockers	15.20%(1,974)	14.16%(79)	14.29%(118)	12.45%(977)	16.62%(3,689)	11.89%(182)	<10%
Angiotensin inhibitors	20.94%(2,719)	20.97%(117)	10.90%(90)	19.77%(1,552)	20.05%(4,450)	20.77%(318)	<25%

Calcium channel blocker	18.62%(2,418)	13.44%(75)	10.41%(86)	17.36%(1,363)	17.71%(3,931)	17.50%(268)	<20%
Polypharmacy							
0	1.76%(229)	2.51%(14)	2.42%(20)	2.88%(226)	2.08%(462)	1.76%(27)	0.00%(0)
1-4	32.01%(4,157)	32.26%(180)	32.32%(267)	35.20%(2,763)	30.11%(6,683)	41.41%(634)	53.33%(8)
>=5	66.23%(8,600)	65.23%(364)	65.25%(539)	61.92%(4,861)	67.81%(15,052)	56.83%(870)	46.67%(7)
Body mass index (kg/m^2)	33(29, 38)	41(36, 46)	31(27, 37)	34(30, 39)	32(28, 36)	32(29, 37)	31(29, 32)
<= 24.9	3.65%(474)	0.00%(0)	9.69%(80)	2.29%(180)	5.50%(1,220)	3.40%(52)	0.00%(0)
25-29.9	17.16%(2,228)	1.08%(6)	13.92%(115)	14.37%(1,128)	18.25%(4,051)	18.88%(289)	*
>= 30	48.89%(6,349)	73.66%(411)	33.17%(274)	59.26%(4,652)	41.54%(9,221)	45.20%(692)	*
Unknown	30.30%(3,935)	25.27%(141)	43.22%(357)	24.08%(1,890)	34.71%(7,705)	32.53%(498)	46.67%(7)
HbA1c (%) **mmol/mol**	8.60(8.00, 9.70) 71(64, 82)	9.00(8.00, 10.30) 75(64, 89)	8.90(7.20, 11.88) 74(55, 107)	8.90(8.10, 10.00) 74(65, 86)	9.10(8.20, 10.50) 76(66, 91)	8.70(8.00, 9.80) 72(64, 84)	9.10(7.85, 10.00) 76(62, 86)
< 7	1.68%(218)	3.94%(22)	16.71%(138)	1.69%(133)	2.21%(490)	1.31%(20)	0.00 %(0)
7- <9	56.38%(7,321)	43.91%(245)	26.88%(222)	49.34%(3,873)	42.76%(9,492)	54.87%(840)	*
>=9	40.11%(5,209)	48.92%(273)	43.34%(358)	47.15%(3,701)	51.16%(11,356)	42.33%(648)	46.67%(7)
Unknown	1.83%(238)	3.23%(18)	13.08%(108)	1.82%(143)	3.87%(859)	1.50%(23)	*
Estimated glomerular filtration rate (m/min/1.73m^2)	94(79, 104)	102(85, 112)	100(77, 116)	99(88, 107)	94(79, 104)	95(80, 104)	89(77, 101)
>= 60	84.54%(10,979)	84.23%(470)	73.24%(605)	91.22%(7,161)	84.67%(18,795)	86.68%(1,327)	60.00%(9)
< 60	7.35%(955)	5.38%(30)	11.99%(99)	1.41%(111)	7.18%(1,594)	4.90%(75)	0.00%(0)
Unknown	8.10%(1,052)	10.39%(58)	14.77%(122)	7.36%(578)	8.15%(1,808)	8.43%(129)	40.00%(6)
High density lipoprotein (mg/dl)	42(35, 49)	39(35, 46)	42(35, 50)	41(35, 48)	41(35, 49)	41(35, 48)	46(42, 50)
<40 (M) or <50 (F)	42.35%(5,499)	47.67%(266)	32.69%(270)	44.19%(3,469)	41.00%(9,101)	41.80%(640)	*
40-59 (M) or 50-59 (F)	24.83%(3,225)	19.71%(110)	15.25%(126)	24.57%(1,929)	22.80%(5,062)	28.35%(434)	*

>=60	5.21%(676)	2.87%(16)	5.33%(44)	4.32%(339)	5.21%(1,156)	4.70%(72)	0.00%(0)
Unknown	27.61%(3,586)	29.75%(166)	46.73%(386)	26.92%(2,113)	30.99%(6,878)	25.15%(385)	53.33%(8)
Total cholesterol (mg/dl)	164(139, 193)	186(155, 220)	182(147, 217)	170(143, 201)	168(143, 201)	166(143, 193)	178(138, 189)
< 200	64.84%(8,420)	49.10%(274)	40.07%(331)	60.88%(4,779)	60.11%(13,343)	66.04%(1,011)	46.67%(7)
200-239	11.97%(1,554)	18.64%(104)	12.47%(103)	14.27%(1,120)	12.61%(2,799)	12.48%(191)	*
>=240	5.85%(760)	12.54%(70)	8.47%(70)	7.10%(557)	8.28%(1,839)	6.60%(101)	*
Unknown	17.34%(2,252)	19.71%(110)	38.98%(322)	17.76%(1,394)	18.99%(4,216)	14.89%(228)	40.00%(6)
Triglyceride (mg/dl)	194(136, 271)	221(151, 319)	188(133, 305)	195(142, 283)	195(142, 284)	200(137, 283)	186(155, 204)
< 150	19.07%(2,477)	15.77%(88)	15.62%(129)	18.39%(1,444)	18.53%(4,114)	15.15%(232)	*
150-499	41.05%(5,331)	46.42%(259)	27.48%(227)	45.77%(3,593)	41.26%(9,159)	33.12%(507)	33.33%(5)
>= 500	2.89%(375)	5.91%(33)	5.21%(43)	4.17%(327)	4.30%(954)	2.74%(42)	*
Unknown	36.99%(4,803)	31.90%(178)	51.69%(427)	31.67%(2,486)	35.91%(7,970)	48.99%(750)	53.33%(8)

The results presented as % (frequency) or median (Interquartile range). DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

C. Baseline characteristics stratified by the class of intensifying combination regimen

Table 5.6 presents the baseline characteristics of the initial-metformin cohort who were treated with two or more ADDs stratified by the antidiabetic class of combination regimens. Male patients accounted for more than 50% of all combination regimens, but for the other-combination group, half of the patients were male and half were female (Table 5.6). Despite that the median age of patients across all combination regimens was less than 65 years, elderly patients (>= 65 years old) accounted for 44.6%(58/130), 36.9%(92/249), 25.5%(25/98), 19.4%(24/124), and 16.87% (28/166) of patients started on SU+insulin, DPP4-I+SU, DPP4-I+SGLT2-I, SGLT2-I+SU, and other-combination groups, respectively.

Of the initial-metformin cohort, patients treated with SU+ insulin had the lowest percent of zero CCI score (62.3%, 81/130). Comparable to the overall cohort and monotherapy groups, HTN and IHD were the most commonly present co-existing diseases across all combination regimens (Table 5.6). HTN, PVD, and liver disease were mostly present among patients treated with SU+ insulin (Table 5.6). On the contrary, IHD and HF were most prevalent among DPP4-I+SGLT2-I (20.4%, 20/98) and SGLT2-I+SU (8.1%, 10/124) users, respectively. Moreover, more than 70% of patients who were treated with any of the studied combination regimens were on five or more concomitant medications at or prior to drug intensification (Table 5.6). Antihyperlipidemic drugs were the most commonly used concomitant medications across all combination regimens, whereas antipsychotic drugs were the least frequently used ones (Table 5.6). The highest percentage of consumption of antihyperlipidemic drugs was observed among patients who started on DPP4-I+SGLT2-I (72.5%, 71/98).

The percentage of obese patients (BMI >= 30kg/m^2) ranged from 21.5%(28/130) of patients who added SU+ insulin to 53.1%(52/98) of patients who received DPP4-I+SGLT2-I. On the contrary, patients who were intensified with SU+ insulin had the highest baseline median HbA1c (11.60[IQR: 9.60-13.80]), with around 73%(95/130) of patients having a high baseline HbA1c of >= 9%.

Although the baseline median eGFR was greater than 60 ml/min/1.73m^2 across all combination regimens, patients with a low baseline eGFR (< 60 ml/min/1.73m^2) were mostly prescribed SU+insulin, accounting for 20.0%(26/130) of patients who were treated with SU+ insulin (Table 5.6).

Table 5.6: Baseline characteristics of the initial-metformin cohort who received combination therapy stratified by class of combination regimens

Characteristics	DPP4-I+ SGLT2-I N=98	DPP4-I+SU N=249	SGLT2-I+SU N=124	SU+ insulin N=130	Other N=166
Sex					
Male	59.18%(58)	52.61%(131)	53.23%(66)	57.69%(75)	50.00%(83)
Female	40.82%(40)	47.39%(118)	46.77%(58)	42.31%(55)	50.00%(83)
Age at prescription					
< 65 years	74.49%(73)	63.05%(157)	80.65%(100)	55.38%(72)	83.13%(138)
>= 65 years	25.51%(25)	36.95%(92)	19.35%(24)	44.62%(58)	16.87%(28)
Urban-rural					
1	36.73%(36)	32.13%(80)	37.90%(47)	31.54%(41)	28.92%(48)
2	40.82%(40)	35.74%(89)	37.10%(46)	34.62%(45)	40.96%(68)
3	*	10.04%(25)	8.87%(11)	8.46%(11)	7.23%(12)
4	0.00%(0)	*	5.65%(7)	0.00%(0)	*
5	*	*	*	0.00%(0)	*
6	10.20%(10)	11.24%(28)	7.26%(9)	16.92%(22)	8.43%(14)
7	*	3.21%(8)	*	*	4.82%(8)
8	*	4.82%(12)	0.00%(0)	*	5.42%(9)
Scottish index of multiple deprivation-quantile					
1	31.63%(31)	29.32%(73)	33.06%(41)	24.62%(32)	27.11%(45)
2	26.53%(26)	22.89%(57)	29.84%(37)	18.46%(24)	24.70%(41)
3	14.29%(14)	21.29%(53)	16.13%(20)	26.15%(34)	28.92%(48)
4	15.31%(15)	13.65%(34)	11.29%(14)	19.23%(25)	12.65%(21)
5	12.24%(12)	12.85%(32)	9.68%(12)	11.54%(15)	6.63%(11)
Prescriber type					

General practitioner (GP)	88.78%(87)	94.78%(236)	93.55%(116)	95.38%(124)	92.77%(154)
Non-GP	11.22%(11)	5.22%(13)	6.45%(8)	4.62%(6)	7.23%(12)
Ischemic heart disease	20.41%(20)	12.45%(31)	18.55%(23)	18.46%(24)	15.06%(25)
Hypertension	21.43%(21)	24.10%(60)	24.19%(30)	36.15%(47)	22.29%(37)
Hear failure	<10%	6.02%(15)	8.06%(10)	6.15%(8)	4.22%(7)
Stroke	<5%	3.61%(9)	4.03%(5)	<5%	3.61%(6)
Peripheral vascular disease	<5%	2.81%(7)	<5%	6.92%(9)	<5%
Liver disease	<5%	4.42%(11)	7.26%(9)	9.23%(12)	5.42%(9)
Retinal disease	0.00%(0)	<5%	<5%	<5%	0.00%(0)
Neuropathy disease	5.10%(5)	4.82%(12)	<5%	<5%	<5%
Charlson comorbidity score- Quan					
0	85.71%(84)	74.30%(185)	70.97%(88)	62.31%(81)	75.30%(125)
1-2	11.22%(11)	18.47%(46)	22.58%(28)	23.08%(30)	18.67%(31)
3-4	*	*	6.45%(8)	6.92%(9)	*
>=5	*	*	0.00%(0)	7.69%(10)	*
Lipid drugs	72.45%(71)	67.47%(168)	62.90%(78)	57.69%(75)	61.45%(102)
Antipsychotics	<10%	5.62%(14)	6.45%(8)	6.15%(8)	4.22%(7)
Thiazide diuretics	<10%	7.23%(18)	4.84%(6)	5.38%(7)	4.22%(7)
Beta-blockers	20.41%(20)	12.85%(32)	16.94%(21)	14.62%(19)	12.05%(20)
Angiotensin inhibitors	19.39%(19)	24.10%(60)	22.58%(28)	16.92%(22)	19.88%(33)
Calcium channel blocker	14.29%(14)	12.45%(31)	12.10%(15)	19.23%(25)	12.65%(21)
Polypharmacy					
0	0.00%(0)	3.61%(9)	0.00%(0)	<4%	<5%
1-4	25.51%(25)	20.88%(52)	17.74%(22)	>20%	>20%

>=5	74.49%(73)	75.50%(188)	82.26%(102)	76.92%(100)	75.30%(125)
Body mass index (kg/m^2)	34(30, 38)	33(28, 38)	33(30, 39)	29(25, 33)	37(31, 42)
<= 24.9	*	5.62%(14)	6.45%(8)	13.08%(17)	*
25-29.9	*	13.25%(33)	9.68%(12)	22.31%(29)	*
>= 30	53.06%(52)	40.16%(100)	50.00%(62)	21.54%(28)	45.78%(76)
Unknown	30.61%(30)	40.96%(102)	33.87%(42)	43.08%(56)	41.57%(69)
HbA1c (%) **mmol/mol**	8.70(8.00, 10.20) 72(64, 88)	9.70(8.50, 11.33) 82(69, 100)	10.00(8.88, 11.70) 86(74, 104)	11.60(9.60, 13.80) 103(81, 127)	10.40(8.97, 12.12) 90(75, 109)
< 7	*	3.61%(9)	*	6.15%(8)	*
7- <9	54.08%(53)	30.92%(77)	25.81%(32)	13.85%(18)	21.08%(35)
>=9	39.80%(39)	57.03%(142)	66.94%(83)	73.08%(95)	66.87%(111)
Unknown	*	8.43%(21)	*	6.92%(9)	*
Estimated glomerular filtration rate (m/min/1.73m^2)	101(89, 109)	93(74, 105)	101(88, 108)	86(64, 103)	98(81, 108)
>= 60	90.82%(89)	75.90%(189)	87.10%(108)	76.15%(99)	74.70%(124)
< 60	*	12.05%(30)	*	20.00%(26)	7.23%(12)
Unknown	*	12.05%(30)	*	3.85%(5)	18.07%(30)
High density lipoprotein (mg/dl)	39(35, 43)	42(35, 48)	39(33, 46)	39(33, 48)	39(35, 46)
<40 (M) or <50 (F)	52.04%(51)	37.75%(94)	53.23%(66)	33.85%(44)	31.33%(52)
40-59 (M) or 50-59 (F)	*	20.08%(50)	20.16%(25)	16.15%(21)	*
>=60	*	4.82%(12)	4.03%(5)	6.15%(8)	*
Unknown	30.61%(30)	37.35%(93)	22.58%(28)	43.85%(57)	51.20%(85)
Total cholesterol (mg/dl)	174(138, 194)	178(147, 212)	178(151, 217)	170(139, 201)	174(147, 217)
< 200	57.14%(56)	47.39%(118)	50.00%(62)	49.23%(64)	43.37%(72)
200-239	10.20%(10)	14.86%(37)	18.55%(23)	10.00%(13)	12.65%(21)

>=240	6.12%(6)	10.84%(27)	10.48%(13)	8.46%(11)	7.23%(12)
Unknown	26.53%(26)	26.91%(67)	20.97%(26)	32.31%(42)	36.75%(61)
Triglyceride (mg/dl)	213(133, 319)	202(151, 309)	239(186, 372)	196(134, 310)	216(159, 326)
< 150	*	13.65%(34)	9.68%(12)	16.92%(22)	8.43%(14)
150-499	39.80%(39)	38.15%(95)	52.42%(65)	27.69%(36)	30.12%(50)
>= 500	*	6.02%(15)	11.29%(14)	4.62%(6)	3.61%(6)
Unknown	38.78%(38)	42.17%(105)	26.61%(33)	50.77%(66)	57.83%(96)

The results presented as % (frequency) or median (Interquartile range). DPP4-I; Dipeptidyl peptidase-4 inhibitors, SU; sulfonylurea, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

5.3.1.2 Baseline characteristics of patients using sulfonylurea as an initial therapy at the point of drug intensification

A. Baseline characteristics of the overall cohort stratified by the regimen type

Table 5.7 presents the baseline characteristics of the initial-SU cohort overall and their distribution by the type of prescribed regimen (monotherapy and combination). Of the 4001 patients who were started on SU, 2333 (58.3%) were male, while the remaining 1668 (41.7%) patients were female, with almost similar distribution across monotherapy and combination therapy groups (Table 5.7). The median age of the initial-SU cohort was higher than the median age of the initial-metformin cohort (64 [IQR: 54-73] vs. 59 [IQR: 51-68] years), with more than one-third of patients (47.7%, 1908/4001) aged 65 years or over at the time of drug intensification. However, patients treated with combination therapy had a lower median age compared to the median age of monotherapy users (58[IQR: 51-69] vs. 64[IQR: 54-74] years), with 35.5%(38/107) of combination therapy users being elderly compared to 48.0%(1870/3894) of monotherapy users.

Regarding the baseline clinical characteristics of the initial-SU cohort, more than two-thirds of patients had a baseline zero CCI score (68.6%, 2745/4001), yet more than two-thirds were on five or more concomitant medications (68.6%, 2744/4001). Similar to the initial-metformin cohort, HTN and IHD were the most prevalent diseases among the overall cohort, monotherapy group, and combination group (Table 5.16). Moreover, antihyperlipidemic medications were the most commonly used among the overall cohort, monotherapy group, and combination group (Table 5.7).

Additionally, of the available baseline BMI data (65.6%), the median BMI of patients who added a combination therapy to initial SU therapy was slightly higher than the overall median BMI and the median BMI of the monotherapy group (30[26-36] vs. 29[26-33] and 29[26-33], respectively). For the baseline eGFR, data was available for 91.88% of the initial-SU cohort, in which the baseline median eGFR of combination

therapy users was slightly lower than the median eGFR of the overall cohort and monotherapy group (84[59-107] vs. 88[66-101] and 88[67-101], respectively).

In contrast, the median HbA1c of patients who were treated with combination therapy was higher than the median HbA1c of the overall cohort and monotherapy group (10.3[8.95-11.85] vs. 9.6[8.2-10.60] and 9.6 [8.2-10.6], respectively).

Table 5.7: Baseline characteristics of the initial-sulfonylurea cohort as overall and stratified by the type of prescribed regimen

Characteristics	Overall N=4,001	Combination N=107	Monotherapy N=3,894
Sex			
Male	58.31%(2,333)	58.88%(63)	58.29%(2,270)
Female	41.69%(1,668)	41.12%(44)	41.71%(1,624)
Age at prescription	64(54, 73)	58(51, 69)	64(54, 74)
< 65 years	52.31%(2,093)	64.49%(69)	51.98%(2,024)
>= 65 years	47.69%(1,908)	35.51%(38)	48.02%(1,870)
Urban-rural			
1	34.59%(1,384)	28.04%(30)	34.77%(1,354)
2	36.22%(1,449)	41.12%(44)	36.08%(1,405)
3	8.87%(355)	4.67%(5)	8.99%(350)
4	2.50%(100)	*	2.52%(98)
5	*	*	*
6	10.45%(418)	12.15%(13)	10.40%(405)
7	3.45%(138)	6.54%(7)	3.36%(131)
8	2.55%(102)	*	2.52%(98)
unknown	*	0.00%(0)	*
Scottish index of multiple deprivation-quantile			
1	26.77%(1,071)	28.04%(30)	26.73%(1,041)
2	24.12%(965)	21.50%(23)	24.19%(942)
3	17.85%(714)	23.36%(25)	17.69%(689)
4	16.87%(675)	16.82%(18)	16.87%(657)
5	14.40%(576)	10.28%(11)	14.51%(565)
Prescriber type			
General practitioner (GP)	93.78%(3,752)	95.33%(102)	93.73%(3,650)
Non-GP	6.22%(249)	4.67%(5)	6.27%(244)
Ischemic heart disease	17.17%(687)	14.95%(16)	17.23%(671)
Hypertension	23.77%(951)	23.36%(25)	23.78%(926)
Hear failure	6.45%(258)	5.61%(6)	6.47%(252)
Stroke	4.30%(172)	4.67%(5)	4.29%(167)

Peripheral vascular disease	5.10%(204)	5.61%(6)	5.08%(198)
Liver disease	6.02%(241)	11.21%(12)	5.88%(229)
Retinal disease	1.2%(48)	<5%	1.16%(45)
Neuropathy disease	2.25%(90)	<5%	2.21%(86)
Charlson comorbidity score-Quan			
0	68.61%(2,745)	68.22%(73)	68.62%(2,672)
1-2	20.02%(801)	16.82%(18)	20.11%(783)
3-4	7.87%(315)	10.28%(11)	7.81%(304)
>=5	3.50%(140)	4.67%(5)	3.47%(135)
Lipid drugs	63.76%(2,551)	55.14%(59)	64.00%(2,492)
Antipsychotics	3.15%(126)	4.67%(5)	3.11%(121)
Thiazide diuretics	5.42%(217)	<5%	5.52%(215)
Beta-blockers	18.95%(758)	21.50%(23)	18.88%(735)
Angiotensin inhibitors	17.70%(708)	16.82%(18)	17.72%(690)
Calcium channel blocker	15.67%(627)	9.35%(10)	15.84%(617)
Polypharmacy			
0	3.25%(130)	5.61%(6)	3.18%(124)
1-4	28.17%(1,127)	21.50%(23)	28.35%(1,104)
>=5	68.58%(2,744)	72.90%(78)	68.46%(2,666)
Body mass index (kg/m^2)	29(26, 33)	30(26, 36)	29(26, 33)
<= 24.9	14.22%(569)	12.15%(13)	14.28%(556)
25-29.9	22.94%(918)	21.50%(23)	22.98%(895)
>= 30	28.47%(1,139)	31.78%(34)	28.38%(1,105)
Unknown	34.37%(1,375)	34.58%(37)	34.36%(1,338)
HbA1c (%) **mmol/mol**	9.20(8.20, 10.60) 77(66, 92)	10.30(8.95, 11.85) 89(74, 106)	9.20(8.20, 10.60) 77(66, 92)
< 7	4.05%(162)	*	4.13%(161)
7- <9	38.52%(1,541)	23.36%(25)	38.93%(1,516)
>=9	52.81%(2,113)	71.96%(77)	52.29%(2,036)
Unknown	4.62%(185)	*	4.65%(181)
Estimated glomerular filtration rate (m/min/1.73m^2)	88(66, 101)	84(59, 104)	88(67, 101)
>= 60	74.81%(2,993)	69.16%(74)	74.96%(2,919)
< 60	17.07%(683)	23.36%(25)	16.90%(658)
Unknown	8.12%(325)	7.48%(8)	8.14%(317)
High density lipoprotein (mg/dl)	42(35, 50)	40(33, 50)	42(35, 50)
<40 (M) or <50 (F)	40.16%(1,607)	31.78%(34)	40.40%(1,573)
40-59 (M) or 50-59 (F)	22.32%(893)	19.63%(21)	22.39%(872)

>=60	6.77%(271)	4.67%(5)	6.83%(266)
Unknown	30.74%(1,230)	43.93%(47)	30.38%(1,183)
Total cholesterol (mg/dl)	170(143, 201)	170(143, 213)	170(143, 201)
< 200	57.89%(2,316)	47.66%(51)	58.17%(2,265)
200-239	13.47%(539)	14.02%(15)	13.46%(524)
>=240	8.30%(332)	8.41%(9)	8.29%(323)
Unknown	20.34%(814)	29.91%(32)	20.08%(782)
Triglyceride (mg/dl)	184(124, 275)	204(124, 298)	183(124, 275)
< 150	22.69%(908)	*	22.83%(889)
150-499	36.77%(1,471)	28.97%(31)	36.98%(1,440)
>= 500	4.05%(162)	*	4.08%(159)
Unknown	36.49%(1,460)	50.47%(54)	36.11%(1,406)

The results presented as % (frequency) or median (Interquantile range)

B. Baseline characteristics stratified by the class of intensifying monotherapy ADD

Table 5.8 describes the baseline characteristics of the initial-SU users who were intensified with a single ADD stratified by the antidiabetic class. Male patients accounted for more than 50% of the initial-SU users who received metformin, insulin, or SGLT2-I as a first intensifying therapy, while female patients accounted for more than half of patients who were treated with DPP4-I, TZD, and the other-monotherapy (Table 5.8). Only patients who received metformin, SGLT2-I, and the other-monotherapy group had a median age of less than 65 years (63[53-73], 60[53-67], and 63[50-67], respectively).

Regarding the baseline comorbid conditions, around 62%(77/124) and 65%(1895/2924) of patients who were prescribed SGLT2-I or metformin as a first intensifying therapy were on five or more concomitant medications, respectively, compared to more than two-thirds of patients who received each of the remaining monotherapy classes (Table 5.8). The lowest percent of the baseline zero CCI score was observed among patients treated with insulin (37.7%, (129/342)). HTN followed by IHD were the most commonly present comorbid conditions across all monotherapy antidiabetic classes, in which the highest prevalence of HTN and IHD was observed among the other-monotherapy group (40.0%, 6/15) and DPP4-I group

(24.3%, 104/428), respectively (Table 5.8). Consistent with the previous findings of the initial-metformin cohort, antihyperlipidemic medications were the most frequently prescribed concomitant medications for all investigated monotherapy groups (Table 5.8).

Additionally, based on the available data on the baseline BMI, the highest median BMI was observed among patients treated with the other-monotherapy ADDs, followed by SGLT2-I (38[IQR: 38-45] and 32[IQR: 28-37], respectively). The median baseline eGFR varied from 67ml/min/1.73m^2 for patients treated with DPP4-Ito 95ml/min/1.73m^2 for patients who received SGLT2-I. Furthermore, patients who were intensified with insulin or other-monotherapy groups had the highest baseline median HbA1c (10.30[IQR: 8.62-12.17] and 10.35[9.07-12.10], respectively).

Table 5.8: Baseline characteristics of the initial-sulfonylurea cohort who received monotherapy groups stratified by antidiabetic class

Characteristics	Biguanide N=2,924	DPP4-I N=428	Insulin N=342	SGLT2-I N=124	TZD N=61	Other N=15
Sex						
Male	60.67%(1,774)	49.07%(210)	54.68%(187)	53.23%(66)	44.26%(27)	40.00%(6)
Female	39.33%(1,150)	50.93%(218)	45.32%(155)	46.77%(58)	55.74%(34)	60.00%(9)
Age at prescription	63(53, 73)	70(60, 79)	65(55, 75)	60(53, 67)	71(60, 79)	63(50, 67)
< 65 years	54.51%(1,594)	34.35%(147)	48.83%(167)	68.55%(85)	34.43%(21)	66.67%(10)
>= 65 years	45.49%(1,330)	65.65%(281)	51.17%(175)	31.45%(39)	65.57%(40)	33.33%(5)
Urban-rural						
1	35.77%(1,046)	31.31%(134)	33.63%(115)	29.84%(37)	26.23%(16)	40.00%(6)
2	35.40%(1,035)	41.36%(177)	34.21%(117)	40.32%(50)	36.07%(22)	>25%
3	8.96%(262)	9.11%(39)	9.94%(34)	5.65%(7)	13.11%(8)	0.00%(0)
4	2.60%(76)	*	*	*	*	*
5	*	*	*	*	*	0.00%(0)
6	10.33%(302)	9.58%(41)	11.11%(38)	10.48%(13)	14.75%(9)	*
7	3.21%(94)	3.74%(16)	4.97%(17)	*	*	0.00%(0)
8	2.26%(66)	2.80%(12)	2.63%(9)	6.45%(8)	*	*
unknown	*	0.00%(0)	0.00%(0)	0.00%(0)	0.00%(0)	0.00%(0)
Scottish index of multiple deprivation-quantile						
1	27.29%(798)	25.23%(108)	26.61%(91)	25.00%(31)	18.03%(11)	*
2	23.26%(680)	23.36%(100)	26.90%(92)	32.26%(40)	36.07%(22)	53.33%(8)
3	17.51%(512)	19.39%(83)	17.84%(61)	17.74%(22)	13.11%(8)	*
4	17.03%(498)	18.46%(79)	16.08%(55)	12.10%(15)	14.75%(9)	*
5	14.91%(436)	13.55%(58)	12.57%(43)	12.90%(16)	18.03%(11)	*

Prescriber type	NA	NA	NA	NA	NA	NA
General practitioner (GP)	93.88%(2,745)	92.52%(396)	96.49%(330)	85.48%(106)	>90%	100.00%(15)
Non-GP	6.12%(179)	7.48%(32)	3.51%(12)	14.52%(18)	<10%	0.00%(0)
Ischemic heart disease	15.63%(457)	24.30%(104)	23.39%(80)	12.90%(16)	21.31%(13)	<10%
Hypertension	20.49%(599)	34.35%(147)	37.13%(127)	20.97%(26)	34.43%(21)	40.00%(6)
Hear failure	4.69%(137)	10.28%(44)	15.79%(54)	6.45%(8)	9.84%(6)	<30%
Stroke	3.76%(110)	6.07%(26)	7.31%(25)	4.03%(5)	0.00%(0)	<10%
Peripheral vascular disease	4.38%(128)	6.54%(28)	10.23%(35)	<10%	<10%	0.00%(0)
Liver disease	4.92%(144)	5.14%(22)	13.45%(46)	10.48%(13)	<10%	<10%
Retinal disease	1.09%(32)	1.64%(7)	<10%	<10%	0.00%(0)	<10%
Neuropathy disease	1.95%(57)	2.10%(9)	3.51%(12)	4.03%(5)	<10%	0.00%(0)
Charlson comorbidity score- Quan						
0	74.01%(2,164)	57.48%(246)	37.72%(129)	71.77%(89)	60.66%(37)	46.67%(7)
1-2	17.65%(516)	26.87%(115)	30.12%(103)	20.16%(25)	29.51%(18)	*
3-4	5.68%(166)	10.75%(46)	21.93%(75)	8.06%(10)	*	*
>=5	2.67%(78)	4.91%(21)	10.23%(35)	0.00%(0)	*	*
Lipid drugs	65.08%(1,903)	69.86%(299)	50.58%(173)	47.58%(59)	78.69%(48)	66.67%(10)
Antipsychotics	3.04%(89)	3.04%(13)	4.39%(15)	<10%	<10%	<10%
Thiazide diuretics	5.68%(166)	7.24%(31)	1.75%(6)	5.65%(7)	<10%	<15%
Beta-blockers	16.76%(490)	28.27%(121)	26.61%(91)	16.13%(20)	18.03%(11)	<15%
Angiotensin inhibitors	18.19%(532)	16.36%(70)	12.57%(43)	20.97%(26)	24.59%(15)	<30%
Calcium channel blocker	15.63%(457)	18.93%(81)	14.33%(49)	14.52%(18)	16.39%(10)	<15%
Polypharmacy						
0	3.76%(110)	1.40%(6)	<5%	<5%	0.00%(0)	0.00%(0)

1-4	31.43%(919)	19.16%(82)	>10%	>30%	26.23%(16)	<10%
>=5	64.81%(1,895)	79.44%(340)	86.26%(295)	62.10%(77)	73.77%(45)	>90%
Body mass index (kg/m^2)	29(26, 33)	30(26, 33)	26(22, 31)	32(28, 37)	28(25, 32)	38(38, 45)
<= 24.9	13.10%(383)	13.79%(59)	28.65%(98)	5.65%(7)	14.75%(9)	0.00%(0)
25-29.9	24.83%(726)	18.69%(80)	14.04%(48)	20.16%(25)	24.59%(15)	<10%
>= 30	29.00%(848)	29.91%(128)	16.67%(57)	38.71%(48)	26.23%(16)	53.33%(8)
Unknown	33.07%(967)	37.62%(161)	40.64%(139)	35.48%(44)	34.43%(21)	>30%
HbA1c (%) **mmol/mol**	9.10(8.10, 10.40) 76(65, 90)	9.20(8.30, 10.40) 77(67, 90)	10.30(8.62, 12.17) 89(71, 110)	9.70(8.40, 10.80) 82(68, 95)	9.75(8.70, 10.97) 84(72, 97)	10.35(9.07, 12.10) 90(76, 109)
< 7	4.58%(134)	3.04%(13)	3.22%(11)	*	*	0.00%(0)
7- <9	41.18%(1,204)	39.25%(168)	23.10%(79)	33.87%(42)	32.79%(20)	*
>=9	50.14%(1,466)	53.74%(230)	63.16%(216)	60.48%(75)	62.30%(38)	73.33%(11)
Unknown	4.10%(120)	3.97%(17)	10.53%(36)	*	*	*
Estimated glomerular filtration rate (m/min/1.73m^2)	90(72, 102)	67(44, 93)	70(42, 98)	95(82, 103)	71(40, 92)	87(52, 95)
>= 60	80.64%(2,358)	52.80%(226)	54.39%(186)	83.87%(104)	59.02%(36)	60.00%(9)
< 60	10.88%(318)	40.19%(172)	38.30%(131)	7.26%(9)	*	*
Unknown	8.48%(248)	7.01%(30)	7.31%(25)	8.87%(11)	*	*
High density lipoprotein (mg/dl)	42(35, 50)	39(35, 49)	43(34, 53)	42(35, 48)	42(35, 50)	42(31, 50)
<40 (M) or <50 (F)	40.77%(1,192)	43.46%(186)	32.75%(112)	40.32%(50)	44.26%(27)	40.00%(6)
40-59 (M) or 50-59 (F)	23.50%(687)	18.46%(79)	16.96%(58)	25.81%(32)	*	*
>=60	6.81%(199)	6.54%(28)	9.06%(31)	4.03%(5)	*	*
Unknown	28.93%(846)	31.54%(135)	41.23%(141)	29.84%(37)	29.51%(18)	40.00%(6)
Total cholesterol (mg/dl)	170(143, 205)	162(139, 201)	158(139, 196)	182(160, 202)	170(155, 189)	174(155, 201)
< 200	58.72%(1,717)	60.05%(257)	51.46%(176)	54.84%(68)	67.21%(41)	40.00%(6)

200-239	14.40%(421)	12.38%(53)	6.43%(22)	12.90%(16)	13.11%(8)	*
>=240	8.31%(243)	8.18%(35)	8.77%(30)	8.87%(11)	*	0.00%(0)
Unknown	18.57%(543)	19.39%(83)	33.33%(114)	23.39%(29)	*	*
Triglyceride (mg/dl)	182(124, 275)	198(142, 248)	159(115, 259)	186(140, 266)	169(127, 328)	232(170, 361)
< 150	23.60%(690)	18.22%(78)	23.68%(81)	20.16%(25)	*	*
150-499	37.41%(1,094)	42.52%(182)	24.85%(85)	41.13%(51)	34.43%(21)	46.67%(7)
>= 500	4.24%(124)	2.10%(9)	3.51%(12)	8.06%(10)	*	*
Unknown	34.75%(1,016)	37.15%(159)	47.95%(164)	30.65%(38)	39.34%(24)	33.33%(5)

The results presented as % (frequency) or median (Interquartile range). DPP4-I; Dipeptidyl peptidase-4 inhibitors, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

C. Baseline characteristics stratified by the class of intensifying combination regimen

Table 5.9 shows the baseline characteristics of the initial-SU users who received two or more ADDs as the first intensifying therapy stratified by the antidiabetic class of combination regimens. Because of the small number of patients in this subgroup, many of the cells within Table 5.18 were replaced with a star (*) to protect patient privacy. Male patients accounted for 61.4%(27/44), 58.8%(20/34), and 55.2%(16/29) of patients who received metformin+DPP4-I, other-combination, and metformin+ insulin, respectively. In addition, it was revealed that patients who received metformin+DPP4-I had a higher median age at prescription (60[51-70] years) than patients treated with metformin+ insulin or other-combination group (56[51-68] and 58[49-68], respectively).

For the clinical characteristics, patients with a zero baseline CCI score accounted for 55.2%(16/29), 67.7%(23/34), and 77.3%(34/44) of patients who were prescribed metformin+ insulin, other-combination group, and metformin+ DPP4-I, respectively, while more than 70% of patients used five or more concomitant medication at or before the index intensification date for all studied combination regimens (Table 5.9). Comparable to the overall cohort and monotherapy groups, HTN and IHD were the most commonly presented co-existing diseases across all combination regimens, and antihyperlipidemic drugs were the most commonly used concomitant medication for all studied combination regimens (Table 5.9). Moreover, the highest baseline median BMI was observed among metformin+ insulin users (32[IQR: 27-39]kg/m^2). Likewise, metformin+ insulin users had the highest baseline median HbA1c (11.4[IQR: 10.25-12.55]), and the baseline median eGFR was higher than 60 ml/min/1.73m^2 for all combination regimens (Table 5.9).

Table 5.9: Baseline characteristics of the initial-sulfonylurea cohort who received combination therapy stratified by class of combination regimens

Characteristics	biguanide+DPP4-I N=44	biguanide+ insulin N=29	Other N=34
Sex			

Male	61.36%(27)	55.17%(16)	58.82%(20)
Female	38.64%(17)	44.83%(13)	41.18%(14)
Age at prescription	60(51, 70)	56(51, 68)	58(49, 68)
< 65 years	59.09%(26)	68.97%(20)	67.65%(23)
>= 65 years	40.91%(18)	31.03%(9)	32.35%(11)
Urban-rural			
1	20.45%(9)	31.03%(9)	35.29%(12)
2	38.64%(17)	44.83%(13)	41.18%(14)
3	*	*	*
4	*	0.00%(0)	*
5	*	0.00%(0)	0.00%(0)
6	22.73%(10)	*	*
7	*	*	*
8	*	*	*
Scottish index of multiple deprivation-quantile			
1	34.09%(15)	27.59%(8)	20.59%(7)
2	22.73%(10)	*	26.47%(9)
3	20.45%(9)	24.14%(7)	26.47%(9)
4	*	20.69%(6)	*
5	*	*	*
Prescriber type	NA	NA	NA
General practitioner (GP)	>90%	>90%	>90%
Non-GP	<10%	<10%	<10%
Ischemic heart disease	13.64%(6)	<20%	20.59%(7)
Hypertension	15.91%(7)	34.48%(10)	23.53%(8)
Hear failure	<15%	<10%	<10%
Stroke	<10%	<10%	<10%
Peripheral vascular disease	<20%	0.00%(0)	<10%
Liver disease	<20%	20.69%(6)	<10%
Retinal disease	<10%	<10%	0.00%(0)
Neuropathy disease	<10%	0.00%(0)	<10%
Charlson comorbidity score- Quan			
0	77.27%(34)	55.17%(16)	67.65%(23)
1-2	13.64%(6)	*	20.59%(7)
3-4	*	20.69%(6)	*
>=5	*	*	*
Lipid drugs	61.36%(27)	41.38%(12)	58.82%(20)

Antipsychotics	<10%	<10%	0.00%(0)
Thiazide diuretics	<10%	0.00%(0)	0.00%(0)
Beta-blockers	22.73%(10)	27.59%(8)	14.71%(5)
Angiotensin inhibitors	15.91%(7)	<20%	20.59%(7)
Calcium channel blocker	<10%	<20%	<10%
Polypharmacy			
0	*	*	*
1-4	*	*	*
>=5	70.45%(31)	75.86%(22)	73.53%(25)
Body mass index (kg/m^2)	30(25, 33)	32(27, 39)	28(26, 36)
<= 24.9	15.91%(7)	*	*
25-29.9	22.73%(10)	*	*
>= 30	31.82%(14)	41.38%(12)	23.53%(8)
Unknown	29.55%(13)	24.14%(7)	50.00%(17)
HbA1c (%) **mmol/mol**	9.60(8.45, 10.95) 81(69, 96)	11.40(10.25, 12.55) 101(88, 114)	10.50(9.05, 11.93) 91(75, 107)
< 7	*	0.00%(0)	*
7- <9	31.82%(14)	*	23.53%(8)
>=9	63.64%(28)	86.21%(25)	70.59%(24)
Unknown	*	*	*
Estimated glomerular filtration rate (m/min/1.73m^2)	82(65, 103)	84(60, 108)	90(56, 100)
>= 60	75.00%(33)	68.97%(20)	61.76%(21)
< 60	*	*	*
Unknown	*	*	*
High density lipoprotein (mg/dl)	41(35, 48)	42(31, 55)	39(32, 49)
<40 (M) or <50 (F)	31.82%(14)	31.03%(9)	32.35%(11)
40-59 (M) or 50-59 (F)	*	*	*
>=60	*	*	*
Unknown	38.64%(17)	48.28%(14)	47.06%(16)
Total cholesterol (mg/dl)	160(134, 200)	186(151, 236)	176(148, 214)
< 200	56.82%(25)	31.03%(9)	50.00%(17)
200-239	*	*	*
>=240	*	*	*
Unknown	22.73%(10)	41.38%(12)	29.41%(10)
Triglyceride (mg/dl)	201(131, 292)	224(124, 298)	204(133, 408)
< 150	20.45%(9)	*	*
150-499	36.36%(16)	24.14%(7)	23.53%(8)

>= 500	0.00%(0)	*	*
Unknown	43.18%(19)	55.17%(16)	55.88%(19)

The results presented as % (frequency) or median (Interquantile range). DPP4-I; Dipeptidyl peptidase-4 inhibitors.

5.3.2 Prescribing pattern of antidiabetic drugs at the stage of first drug intensification

Of the individuals who were started on metformin monotherapy and intensified with one or more antidiabetic classes (N=46730), a total of 45963 (98.4%) patients were intensified with single ADD (monotherapy), and only 1.6%(N=767) of patients were treated with combination therapy over the studied 11 years (Table 5.10, Figure 5.2). Similar to the first line study (Chapter 4), the addition of a combination regimen as a first intensifying therapy to initial metformin has significantly increased over the study period compared to the addition of a monotherapy regimen (Combination vs. monotherapy: from 1.1%(7/767) to 2.3%(122/767) vs. 98.9%(624/45963) to 97.7%(5298/45963) in 2010 to 2020, Z = 4.74, p-value < 0.001). Likewise, the majority of patients who were started on SU and intensified with one or more ADDs (N=4001) received one additional antidiabetic class as a first intensifying therapy (3894/4001, 97.3%), while the remaining 2.7%(107/4001) of patients were intensified with combination regimen (Figure 5.2, Table 5.11), which was higher than the percentage of combination therapy among patients initiated on metformin (1.6%). Unlike patients started on metformin, those started on SU showed no significant change in the prescribing trend of combination therapy as a first intensifying therapy compared to monotherapy over the study period (Z = 0.28, p-value = 0.781).

Table 5.10: Prescribing patterns of antidiabetic regimen type at the stage of first drug intensification for patients starting on metformin monotherapy

Prescription Year	Monotherapy	Combination therapy	Total per year
2010	624 (98.89%)	7(1.11%)	(N=631)
2011	2056 (98.14%)	39 (1.86%)	(N=2095)
2012	3121 (99.05%)	30 (0.95%)	(N=3151)
2013	3840 (98.77%)	48 (1.23%)	(N=3888)
2014	4061 (98.81%)	49 (1.19%)	(N=4110)
2015	5030 (98.55%)	74 (1.45%)	(N=5104)
2016	5090 (98.38%)	84 (1.62%)	(N=5174)
2017	5336 (97.94%)	112 (2.06%)	(N=5448)
2018	5442 (98.27%)	96 (1.73%)	(N=5538)
2019	6065 (98.28%)	106 (1.72%)	(N=6171)
2020	5298(97.75%)	122 (2.25%)	(N=5420)
Total per regimen	45963 (98.36%)	767 (1.64%)	(N=46730)
Absolute change	4674	115	
Relative change	7.49	16.43	
Trend test*	Z = 4.74, p-value **< 0.001**		

*Using Cochran-Armitage test for trend compared combination therapy to monotherapy

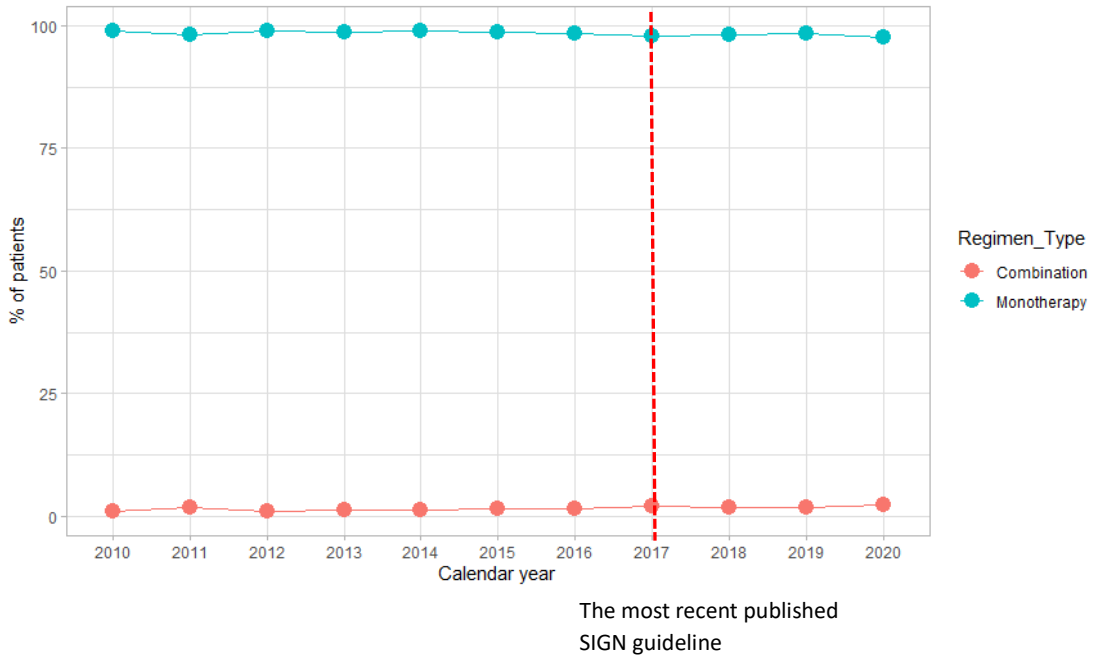

Figure 5.2: Line plot of the change in prescribing pattern of first intensifying regimen type for patients starting on metformin monotherapy over the study period

Table 5.11: Prescribing pattern of antidiabetic regimen type at the stage of first drug intensification for patients starting on sulfonylurea monotherapy

Prescription Year	Monotherapy	Combination therapy	Total per year
2010	>95%	<5%	(N=106)
2011	272 (96.45%)	10 (3.55%)	(N=282)
2012	>95%	<5%	(N=408)
2013	438 (97.33%)	12 (2.67%)	(N=450)
2014	438 (96.26%)	17 (3.74%)	(N=455)
2015	413 (97.64%)	10 (2.36%)	(N=423)
2016	446 (97.38%)	12 (2.62%)	(N=458)
2017	396 (98.26%)	7 (1.74%)	(N=403)
2018	382 (97.45%)	10 (2.55%)	(N=392)
2019	372 (97.13%)	11 (2.87%)	(N=383)
2020	232 (96.27%)	9 (3.73%)	(N=241)
Total per regimen	3894 (97.33%)	107 (2.67%)	(N=4001)
Absolute change	128	7	
Relative change	1.23	3.50	
Trend test*	Z = 0.28, p-value = 0.781		

*Using Cochran-Armitage test for trend compared combination therapy to monotherapy

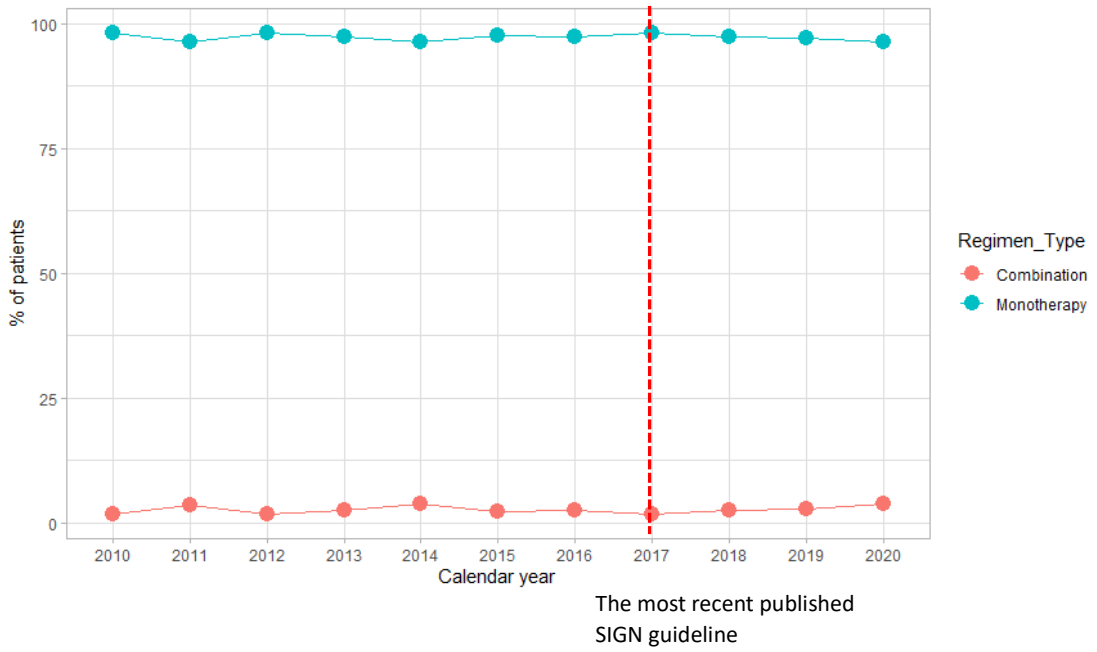

Figure 5.3: Line plot of the change in prescribing pattern of first intensifying regimen type for patients starting on sulfonylurea monotherapy over the study period

Among patients who were started on metformin and intensified with antidiabetic monotherapy (N= 45963), SU was the most frequently added ADD (Figure 5.4), which was used by 48.3%(22197/45963) of patients over the entire study period, followed by DPP4-I (12986/45963, 28.3%) and SGLT2-I (7850/45963, 17.1%). In line with the first-line study (Chapter 4), the use of SU as a first intensifying therapy significantly decreased over time from 65.4%(408/624) in 2010 to 29.8%(1581/5298) in 2020 (Z = -61.25, p-value < 0.001), whereas the use of DPP4-I and SGLT2-I significantly increased over time (Tables 5.12 and 5.7); SGLT2-I showed the most significant increase in the prescribing trend (from 0.0%(0/624) in 2010 to 39.6% (2098/5298) in 2020, Z = 77.70, p-value < 0.001), replacing SU as the most common first intensifying therapy in 2019 (SGLT2-I vs. SU: 33.6% vs. 31.7%). The proportional prescription and prescribing trend of the remaining monotherapy groups are summarised in Tables 5.12 and 5.13, in which the change in the prescribing patterns has decreased over time for all of the remaining classes, yet the decline in the prescribing patterns of GLP1-RA was non-significant.

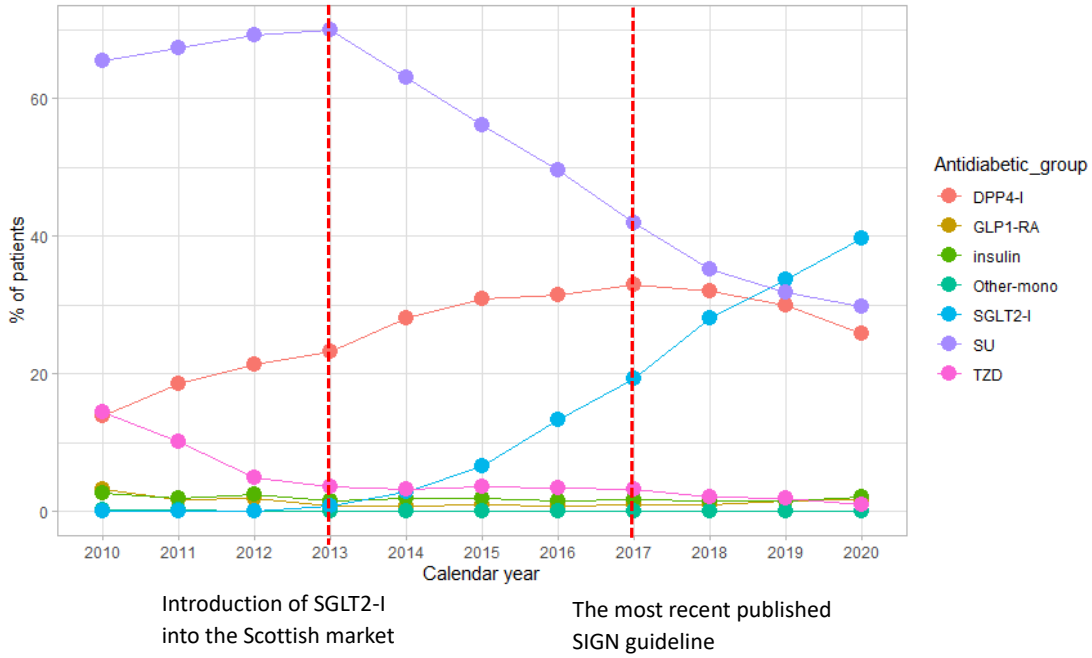

Figure 5.4: The change in prescribing pattern of monotherapy groups for patients starting on metformin over the study period. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors, SIGN; Scottish Intercollegiate Guidelines Network.

Table 5.12: Frequency and percentage of the individual class of antidiabetic drugs prescribed as a monotherapy for patients starting on metformin over the study period

Antidiabetic group	2010 (N=624)	2011 (N=2056)	2012 (N=3121)	2013 (N=3840)	2014 (N=4061)	2015 (N=5030)	2016 (N=5090)	2017 (N=5336)	2018 (N=5442)	2019 (N=6065)	2020 (N=5298)	Overall (N=45963)
DPP4-I	87 (13.94%)	380 (18.48%)	667 (21.37%)	890 (23.18%)	1139 (28.05%)	1548 (30.78%)	1596 (31.36%)	1759 (32.96%)	1744 (32.05%)	1811 (29.86%)	1365 (25.76%)	12986 (28.25%)
GLP1-RA	20 (3.21%)	35 (1.70%)	*	30 (0.78%)	*	49 (0.97%)	42 (0.83%)	*	54 (0.99%)	88 (1.45%)	90 (1.70%)	558 (1.21%)
Insulin	*	41(1.99%)	75(2.40%)	62(1.61%)	79(1.95%)	98(1.95%)	*	89(1.67%)	*	89(1.47%)	113(2.13%)	826 (1.80%)
SU	408 (65.38%)	1385 (67.36%)	2160 (69.21%)	2688 (70.00%)	2561 (63.06%)	2822 (56.10%)	2519 (49.49%)	2231 (41.81%)	1918 (35.24%)	1924 (31.72%)	1581 (29.84%)	22197 (48.29%)
TZD	90 (14.42%)	209 (10.17%)	155 (4.97%)	138 (3.59%)	133 (3.28%)	185 (3.68%)	171 (3.36%)	170 (3.19%)	115 (2.11%)	114 (1.88%)	51 (0.96%)	1531 (3.33%)
SGLT2-I	0 (0.00%)	0 (0.00%)	0 (0.00%)	32 (0.83%)	113 (2.78%)	328 (6.52%)	680 (13.36%)	1032 (19.34%)	1528 (28.08%)	2039 (33.62%)	2098 (39.60%)	7850 (17.08%)
Other	*	6 (0.29%)	*	0 (0.00%)	*	0 (0.00%)	*	*	*	0 (0.00%)	0 (0.00%)	15 (0.03%)

*; Those values were removed either because they are very small (<5) or to no disclose a very small value because of the high risk of patient's identification. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

Table 5.13: The change in prescribing pattern of the individual class of antidiabetic drug prescribed as monotherapy for patients starting on metformin

Antidiabetic group	Absolute change	Relative change	Trend-test*
DPP4-I	1278	14.69	Z = 12.48, **p-value < 0.001**
GLP1-RA	70	3.50	Z = -0.28, p-value = 0.783
Insulin	96	5.65	Z = -2.00, **p-value = 0.045**
SGLT2-I	2098	64.56	Z = 77.70, **p-value < 0.001**
SU	1173	2.88	Z = -61.25, **p-value < 0.001**
TZD	-39	-0.43	Z = -21.53, **p-value < 0.001**
Other	-2	1.00	Z = -4.94, **p-value < 0.001**

*Using Cochran-Armitage test for trend (each group was compared to all other groups). DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

A total of 767 (1.6%) patients who received metformin as initial therapy were treated with combination ADDs as the first intensifying therapy over the entire study period. Of those, about one-third of patients (249/767, 32.5%) were treated with DPP4-I+SU, while SU+ insulin, SGLT2-I+SU, and DPP4-I+SGLT2-I accounted for 16.9%(130/767), 16.2%(124/767), and 12.8%(98/767) of the initial metformin users, respectively (Table 5.14, Figure 5.5). Nonetheless, the use of SGLT2-I-based combination regimens as a first intensifying therapy for the initial-metformin users has significantly increased over the study period, including SGLT2-I+SU (from 0%(0/7) in 2010 to 24.6%(30/122) in 2020, Z = 6.13, p-value < 0.001) and DPP4-I+SGLT2-I (from 0%(0/7) in 2010 to 18.9%(23/122) in 2020, Z = 5.87, p-value <0.001). On the contrary, there was a significant reduction in the prescribing trend of DPP4-I+SU and SU+ insulin (Tables 5.14 and 5.15, Figure 5.5).

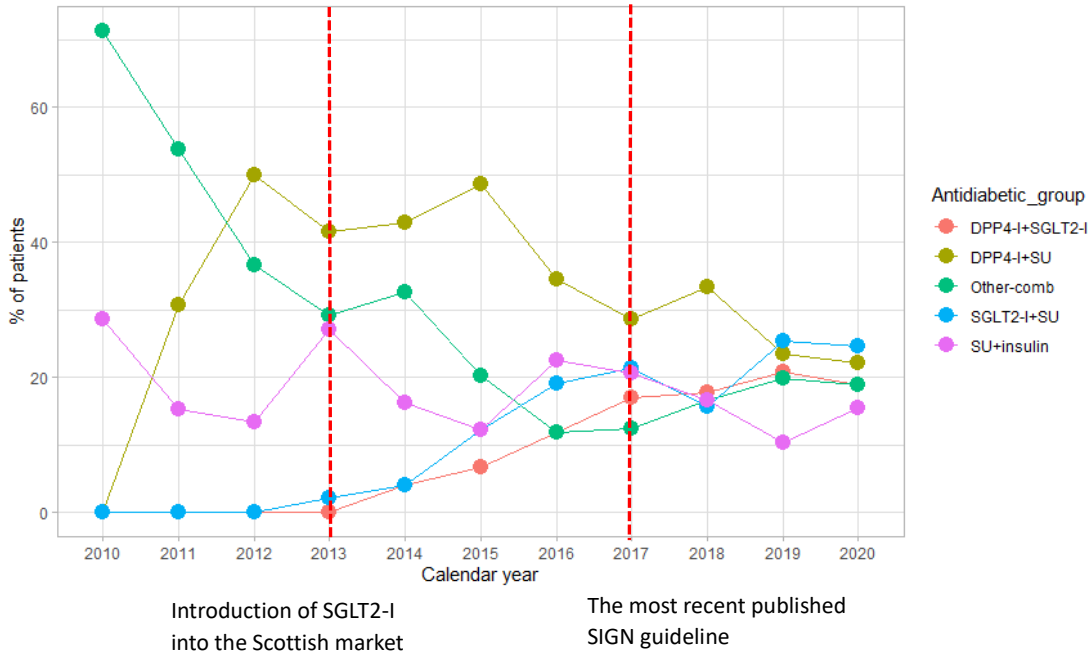

Figure 5.5: The change in the prescribing pattern of combination therapy groups for patients starting on metformin over the study period. DPP4-I; Dipeptidyl peptidase-4 inhibitors, SU; sulfonylurea, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

Table 5.14: Frequency and percentage of the individual class of antidiabetic drugs prescribed as a combination therapy for patients starting on metformin over the study period

Antidiabetic group	2010 (N=7)	2011 (N=39)	2012 (N=30)	2013 (N=48)	2014 (N=49)	2015 (N=74)	2016 (N=84)	2017 (N=112)	2018 (N=96)	2019 (N=106)	2020 (N=122)	Overall (N=767)
SU+ insulin	*	6 (15.38%)	*	13 (27.08%)	8 (16.33%)	9 (12.16%)	19 (22.62%)	23 (20.54%)	16 (16.67%)	11 (10.38%)	19 (15.57%)	130 (16.95%)
DPP4-I+SU	*	12 (30.77%)	*	20 (41.67%)	21 (42.86%)	36 (48.65%)	29 (34.52%)	32 (28.57%)	32 (33.33%)	25 (23.58%)	27 (22.13%)	249 (32.46%)
SGLT2-I+SU	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	9 (12.16%)	16 (19.05%)	24 (21.43%)	15 (15.63%)	27 (25.47%)	30 (24.59%)	124 (16.17%)
DPP4-I+ SGLT2-I	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	5 (6.76%)	10 (11.90%)	19 (16.96%)	17 (17.71%)	22 (20.75%)	23 (18.85%)	98 (12.78%)
Other	5 (71.43%)	21 (53.85%)	11 (36.67%)	14 (29.17%)	16 (32.65%)	15 (20.27%)	10 (11.90%)	14 (12.50%)	16 (16.67%)	21 (19.81%)	23 (18.85%)	166 (21.64%)

DPP4-I; Dipeptidyl peptidase-4 inhibitors, SU; sulfonylurea, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

Table 5.15: The change in the prescribing pattern of the individual class of antidiabetic drug prescribed as combination therapy for patients starting on metformin.

Antidiabetic group	Absolute change	Relative change	Trend-test*
DPP4-I+SGLT2-I	23	10.50	Z = 5.87, p-value **<0.001**
DPP4-I+SU	27	1.25	Z = -3.46, p-value = **0.001**
SGLT2-I+SU	30	29.00	Z = 6.13, p-value **< 0.001**
SU+ insulin	17	8.50	Z = -1.15, p-value = 0.252
Other	18	3.60	Z = -5.26, p-value **<0.001**

*Using Cochran-Armitage test for trend (each group was compared to all other groups) DPP4-I; Dipeptidyl peptidase-4 inhibitors, SU; sulfonylurea, SGLT2-i; Sodium-glucose co-transporter-2 inhibitors.

On the other hand, of patients who were started on SU and intensified with one ADD (N=3894), about three-quarters (2924/3894, 75.09%) were treated with metformin as a first intensifying therapy; however, the use of metformin has significantly decreased from 75%(78/104) in 2010 to 68.5%(159/232) in 2020 (Z = -2.60, p-value = 0.009). DPP4-I, insulin, and SGLT2-I contributed to 11.0%(428/3894), 8.8%(342/3894), and 3.2%(124/3894), respectively, while the remaining classes accounted for 2% of all monotherapy groups among patients started on SU (Table 5.16). Nevertheless, only the prescribing trend of SGLT2-I showed a significant increase over time (Z = 10.27, p-value < 0.001), while the use of insulin and TZD significantly decreased (Z = -2.31, p-value = 0.021 and Z = -4.82, p-value < 0.001). The proportional prescriptions and prescribing trend of intensifying monotherapy groups among patients starting on SU are summarised in Tables 5.16 and 5.17 and displayed in Figure 5.6.

Among the initial SU users (4001), only 107 (2.7%) patients were intensified with a combination regimen. Table 5.18 presents the change in the prescribing patterns of combination antidiabetic regimens that were prescribed for patients who started on SU in terms of the overall prescription, absolute/relative change, and trend test. Only the overall frequency (percentage) was reported to protect patient privacy because of the wide range of different prescribed combination regimens and the low frequency of the individual regimen per calendar year, increasing the risk of patient disclosure. Metformin+DPP4-I was the most commonly prescribed combination regimen as a first intensifying therapy for patients who started on SU, which was used by 44 out of 107 patients (41.1%), and it was followed by metformin+ insulin accounting for 27.1% of patients (29/107), Figure 5.7. However, the Cochrane-Armitage test revealed no significant change in the prescribing patterns of metformin+DPP4-I and metformin+ insulin over the studied 11 years (Z = -0.52, p-value = 0.599 and Z = -1.68, p-value = 0.092, respectively).

Table 5.16: Frequency and percentage of the individual class of antidiabetic drugs prescribed as a monotherapy for patients starting on sulfonylurea over the study period

Antidiabetic group	2010 (N=104)	2011 (N=272)	2012 (N=401)	2013 (N=438)	2014 (N=438)	2015 (N=413)	2016 (N=446)	2017 (N=396)	2018 (N=382)	2019 (N=372)	2020 (N=232)	Overall (N=3894)
Biguanide	78 (75.00%)	218 (80.15%)	309 (77.06%)	332 (75.79%)	328 (74.89%)	324 (78.45%)	329 (73.77%)	272 (68.9%)	300 (78.53%)	275 (73.92%)	159 (68.53%)	2924 (75.09%)
DPP4-I	9 (8.65%)	14 (5.15%)	41 (10.22%)	48 (10.96%)	52 (11.87%)	44 (10.65%)	69 (15.47%)	57 (14.39%)	29 (7.59%)	40 (10.75%)	25 (10.78%)	428 (10.99%)
Insulin	14 (13.46%)	21 (7.72%)	38 (9.48%)	53 (12.10%)	47 (10.73%)	34 (8.23%)	26 (5.83%)	32 (8.08%)	33 (8.64%)	21 (5.65%)	23 (9.91%)	342 (8.78%)
TZD	*	*	*	*	*	*	*	*	*	*	*	61 (1.57%)
SGLT2-I	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	7 (1.69%)	14 (3.14%)	27 (6.82%)	18 (4.71%)	29 (7.80%)	22 (9.48%)	124 (3.18%)
Other [a]	*	*	*	*	*	*	*	*	*	*	*	15 (0.39%)

DPP4-I; Dipeptidyl peptidase-4 inhibitors, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors. a, include Glucagon-like peptide receptors agonist, alpha glucosidase, meglitinide. *; Those values were removed either because they are very small (<5) or to no disclose a very small value because of the high risk of patient's identification.

Table 5.17: The change in prescribing pattern of the individual class of antidiabetic drug prescribed as monotherapy for patients starting on sulfonylurea

Antidiabetic group	Absolute change	Relative change	Trend-test*
Biguanide	81	1.04	Z = -2.60, p-value = **0.009**
DPP4-I	16	1.78	Z = 1.54, p-value = 0.123
Insulin	9	0.64	Z = -2.31, p-value = **0.021**
TZD	-2	-0.67	Z = -4.82, p-value **< 0.001**
SGLT2-I	22	21.00	Z = 10.27, p-value **< 0.001**
Other	2	1.00	Z = 1.45, p-value = 0.147

*Using Cochran-Armitage test for trend (each group was compared to all other groups). DPP4-I; Dipeptidyl peptidase-4 inhibitors, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

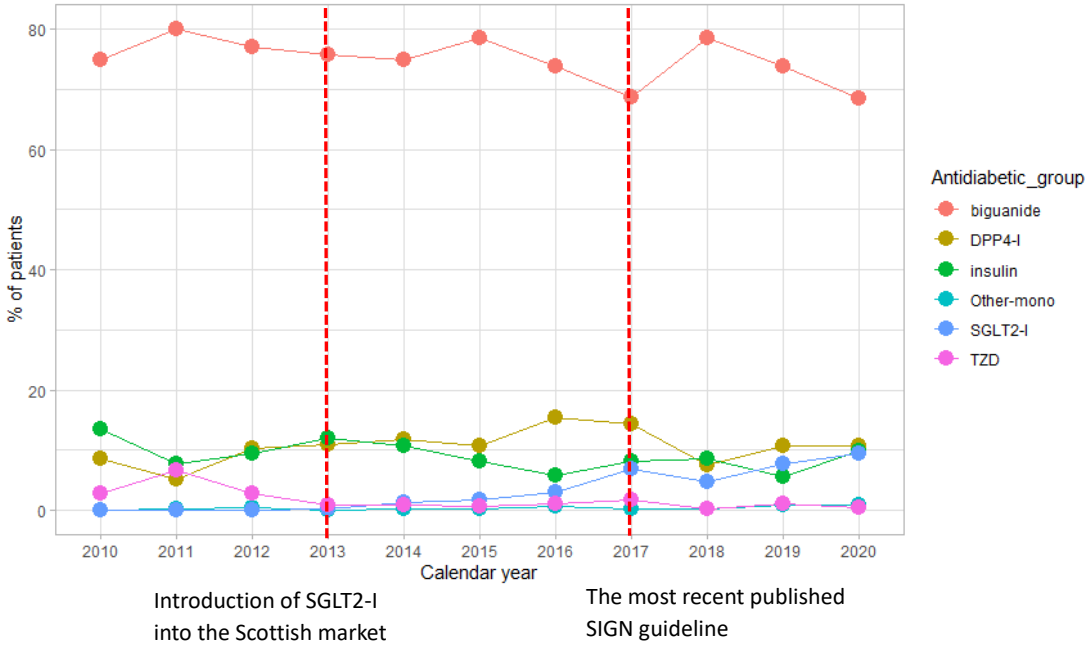

Figure 5.6: The change in the prescribing pattern of monotherapy groups for patients starting on sulfonylurea over the study period. DPP4-I; Dipeptidyl peptidase-4 inhibitors, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

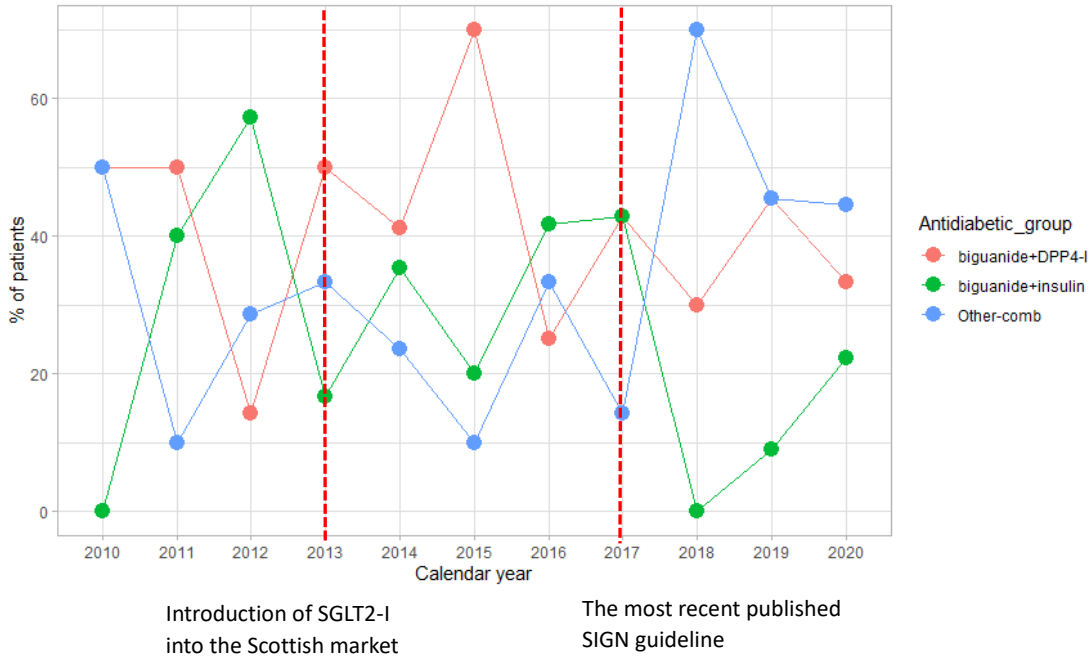

Figure 5.7: The change in the prescribing pattern of combination therapy groups for patients starting on sulfonylurea over the study period. DPP4-I; Dipeptidyl peptidase-4 inhibitors

Table 5.18: The change in the prescribing patterns of the individual class of antidiabetic drug prescribed as combination therapy for patients starting on sulfonylurea

Antidiabetic group	Overall (N=107)	Absolute change	Relative change	Trend test*
Biguanide+DPP4-I	44 (41.12%)	2	2	Z = -0.53, p-value = 0.599
Biguanide+ insulin	29 (27.10%)	2	-0.5	Z = -1.68, p-value = 0.092
Other [a]	34 (31.78%)	3	3	Z = 2.16, p-value = **0.031**

a; Other comb including metformin+SGLT2-I (n=6). DPP4-I; Dipeptidyl peptidase-4 inhibitors.

5.3.3 Factors influencing prescribing choice of first intensifying antidiabetic drugs

5.3.3.1 Initial metformin cohort (cohort 2a)

A. Factors influencing the prescribing choice of the regimen type (combination therapy vs. monotherapy)

The results of the univariable and multivariable binomial logistic regression of factors associated with the prescribing choice of the regimen type for patients who were initiated on metformin are presented in Table 5.19. Both of the demographic factors (age at index prescription and sex) showed a significant influence on the prescribing choice of the regimen type among initial-metformin users in the univariable and multivariable analyses, in which elderly patients (age >= 65 years) were significantly less likely to add a combination regimen than a monotherapy regimen to initial metformin for T2DM management compared to younger individuals (OR[95%CI]: unadjusted: 0.83[0.71-0.97], adjusted: 0.72[0.60-0.86]). On the other hand, female patients were significantly more likely to be treated with combination therapy compared to their counterparts in the univariable and multivariable analyses, yet the significance of influence has weakened under the adjustment of all baseline characteristics (OR[95%CI]: unadjusted: 1.29[1.12-1.49], p<0.001 vs. adjusted: 1.19[1.02-1.38], p=0.028).

Of the clinical-related factors, being diagnosed with HTN or liver disease, using CCB, being overweight/obese (BMI: 25-29.9 and >= 30kg/m^2), having HbA1c in a range of 7-9%, and having a low eGFR (<60ml/min/1.73m^2) had significant associations with the prescribing choice of the regimen type in both the univariable and multivariable analyses. For instance, patients who had HTN or liver disease at or prior to the index intensification date were 22% and 51% more likely to add combination therapy than monotherapy to initial metformin compared to patients without the disease under the adjustment of all other baseline characteristics (adjusted OR[95%CI]: 1.22[1.01-1.48] and 1.51[1.05-2.13], respectively). Likewise, patients with a low baseline eGFR (<60ml/min/1.73m2) had a 55% greater likelihood to be treated with combination therapy than monotherapy as a first intensifying therapy compared to their counterparts (adjusted OR[95%CI]: 1.55[1.18-2.01]). In contrast, those being

overweight/obese or had HbA1c level of 7-9% had lower odds of receiving combination therapy after initial metformin compared to their counterparts. On the other hand, the significant associations of IHD, HF, CCI-score, antihyperlipidemic drugs, antipsychotic medications, HDL, TG, and total cholesterol levels with the prescribing decision of the regimen type have turned non-significant after the adjustment of all baseline characteristics in the multivariable analysis (Table 5.19).

While thiazide diuretics and beta-blockers showed non-significant associations with the prescribing choice of the regimen type in the univariable analysis (unadjusted OR[95%CI]: 0.76[0.54-1.03] and 0.95[0.77-1.16], respectively), the multivariable analysis showed statistically significant negative results (adjusted OR[95%CI]: 0.69[0.48-0.95] and 0.7[0.54-0.89], respectively). Moreover, the multivariable analysis showed that monotherapy patients were significantly more likely to be on five or more concomitant medications at or prior to the index intensification date (Table 5.19). The remaining clinical-related factors, socioeconomic factors, and prescriber related-factor had non-significant associations with the prescribing choice of the regimen type for patients who were initiated on metformin both in the univariable and the multivariable analyses (Table 5.19).

Table 5.19: Univariable and multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type (combination therapy vs. monotherapy) for initial-metformin cohort (Cohort-2a: N=46,730)

Studied factor	Combination regimen	
	Univariable	Multivariable
1- Demographic factors		
Age at prescription	0.017	<0.001
>= 65 vs. < 65 years	0.83[0.71, 0.97]	0.72[0.60, 0.86]
Sex	<0.001	0.028
Female vs. Male	1.29[1.12, 1.49]	1.19[1.02, 1.38]
2- Socioeconomic factors		
Urban-rural	0.8	0.8
1	1	1
2	0.95[0.80, 1.13]	0.97[0.81, 1.15]
3	0.95[0.71, 1.25]	0.98[0.73, 1.29]
4	0.94[0.55, 1.50]	0.96[0.56, 1.54]
5	0.6[0.23, 1.23]	0.6[0.24, 1.25]
6	0.97[0.75, 1.25]	1.03[0.79, 1.34]
7	1.2[0.80, 1.71]	1.23[0.82, 1.79]
8	1.2[0.79, 1.76]	1.18[0.76, 1.77]
Scottish index of multiple deprivation-quantile	0.4	0.9
1	1	1
2	0.96[0.78, 1.16]	1[0.82, 1.23]
3	1.05[0.85, 1.28]	1.09[0.88, 1.36]
4	0.83[0.66, 1.05]	0.94[0.73, 1.19]
5	0.86[0.66, 1.11]	1.02[0.78, 1.32]
3- Prescriber-related factor		
Prescriber type	0.4	>0.9
Non-general practitioner (GP) vs. GP	0.9[0.66, 1.18]	0.99[0.73, 1.31]
4- Clinical-related factors		
Ischemic heart disease	0.023	0.5
Yes vs. No	1.26[1.03, 1.53]	1.08[0.85, 1.35]
Hypertension	<0.001	0.04
Yes vs. No	1.38[1.17, 1.62]	1.22[1.01, 1.48]
Heart failure	<0.001	0.2
Yes vs. No	1.8[1.30, 2.43]	1.3[0.89, 1.87]
Stroke	0.2	0.9
Yes vs. No	1.33[0.87, 1.94]	1.03[0.67, 1.53]
Peripheral vascular disease	0.3	>0.9
Yes vs. No	1.23[0.79, 1.83]	0.98[0.62, 1.48]
Liver disease	<0.001	0.029

Yes vs. No	2.06[1.48, 2.78]	1.51[1.05, 2.13]
Charlson comorbidity index score	<0.001	0.8
0	1	1
1-2	1.51[1.25, 1.81]	1.09[0.88, 1.33]
3-4	2.18[1.56, 2.96]	1.14[0.77, 1.66]
>= 5	1.67[0.97, 2.67]	0.98[0.56, 1.63]
Antihyperlipidemic drugs	0.002	0.6
Yes vs. No	0.79[0.68, 0.92]	0.96[0.80, 1.14]
Antipsychotic	0.002	0.2
Yes vs. No	1.72[1.23, 2.34]	1.27[0.90, 1.75]
Thiazide diuretics	0.076	0.023
Yes vs. No	0.76[0.54, 1.03]	0.69[0.48, 0.95]
Beta-blockers	0.6	0.003
Yes vs. No	0.95[0.77, 1.16]	0.7[0.54, 0.89]
Angiotensin inhibitors	0.5	0.7
Yes vs. No	1.06[0.89, 1.26]	0.96[0.79, 1.18]
Calcium channel blocker	0.004	<0.001
Yes vs. No	0.74[0.60, 0.91]	0.66[0.52, 0.84]
Number of concomitant medications	<0.001	<0.001
0	1	1
1-4	0.93[0.54, 1.76]	1.14[0.65, 2.18]
>= 5	1.58[0.93, 2.98]	1.92[1.10, 3.68]
Body mass index (kg/m^2)	<0.001	0.016
<=24.9	1	1
25-29.9	0.62[0.44, 0.89]	0.64[0.45, 0.92]
>= 30	0.67[0.49, 0.93]	0.63[0.46, 0.88]
Unknown	0.94[0.69, 1.31]	0.75[0.55, 1.06]
HbA1c (%)	<0.001	<0.001
< 7	1	1
7- < 9	0.48[0.31, 0.77]	0.57[0.37, 0.93]
>=9	1.06[0.70, 1.70]	1.17[0.77, 1.89]
Unknown	2.13[1.31, 3.60]	1.7[1.03, 2.93]
Estimated glomerular filtration rate (ml/min/1.73m^2)	<0.001	0.008
< 60 vs. >= 60	1.67[1.30, 2.12]	1.55[1.18, 2.01]
Unknown vs. < 60	1.45[1.14, 1.81]	1[0.76, 1.30]
High density lipoprotein (mg/dl)	<0.001	0.8
<40 (M) or <50 (F)	1	1
40-59 (M) or 50-59 (F)	0.78[0.64, 0.96]	0.91[0.73, 1.12]
>= 60	0.84[0.57, 1.20]	0.89[0.59, 1.29]

Unknown	1.36[1.16, 1.60]	0.94[0.71, 1.24]
Triglyceride (mg/dl)	<0.001	0.4
< 150	1	1
150-499	1.27[1.01, 1.60]	1.11[0.87, 1.42]
>= 500	2.1[1.46, 2.99]	1.39[0.93, 2.06]
Unknown	1.73[1.38, 2.17]	1.16[0.86, 1.55]
Total cholesterol (mg/dl)	<0.001	0.087
< 200	1	1
200-239	1.34[1.07, 1.66]	1.14[0.91, 1.43]
>=240	1.54[1.18, 1.98]	1.15[0.86, 1.52]
Unknown	1.97[1.66, 2.33]	1.45[1.07, 1.97]

The results presented as OR[95%CI] along with the global p value.

B. Factors influencing the prescribing choice of antidiabetic class

Table 5.20 shows the results of the multivariable multinomial logistic regression of factors associated with the prescribing decision of antidiabetic classes for the initial-metformin cohort (Cohort 2a). The results of the univariable analysis are presented in Appendix S.5.3. All monotherapy and combination therapy regimens described in section 5.3.1 for patients initiated on metformin (cohort 2a) were included in the regression model except the other-monotherapy (N=15) and the other-combination therapy (N=166) groups, providing a total of 46549 out of 46730 patients included in the regression models of antidiabetic classes. The other-monotherapy and other-combination therapy groups were excluded because they included a wide range of regimens with small sample sizes, making the interpretation of the analysis results complex and not clinically meaningful. Several factors showed a significant influence on the prescribing choice of each investigated antidiabetic class compared to SU. Patient age at prescription and sex had significant associations with the prescribing choice of six and three out of nine studied antidiabetic regimens, respectively. Patients aged 65 years or older at the index intensification date were significantly less likely to be treated with DPP4-I, GLP1-RA, insulin, SGLT2-I, TZD, DPP4-I+SGLT2-I, and SGLT2-I+SU than SU compared to younger individuals (Table 5.20), where GLP1-RA was the least likely to be prescribed for elderly patients among the studied antidiabetic classes (Adjusted OR[95%CI]: 0.23[0.17-0.30]). In the multivariable analysis, patient sex had a significant association with prescribing of GLP1-RA, insulin, TZD, and DPP4-I; female patients were significantly more likely to add GLP1-

RA and insulin than SU to initial metformin compared to male patients (Adjusted OR[95%CI]: 1.84[1.58-2.15] and 1.4[1.17-1.67]), but significantly less likely to be treated with TZD and DPP4-I (Adjusted OR[95%CI]: 0.8[0.71-0.90] and 0.94[0.90-0.99]).

Furthermore, the impact of UR and SIMD-Q on the prescribing choice was diverse by the class of ADDs and levels of the variable (Table 5.20). For example, the multivariable analysis showed that patients living in more rural areas were significantly more likely to be treated with DPP4-I (UR rank 3, 6, and 8), GLP1-RA (UR rank 4 and 8), SGLT2-I (UR rank 5), TZD (UR rank 3, 6, and 8), and DPP4-I+SU (UR rank 8), yet significantly less likely to be treated with insulin (UR rank 5) compared to patients who lived in a large urban area with UR rank 1 (Table 5.20). In addition, patients who resided in less deprived areas were less likely to be prescribed DPP4-I (SIMD-Q rank 2, 3, 4, and 5), GLP1-RA (SIMD-Q rank 4), SGLT2-I (SIMD-Q rank 2, 3, and 4), and TZD (SIMD-Q rank 4) than SU compared to patients living in the most deprived area with SIMD-Q rank 1 (Table 5.20). Regarding prescriber type, the multivariable analysis revealed that non-GPs had a statistically significant greater likelihood of prescribing DPP4-I and SGLT2-I over SU for patients with T2DM who started on metformin, yet were significantly less likely to prescribe TZD (Table 5.20).

Of the studied clinical-related factors, several baseline comorbid conditions had a statistically significant association with the prescribing choice of multiple antidiabetic classes prescribed for patients who started on metformin monotherapy. For instance, the multivariable analysis revealed that patients who were diagnosed with IHD had 11% and 29% lower odds of prescribing DPP4-I and TZD than SU, respectively (Adjusted OR[95%CI]: 0.89[0.82-0.96] and 0.71[0.58-0.87]). Likewise, patients who had PVD were significantly less likely to receive DPP4-I as a first intensifying therapy after initial metformin (Adjusted OR[95%CI]: 0.85[0.73-0.98]). In addition, a diagnosis of HTN had a statistically significant negative association with the prescribing choice of SGLT2-I (Adjusted OR[95%CI]: 0.86[0.79-0.93]), but significant positive associations with insulin and SU+ insulin (Adjusted OR[95%CI]: 1.47[1.20- 1.79] and 1.64[1.15-2.35]). On the other hand, patients with a diagnosis

of HF were 36% and 2.46 times significantly more likely to add SGLT2-I or SGLT2-I+SU over SU to initial metformin, respectively (Adjusted OR[95%CI]: 1.36[1.12-1.66] and 2.46[1.16, 5.21]), yet 90% less likely to be intensified with TZD (Adjusted OR[95%CI]: 0.1[0.03-0.37]). Liver disease had a significant positive association with the prescribing choice of TZD and insulin over SU (Adjusted OR[95%CI]: 2.53[1.78-3.60] and 1.59[1.13-2.24]). A baseline diagnosis of stroke had only a statistically significant association with the prescribing choice of TZD (Adjusted OR[95%CI]: 0.58[0.37-0.92]). Moreover, patients with higher baseline CCI scores (1-2. 3-4, and >=5) were significantly less likely to receive DPP4-I, SGLT2-I, or TZD over SU as a first-intensifying therapy. However, patients with a CCI score of >=5 had greater odds of adding insulin or SU+ insulin than SU alone to initial metformin (Table 5.20).

The association of concomitant medications with the prescribing choice of ADDs was highly variable across antidiabetic groups, in which the most significant impact was observed with SGLT2-I and insulin. For instance, baseline CCI score (>=5), antihyperlipidemic, thiazide diuretics, angiotensin inhibitors, and CCB were significantly associated with insulin prescription; the association was negative for all factors except the baseline CCI score. Additionally, baseline CCI score (1-2, 3-4, and >=5), antipsychotic drugs, angiotensin inhibitors, and CCB had significant associations with the prescribing choice of SGLT2-I (Table 5.20).

Moreover, the multivariable regression analyses showed that overweight (BMI 25-29.9 kg/m^2) and obese (>= 30 kg/m^2) patients had a greater likelihood of adding a prescription of DPP4-I, GLP1-RA, SGLT2-I, and TZD than SU to initial metformin compared to patients with low/normal BMI (<= 24.9 kg/m2). However, they were less likely to get insulin prescriptions (Table 5.20). For patients with a low eGFR of < 60 ml/min/1.73m^2, the odds of receiving DPP4-I, insulin, and SU+ insulin were 19%, 88%, and 2.43 times greater than patients with a baseline eGFR of >= 60 ml/min/1.73m^2, respectively (Adjusted OR[95%CI]: 1.19[1.09, 1.30], 1.88[1.46, 2.43], and 2.03[1.30, 3.15], respectively), whereas the odds of getting SGLT2-I prescriptions was 0.27[0.22-0.33] for patients with eGFR of <60 ml/min/1.73m^2 compared to their counterparts. The results relevant to the association of the

baseline HbA1c level with the prescribing choice of ADDs for the initial-metformin cohort showed that patients with a baseline HbA1c in a range of 7-9% had a greater likelihood to be intensified with DPP4-I, SGLT2-I, and TZD than SU compared to patients with a baseline HbA1c of < 7%, but they had a lower likelihood of getting GLP1-RA, insulin, and DPP4-I+SU prescriptions (Table 5.20).

Regarding the influence of the baseline lipid profile on the prescribing decision of ADDs, baseline HDL had the least impact on ADD prescribing, while total cholesterol had the most impact on the prescribing decision. Baseline HDL level had only a significant impact on DPP4-I+SGLT2-I prescription, in which the multivariable analysis indicated that patients with a medium level of HDL (40-59 (M) or 50-59 (F) mg/dl) were significantly less likely to receive DPP4-I+SGLT2-I than SU compared to patients with a low HDL level (<40 (M) or <50 (F) mg/dl) (Table 5.20). On the other hand, it was found that a baseline total cholesterol of 200-239 mg/dl was positively and significantly associated with GLP1-RA and SU+SGLT2-I prescriptions yet negatively and significantly associated with DPP4-I and TZD prescriptions.

Similarly, a baseline total cholesterol level of >= 240 mg/dl had a positive and significant association with insulin prescription but a significant negative impact on DPP4-I, SGLT2-I, and TZD prescriptions (Table 5.20). Lastly, the multivariable analysis showed a significant association of the baseline TG level with the prescribing decision of insulin, DPP4-I, and SU+SGLT2-I. For instance, patients with a baseline TG level of 150-499 mg/dl were 25% significantly less likely to add insulin than SU to initial metformin compared to patients with a TG level of < 150 mg/dl (Adjusted OR[95%CI]: 0.75[0.60, 0.94]). Additionally, patients with a very high baseline TG level (>= 500 mg/dl) had a significantly lower likelihood of receiving DPP4-I than SU compared to the normal TG level of < 150 mg/dl (adjusted OR[95%CI]: 0.73[0.63, 0.84]). Additionally, the odds of SU+SGLT2-I prescription for patients who had a baseline TG level of 150-499 and >= 500 mg/dl were 1.89[1.08-3.30] and 2.43[1.11-5.32], respectively.

Table 5.20: Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to SU) for initial-metformin cohort (Cohort-2a: N=46549)

Studied factor	DPP4-I	GLP1-RA	Insulin	SGLT2-I	TZD	DPP4-I+SGLT2-I	DPP4-I+ SU	SGLT2-I+SU	SU+ Insulin	P-value
1- Demographic factors										
Age at prescription										**<0.001**
>= 65 vs. < 65 years	**0.92[0.87, 0.97]**	**0.23[0.17, 0.30]**	**0.53[0.44, 0.64]**	**0.48[0.45, 0.52]**	**0.86[0.76, 0.97]**	**0.61[0.41, 0.90]**	0.82[0.63, 1.06]	**0.43[0.28, 0.64]**	**0.67[0.47, 0.94]**	
Sex										**0.110**
Female vs. Male	**0.94[0.90, 0.99]**	**1.4[1.17, 1.67]**	**1.84[1.58, 2.15]**	0.96[0.90, 1.02]	**0.8[0.71, 0.90]**	1.2[0.85, 1.70]	1.12[0.89, 1.41]	1.34[0.97, 1.85]	0.8[0.59, 1.09]	
2- Socioeconomic factors										
Urban-rural										**<0.001**
2 vs. 1	**1.3[1.23, 1.37]**	0.99[0.81, 1.21]	1[0.84, 1.19]	1.06[0.98, 1.13]	**2.86[2.47, 3.32]**	0.89[0.60, 1.32]	1.01[0.78, 1.32]	0.96[0.67, 1.39]	0.92[0.64, 1.31]	
3 vs. 1	**1.1[1.01, 1.20]**	0.91[0.65, 1.28]	0.78[0.58, 1.05]	**0.72[0.64, 0.81]**	**2.32[1.89, 2.84]**	0.74[0.38, 1.45]	0.95[0.62, 1.45]	1.14[0.65, 1.98]	1.18[0.71, 1.96]	
4 vs. 1	**0.8[0.69, 0.94]**	**1.59[1.01, 2.51]**	1.09[0.71, 1.68]	**0.74[0.60, 0.90]**	0.6[0.34, 1.05]	0.35[0.06, 1.87]	0.78[0.36, 1.72]	1.83[0.86, 3.90]	0.24[0.04, 1.39]	
5 vs. 1	1.19[0.97, 1.45]	1.58[0.82, 3.04]	**0.29[0.09, 0.93]**	**1.32[1.03, 1.70]**	**0.17[0.04, 0.77]**	0.9[0.19, 4.31]	0.81[0.25, 2.57]	0.81[0.16, 4.01]	0.21[0.02, 2.74]	
6 vs. 1	**1.14[1.05, 1.24]**	0.82[0.59, 1.16]	0.81[0.62, 1.07]	1[0.90, 1.11]	**2.53[2.07, 3.08]**	1.02[0.57, 1.85]	1.05[0.70, 1.56]	0.95[0.53, 1.70]	1.17[0.72, 1.91]	
7 vs. 1	0.99[0.86, 1.13]	1.29[0.81, 2.04]	1.09[0.73, 1.62]	0.96[0.81, 1.14]	0.84[0.55, 1.29]	1.34[0.58, 3.11]	1.04[0.55, 1.95]	0.76[0.28, 2.08]	1.71[0.89, 3.31]	
8 vs. 1	**1.21[1.05, 1.40]**	**2.17[1.40, 3.35]**	1.36[0.91, 2.05]	1.15[0.96, 1.38]	**2.41[1.74, 3.33]**	1.35[0.53, 3.48]	**2.56[1.53, 4.27]**	0.31[0.05, 1.78]	0.84[0.32, 2.22]	
Unknown vs. 1	2.89[0.83, 10.0]	0.45[0.00, 3,120]	**10.3[1.33, 80.4]**	0.54[0.06, 4.83]	0.41[0.00, 805]	0.84[0.00, 47,976]	0.76[0.00, 12,559]	0.87[0.00, 31,834]	0.89[0.00, inf]	
Scottish index of multiple deprivation-Quantile										**<0.001**

2 vs. 1	**0.86[0.81, 0.92]**	0.92[0.73, 1.15]	0.92[0.76, 1.13]	**0.82[0.75, 0.89]**	0.9[0.78, 1.05]	0.72[0.45, 1.15]	0.85[0.63, 1.16]	0.92[0.61, 1.38]	1.17[0.77, 1.79]	
3 vs. 1	**0.84[0.78, 0.90]**	0.94[0.73, 1.22]	0.91[0.73, 1.14]	**0.88[0.80, 0.96]**	0.9[0.76, 1.06]	0.75[0.44, 1.26]	0.88[0.63, 1.23]	0.92[0.58, 1.46]	1.04[0.66, 1.66]	
4 vs. 1	**0.82[0.76, 0.88]**	**0.74[0.55, 0.99]**	0.97[0.77, 1.22]	**0.87[0.79, 0.96]**	**0.81[0.68, 0.97]**	0.88[0.52, 1.49]	0.87[0.61, 1.25]	0.83[0.50, 1.38]	1.34[0.84, 2.15]	
5 vs. 1	**0.82[0.76, 0.89]**	0.94[0.69, 1.28]	0.77[0.59, 1.01]	0.95[0.86, 1.05]	1.06[0.88, 1.26]	1.12[0.66, 1.91]	0.95[0.65, 1.39]	0.96[0.55, 1.65]	1.38[0.84, 2.27]	
Unknown vs. 1	1.06[0.19, 5.80]	0.6[0.00, 2,513]	0.28[0.00, 45.6]	1.48[0.10, 22.3]	0.28[0.00, 54.4]	0.97[0.00, 36,106,459]	0.77[0.00, 1,460]	0.95[0.00, 4,418,992]	0.88[0.00, 565,706]	
3- Prescriber-related factors										
Prescriber type										**0.007**
Non-general practitioner (GP) vs. GP	**1.35[1.23, 1.47]**	0.86[0.60, 1.23]	**0.5[0.33, 0.77]**	**1.32[1.19, 1.47]**	**0.74[0.59, 0.94]**	1.38[0.77, 2.47]	1.09[0.69, 1.73]	1.02[0.55, 1.90]	0.88[0.45, 1.72]	
4- Clinical-related factors										
Ischemic heart disease	<0.001									**<0.001**
Yes vs. No	**0.89[0.82, 0.96]**	0.72[0.52, 1.01]	1.13[0.89, 1.45]	1.03[0.93, 1.14]	**0.71[0.58, 0.87]**	1.35[0.81, 2.24]	0.72[0.49, 1.05]	1.35[0.85, 2.16]	0.99[0.64, 1.54]	
Hypertension										**<0.001**
Yes vs. No	0.95[0.89, 1.01]	1.11[0.87, 1.42]	**1.47[1.20, 1.79]**	**0.86[0.79, 0.93]**	1.14[0.98, 1.33]	0.85[0.53, 1.35]	1.22[0.92, 1.63]	0.94[0.62, 1.43]	**1.64[1.15, 2.35]**	
Heart Failure										**<0.001**
Yes vs. No	1.03[0.90, 1.19]	1.32[0.74, 2.35]	0.86[0.57, 1.29]	**1.36[1.12, 1.66]**	**0.1[0.03, 0.37]**	1.16[0.40, 3.34]	1.59[0.91, 2.75]	**2.46[1.16, 5.21]**	0.8[0.37, 1.74]	
Stroke										**0.634**
Yes vs. No	0.95[0.82, 1.09]	0.64[0.29, 1.41]	0.86[0.53, 1.39]	0.88[0.72, 1.08]	**0.58[0.37, 0.92]**	0.68[0.20, 2.36]	1.09[0.60, 1.98]	1.26[0.54, 2.95]	0.43[0.14, 1.29]	
Peripheral vascular disease										**< 0.001**
Yes vs. No	**0.85[0.73,**	0.96[0.48,	1.18[0.77,	0.83[0.67,	0.83[0.55,	0.48[0.12, 2.00]	0.98[0.51,	0.47[0.13,	1.69[0.90, 3.17]	

	0.98]	1.90]	1.81]	1.02]	1.24]		1.86]	1.68]		
Liver disease										**0.001**
Yes vs. No	0.97[0.83, 1.13]	0.74[0.40, 1.37]	**1.59[1.13, 2.24]**	1.07[0.89, 1.30]	**2.53[1.78, 3.60]**	0.57[0.14, 2.36]	1.31[0.73, 2.34]	1.8[0.85, 3.80]	1.61[0.86, 3.04]	
Charlson comorbidity index										**<0.001**
1-2 vs. 0	**0.87[0.81, 0.93]**	0.77[0.58, 1.02]	1.02[0.82, 1.26]	**0.76[0.69, 0.83]**	**0.56[0.46, 0.69]**	0.66[0.38, 1.13]	0.86[0.63, 1.19]	0.93[0.59, 1.45]	1.14[0.77, 1.69]	
3-4 vs. 0	**0.78[0.67, 0.92]**	0.95[0.52, 1.74]	1.07[0.72, 1.60]	**0.78[0.64, 0.96]**	**0.22[0.11, 0.44]**	0.6[0.17, 2.07]	1.05[0.60, 1.86]	0.75[0.31, 1.80]	0.79[0.35, 1.79]	
>= 5 vs. 0	**0.61[0.49, 0.75]**	0.84[0.38, 1.87]	**2.01[1.37, 2.94]**	**0.5[0.38, 0.66]**	**0.14[0.05, 0.42]**	0.64[0.15, 2.78]	0.53[0.21, 1.34]	0.14[0.01, 1.76]	**2.31[1.17, 4.54]**	
Antihyperlipidemic drugs										**<0.001**
Yes vs. No	1.05[1.0, 1.11]	**0.68[0.56, 0.83]**	**0.46[0.39, 0.54]**	1.02[0.95, 1.10]	1.11[0.97, 1.27]	1.19[0.79, 1.81]	0.86[0.66, 1.11]	1.24[0.85, 1.81]	**0.58[0.41, 0.80]**	
Antipsychotic										**0.475**
Yes vs. No	0.88[0.77, 1.00]	1.19[0.81, 1.74]	0.94[0.65, 1.37]	**0.71[0.60, 0.85]**	0.7[0.49, 1.00]	0.91[0.37, 2.22]	1.34[0.84, 2.15]	1.08[0.55, 2.15]	1.59[0.86, 2.96]	
Thiazide diuretics										**<0.001**
Yes vs. No	**1.3[1.19, 1.43]**	0.83[0.55, 1.25]	**0.65[0.46, 0.93]**	1.14[1.00, 1.31]	1.14[0.93, 1.40]	0.77[0.34, 1.74]	1.04[0.68, 1.61]	0.78[0.36, 1.69]	0.63[0.31, 1.31]	
Beta-blockers										**<0.001**
Yes vs. No	**1.09[1.01, 1.17]**	1.21[0.92, 1.60]	0.85[0.67, 1.08]	1.02[0.92, 1.13]	0.85[0.70, 1.02]	1.21[0.73, 2.00]	**0.66[0.46, 0.96]**	0.86[0.52, 1.42]	**0.56[0.33, 0.95]**	
Angiotensin inhibitors										**0.003**
Yes vs. No	**1.2[1.12, 1.28]**	1.21[0.96, 1.52]	**0.57[0.45, 0.72]**	**1.34[1.23, 1.45]**	1.02[0.88, 1.17]	0.83[0.50, 1.36]	1.08[0.81, 1.46]	1.46[0.97, 2.20]	0.84[0.55, 1.29]	
Calcium channel blocker										**<0.001**
Yes vs. No	**1.1[1.03, 1.18]**	0.99[0.75, 1.30]	**0.69[0.55, 0.88]**	**1.22[1.11, 1.33]**	0.98[0.83, 1.15]	0.7[0.41, 1.21]	**0.69[0.48, 0.99]**	0.66[0.38, 1.13]	0.93[0.61, 1.43]	

Number of concomitant medications										**<0.001**
1-4 vs. 0	1.03[0.86, 1.22]	1.74[0.86, 3.54]	**2.28[1.31, 3.96]**	**0.79[0.66, 0.96]**	0.77[0.55, 1.09]	3.6[0.40, 32.5]	0.83[0.37, 1.84]	4.11[0.32, 52.7]	2.42[0.54, 10.8]	
>= 5 vs. 0	1[0.84, 1.19]	2.02[0.99, 4.11]	**1.76[1.01, 3.09]**	**0.74[0.61, 0.90]**	**0.69[0.49, 0.98]**	4.51[0.50, 40.9]	1.37[0.61, 3.05]	7.25[0.57, 92.5]	3.83[0.86, 17.1]	
Body mass index										**<0.001**
25-29.9 vs. <=24.9	**1.31[1.16, 1.48]**	**4.17[0.19, 94.0]**	**0.69[0.51, 0.93]**	**1.66[1.39, 1.99]**	**2.13[1.49, 3.04]**	1.3[0.52, 3.25]	1.29[0.69, 2.42]	0.75[0.31, 1.82]	1.57[0.80, 3.08]	
>= 30 vs. <=24.9	**1.81[1.62, 2.03]**	**104[5.10, 2,138]**	**0.62[0.47, 0.82]**	**3.57[3.02, 4.22]**	**2.17[1.53, 3.07]**	1.76[0.74, 4.19]	1.57[0.87, 2.84]	1.34[0.60, 2.99]	0.8[0.41, 1.58]	
Unknown vs. <= 24.9	**1.52[1.35, 1.70]**	**49.5[2.41, 1,016]**	**0.53[0.40, 0.70]**	**2.23[1.87, 2.64]**	**2.57[1.81, 3.65]**	1.58[0.65, 3.85]	1.65[0.91, 2.99]	1.25[0.55, 2.82]	1.09[0.56, 2.11]	
HbA1c										**<0.001**
7- <9% vs. < 7%	**1.84[1.56, 2.16]**	**0.41[0.28, 0.60]**	**0.2[0.15, 0.26]**	**1.68[1.34, 2.12]**	**3.8[2.09, 6.91]**	3.21[0.59, 17.5]	**0.27[0.17, 0.42]**	2.14[0.42, 11.0]	**0.26[0.14, 0.49]**	
>=9% vs. < 7%	1.06[0.90, 1.25]	**0.3[0.20, 0.43]**	**0.23[0.18, 0.29]**	1.08[0.86, 1.36]	**2.67[1.47, 4.87]**	1.81[0.33, 9.85]	**0.36[0.23, 0.57]**	2.62[0.52, 13.3]	**0.48[0.27, 0.87]**	
Unknown vs. < 7%	**0.86[0.69, 1.07]**	**0.38[0.21, 0.68]**	**0.7[0.51, 0.98]**	**0.87[0.65, 1.17]**	**2.89[1.47, 5.67]**	**2.88[0.43, 19.4]**	**0.85[0.47, 1.52]**	**2.98[0.51, 17.5]**	**0.44[0.18, 1.06]**	
Estimated glomerular filtration rate										**<0.001**
< 60 vs. >= 60	**1.19[1.09, 1.30]**	1.08[0.70, 1.69]	**1.88[1.46, 2.43]**	**0.27[0.22, 0.33]**	1[0.78, 1.28]	0.66[0.29, 1.51]	1.37[0.93, 2.02]	0.52[0.22, 1.25]	**2.03[1.30, 3.15]**	
Unknown vs. < 60	1.15[1.05, 1.27]	1.47[1.05, 2.05]	0.84[0.64, 1.09]	1.12[0.99, 1.26]	1.37[1.11, 1.70]	0.47[0.20, 1.09]	0.77[0.49, 1.20]	1.64[0.91, 2.96]	0.36[0.16, 0.78]	
High density lipoprotein										**>0.9**
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.98[0.92, 1.04]	0.94[0.74, 1.18]	1.12[0.90, 1.39]	0.93[0.86, 1.00]	1.1[0.96, 1.25]	**0.55[0.34, 0.88]**	1.04[0.76, 1.41]	0.73[0.47, 1.13]	0.99[0.64, 1.51]	
>= 60 vs. <40 (M) or <50 (F)	0.99[0.89, 1.11]	0.79[0.49, 1.28]	1.31[0.95, 1.81]	0.98[0.85, 1.14]	1[0.77, 1.30]	0.7[0.31, 1.60]	0.97[0.56, 1.69]	1.07[0.51, 2.25]	1.37[0.71, 2.65]	
Unknown vs. <40 (M) or	0.79[0.72,	0.86[0.63,	0.88[0.66,	0.83[0.74,	0.49[0.40,	0.45[0.23, 0.87]	1.05[0.70,	0.48[0.24,	1.03[0.61, 1.74]	

<50 (F)	0.86]	1.18]	1.18]	0.93]	0.60]		1.57]	0.97]		
Triglyceride										**<0.001**
150-499 vs. < 150	0.94[0.88, 1.00]	1.21[0.92, 1.58]	**0.75[0.60, 0.94]**	1[0.92, 1.09]	1.07[0.91, 1.27]	0.86[0.53, 1.40]	1.14[0.80, 1.60]	**1.89[1.08, 3.30]**	0.75[0.47, 1.20]	
>= 500 vs. < 150	**0.73[0.63, 0.84]**	1.16[0.73, 1.82]	0.95[0.62, 1.45]	0.92[0.78, 1.09]	1.02[0.72, 1.43]	0.47[0.15, 1.49]	1.48[0.83, 2.64]	**2.43[1.11, 5.32]**	1.36[0.66, 2.83]	
Unknown vs. < 150	1.19[1.10, 1.29]	0.98[0.70, 1.37]	0.86[0.65, 1.14]	0.9[0.81, 1.00]	2.58[2.17, 3.07]	1.38[0.77, 2.45]	0.95[0.61, 1.48]	1.46[0.72, 2.96]	1.46[0.86, 2.48]	
Total cholesterol										**0.001**
200-239 vs. < 200	**0.87[0.81, 0.94]**	**1.41[1.11, 1.78]**	1.06[0.84, 1.34]	0.96[0.87, 1.05]	**0.84[0.71, 0.99]**	0.92[0.53, 1.59]	1.18[0.85, 1.64]	**1.69[1.12, 2.55]**	0.97[0.60, 1.57]	
>=240 vs. < 200	**0.73[0.67, 0.81]**	1.33[0.99, 1.77]	**1.32[1.01, 1.72]**	**0.73[0.64, 0.82]**	**0.73[0.59, 0.92]**	1.02[0.53, 1.98]	1.02[0.67, 1.55]	0.92[0.52, 1.66]	1.56[0.96, 2.55]	
Unknown vs. < 200	0.8[0.73, 0.88]	1.09[0.74, 1.60]	1.93[1.41, 2.65]	0.93[0.81, 1.05]	0.66[0.52, 0.83]	1.29[0.62, 2.70]	1.26[0.79, 2.00]	1.73[0.78, 3.86]	1.16[0.68, 1.99]	

The results presented as OR[95%CI] along with the global p value. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

C. Sensitivity analysis: factors influencing prescribing choice after addressing missing data

Because of the substantial missingness in some of the investigated variables (Table 5.2), the LOCF method and multiple imputation were applied to account for data missingness. Thereby, as a sensitivity analysis, multivariable regression analyses were performed on the imputed cohort. Tables 5.21 and 5.22 include the results of multivariable logistic regression applied to the imputed initial-metformin cohort for the regimen type and antidiabetic class, respectively. No significant change was observed in the extent and direction of the association of the studied factors with the prescribing choice of the regimen type after accounting for missing data (Tables 5.19 and 5.21). However, a slight decline was noted in the extent of association of baseline BMI value (>= 30 kg/m^2) and total cholesterol level (>=240 mg/dl) with the choice of the regimen type in the multivariable analysis of the imputed cohort compared to the original cohort (Adjusted OR[95%CI]: before adjusting for missing data vs. after adjusting for missing data: baseline BMI of >=30: 0.63[0.46-0.88] vs. 0.72[0.54-0.96], baseline total cholesterol of >= 240 mg/dl: 1.15[0.86-1.52] vs. 1.05[0.81-1.73]). On the contrary, the association of the baseline TG level of >=500 mg/dl with the choice of the regimen type for the initial-metformin cohort has slightly increased after adjusting for missing data (Adjusted OR[95%CI]: before addressing for missing data vs. after addressing for missing data: 1.39[0.93-2.06] vs. 1.48[1.04-2.09]).

Table 5.21: Multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type (combination therapy vs. monotherapy) for initial-metformin cohort after imputation (Cohort-2a: N=46,730)

Studied factor	OR[95%CI]	Overall p value
Age at prescription >= 65 vs. < 65 years	0.74[0.62,0.89]	0.001
Sex Female vs. Male	1.2[1.03,1.4]	0.022
Urban-rural		0.792
1	1	
2	0.97[0.82,1.15]	
3	0.99[0.75,1.31]	
4	0.95[0.57,1.56]	
5	0.6[0.27,1.37]	
6	1.03[0.79,1.35]	
7	1.26[0.85,1.86]	
8	1.22[0.8,1.85]	
Scottish index of multiple deprivation-quantile		0.889
1	1	
2	1.01[0.83,1.24]	
3	1.1[0.89,1.37]	
4	0.94[0.73,1.19]	
5	1.04[0.8,1.35]	
Prescriber type Non-GP vs. GP	0.93[0.7,1.25]	0.649
Ischemic heart disease Yes vs. No	1.07[0.85,1.34]	0.577
Hypertension Yes vs. No	1.24[1.02,1.5]	0.028
Heart failure Yes vs. No	1.29[0.89,1.88]	0.175
Stroke Yes vs. No	1.08[0.72,1.64]	0.708
Peripheral vascular disease Yes vs. No	1[0.65,1.54]	0.994
Liver disease Yes vs. No	1.47[1.03,2.1]	0.033
Charlson comorbidity index-score		0.510
0	1	
1-2	1.12[0.91,1.38]	
3-4	1.22[0.83,1.8]	

>= 5	1.09[0.64,1.86]	
Antihyperlipidemic drugs Yes vs. No	0.91[0.76,1.09]	0.295
Antipsychotic Yes vs. No	1.28[0.92,1.78]	0.141
Thiazide diuretics Yes vs. No	0.66[0.47,0.93]	0.018
Beta-blockers Yes vs. No	0.69[0.54,0.88]	0.003
Angiotensin inhibitors Yes vs. No	0.94[0.77,1.15]	0.547
Calcium channel blocker Yes vs. No	0.65[0.51,0.83]	<0.001
Number of concomitant medications		0.084
0	1	
1-4	1.14[0.63,2.08]	
>= 5	1.94[1.07,3.53]	
Body mass index (kg/m^2)		0.014
<= 24.9	1	
25-29.9	0.69[0.49,0.98]	
>= 30	0.72[0.54,0.96]	
HbA1c (%)		0.049
< 7	1	
7-< 9	0.57[0.36,0.89]	
>= 9	1.12[0.71,1.77]	
Estimated glomerular filtration rate (ml/min/1.73m^2) < 60 vs. >= 60	1.6[1.23,2.07]	<0.001
HDL (mg/dl)		0.545
<40 (M) or <50 (F)	1	
40-59 (M) or 50-59 (F)	0.92[0.76,1.1]	
>= 60	0.91[0.65,1.26]	
Triglyceride (mg/dl)		0.024
< 150	1	
150-499	1.18[0.97,1.42]	
>= 500	1.48[1.04,2.09]	
Total cholesterol (mg/dl)		0.686
< 200	1	
200-239	1.09[0.88,1.35]	
>=240	1.05[0.81,1.37]	

The results are presented as OR[95%CI] along with the global p-value.

Despite that the majority of the results of factors associated with the prescribing choice of antidiabetic class were not changed after imputation in terms of the direction and extent of association, several differences were observed for multiple of the studied factors (Tables 5.20 and 5.22). Most of these differences were related to the change in the magnitude or extent of association, with only the number of concomitant medications (1-4 and >= 5) associated with TZD prescribing showing a change in the direction of association from negative (1-4: 0.77[95%CI: 0.55-1.09], >=5: 0.69[95%CI: 0.49-0.98]) to positive after imputation (1-4: 2.77[95%CI: 1.37-5.62], >=5: 2.11[95%CI: 0.85-5.22]). For instance, the negative association of patient age with the likelihood of prescribing SU+ insulin relative to SU monotherapy has changed to non-significant after imputation (0.67[95%CI: 0.47-0.94] vs. 0.99[95%CI: 0.58-1.67]). The same applied to the association of IHD with TZD prescribing, number of concomitant medications (1-4 and >=5) with SGLT2-I prescribing, HbA1c with DPP4-I+SU prescribing, and others (Tables 5.20 and 5.22). An increment in the magnitude of association was observed in other situations, such as the negative association of the baseline BMI of >= 30 kg/m^2 with SU+ insulin prescribing (before vs. after imputation: 0.8[95%CI: 0.41-1.58] vs. 0.41[95%CI: 0.22-0.79]). In addition, the extent of the positive association of a low baseline eGFR level (< $60ml/min/1.73m^2$) with insulin prescription has increased from 1.88[95%CI: 1.46-2.43] to 2.16[95%CI: 1.53-3.05] after imputation.

Moreover, the results of the complete case analysis including only complete cases of initial metformin users showed some variability relative to the analysis of the original cohort for both the regimen type and antidiabetic class (Appendix S.5.4). Nevertheless, most differences were in the significance or extent of association rather than the direction of the results. For effect sizes that showed a change in the direction of association, the results remained statistically non-significant in the two situations. For example, IHD and stroke association with SGLT2-I+SU prescribing has changed from positive non-significant (IHD: 1.35[95%CI: 0.85-2.16], stroke: 1.26[95%CI: 0.52-2.95]) to negative non-significant (IHD: 0.63[95%CI: 0.28-1.42], stroke: 0.81[95%CI: 0.16-4.14]). Furthermore, an observed reduction in the

magnitude and significance of association was noted with HTN association with SU+ insulin prescribing (from 1.64[95%CI: 1.15-2.35] to 1.32[0.71-2.45]), HF association with SGLT2-I prescribing (from 1.36[95%CI: 1.12-1.66] to 1.12[0.83-1.52]), liver disease association with insulin and TZD prescribing (insulin: from 1.59[95%CI: 1.13-2.24] to 1.37[0.76-2.47], TZD: from 2.53 [95%CI: 1.78-3.60] to 1.45[0.74-2.86]), and others (Table 5.20 and Appendix S.5.4).

Table 5.22: Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to SU) for initial-metformin cohort after imputation (Cohort-2a: N=46549)

Studied factors	DPP4-I	GLP1-RA	Insulin	SGLT2-I	TZD	DPP4-I+SGLT2-I	DPP4-I+SU	SGLT2-I+SU	SU+ insulin
Age at prescription	0.583	**<0.001**	**0.001**	**<0.001**	0.458	**0.028**	0.741	**<0.001**	>0.9
>= 65 vs. < 65 years	0.97[0.87,1.08]	**0.27[0.19,0.4]**	**0.54[0.41,0.72]**	**0.5[0.46,0.55]**	0.91[0.73,1.15]	**0.59[0.37,0.94]**	0.94[0.67,1.33]	**0.42[0.27,0.66]**	0.99[0.58,1.67]
Sex	0.753	**0.001**	**<0.001**	>0.9	**0.002**	0.394	0.266	0.418	0.678
Female vs. Male	0.99[0.92,1.06]	**1.43[1.16,1.76]**	**2[1.54,2.58]**	1[0.93,1.08]	**0.79[0.68,0.91]**	0.84[0.56,1.25]	1.21[0.87,1.7]	1.16[0.81,1.65]	0.92[0.61,1.38]
Urban-rural	**<0.001**	**0.001**	0.506	**<0.001**	**<0.001**	0.871	0.602	0.601	0.860
2 vs. 1	**1.31[1.22,1.4]**	0.85[0.68,1.07]	1.05[0.85,1.31]	1[0.93,1.08]	**3.41[2.34,4.98]**	0.94[0.59,1.49]	1.1[0.8,1.51]	0.87[0.58,1.33]	1.02[0.66,1.57]
3 vs. 1	1.07[0.94,1.22]	0.7[0.48,1]	0.86[0.64,1.15]	**0.77[0.65,0.92]**	**2.66[1.91,3.7]**	0.69[0.31,1.51]	1.21[0.74,1.97]	1.27[0.7,2.32]	1.06[0.57,1.97]
4 vs. 1	0.88[0.74,1.04]	1.42[0.83,2.42]	1.04[0.61,1.76]	0.85[0.66,1.08]	1.41[0.64,3.11]	0.2[0.02,2.43]	0.77[0.29,2.08]	1.6[0.66,3.88]	0.11[0.01,2.12]
5 vs. 1	1.18[0.94,1.48]	1.36[0.68,2.73]	0.31[0.1,0.94]	1.29[0.99,1.69]	0.14[0.02,1.01]	0.8[0.13,4.84]	0.75[0.17,3.23]	0.67[0.11,4.08]	0.13[0,5.09]
6 vs. 1	1.13[0.98,1.3]	0.77[0.55,1.1]	0.83[0.58,1.18]	0.88[0.75,1.02]	**2.88[2,4.16]**	1.19[0.55,2.57]	1.34[0.83,2.18]	1.1[0.59,2.07]	1.34[0.77,2.34]
7 vs. 1	1[0.85,1.17]	1.34[0.82,2.19]	1.27[0.85,1.89]	0.87[0.72,1.06]	0.74[0.31,1.75]	1.28[0.49,3.35]	0.84[0.34,2.06]	0.87[0.31,2.39]	1.33[0.58,3.06]
8 vs. 1	1.18[0.99,1.41]	**1.99[1.26,3.14]**	1.32[0.84,2.08]	1.02[0.8,1.29]	1.63[0.78,3.39]	1.39[0.49,3.94]	**2.28[1.01,5.17]**	0.17[0.02,1.89]	0.89[0.33,2.42]
Scottish index of multiple deprivation-quantile	**<0.001**	0.102	**0.014**	**<0.001**	0.251	0.654	0.468	0.786	0.695
2 vs. 1	**0.88[0.81,0.95]**	0.93[0.73,1.19]	0.92[0.76,1.12]	**0.85[0.76,0.96]**	1.12[0.81,1.55]	0.84[0.51,1.39]	0.74[0.5,1.1]	1.03[0.65,1.64]	0.92[0.51,1.64]
3 vs. 1	**0.86[0.8,0.93]**	0.78[0.58,1.05]	0.78[0.59,1.03]	0.9[0.79,1.03]	1.32[0.93,1.86]	0.67[0.37,1.21]	0.75[0.51,1.11]	1.06[0.62,1.8]	1.27[0.74,2.16]
4 vs. 1	0.87[0.73,1.03]	**0.61[0.43,0.86]**	0.82[0.64,1.06]	0.92[0.78,1.09]	1.1[0.76,1.59]	0.77[0.42,1.42]	**0.59[0.35,0.99]**	0.88[0.5,1.57]	1.19[0.7,2.03]

5 vs. 1	**0.87[0.76,0.99]**	0.74[0.52,1.05]	**0.68[0.49,0.96]**	1.03[0.89,1.19]	1.29[0.95,1.73]	1.06[0.57,1.98]	0.9[0.54,1.49]	1.47[0.82,2.64]	0.91[0.43,1.9]
Prescriber type	0.094	0.464	**0.003**	**0.004**	0.056	0.610	0.712	0.885	0.731
Non-general practitioner (GP) vs. GP	**1.3[1.01,1.67]**	0.87[0.61,1.26]	**0.4[0.22,0.7]**	**1.33[1.13,1.56]**	0.78[0.6,1]	1.23[0.56,2.71]	0.9[0.5,1.6]	0.95[0.48,1.9]	0.88[0.42,1.84]
Ischemic heart disease	0.745	**0.020**	0.568	0.149	**0.001**	0.456	0.148	0.617	0.876
Yes vs. No	0.97[0.8,1.17]	**0.65[0.46,0.93]**	1.09[0.81,1.46]	1.09[0.97,1.22]	**0.59[0.44,0.79]**	1.24[0.7,2.2]	0.71[0.45,1.13]	1.15[0.66,2.01]	1.04[0.64,1.69]
Hypertension	0.257	0.667	**<0.001**	**0.007**	0.521	0.899	0.657	0.634	0.088
Yes vs. No	0.95[0.87,1.03]	1.07[0.8,1.43]	**1.62[1.28,2.05]**	**0.86[0.78,0.96]**	0.94[0.79,1.13]	0.97[0.57,1.64]	1.09[0.76,1.56]	1.11[0.72,1.73]	1.58[0.95,2.63]
Heart failure	0.635	0.136	0.410	0.067	0.359	0.756	0.108	**0.028**	0.759
Yes vs. No	1.04[0.88,1.24]	1.56[0.87,2.78]	0.84[0.55,1.28]	1.28[0.99,1.65]	0.18[0.01,5.3]	1.2[0.39,3.67]	1.74[0.89,3.4]	**2.47[1.1,5.52]**	0.87[0.37,2.06]
Stroke	0.205	0.389	0.335	0.057	0.158	0.594	0.934	0.631	0.189
Yes vs. No	0.91[0.78,1.05]	0.7[0.31,1.57]	0.75[0.42,1.34]	0.82[0.67,1.01]	0.67[0.39,1.16]	0.7[0.19,2.56]	0.97[0.45,2.07]	1.24[0.51,3]	0.42[0.12,1.53]
Peripheral vascular disease	**0.012**	0.950	0.380	0.079	0.184	0.319	0.577	0.284	0.163
Yes vs. No	**0.83[0.71,0.96]**	0.98[0.49,1.94]	1.21[0.79,1.86]	0.83[0.67,1.02]	0.72[0.44,1.17]	0.45[0.09,2.16]	0.78[0.33,1.85]	0.47[0.12,1.86]	1.64[0.82,3.26]
Liver disease	0.501	0.214	0.354	0.319	0.144	0.382	0.695	0.188	0.731
Yes vs. No	0.94[0.79,1.12]	0.61[0.28,1.33]	1.2[0.82,1.75]	1.13[0.9,1.41]	2.34[0.88,6.18]	0.5[0.11,2.37]	1.16[0.56,2.4]	1.73[0.76,3.93]	1.16[0.49,2.77]
Charlson comorbidity index score	**<0.001**	0.411	**<0.001**	**<0.001**	**<0.001**	0.275	0.904	0.987	**0.028**
1-2 vs. 0	**0.85[0.78,0.93]**	0.74[0.48,1.12]	1.13[0.92,1.39]	**0.69[0.6,0.79]**	**0.57[0.41,0.8]**	0.73[0.38,1.42]	0.99[0.65,1.49]	0.95[0.58,1.54]	0.98[0.53,1.82]
3-4 vs. 0	**0.71[0.58,0.85]**	0.94[0.5,1.78]	1.14[0.69,1.87]	**0.65[0.49,0.86]**	0.22[0.04,1.25]	0.57[0.15,2.24]	1.03[0.51,2.07]	0.7[0.27,1.79]	0.74[0.26,2.13]
>= 5 vs. 0	**0.57[0.45,0.72]**	0.94[0.41,2.16]	**2.32[1.58,3.41]**	**0.44[0.31,0.61]**	0.75[0.12,4.87]	0.62[0.11,3.45]	0.43[0.11,1.64]	0.07[0,2.84]	**2.34[1.03,5.3]**
Antihyperlipidemic drugs	**0.048**	**0.017**	**<0.001**	0.134	0.387	0.534	0.940	0.394	**0.004**

Yes vs. No	**1.09[1.01,1.18]**	**0.74[0.58,0.94]**	**0.36[0.3,0.43]**	1.06[0.98,1.14]	1.09[0.9,1.33]	1.18[0.71,1.97]	1.01[0.73,1.4]	0.84[0.55,1.26]	**0.51[0.33,0.79]**
Antipsychotic	0.155	0.618	>0.9	**0.003**	0.145	0.749	0.477	0.640	0.203
Yes vs. No	0.89[0.75,1.04]	1.11[0.73,1.69]	1[0.69,1.45]	**0.69[0.55,0.86]**	0.75[0.51,1.1]	0.86[0.33,2.22]	1.23[0.69,2.2]	1.19[0.57,2.47]	1.59[0.78,3.24]
Thiazide diuretics	**0.007**	0.652	**<0.001**	0.089	**0.035**	0.544	0.672	0.883	0.292
Yes vs. No	**1.17[1.05,1.31]**	1.1[0.73,1.66]	**0.42[0.28,0.63]**	1.14[0.98,1.31]	**1.29[1.02,1.62]**	0.76[0.31,1.85]	0.88[0.5,1.57]	0.94[0.43,2.05]	0.63[0.26,1.49]
Beta blocker	0.878	0.451	**0.005**	0.630	0.245	0.918	0.141	0.587	0.666
Yes vs. No	0.99[0.87,1.12]	1.12[0.83,1.51]	**0.7[0.55,0.89]**	0.97[0.87,1.09]	0.83[0.62,1.12]	1.03[0.59,1.81]	0.69[0.42,1.13]	0.86[0.49,1.5]	0.86[0.44,1.68]
Angiotensin inhibitors	**<0.001**	0.317	**<0.001**	**<0.001**	0.439	0.630	0.440	0.208	0.541
Yes vs. No	**1.13[1.06,1.21]**	1.15[0.88,1.5]	**0.44[0.35,0.57]**	**1.2[1.1,1.31]**	0.94[0.79,1.11]	0.87[0.5,1.51]	1.16[0.8,1.67]	1.35[0.85,2.13]	0.84[0.49,1.45]
Calcium channel blocker	0.364	0.580	**<0.001**	0.068	0.525	0.300	0.104	0.367	0.746
Yes vs. No	1.06[0.94,1.21]	0.92[0.7,1.22]	**0.5[0.39,0.65]**	1.12[1,1.26]	1.06[0.88,1.29]	0.73[0.41,1.32]	0.69[0.45,1.08]	0.77[0.43,1.37]	0.91[0.53,1.57]
Number of concomitant medications	0.046	0.614	**0.005**	0.216	**0.038**	>0.9	0.083	>0.9	0.227
1-4 vs. 0	1.23[1,1.51]	1.66[0.84,3.27]	**1.97[1.12,3.46]**	0.97[0.73,1.29]	**2.77[1.37,5.62]**	4.59[0.39,53.57]	0.53[0.21,1.32]	7.56[0.35,163.46]	4.56[0.59,35.03]
>= 5 vs. 0	1.15[0.94,1.41]	1.63[0.82,3.27]	**1.87[1.08,3.24]**	0.9[0.7,1.17]	2.11[0.85,5.22]	5.83[0.5,67.81]	0.94[0.39,2.26]	12.99[0.6,279.64]	5.74[0.77,42.71]
Body mass index (kg/m^2)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.015**	0.154	0.811	0.459	**0.005**
25-29.9 vs. <=24.9	**1.23[1.06,1.44]**	1.16[0.22,6.07]	**0.61[0.41,0.91]**	**1.74[1.45,2.08]**	1.27[0.61,2.67]	2.17[0.73,6.43]	1.03[0.52,2.01]	1.38[0.48,3.93]	0.62[0.32,1.21]
>= 30 vs. <=24.9	**1.58[1.4,1.78]**	**10.1[2.2,46.47]**	**0.57[0.43,0.77]**	**3.03[2.56,3.6]**	1.34[0.73,2.46]	2.7[0.95,7.71]	1.27[0.61,2.62]	1.49[0.55,4.03]	**0.41[0.22,0.79]**
HbA1c (%)	**<0.001**	**<0.001**	**<0.001**	**0.009**	**0.015**	0.751	0.121	0.489	**<0.001**
7-9 vs. < 7	**1.55[1.25,1.92]**	**0.55[0.35,0.89]**	**0.13[0.09,0.19]**	1.18[0.85,1.62]	**3.72[1.06,12.99]**	2.96[0.34,25.38]	**0.45[0.21,0.96]**	2.76[0.3,25.27]	**0.27[0.11,0.67]**
>=9 vs. < 7	0.93[0.76,1	**0.42[0.25,0**	**0.15[0.11,0**	0.79[0.58,1	2.67[0.79,9.	2.19[0.26,1	0.64[0.3,1.	4.17[0.46,38.	0.68[0.31,1.

	.14]	**.68]**	**.2]**	.07]	04]	8.85]	38]	06]	52]
Estimated glomerular filtration rate (ml/min/1.73m^2)	0.584	0.483	**0.001**	**<0.001**	0.648	0.361	0.145	0.295	0.280
< 60 vs. >= 60	1.04[0.9,1.2]	1.18[0.75,1.85]	**2.16[1.53,3.05]**	**0.33[0.25,0.43]**	0.93[0.67,1.28]	0.65[0.26,1.64]	1.42[0.89,2.29]	0.62[0.25,1.52]	1.82[0.67,4.98]
High density lipoprotein (mg/dl)	0.396	0.115	0.142	0.163	0.811	0.181	0.971	0.939	0.670
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.98[0.92,1.05]	0.85[0.66,1.09]	0.86[0.66,1.12]	0.99[0.91,1.08]	1.08[0.94,1.24]	0.65[0.42,1]	0.94[0.66,1.34]	0.86[0.58,1.28]	0.72[0.42,1.26]
>= 60 vs. <40 (M) or <50 (F)	0.92[0.77,1.09]	0.66[0.41,1.06]	0.81[0.59,1.11]	0.89[0.76,1.04]	0.95[0.73,1.22]	0.66[0.28,1.58]	0.96[0.51,1.81]	0.71[0.32,1.58]	0.62[0.27,1.46]
Triglyceride (mg/dl)	**0.013**	0.856	0.342	0.367	0.365	0.873	0.328	**0.002**	0.772
150-499 vs. < 150	0.99[0.93,1.04]	0.94[0.72,1.22]	0.86[0.65,1.12]	1.03[0.95,1.11]	1.04[0.91,1.19]	0.8[0.4,1.58]	1.16[0.81,1.65]	1.07[0.68,1.68]	0.83[0.51,1.35]
>= 500 vs. < 150	**0.82[0.71,0.93]**	0.96[0.6,1.53]	1.01[0.7,1.44]	0.93[0.77,1.12]	0.83[0.62,1.11]	1.04[0.47,2.34]	1.3[0.67,2.52]	**2.06[1.07,3.96]**	1.23[0.6,2.52]
Total cholesterol (mg/dl)	**<0.001**	**0.004**	0.677	**0.005**	0.223	0.917	0.578	0.849	0.723
200-239 vs. < 200	0.92[0.83,1.02]	1.28[1,1.66]	1.06[0.86,1.32]	0.99[0.91,1.09]	0.94[0.8,1.1]	0.96[0.5,1.86]	1.17[0.81,1.69]	1.1[0.68,1.79]	0.81[0.47,1.39]
>=240 vs. < 200	**0.75[0.65,0.87]**	**1.49[1.11,1.99]**	1.13[0.82,1.55]	**0.81[0.72,0.91]**	0.86[0.68,1.09]	1.45[0.65,3.21]	1.19[0.69,2.03]	0.81[0.42,1.56]	1.14[0.48,2.72]

The results are presented as OR[95%CI] along with the global p-value. DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

5.3.3.2 Initial sulfonylurea cohort (cohort 2b)

A. Factors influencing the prescribing choice of the regimen type (combination therapy vs. monotherapy)

For patients who started on SU (N= 4001), univariable and multivariable logistic regression analyses of factors associated with the prescribing choice of the regimen type were conducted; the results are summarised in Table 5.23. The odds of receiving combination therapy than monotherapy after an initial SU was 50% significantly less likely for elderly patients (>= 65 years old) compared to younger individuals (Adjusted OR[95%CI]: 0.5[0.31-0.81]), yet there was no significant difference in the prescription of combination therapy and monotherapy for female patients compared to male patients (Table 5.23). Additionally, compared to patients living in a large urban area (UR rank 1), only patients who lived in a rural area of UR rank 7 showed a significant positive association with the choice of combination therapy over monotherapy for patients who started on SU (adjusted OR[95%CI]: 2.67[1.01-6.27]). Likewise, SIMD-Q and prescriber type had no significant impact on the choice of regimen type for the initial-SU cohort.

Of the clinical-related factors, only liver disease, baseline HbA1c level (>= 9% vs. < 7%), and baseline eGFR value (<60ml/min/1.73m^2) had significant associations with the prescribing choice of the regimen type, in which patients with a baseline HbA1c level of >= 9% were 6.9 times more likely to add combination therapy to initial SU compared to patients with a baseline HbA1c level of < 7%(Adjusted OR[95%CI]: 6.9[1.47, 123]). In addition, the odds of adding combination therapy over monotherapy to initial SU for patients with liver disease was 2.29[1.01-4.89]. Regarding the baseline eGFR, the multivariable analysis showed a 2.33 times greater likelihood of prescribing combination therapy to initial SU for patients with a low baseline eGFR (< 60ml/min/1.73m^2) compared to patients with eGFR of > 60ml/min/1.73m^2 (adjusted OR[95%CI]: 2.33[1.31, 4.09]).

Table 5.23: Univariable and multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type (combination therapy vs. monotherapy) for initial-sulfonylurea cohort (Cohort-2b: N=4001)

Studied factor	Combination regimen	
	Univariate	Multivariate
1- Demographic factors		
Age at prescription	0.01	0.004
>= 65 vs. < 65 years	0.6[0.40, 0.88]	**0.5[0.31, 0.81]**
Sex	>0.9	0.8
Female vs. Male	0.98[0.66, 1.44]	0.95[0.62, 1.45]
2- Socioeconomic factors		
Urban-rural	0.4	0.4
1	1	1
2	1.41[0.89, 2.28]	1.43[0.88, 2.35]
3	0.64[0.22, 1.53]	0.66[0.22, 1.60]
4	0.92[0.15, 3.11]	1.1[0.17, 3.90]
5	1.74[0.28, 5.96]	1.84[0.28, 7.09]
6	1.45[0.72, 2.74]	1.62[0.77, 3.25]
7	2.41[0.96, 5.30]	2.67[1.01, 6.27]
8	1.84[0.54, 4.78]	1.98[0.54, 5.64]
Unknown	0[NA]	0[NA]
Scottish index of multiple deprivation-quantile	0.5	0.8
1	1	1
2	0.85[0.48, 1.46]	0.81[0.45, 1.43]
3	1.26[0.73, 2.16]	1.13[0.62, 2.05]
4	0.95[0.52, 1.70]	1.04[0.54, 1.94]
5	0.68[0.32, 1.32]	0.84[0.39, 1.69]
3- Prescriber-related factor		
Prescriber type	0.5	0.4
Non-general practitioner (GP) vs. GP	0.73[0.26, 1.64]	0.7[0.24, 1.63]
4- Clinical-related factors		
Ischemic heart disease	0.5	0.6
Yes vs. No	0.84[0.48, 1.40]	0.84[0.44, 1.55]
Hypertension	>0.9	>0.9
Yes vs. No	0.98[0.61, 1.51]	0.97[0.56, 1.65]
Heart failure	0.7	0.4
Yes vs. No	0.86[0.33, 1.81]	0.67[0.23, 1.70]
Stroke	0.8	0.8
Yes vs. No	1.09[0.38, 2.46]	1.16[0.39, 2.77]
Peripheral vascular disease	0.8	>0.9
Yes vs. No	1.11[0.43, 2.35]	1.04[0.39, 2.36]

Liver disease	0.039	0.048
Yes vs. No	2.02[1.04, 3.60]	2.29[1.01, 4.89]
Charlson comorbidity index score	0.6	0.6
0	1	1
1-2	0.84[0.48, 1.39]	0.67[0.36, 1.19]
3-4	1.32[0.66, 2.42]	0.79[0.32, 1.82]
>= 5	1.36[0.47, 3.09]	0.87[0.26, 2.36]
Antihyperlipidemic drugs	0.064	0.6
Yes vs. No	0.69[0.47, 1.02]	0.88[0.56, 1.39]
Antipsychotic	0.4	0.7
Yes vs. No	1.53[0.53, 3.46]	1.22[0.41, 2.87]
Thiazide diuretics	0.059	0.079
Yes vs. No	0.33[0.05, 1.04]	0.33[0.05, 1.12]
Beta-blockers	0.5	0.8
Yes vs. No	1.18[0.72, 1.85]	0.93[0.51, 1.68]
Angiotensin inhibitors	0.8	0.8
Yes vs. No	0.94[0.55, 1.53]	0.94[0.51, 1.67]
Calcium channel blocker	0.052	0.055
Yes vs. No	0.55[0.27, 1.00]	0.51[0.23, 1.01]
Number of concomitant medications	0.2	0.14
0	1	1
1-4	0.43[0.18, 1.18]	0.53[0.21, 1.51]
>= 5	0.6[0.28, 1.58]	0.85[0.34, 2.45]
Body mass index (kg/m^2)	0.8	0.9
<=24.9	1	1
25-29.9	1.1[0.56, 2.25]	1.09[0.54, 2.28]
>= 30	1.32[0.71, 2.61]	1.28[0.66, 2.62]
Unknown	1.18[0.64, 2.33]	1.06[0.55, 2.15]
HbA1c (%)	<0.001	<0.001
< 7	1	1
7- < 9	2.66[0.56, 47.6]	3.06[0.62, 55.4]
>=9	6.09[1.34, 108]	6.9[1.47, 123]
Unknown	3.56[0.52, 70.0]	2.35[0.33, 47.4]
Estimated glomerular filtration rate (ml/min/1.73m^2)	0.2	0.014
< 60 vs. >= 60	1.5[0.93, 2.34]	2.33[1.31, 4.09]
Unknown vs. < 60	1[0.44, 1.96]	0.86[0.35, 1.88]
High density lipoprotein (mg/dl)	0.033	0.6
<40 (M) or <50 (F)	1	1
40-59 (M) or 50-59 (F)	1.11[0.63, 1.92]	1.16[0.64, 2.06]

>= 60	0.87[0.30, 2.05]	0.96[0.31, 2.41]
Unknown	1.84[1.18, 2.90]	1.56[0.76, 3.10]
Triglyceride (mg/dl)	0.03	0.5
< 150	1	1
150-499	1.01[0.57, 1.82]	0.87[0.47, 1.64]
>= 500	0.88[0.21, 2.63]	0.57[0.12, 1.94]
Unknown	1.8[1.08, 3.13]	1.28[0.63, 2.63]
Total cholesterol (mg/dl)	0.091	>0.9
< 200	1	1
200-239	1.27[0.69, 2.22]	1.13[0.59, 2.06]
>=240	1.24[0.56, 2.42]	1.09[0.47, 2.28]
Unknown	1.82[1.15, 2.83]	1.08[0.54, 2.27]

The results are presented as OR[95%CI] along with the global p-value.

B. Factors influencing the prescribing choice of antidiabetic class

Table 5.24 presents the results of the multivariable multinomial logistic regression of factors associated with the prescribing decision of antidiabetic classes compared to metformin for patients who started on SU (Cohort 2b). The results of the univariable multinomial logistic regression analysis are summarised in Appendix S.5.5 Of the entire cohort of patients started on SU (N=4001), 49 patients who were started on other monotherapy (N=15) and other combination therapy (N=34) were not included in the regression model, leaving a total of 3952 patients included in the regression model. The other-monotherapy and the other-combination therapy groups were excluded for the same reasons mentioned with the initial-metformin cohort, which are related to the inclusion of a wide range of regimens with a small sample size, as well as the clinical relevance and complexity of interpreting the results.

Generally, patients who started on SU had fewer variables connected with the prescribing decision of antidiabetic classes than patients who started on metformin (section 5.3.3.1). The multivariable analysis revealed that patient age at the index intensification date had only significant associations with insulin and SGLT2-I prescription, in which patients aged 65 years or over had 47% and 46% lower likelihood to receive insulin and SGLT2-I than metformin as a first intensifying therapy to initial SU, respectively (Adjusted OR[95%CI]: 0.53[0.39-0.71] and

0.54[0.35-0.86], respectively). Furthermore, patient sex was only significantly associated with SGLT2-I according to the multivariable analysis; SGLT2-I was 28% more likely than metformin to be prescribed for female patients compared to male patients (adjusted OR[95%CI]: 1.72[1.14-2.58]).

Moreover, a statistically significant positive correlation between UR location and the prescription of DPP4-I (UR rank 2), SGLT2-I (UR rank 8), metformin+DPP4-I (UR rank 5, 6, and 7), and insulin was also found (UR rank 6 and 7), Table 5.24 Conversely, the multivariable analysis revealed that SIMD-Q had no significant impact on the decision to prescribe any of the examined antidiabetic classes. For patients who started on SU, it was shown that DPP4-I and SGLT2-I were prescribed more frequently than metformin by non-GPs than by GPs (adjusted OR[95%CI]: 1.6[1.05, 2.43] and 2.14[1.18, 3.87], respectively).

Of the studied comorbid conditions, only liver disease and CCI score had a significant association with the prescribing choice of ADDs according to the multivariable analyses, in which patients with liver disease were significantly more likely to be treated with SGLT2-I and metformin+ DPP4-I than metformin alone as a first intensifying therapy to initial SU compared to patients without the disease (Adjusted OR[95%CI]: 2.68[1.23-5.83] and 3.92[1.07-14.4], respectively). For concomitant medications, antihyperlipidemic drugs, thiazide diuretics, beta-blockers, and the number of concomitant medications showed a statistically significant association with the prescribing choice of ADDs. Patients who were on antihyperlipidemic drugs were 51% and 54% significantly less likely to receive insulin and SGLT2-I than metformin after an initial SU (Adjusted OR[95%CI]: 0.49[0.37-0.65] and 0.56[0.36-0.86], respectively), while patients who were on beta blocker had a 58% greater likelihood to get a prescription of DPP4-I than metformin as a first intensifying therapy compared to their counterparts (Adjusted OR[95%CI]: 1.58[1.15-2.19]). Moreover, the odds of prescribing insulin as a first intensifying therapy after initial SU for patients who were on thiazide diuretics or on five or more concomitant medications were 0.35[0.14-0.84] and 3.87[1.32-11.3], respectively.

Moreover, it was found that overweight (BMI 24.9-29.9 kg/m^2) and obese (BMI >= 30 kg/m^2) patients were significantly less likely to receive insulin (Adjusted OR[95%CI]: 0.22[0.14-0.33] and 0.19[0.13-0.28], respectively), while obese patients were significantly more likely to be treated with SGLT2-I than metformin compared to patients with a low/normal BMI (OR[95%CI]: unadjusted: 3.1[1.39-6.91], adjusted: 2.42[1.04-5.66]). The multivariable analysis also revealed that overweight patients were 42% significantly less likely to receive DPP4-I than metformin compared to patients with a low/normal BMI (adjusted OR[95%CI]: 0.58[0.40, 0.85]). Baseline HbA1c value was only significantly associated with insulin prescription under the adjustment of all baseline characteristics; patients with a baseline HbA1c value of >=9% were 2.37 times significantly more likely to add insulin than metformin to initial SU compared to patients with a baseline HbA1c of <7%(adjusted OR[95%CI]: 2.37[1.17-4.81]).

The multivariable analysis also revealed that baseline total cholesterol was considerably and negatively linked with insulin prescription, but baseline TG level was significantly and positively associated with the prescription of SGLT2-I and DPP4-I. For instance, compared to patients with a normal TG level (150 mg/dl), the likelihood of adding DPP4-I for patients with baseline TG levels of 150-499 mg/dl and SGLT2-I for patients with TG levels of >= 500 mg/dl over metformin to initial SU were 1.37[1.01-1.88] and 2.94[1.13-7.62], respectively. In contrast, patients with a baseline total cholesterol level between 200 and 239 mg/dl had a 50% lower likelihood of receiving an insulin prescription than those with a baseline total cholesterol level under 200 mg/dl (Adjusted OR[95%CI: 0.5[0.30-0.82]). Nevertheless, the results of the multivariable analysis indicated that baseline HDL level had no statistically significant influence on the prescribing decision of antidiabetic classes for patients who started on SU.

Table 5.24: Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to metformin) for initial-sulfonylurea cohort (Cohort-2b: N=3952)

Studied factors	DPP4-I	insulin	SGLT2-I	TZD	biguanide+ DPP4-I	biguanide+ insulin	P-value
1- Demographic factors							
Age at prescription	0.15	<0.001	0.011	0.4	0.3	0.021	<0.001
>= 65 vs. < 65 years	1.25[0.97, 1.61]	**0.53[0.39, 0.71]**	**0.54[0.35, 0.86]**	1.35[0.72, 2.54]	0.7[0.34, 1.45]	**0.34[0.12, 0.93]**	
Sex	0.066	>0.9	0.01	0.038	0.8	0.9	0.04
Female vs. Male	1.22[0.97, 1.53]	1.02[0.78, 1.34]	**1.72[1.14, 2.58]**	1.7[0.95, 3.03]	1.03[0.52, 2.02]	1.17[0.50, 2.73]	
2- Socioeconomic factors							
Urban-rural	0.2	0.4	0.066	0.5	0.018	0.6	0.082
2 vs. 1	1.33[1.03, 1.73]	1.07[0.79, 1.46]	1.31[0.81, 2.10]	1.32[0.66, 2.61]	2.09[0.90, 4.83]	1.61[0.63, 4.13]	
3 vs. 1	1.09[0.72, 1.64]	1.33[0.84, 2.12]	0.65[0.27, 1.54]	1.94[0.78, 4.84]	0.53[0.07, 4.21]	0.46[0.05, 3.97]	
4 vs. 1	0.66[0.27, 1.60]	0.96[0.39, 2.34]	1.29[0.41, 4.05]	2.79[0.70, 11.0]	1.93[0.23, 16.2]	0.01[0.00, inf]	
5 vs. 1	0.42[0.12, 1.45]	1.19[0.37, 3.82]	1.07[0.21, 5.38]	2.79[0.32, 24.4]	**8.66[1.54, 48.6]**	0.01[0.00, inf]	
6 vs. 1	1.2[0.80, 1.81]	**1.62[1.03, 2.56]**	1.2[0.59, 2.44]	2.41[0.98, 5.93]	**5.91[2.14, 16.4]**	0.77[0.15, 4.06]	
7 vs. 1	1.28[0.71, 2.34]	**1.97[1.03, 3.80]**	1.12[0.32, 3.91]	0.71[0.08, 6.00]	**5.65[1.36, 23.4]**	2.61[0.45, 15.3]	
8 vs. 1	1.29[0.64, 2.59]	1.79[0.78, 4.11]	**5.43[2.13, 13.8]**	1.06[0.13, 8.79]	2.49[0.28, 22.4]	2.9[0.42, 20.1]	
Unknown vs. 1	0.09[0.00, inf]	0.32[0.00, inf]	0.3[0.00, inf]	0.99[0.00, inf]	0.98[0.00, inf]	1.02[0.89, 1.17]	
Scottish index of multiple deprivation-quantile	0.8	0.6	0.4	0.2	0.3	0.5	0.5
2 vs. 1	0.97[0.71, 1.33]	1.22[0.86, 1.74]	1.46[0.87, 2.46]	1.95[0.89, 4.25]	0.58[0.25, 1.35]	0.64[0.17, 2.43]	
3 vs. 1	1.08[0.77, 1.51]	0.98[0.65, 1.48]	1.02[0.54, 1.93]	0.93[0.35, 2.48]	0.55[0.22, 1.39]	1.6[0.48, 5.35]	
4 vs. 1	1.19[0.84, 1.67]	1.09[0.72, 1.64]	0.76[0.38, 1.52]	1.22[0.47, 3.20]	0.64[0.25, 1.67]	1.86[0.53, 6.50]	
5 vs. 1	0.98[0.68, 1.41]	1.05[0.68, 1.63]	1.19[0.61, 2.31]	1.71[0.69, 4.22]	0.23[0.05, 1.05]	2.04[0.52, 7.96]	
3- Prescriber-related factors							
Prescriber type	0.039	0.5	0.028	>0.9	0.4	0.4	0.058

Non-general practitioner (GP) vs. GP	**1.6[1.05, 2.43]**	0.78[0.41, 1.49]	**2.14[1.18, 3.87]**	0.86[0.25, 2.95]	0.52[0.11, 2.32]	2.04[0.42, 9.97]	
4- Clinical-related factors							
Ischemic heart disease	>0.9	0.4	0.7	0.8	0.3	0.2	0.9
Yes vs. No	1[0.75, 1.35]	0.87[0.61, 1.24]	0.89[0.47, 1.68]	0.93[0.43, 2.05]	0.57[0.20, 1.61]	0.53[0.13, 2.20]	
Hypertension	0.3	0.3	>0.9	0.15	0.4	0.2	0.3
Yes vs. No	1.14[0.87, 1.48]	1.26[0.93, 1.72]	1.03[0.61, 1.75]	1.7[0.91, 3.20]	0.66[0.26, 1.67]	1.73[0.64, 4.66]	
Heart failure	0.5	>0.9	0.12	0.3	0.2	0.3	0.3
Yes vs. No	0.88[0.56, 1.39]	0.97[0.61, 1.54]	2.22[0.87, 5.66]	1.42[0.46, 4.38]	2.84[0.73, 11.0]	0.23[0.02, 2.43]	
Stroke	0.6	0.2	0.7	0.007	0.8	0.6	0.072
Yes vs. No	1.18[0.73, 1.91]	1.42[0.85, 2.37]	1.22[0.45, 3.33]	0[0.00, inf]	1.37[0.30, 6.29]	0.82[0.09, 7.78]	
Peripheral vascular disease	0.8	0.4	0.4	>0.9	0.4	0.2	0.5
Yes vs. No	0.97[0.61, 1.54]	1.29[0.82, 2.04]	0.69[0.21, 2.34]	1.14[0.37, 3.52]	2.02[0.64, 6.42]	0[0.00, inf]	
Liver disease	0.6	0.3	0.026	0.9	0.043	0.2	0.09
Yes vs. No	0.91[0.54, 1.54]	1.19[0.75, 1.89]	**2.68[1.23, 5.83]**	1.39[0.37, 5.24]	**3.92[1.07, 14.4]**	2.23[0.58, 8.65]	
Charlson comorbidity index score	0.011	<0.001	0.049	0.5	0.4	0.4	<0.001
1-2 vs. 0	1.3[0.98, 1.72]	**2.2[1.58, 3.05]**	1.03[0.59, 1.79]	1.51[0.77, 2.97]	0.47[0.17, 1.31]	1.17[0.35, 3.89]	
3-4 vs. 0	1.5[0.95, 2.37]	**3.98[2.52, 6.29]**	0.91[0.36, 2.28]	0.81[0.23, 2.81]	0.41[0.09, 1.82]	3.97[0.89, 17.8]	
>= 5 vs. 0	**2.14[1.22, 3.75]**	**4.24[2.47, 7.27]**	0[0.00, inf]	0.5[0.06, 4.52]	0.41[0.04, 4.05]	1.95[0.34, 11.4]	
Antihyperlipidemic drugs	0.6	<0.001	0.009	0.12	>0.9	0.2	<0.001
Yes vs. No	0.92[0.71, 1.19]	**0.49[0.37, 0.65]**	**0.56[0.36, 0.86]**	1.6[0.79, 3.22]	0.99[0.48, 2.05]	0.53[0.22, 1.27]	
Antipsychotic	0.5	0.9	0.4	0.3	0.4	0.2	0.8
Yes vs. No	0.89[0.48, 1.66]	1.22[0.65, 2.28]	0.5[0.12, 2.16]	0.6[0.08, 4.71]	1.87[0.53, 6.62]	2.04[0.40, 10.3]	
Thiazide diuretics	0.2	0.013	0.3	0.6	0.7	0.028	0.018

Yes vs. No	1.39[0.87, 2.21]	**0.35[0.14, 0.84]**	1.55[0.65, 3.71]	0.64[0.17, 2.36]	0.84[0.18, 3.88]	0[0.00, inf]	
Beta-blockers	0.003	0.7	0.4	0.3	0.8	0.4	0.13
Yes vs. No	**1.58[1.15, 2.19]**	1.08[0.75, 1.55]	1.38[0.73, 2.60]	0.7[0.30, 1.63]	1.18[0.47, 2.93]	1.36[0.44, 4.21]	
Angiotensin inhibitors	0.4	0.3	0.2	>0.9	>0.9	0.7	0.6
Yes vs. No	1.14[0.81, 1.59]	0.82[0.54, 1.22]	1.55[0.90, 2.68]	1.07[0.51, 2.24]	0.9[0.35, 2.28]	0.74[0.20, 2.73]	
Calcium channel blocker	0.1	0.2	0.5	0.3	0.3	0.7	0.3
Yes vs. No	1.28[0.91, 1.79]	0.78[0.52, 1.17]	1.33[0.71, 2.47]	0.75[0.33, 1.74]	0.54[0.17, 1.72]	0.62[0.15, 2.57]	
Number of concomitant medications	0.6	<0.001	0.5	0.3	0.3	0.4	0.001
1-4 vs. 0	1.43[0.59, 3.43]	1.64[0.55, 4.88]	1.79[0.59, 5.40]	155[0.00, inf]	0.39[0.10, 1.59]	0.42[0.07, 2.59]	
>= 5 vs. 0	1.55[0.64, 3.77]	**3.87[1.32, 11.3]**	1.4[0.45, 4.35]	130[0.00, inf]	0.63[0.15, 2.61]	0.77[0.13, 4.65]	
Body mass index (kg/m^2)	0.13	<0.001	0.2	0.8	0.8	0.2	<0.001
25-29.9 vs. <=24.9	**0.58[0.40, 0.85]**	**0.22[0.14, 0.33]**	1.82[0.75, 4.38]	0.92[0.38, 2.24]	0.7[0.26, 1.93]	2.19[0.41, 11.7]	
>= 30 vs. <=24.9	0.72[0.50, 1.03]	**0.19[0.13, 0.28]**	**2.42[1.04, 5.66]**	0.64[0.26, 1.58]	0.81[0.30, 2.14]	2.82[0.54, 14.6]	
Unknown vs. <= 24.9	0.76[0.53, 1.07]	0.34[0.24, 0.47]	2.27[0.97, 5.34]	0.77[0.33, 1.82]	0.65[0.24, 1.75]	0.98[0.18, 5.34]	
HbA1c (%)	0.3	<0.001	0.3	0.03	0.3	<0.001	<0.001
7- <9 vs. < 7	1.59[0.85, 2.95]	1.1[0.53, 2.27]	1.88[0.55, 6.43]	261[0.00, inf]	1.47[0.20, 11.0]	43.3[0.00, inf]	
>=9 vs. < 7	1.69[0.91, 3.12]	**2.37[1.17, 4.81]**	2.5[0.74, 8.42]	442[0.00, inf]	2.3[0.32, 16.6]	423[0.00, inf]	
Unknown vs. < 7	1.47[0.64, 3.35]	2.23[0.97, 5.15]	1.47[0.29, 7.43]	591[0.00, inf]	0.71[0.04, 12.3]	76[0.00, inf]	
Estimated glomerular filtration rate ($ml/min/1.73m^2$)	<0.001	<0.001	0.5	<0.001	0.032	0.053	<0.001
< 60 vs. >= 60	**4.06[3.11, 5.30]**	**4.93[3.55, 6.85]**	0.73[0.34, 1.57]	**3.41[1.78, 6.52]**	**3.2[1.30, 7.84]**	**3.31[1.07, 10.2]**	
Unknown vs. < 60	1.48[0.93, 2.37]	0.91[0.53, 1.57]	1.58[0.72, 3.45]	0.34[0.07, 1.73]	0.56[0.12, 2.63]	0.56[0.10, 3.20]	
High-density lipoprotein (mg/dl)	0.7	0.4	0.5	0.8	0.3	0.3	0.6
40-59 (M) or 50-59 (F)	0.93[0.68, 1.26]	0.97[0.66, 1.42]	1.44[0.86, 2.40]	0.95[0.46, 1.99]	1.52[0.67, 3.48]	0.71[0.18, 2.89]	

vs. <40 (M) or <50 (F)							
>= 60 vs. <40 (M) or <50 (F)	0.88[0.55, 1.40]	1.42[0.86, 2.36]	0.75[0.27, 2.04]	0.74[0.21, 2.61]	0.4[0.05, 3.17]	2.54[0.56, 11.6]	
Unknown vs. <40 (M) or <50 (F)	1.15[0.78, 1.69]	0.77[0.46, 1.28]	1.33[0.56, 3.13]	1.32[0.56, 3.11]	2.07[0.72, 5.97]	0.69[0.12, 3.81]	
Triglyceride (mg/dl)	0.014	0.6	0.04	0.8	0.3	0.7	0.034
150-499 vs. < 150	**1.37[1.01, 1.88]**	0.76[0.53, 1.11]	1.28[0.74, 2.21]	0.86[0.40, 1.86]	1.03[0.43, 2.47]	0.57[0.15, 2.13]	
>= 500 vs. < 150	0.54[0.24, 1.21]	0.77[0.35, 1.70]	**2.94[1.13, 7.62]**	1.18[0.26, 5.33]	0[0.00, inf]	0.41[0.03, 5.18]	
Unknown vs. < 150	1.2[0.81, 1.77]	0.97[0.62, 1.52]	0.54[0.23, 1.28]	1.16[0.50, 2.71]	0.99[0.34, 2.89]	1.14[0.24, 5.41]	
Total cholesterol (mg/dl)	0.6	0.003	0.2	0.5	0.9	0.2	0.024
200-239 vs. < 200	1.01[0.72, 1.43]	**0.5[0.30, 0.82]**	0.59[0.32, 1.10]	1.07[0.45, 2.51]	1.15[0.47, 2.84]	1.36[0.37, 5.05]	
>=240 vs. < 200	1.21[0.79, 1.86]	1.1[0.67, 1.81]	0.6[0.28, 1.30]	0.78[0.24, 2.49]	0.61[0.14, 2.76]	2.85[0.69, 11.8]	
Unknown vs. < 200	0.78[0.50, 1.22]	1.74[1.02, 2.96]	1.62[0.61, 4.31]	0.48[0.16, 1.44]	0.9[0.30, 2.73]	5.82[0.90, 37.6]	

The results presented as OR[95%CI] along with the global p value. DPP4-I; Dipeptidyl peptidase-4 inhibitors, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

C. Sensitivity analysis: factors influencing prescribing choice after addressing missing data

Similar to the initial-metformin cohort, a sensitivity analysis of multivariable logistic regression was conducted for the initial-SU cohort by repeating the analysis on the imputed cohort to assess the change in effect sizes after accounting for missing data. The results are included in Table 5.25 for regimen type regression and Table 5.26 for antidiabetic classes. There was no significant difference in the extent and direction of the association before and after imputation for both the regimen type and antidiabetic class. The direction of association has changed in some factors, including HTN, CCI score (>=5), and HDL medium level of the regimen type; nevertheless, the results were statistically non-significant in the two situations, before and after imputation (Tables 5.23 and 5.25). In addition, a change in the direction of association was observed with the association of patient sex and total cholesterol level (>=240 mg/dl) with metformin+DPP4-I prescribing, HF with insulin prescribing, and HDL level (>= 60 mg/dl) with TZD prescribing (Tables 5.24 and 5.26). A change in the magnitude and significance of association was identified with baseline BMI of >=30 kg/m^2 with SGLT2-I prescribing (from 2.42[95%CI: 1.04-5.66] TO 1.98[0.89-4.39]).

Regarding the results of complete case analyses of the regimen type and antidiabetic class (Appendix S.5.6), multiple differences were observed in the extent and direction of associations because of the substantial decrease in the sample size. Multiple factors showed a change in the direction of association with the regimen type, including prescriber type, IHD, HTN, HF, PVD, and BMI value of 25-29.9 kg/m^2 (Table 5.23 and Appendix S.5.6). Likewise, a change in the direction of association was identified with multiple factors, such as patient sex with DPP4-I, metformin+DPP4-I, and metformin+ insulin, prescriber type with insulin, IHD with DPP4-I, TZD, and metformin+ insulin, and others (Table 5.24 and Appendix S.5.6).

Table 5.25: Multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type (combination therapy vs. monotherapy) for initial-sulfonylurea cohort after imputation (Cohort-2b: N= 4001)

Studied factor	OR[95%CI]	Overall p-value
Age at prescription		0.045
>= 65 vs. < 65 years	0.62[0.39,0.99]	
Sex		0.583
Female vs. Male	0.89[0.58,1.35]	
Urban-rural		0.105
1	1	
2	1.56[0.97,2.5]	
3	0.66[0.25,1.74]	
4	1.06[0.24,4.64]	
5	1.82[0.39,8.34]	
6	1.54[0.76,3.12]	
7	2.53[1.04,6.16]	
8	2.06[0.67,6.35]	
Scottish index of multiple deprivation-quantile		0.984
1	1	
2	0.91[0.52,1.58]	
2	1.12[0.62,2.01]	
2	1.07[0.57,1.99]	
2	0.9[0.45,1.82]	
Prescriber type		0.604
Non-general practitioner (GP) vs. GP	0.8[0.34,1.88]	
Ischemic heart disease		0.348
Yes vs. No	0.74[0.4,1.38]	
Hypertension		0.849
Yes vs. No	1.05[0.63,1.77]	
Heart failure		0.528
Yes vs. No	0.73[0.28,1.93]	
Stroke		0.841
Yes vs. No	1.1[0.42,2.86]	
Peripheral vascular disease		0.866
Yes vs. No	1.08[0.44,2.63]	
Liver disease		0.026
Yes vs. No	2.37[1.11,5.05]	
Charlson comorbidity index-score		0.349
0	1	
1-2	0.6[0.33,1.08]	
3-4	0.75[0.32,1.77]	
>= 5	1.06[0.39,2.9]	
Antihyperlipidemic drugs		0.714
Yes vs. No	0.92[0.59,1.44]	

Antipsychotic		0.756
Yes vs. No	1.16[0.45,3]	
Thiazide diuretics		0.102
Yes vs. No	0.3[0.07,1.27]	
Beta-blockers		0.768
Yes vs. No	0.92[0.51,1.63]	
Angiotensin inhibitors		0.509
Yes vs. No	0.82[0.46,1.47]	
Calcium channel blocker		0.089
Yes vs. No	0.55[0.28,1.1]	
Number of concomitant medications		0.522
0	1	
1-4	0.57[0.22,1.49]	
>= 5	0.97[0.37,2.53]	
Body mass index (kg/m^2)		0.468
<= 24.9	1	
25-29.9	1.45[0.77,2.75]	
>= 30	1.45[0.72,2.93]	
HbA1c (%)		0.093
< 7	1	
7-9	3.14[0.42,23.55]	
>= 9	6.75[0.92,49.55]	
Estimated glomerular filtration rate (ml/min/1.73m^2)		
< 60 vs. >= 60	2.03[1.18,3.5]	0.010
High density lipoprotein (mg/dl)		0.929
<40 (M) or <50 (F)	1	
40-59 (M) or 50-59 (F)	0.96[0.56,1.65]	
>= 60	0.86[0.4,1.85]	
Triglyceride (mg/dl)		0.523
< 150	1	
150-499	0.81[0.5,1.33]	
>= 500	0.64[0.21,1.92]	
Total cholesterol (mg/dl)		0.710
< 200	1	
200-239	1.15[0.67,1.97]	
>=240	1.25[0.64,2.47]	

The results presented as OR[95%CI] along with the global p value.

Table 5.26: Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to metformin) for initial-sulfonylurea cohort after imputation (Cohort-2b: N=3952)

Studied factors	DPP4-I	Insulin	SGLT2-I	TZD	biguanide+DPP4-I	biguanide+ insulin
Age at prescription	0.064	<0.001	0.015	0.300	0.435	0.059
>= 65 vs. < 65 years	1.27[0.99,1.63]	0.55[0.41,0.73]	0.57[0.36,0.89]	1.39[0.75,2.59]	0.75[0.36,1.55]	0.39[0.15,1.03]
Sex	0.091	0.745	0.011	0.116	0.879	0.829
Female vs. Male	1.22[0.97,1.54]	1.05[0.8,1.37]	1.71[1.13,2.57]	1.59[0.89,2.85]	0.95[0.48,1.89]	1.1[0.47,2.54]
Urban-rural	0.170	0.124	0.038	0.152	<0.001	0.476
2 vs. 1	1.34[1.03,1.73]	1.1[0.81,1.5]	1.24[0.78,1.97]	1.36[0.69,2.69]	2.08[0.9,4.78]	1.8[0.71,4.55]
3 vs. 1	1.08[0.72,1.62]	1.35[0.85,2.14]	0.62[0.26,1.47]	1.93[0.78,4.78]	0.54[0.07,4.33]	0.41[0.05,3.63]
4 vs. 1	0.66[0.27,1.59]	0.9[0.37,2.18]	1.21[0.39,3.72]	2.57[0.64,10.27]	2.02[0.24,17.16]	0.01[0, inf]
5 vs. 1	0.37[0.11,1.33]	0.9[0.26,3.14]	0.99[0.2,4.83]	2.67[0.31,23.01]	7.03[1.29,38.5]	0.01[0, inf]
6 vs. 1	1.19[0.79,1.79]	1.72[1.09,2.72]	1.08[0.53,2.19]	2.35[0.96,5.74]	5.64[2.05,15.48]	0.94[0.18,4.92]
7 vs. 1	1.22[0.67,2.23]	1.8[0.94,3.44]	1.01[0.29,3.51]	0.67[0.08,5.64]	5.28[1.29,21.72]	2.93[0.52,16.54]
8 vs. 1	1.25[0.62,2.51]	1.81[0.8,4.13]	5.07[2,12.85]	0.9[0.11,7.57]	2.39[0.27,21.54]	4.42[0.7,28.14]
Scottish index of multiple deprivation-quantile	0.858	0.607	0.602	0.345	0.132	0.683
2 vs. 1	1[0.73,1.36]	1.26[0.89,1.78]	1.5[0.89,2.52]	1.97[0.91,4.27]	0.6[0.26,1.42]	0.74[0.2,2.77]
3 vs. 1	1.1[0.78,1.55]	1[0.66,1.51]	1.07[0.57,2.02]	0.94[0.35,2.51]	0.56[0.22,1.44]	1.56[0.48,5.06]
4 vs. 1	1.18[0.84,1.66]	1.03[0.68,1.57]	0.76[0.38,1.52]	1.27[0.49,3.3]	0.62[0.24,1.63]	1.82[0.54,6.14]
5 vs. 1	0.99[0.68,1.42]	1.05[0.67,1.63]	1.23[0.63,2.37]	1.8[0.73,4.41]	0.24[0.05,1.1]	1.87[0.5,7.05]
Prescriber type	0.042	0.316	0.011	0.782	0.380	0.533
Non-general practitioner (GP) vs. GP	1.55[1.02,2.35]	0.72[0.37,1.37]	2.14[1.19,3.85]	0.84[0.25,2.87]	0.51[0.12,2.28]	1.66[0.33,8.28]
Ischemic heart disease	0.974	0.355	0.716	0.763	0.242	0.282
Yes vs. No	1[0.74,1.34]	0.85[0.6,1.2]	0.89[0.47,1.68]	0.89[0.41,1.92]	0.54[0.19,1.52]	0.46[0.11,1.88]
Hypertension	0.313	0.048	0.980	0.084	0.363	0.159

Yes vs. No	1.15[0.88,1.49]	1.37[1,1.87]	1.01[0.59,1.71]	1.74[0.93,3.26]	0.65[0.26,1.64]	1.98[0.77,5.12]
Heart failure	0.804	0.617	0.131	0.518	0.138	0.289
Yes vs. No	0.94[0.6,1.48]	1.12[0.71,1.78]	2.05[0.81,5.19]	1.45[0.47,4.48]	2.73[0.72,10.3]	0.29[0.03,2.85]
Stroke	0.621	0.294	0.570	0.877	0.619	0.987
Yes vs. No	1.13[0.7,1.83]	1.33[0.78,2.24]	1.33[0.49,3.62]	0[0, inf]	1.47[0.32,6.64]	0.98[0.11,8.62]
Peripheral vascular disease	0.810	0.193	0.600	0.840	0.221	0.870
Yes vs. No	0.95[0.6,1.5]	1.36[0.86,2.15]	0.72[0.21,2.44]	1.12[0.37,3.44]	2.06[0.65,6.54]	0[0, inf]
Liver disease	0.715	0.347	0.016	0.665	0.047	0.151
Yes vs. No	0.91[0.54,1.53]	1.25[0.79,1.97]	2.61[1.2,5.68]	1.34[0.35,5.08]	3.73[1.02,13.67]	2.61[0.7,9.71]
Charlson comorbidity index score	0.002	<0.001	>0.9	0.711	0.222	0.288
1-2 vs. 0	1.29[0.97,1.71]	2.16[1.54,3.05]	1.03[0.59,1.79]	1.39[0.71,2.71]	0.45[0.16,1.25]	1.04[0.32,3.4]
3-4 vs. 0	1.41[0.89,2.23]	3.87[2.43,6.18]	0.92[0.36,2.3]	0.77[0.22,2.65]	0.44[0.1,1.94]	3.68[0.89,15.18]
>= 5 vs. 0	2.02[1.15,3.55]	4.33[2.54,7.38]	0[0, inf]	0.49[0.05,4.34]	0.44[0.04,4.34]	2.09[0.37,12]
Antihyperlipidemic drugs	0.571	<0.001	0.006	0.147	0.820	0.103
Yes vs. No	0.93[0.71,1.21]	0.47[0.35,0.63]	0.55[0.35,0.84]	1.69[0.83,3.44]	1.09[0.52,2.28]	0.48[0.2,1.16]
Antipsychotic	0.757	0.380	0.320	0.621	0.295	0.334
Yes vs. No	0.91[0.49,1.69]	1.33[0.71,2.49]	0.48[0.11,2.05]	0.6[0.08,4.62]	1.97[0.55,6.99]	2.2[0.44,10.85]
Thiazide diuretics	0.171	0.022	0.332	0.496	0.849	0.886
Yes vs. No	1.39[0.87,2.21]	0.35[0.15,0.86]	1.54[0.64,3.69]	0.64[0.17,2.33]	0.86[0.19,4]	0[0, inf]
Beta blocker	0.005	0.846	0.275	0.383	0.683	0.501
Yes vs. No	1.59[1.15,2.2]	1.04[0.72,1.49]	1.43[0.75,2.7]	0.69[0.29,1.6]	1.21[0.48,3.03]	1.47[0.48,4.48]
Angiotensin inhibitors	0.468	0.159	0.085	0.948	0.754	0.691
Yes vs. No	1.13[0.81,1.59]	0.74[0.49,1.12]	1.62[0.94,2.79]	1.02[0.49,2.14]	0.86[0.34,2.18]	0.77[0.22,2.76]
Calcium channel blocker	0.136	0.189	0.403	0.495	0.290	0.616
Yes vs. No	1.29[0.92,1.81]	0.76[0.51,1.14]	1.3[0.7,2.42]	0.75[0.33,1.72]	0.53[0.17,1.71]	0.7[0.17,2.84]

Number of concomitant medications	0.529	0.017	0.567	> 0.9	0.407	0.522
1-4 vs. 0	1.4[0.58,3.37]	1.73[0.58,5.15]	1.73[0.57,5.2]	283.4[0, inf]	0.41[0.1,1.65]	0.45[0.08,2.7]
>= 5 vs. 0	1.53[0.63,3.7]	4.24[1.45,12.37]	1.36[0.44,4.2]	248.13[0, inf]	0.68[0.16,2.79]	0.8[0.14,4.7]
Body mass index (kg/m^2)	0.096	<0.001	0.182	0.928	0.689	0.510
25-29.9 vs. <=24.9	0.68[0.5,0.93]	0.35[0.24,0.53]	1.45[0.62,3.39]	1.1[0.47,2.6]	0.68[0.23,1.99]	1.76[0.42,7.38]
>= 30 vs. <=24.9	0.76[0.54,1.08]	0.28[0.17,0.44]	1.98[0.89,4.39]	0.9[0.41,1.98]	0.9[0.33,2.44]	1.88[0.48,7.39]
HbA1c (%)	0.124	0.203	0.311	> 0.9	0.705	> 0.9
7-9 vs. < 7	1.59[0.84,2.99]	0.98[0.49,1.99]	1.75[0.52,5.93]	612.27[0, inf]	1.36[0.18,10.37]	81.56[0, inf]
>=9 vs. < 7	1.6[0.85,3]	2.07[1.04,4.1]	2.19[0.66,7.34]	1026.91[0, inf]	2.19[0.29,16.27]	671.63[0, inf]
Estimated glomerular filtration rate (ml/min/1.73m^2)	<0.001	<0.001	0.424	<0.001	0.027	0.035
< 60 vs. >= 60	3.71[2.85,4.85]	4.21[3.03,5.84]	0.75[0.36,1.53]	3.46[1.84,6.49]	2.74[1.12,6.68]	3.26[1.09,9.73]
High density lipoprotein (mg/dl)	0.888	0.680	0.609	0.892	0.698	0.475
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.95[0.71,1.27]	1.02[0.69,1.49]	1.19[0.75,1.89]	0.84[0.42,1.67]	1.02[0.45,2.29]	0.53[0.16,1.74]
>= 60 vs. <40 (M) or <50 (F)	0.97[0.62,1.54]	1.25[0.8,1.96]	0.75[0.32,1.76]	1.02[0.38,2.77]	0.49[0.11,2.21]	1.26[0.28,5.66]
Triglyceride (mg/dl)	0.122	0.645	0.043	0.827	0.812	0.758
150-499 vs. < 150	1.29[0.99,1.67]	0.85[0.63,1.15]	1.26[0.76,2.09]	0.85[0.44,1.64]	0.78[0.27,2.2]	0.6[0.22,1.63]
>= 500 vs. < 150	0.71[0.35,1.45]	1[0.47,2.09]	2.83[1.23,6.53]	1.16[0.27,5.01]	0[0, inf]	1[0.14,7.11]
Total cholesterol (mg/dl)	0.787	0.136	0.371	0.787	0.686	0.482
200-239 vs. < 200	1.01[0.73,1.39]	0.62[0.41,0.92]	0.79[0.46,1.35]	1.17[0.49,2.81]	1.44[0.55,3.76]	1.78[0.56,5.61]
>=240 vs. < 200	1.2[0.8,1.81]	1.02[0.6,1.74]	0.65[0.32,1.31]	0.86[0.28,2.6]	1.36[0.32,5.86]	1.93[0.46,8.05]

The results presented as OR[95%CI]. DPP4-I; Dipeptidyl peptidase-4 inhibitors, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors.

5.4 Discussion

This study aimed to provide a comprehensive description of the change in the prescribing patterns of the first intensifying ADDs after initial metformin or SU and explore a wide variety of factors affecting the prescribing decision of ADDs at the stage of first drug intensification in Scotland between January 2010 and December 2020.

5.4.1 Key findings

Generally, this study showed that prescribing ADDs for T2DM management at the first intensification stage is rapidly changing towards using the newer ADDs, particularly DPP4-I and SGLT2-I, over the older ones (SU, TZD, and insulin). It was found that the majority of patients who were started on metformin (N= 45963/46730, 98.4%) or SU (3894/4001, 97.3%) were treated with single additional ADD after at least three months of the initial therapy, while only 1.6% and 2.7% of the initial metformin and SU users were intensified with combination therapy, respectively. While using a combination regimen as a first intensifying therapy showed a statistically significant increment throughout the study period for patients starting on metformin, no significant change was observed among the initial SU users. Of the initial metformin users, SU was the most frequently added ADD (48.3%, N=22197), followed by DPP4-I (28.3%, N= 12986) and SGLT2-I (17.1%, N= 7850). However, the use of SU as the first intensifying therapy has significantly fallen between 2010 (65.4%, N= 408/624) and 2020 (29.8%, N= 1581/5298), whereas the use of DPP4-I and SGLT2-I has significantly increased (Tables 5.6 and 5.7). SGLT2-I replaced SU as the most common first intensifying therapy in 2019 (SGLT2-I vs. SU: 33.6% vs. 31.7%). DPP4-I+SU was the most commonly prescribed combination regimen for patients who added combination therapy to initial metformin (32.5%, N=249/767). Nonetheless, the use of SGLT2-I-based combination regimens, including SGLT2-I+SU and DPP4-I+SGLT2-I as the first intensifying therapy for the initial-metformin users, has significantly risen over the study period. However, a

statistically significant reduction was observed in prescribing DPP4-I+SU and SU+ insulin (Tables 14 and 15).

On the other hand, about three-quarters (75.09%, N= 2924/3894) of the initial SU users who were intensified with monotherapy received metformin as the first intensifying therapy. However, the use of metformin, insulin, and TZD has significantly decreased (Tables 5.16 and 5.17), with only the prescribing trends of SGLT2-I showing a significant increase over the study period (Z= 10.27, p-value < 0.001). The most often prescribed combination regimen for patients starting on SU was metformin+DPP4-I (41.1%), N= 44/107), followed by metformin+ insulin (27.1%, N=29/107). Still, there was no significant change in the prescribing patterns of metformin+DPP4-I and metformin+ insulin over the studied 11 years.

Furthermore, for patients who were started on either metformin or SU, a number of characteristics were shown to be associated with the prescription decision of the regimen type and the antidiabetic class at the stage of first drug intensification. This study demonstrated that there was a choice between the old well-known and the new ADDs, considering multiple demographic, socioeconomic, prescriber, and clinical factors for choosing among the available ADDs for T2DM management. The magnitude and significance of the effects of the individual factor on the prescribing decision varied by the class of ADDs. Additionally, it was observed that the identified factors had more significant associations with the prescribing choice of the first intensifying ADDs among initial-metformin users compared to the initial-SU users. Nevertheless, for both studied cohorts, age, baseline HbA1c, baseline eGFR, and baseline BMI had the most significant impact on the prescribing decision of ADDs, manifested by the number of antidiabetic regimens influenced by each of the studied factors (Section 5.3.3).

5.4.2 Baseline characteristics of the study cohort

The baseline demographic characteristics of the first cohort of this study (initial-metformin users: median age: 59[51-68] years, male: 60.05%) was close to what have been reported by Wilkinson et al. (2018) and Strain et al. (2020), which were

conducted in the UK, where the mean age of patients who used metformin monotherapy as a first-line treatment was 60 and 60.57 years, while male patients accounted for 59.68% and 59.69%, respectively *(Strain et al., 2020, Wilkinson et al., 2018b)*. However, the proportion of male patents in this study was higher than the other studies conducted in the USA *(Montvida et al., 2018, Ackermann et al., 2017),* Germany *(Kostev et al., 2014),* Korea *(Kim et al., 2019a)*, and Globally *(Nicolucci et al., 2019)*. In addition, a higher percentage of elderly patients (>=65 years old) was reported in this study (33.6%) compared to 25.7% in Ackermann study *(Ackermann et al., 2017)*, yet it was lower than the percentage reported by Kim and colleagues (37.6%) *(Kim et al., 2019a)*. The variability in the demographic characteristics across studies could be related to the differences in the features of the utilised data sources, such as using an insurance-based database versus a national database, the characteristics of the study population, including the prevalence of diabetes risk factors across different age groups and sex, as well as the study sample size.

In terms of socioeconomic characteristics, the proportion of initial metformin users who resided in the least and most deprived areas (11.8% and 27.7%, respectively) were higher than the one mentioned in Wilkinson et al. (2018) study (least deprived area: 9.3%, most deprived area: 10.8%). However, both showed a higher percentage of patients living in the most deprived areas compared to those living in the least deprived areas *(Wilkinson et al., 2018b)*. The difference in the proportion of patients living in the least and most deprived areas between this study and Wilkinson et al. (2018) could be related to the variability in the percentage of missing data, in which the deprivation level is almost complete in this study, while a more significant proportion of the deprivation level was missing in the latter study *(Wilkinson et al., 2018b)*. The higher proportion of initial-metformin users who lived in the most deprived areas is likely related to the higher prevalence of T2DM in the more deprived locations since deprivation is strongly linked with several risk factors associated with T2DM, including obesity, smoking, unhealthy diet, and physical inactivity *(Connolly et al., 2000, Jacobs et al., 2019).*

Moreover, of the described baseline clinical characteristics at drug intensification, the median BMI (68.3%, 31898/46730) in this study was greater than 30 kg/m^2, and it was in keeping with previous studies *(Kostev et al., 2014, Montvida et al., 2018, Strain et al., 2020, Wilkinson et al., 2018c)*. Although, the percentage of obese patients at the time of drug intensification in this study (46.9%) is lower than the ones identified in the UK (61%) *(Wilkinson et al., 2018b)* and USA (70%) *(Montvida et al., 2018)*. Contrastingly, a greater percentage of patients with a high baseline HbA1c of >=9% was observed in this study compared to Wilkinson et al. (2018) study (47.1% vs. 27.4%) *(Wilkinson et al., 2018c).* In addition, a high baseline eGFR was identified in this study (median: 95[81-105]), which is higher than the one mentioned in Kostev et al. (2014) and Strain et al. (2020) (mean: 81.1(18.8) and 71.8(14.83), respectively) *(Kostev et al., 2014, Strain et al., 2020)*. Nonetheless, the percentage of patients with a low eGFR of <60 ml/min/1.73m^2 is comparable to what has been reported by Wilkinson and colleagues (6.3% vs. 6.4%) *(Wilkinson et al., 2018c).* Regarding the baseline lipid profile at drug intensification, limited studies have described the baseline lipid profile for patients with T2DM who received metformin as an initial therapy. For instance, a lower baseline HDL level was observed in this study compared to other studies conducted in the UK and USA *(Strain et al., 2020, Montvida et al., 2018)*. On the other hand, the baseline TG was comparable to the value reported by Strain and colleagues, a UK-based study *(Strain et al., 2020)*, but higher than the value reported in the USA study *(Montvida et al., 2018).* Of note, the baseline laboratory values of BMI, HbA1c, eGFR, and lipid profile were measured as median [IQR] in the current study but as mean (SD) in previous studies. All previous differences in the baseline laboratory data across studies are likely related to the variability in the population characteristics across countries, study duration, the quality and completeness level of analysed data, inclusion/exclusion criteria (selection bias), study sample size, the investigated antidiabetic classes, and the representativeness of the utilised data source. For instance, the USA was ranked among the countries with the highest rate of obesity *(Boutari and Mantzoros, 2022)*; thus, this might justify the greater percentage of obese patients observed in

Montvida et al. (2018) compared to this study (70.0% vs. 46.9%). Furthermore, data were collected over different time intervals across studies; the baseline laboratory data in this study was based on data collected between 2010 and 2020, whereas, in Wilkinson et al. (2018), Montvida et al. (2018), and Kostev et al. (2014), data were collected over the periods of 2000-2017, 2005-2016, and 2003-2012, respectively *(Kostev et al., 2014, Montvida et al., 2018, Wilkinson et al., 2018c)*. Additionally, the percentage of missingness in the laboratory variables varied across studies; for instance, 3.1% and 31.7% of HbA1c and BMI data were missing in this study compared to 36.2% and 1.6% missingness in Wilkinson et al. (2018) study *(Wilkinson et al., 2018c)*. While this study investigated all classes of ADDs, Wilkinson and colleagues only examined SU, DPP4-I, and SGLT2-I *(Wilkinson et al., 2018c).*

For the other clinical characteristics, the majority of patients had a zero baseline CCI score (81.6%), and the most commonly prevalent disease was HTN (19.9%), followed by IHD (13.2%). Additionally, about two-thirds (66.1%) of patients were on five or more comedications, with antihyperlipidemic drugs and angiotensin inhibitors representing the most frequently utilised concomitant medications (69.6% and 20.1%, respectively). As discussed in Chapter 4, the highest prevalence of HTN and IHD among patients with T2DM in this study could be related to the fact that HTN and T2DM are commonly present concurrently since the risk of T2DM is higher among hypertensive patients, and both HTN and T2DM are the main risk factors for CVD *(Long and Dagogo-Jack, 2011, Petrie et al., 2018)*. The prevalence of IHD in this study (13.2%) was comparable to the proportion of patients with CVD in the UK and Korea (13.6% and 13.1%, respectively) *(Wilkinson et al., 2018b, Kim et al., 2019a)*; still, it is lower than the prevalence reported in the USA and Germany (21.0% and 28.7%, respectively) *(Kostev et al., 2014, Montvida et al., 2018)*. Likewise, a lower proportion of patients had HTN at drug intensification in this study (19.93%) compared to studies conducted in Korea (51.5%) and Germany (81.1%) *(Kim et al., 2019a, Kostev et al., 2014)*. The prevalence of HF in this study (3.2%) is close to the one reported by Kim and colleagues (3.4%) *(Kim et al., 2019a)*, yet it is significantly lower than the prevalence of HF in a study conducted in Germany (13.1%) *(Kostev et al., 2014),* and it

is higher than the one reported in the UK (1.33%) *(Wilkinson et al., 2018c).* Lastly, a lower percentage of angiotensin inhibitors (20.1%) was found in this study versus other studies conducted in the UK (54.7%) and Germany (65.6%) *(Kostev et al., 2014, Wilkinson et al., 2018c).* Overall, the differences in the baseline comorbid conditions across studies cannot be attributed to a single reason. However, several factors could be implicated, including the methodological differences across studies relevant to the characteristics and representativeness of the utilised data source, the degree of capturing comorbid conditions, study duration, and study sample size. Furthermore, the differences in socioeconomic status, educational level, social stress, smoking prevalence, and alcohol consumption might have contributed to the differences in CVD, including HF and IHD *(Khan et al., 2020)*.

Similar to the change in the prescribing patterns of add-on ADDs to initial SU (cohort-2b), the baseline characteristics of the initial-SU cohort at drug intensification were not described previously; thus, the baseline characteristics reported in this study relevant to the initial SU users were not compared to the previous literature. Nevertheless, compared to the initial-metformin users, the initial SU users had a higher baseline median age at drug intensification (64 [54-73] vs. 59[51-68]), with 47.69% of patients aged >=65 years at drug intensification compared to 33.6% of the initial-metformin users. That could be explained by the previous finding of the first-line study (Table 4.6, Chapter 4) that the age of patients starting on SU was higher than those starting on metformin; hence initial SU users will be intensified at an older age. All other baseline characteristics at drug intensification (Table 5.4: initial-metformin users, Table 5.7: initial-SU users) were consistent with the distribution of the baseline characteristics of patients receiving metformin and those treated with SU as a first-line therapy (Table 4.14, Chapter 4).

5.4.3 Prescribing patterns of first intensifying ADDs for patients starting on metformin or SU

The first cohort of this study (cohort 2-a, initial metformin users) demonstrated similar prescribing patterns of the regimen type and antidiabetic class at the stage of first drug intensification to the one observed with the first-line study (Chapter 4).

First, although only 1.6% of the initial metformin users were intensified with a combination regimen, a statistically significant rise was observed in the use of combination therapy compared to monotherapy over the study period. That observation could be explained by the recommendation of some clinical guidelines to start patients with an HbA1c value that is above the target by >=1.5% on combination therapy *(Lipscombe et al., 2020, American Diabetes Association, 2021)*; however, this recommendation is not clearly stated in SIGN or NICE guidelines *(National Institute of Health and Care Excellence, 2021, Network, 2017)*. That is also likely due to the potential benefits of using a combination regimen in attaining and maintaining the targeted glycaemic control, as well as achieving the benefits of weight loss and cardio/reno-protective effects, especially with the current availability of newer ADDs with positive extra-glycaemic outcomes *(American Diabetes Association, 2021, Levin, 2016, National Institute of Health and Care Excellence, 2021, Singh et al., 2021, The Scottish Intercollegiate Guidelines Network, 2017).* In addition, clinical guidelines recommended incorporating one of the GLP1-RA or SGLT2-I with proven cardiovascular benefits into T2DM management for patients with established CVD or indicators for CVD *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021).* That finding was in line with previous studies conducted in Korea and Taiwan, which reported a significant increase in combination therapy use for T2DM management; however, these studies did not mention at which stage of treatment the prescribing pattern was observed *(Chu et al., 2017, Lee et al., 2021).*

Likewise, the change in the prescribing patterns of antidiabetic monotherapy was to some extent consistent with the findings of the first-line study (Chapter 4), in which the use of older ADDs (SU, insulin, and TZD) as a first intensifying therapy significantly decreased over the study period, while the use of the newer options (DPP4-I and SGLT2-I) increased, with no significant change in the use of GLP1-RA. The previous findings reflect that the newer ADDs, particularly SGLT2-I, have indeed affected the use of the older groups; since the decline in the prescribing of the older ADDs mainly commenced in 2013, the year of starting the use of SGLT2-I in

Scotland. Those also possibly indicate the familiarity of prescribers with the newly available treatment options for patients with T2DM; thus, enabling evidence-based management of T2DM. Besides, the non-inferior efficacy, weight-neutral effects, and low risk of hypoglycaemia of DPP4-I are thought to be responsible for the increasing use of DPP4-I for T2DM management *(Mishriky et al., 2015, Gadsby, 2007).* The decline in SU prescribing might be related to the associated risk of hypoglycaemia and weight gain, and this class showed no reduction in the incidence and progression of diabetes-related complications, including cardiovascular complications *(Azoulay and Suissa, 2017, Douros et al., 2018, Nunes et al., 2017)*. Likewise, the improved awareness of TZD-related side effects, such as weight gain, fracture, and the cardiovascular risk linked with rosiglitazone, might discourage prescribers from prescribing TZD despite its effectiveness *(Lipscombe et al., 2007, Loke et al., 2011, Rizos et al., 2009)*. All aforementioned drug characteristics were published before the start of this study (2010), suggesting a possible linkage between these characteristics and the observed change in the prescribing patterns of ADDs. The same reasons could explain the significant increment in the use of SGLT2-I-based combination regimens (SGLT2-I+SU and DPP4-I+SGLT2-I) and the reduction in prescribing DPP4-I+SU and SU+ insulin regimens. The non-significant change in GLP1-RA prescribing as a first intensifying therapy in spite of its favourable effect on body weight and renal/cardiovascular outcomes could be related to the fact that GLP1-RA is recommended as a third or fourth-line agent in the SIGN guideline *(Network, 2017)*, in addition to its high cost and the limitations associated with the use of the injecTable dosage form, since the oral form of GLP1-RA (semaglutide) became only available in Scotland in 2020 *(NHS Scotland, 2020)*.

The identified changes in the prescribing patterns of the first intensifying therapy after initial metformin in this study were in agreement with the findings of multiple UK-based studies, which were conducted over different time intervals *(Curtis et al., 2018, Dennis et al., 2018, Sharma et al., 2016, Wilkinson et al., 2018a)*. These studies showed that SU and TZD prescribing as first-intensifying or second-line therapy decreased over time, while the use of DPP4-I and SGLT2-I markedly increased. For

instance, two UK-based studies, Dennis et al. (2019) and Wilkinson et al. (2018), documented that SU prescribing fell from 53% in 2010 to 29% in 2017, and declined from 63.04% to 30.01% over a similar time interval, respectively *(Sharma et al., 2016, Wilkinson et al., 2018a)* compared to a reduction in SU prescribing in this study from 65.4% in 2010 to 41.8% in 2017 (29.8% in 2020). That variability might suggest a slower reduction in SU use as first-intensifying therapy in Scotland than in other UK-based studies. In addition, a difference in the overall consumption of DPP4-I was observed in this study compared to Dennis et al. (2019) and Wilkinson et al. (2018) during a similar time interval. The proportional share of DPP4-I in this study (2010: 13.9%, 2017: 33.0%) was lower than the one reported by Dennis et al. (2019) study (2010: 22%, 2017: 41%) and Wilkinson et al. (2018) study (2010: 21.38%, 2017: 42.43%) *(Dennis et al., 2019, Wilkinson et al., 2018a).* On the contrary, the utilisation of SGLT2-I in this study (19.3% in 2017) was comparable to Dennis et al. (17% in 2019) and Wilkinson et al. (21.94%) *(Dennis et al., 2019, Wilkinson et al., 2018a).* Likewise, the utilisation of GLP1-RA in this study was consistent with the other studies conducted in the UK, in which GLP1-RA prescribing as a first intensifying therapy was low across all studies *(Curtis et al., 2018, Dennis et al., 2019, Sharma et al., 2016, Wilkinson et al., 2018a)*. Moreover, this study revealed that SU remained the most frequently prescribed add-on therapy to initial metformin from the start of the study until 2019, when SGLT2-I surpassed SU as the most commonly prescribed first intensifying therapy. However, previous studies conducted in the UK reported that DPP4-I replaced SU as the most common second-line therapy at the end of the study interval *(Curtis et al., 2018, Dennis et al., 2019, Sharma et al., 2016, Wilkinson et al., 2018a)*. That variability could be related to the difference in the study time interval, which lasted for up to 2016 *(Curtis et al., 2018)* or 2017 *(Dennis et al., 2019, Wilkinson et al., 2018a)* in previous studies, while the time interval of this study lasted until December 2020; thus, this study was more likely to capture SGLT2-I prescriptions, which has been introduced into the UK, including Scotland. in 2013.

The results relevant to the change in the prescribing trend were also comparable to international studies conducted in the USA *(Montvida et al., 2018),* Korea *(J. Kim et al.,*

2019), and Canada *(Carney et al., 2022).* However, the results relevant to the consumption (percentage of utilisation) of ADDs are quite variable. For example, the proportional share of SGLT2-I and DPP4-I prescriptions in this study was higher (2016: 13.4% and 31.4%, 2020: 39.6% and 25.8%) than the one reported in the USA (2016: 7% and 20%) and Canada (2016:23.2% and 14.8%, 2020: 20.2% and 8%) *(Carney et al., 2022, Montvida et al., 2018)*. Additionally, DPP4-I was identified as the most frequent second-line ADD according to a study conducted in Korea and a global study that included 38 countries *(Kim et al., 2019a, Nicolucci et al., 2019)*. These studies also reported a lower rate of SGLT2-I use as a first intensifying therapy to initial metformin than the one stated in this study, in which the overall consumption of SGLT2-I between 2014 and 2016 in Kim et al. (2019) and Nicolucci et al. (2019) were 4.6% and 4.3%, respectively *(Kim et al., 2019a, Nicolucci et al., 2019)* compared to 7.9% in this study over a similar time interval (from 2014 to 2016). In contrast, a study conducted in Italy showed that the most frequent addition to an initial metformin was insulin (33.7%), followed by SU (26.6%), DPP4-I (20.7%), and SLGT2-I (10.1%) *(Moreno Juste et al., 2019).*

All previous differences are likely due to the variability in the time interval of data collection, clinical guidelines of each country, the available treatment options, the time of introduction of ADDs into the market, sample size of the study, and the utilised data sources. For instance, the time interval of most previous studies was up to 2017, and only Carney et al. (2020) was comparable to this study which was conducted until 2020 *(Carney et al., 2022)*. In addition, treatment guidelines in the USA and Canada provide more detailed treatment algorithms compared to the NICE and SIGN guidelines (National Institute of Health and Care Excellence, 2021, Network, 2017, Lipscombe et al., 2020, American Diabetes Association, 2021). Compared to the data source of previous studies, the utilised data source in this study covered all patients with T2DM who were registered with a GP in Scotland, providing more representative findings. Similar findings of the trend analysis were reported in other studies which examined prescribing trends without specifying at which stage of

treatment the outcome was observed *(Chu et al., 2017, Christensen et al., 2016, Engler et al., 2020).*

The second cohort of this study (cohort-2b) represents patients who received SU as a first-line therapy and were intensified with one or more ADDs. Interestingly, although patients who received SU as a first-line therapy may represent patients with T2DM who have a metformin contraindication (e.g., renal impairment, cardiac failure, lactic acidosis) or cannot tolerate metformin, about 75% of patients received metformin as add-on therapy to the initial SU. That is probably related to the fact that those patients might have had a relative contraindication to metformin that is resolved afterwards, including acute HF exacerbation that is stabilised, transient elevation in serum creatinine, intravenous administration of contrast agents, acute MI, dehydration, and any conditions that transiently increase the risk of lactic acidosis *(Tahrani et al., 2007)*. The dominant prescription of metformin as add-on therapy to initial SU reflects the concordance of the clinical practice with guidelines recommendations of starting metformin for all patients with T2DM as soon as possible after disease diagnosis and once the contraindication, if present, is resolved. As stated previously, metformin is recommended as a drug of choice because of its multiple positive outcomes, including glycaemic control, weight neutral to weight loss effects, cardiovascular risk and mortality reduction, as well as its low cost and low hypoglycaemic risk *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021)*. Notably, among the studied ADDs, only SGLT2-I addition to the initial SU showed a significant increment over the study period. That is likely due to the previous findings that the addition of SGLT2-I to SU enhances glycaemic control, reduces body weight, as well as improves blood pressure and cardiovascular risk. Furthermore, the risk of hypoglycaemia associated with the addition of SGLT2-I to SU is not significantly increased *(Kashiwagi et al., 2015, Strojek et al., 2011, Van den Noortgate et al., 2015)* and can be attenuated by decreasing the SU dose *(Jiang et al., 2021).*

The prescribing patterns of first intensifying ADDs after initial SU were less frequently examined in the literature since the majority of patients are usually started on metformin, with only a small percentage of newly diagnosed patients with T2DM starting on non-metformin ADDs, primarily SU. Nevertheless, Grimes and colleagues reported a similar result with metformin and DPP4-I identified as the most common and the second most commonly added ADDs to initial SU *(Grimes et al., 2015).* On the other hand, some studies showed that metformin was the most common first intensifying treatment for patients starting on SU; however, insulin was observed as the second most frequently added drug compared to DPP4-I in this study *(Geier et al., 2014, Moreno Juste et al., 2019, Sharma et al., 2016).* The difference in the studied time interval could be the reason behind this variability; for instance, the current study covered more recent years (from 2010 to 2020), whereas Sharma et al. (2016) and Geier et al. (2014) investigated the prescribing patterns for up to 2013 and 2009, respectively. Accordingly, these studies were conducted before the publication of the current update in the clinical guideline and only a few years after the introduction of DPP4-I in Sharma et al. (2016), while before the start of using DPP4-I in Geier et al. (2014) study (Geier et al., 2014, Sharma et al., 2016). Furthermore, according to Moreno and colleagues, none of the patients who were initially treated with SU received SGLT2-I as a first-intensifying therapy *(Moreno Juste et al., 2019).*

5.4.4 Factors influencing the prescribing choice of first intensifying therapy

Several baseline patient characteristics at first drug intensification (demographic, socioeconomic, clinical, and prescriber) were found to be associated with the prescribing choice of the regimen type (combination therapy versus monotherapy) and antidiabetic class (each class vs. SU) after the initial metformin. Of all studied factors, sex (F: M), having HTN, having liver disease, using five or more concomitant medications, and having a low eGFR of < 60 ml/min/1.73m^2 were positively associated with adding combination ADDs over single therapy to initial metformin. On the other hand, older age (>= 65 years vs. < 65 years), using thiazide diuretics or CCB, being overweight or obese, and having a baseline HbA1c of 7-9% had lower

odds of prescribing a combination regimen to initial metformin. The decreasing odds of adding combination therapy over monotherapy for elderly patients (>= 65 years old) to initial metformin could be driven by the preference of a less strict glycaemic goal for elderly patients, especially in the presence of comorbid conditions because of the high risk of hypoglycaemia and associated *(American Diabetes Association, 2020, National Institute of Health and Care Excellence, 2021).*

In addition, the lower likelihood of prescribing a combination regimen for overweight/obese patients is likely due to the fear of patients' non-adherence to combination therapy, especially if the combined drugs are known to exert weight gain. Nevertheless, the weight change effect of the individual antidiabetic class should be taken into account to select the most appropriate combination of drugs for patients with high BMI since prescribing medications with weight loss effect could reflect positively on patient's adherence *(Grandy et al., 2013)*.The lower likelihood of prescribing a combination regimen for patients with higher HbA1c at drug intensification (7-< 9%) compared to patients with HbA1c of < 7% is unexpected. Prescribing a combination regimen is recommended for patients with very high HbA1c value of >= 9%, for those who are away from the glycaemic goal by >=1.5%, or to get the extra-glycaemic benefits of combined drugs such as reducing the cardiovascular risk *(American Diabetes Association, 2021)*.

On the contrary, the greater likelihood of adding combination therapy over monotherapy to initial metformin for patients who had a low baseline eGFR of < 60 or liver disease could be explained by the requirement of lower adjusted doses of medications in case of impaired kidney or liver function; thus, patients might require more than one ADD to achieve the targeted glycaemic goal. In addition, the greater odds of prescribing combination therapy over monotherapy for patients who were using thiazide diuretics could be explained by the negative impact of thiazide diuretics on glucose level and insulin sensitivity, increasing the need to use combination therapy to achieve the desired glycaemic goal *(Zillich et al., 2006)*. Lastly, the positive association between using CCB and receiving a combination regimen

could be related to the potential cardiovascular and renal benefits of CCBs, conditions which are more likely to occur for patients with less controlled diabetes *(Nosadini and Tonolo, 2002)*, and patients receiving a combination therapy are more likely to have more severe disease. Previous studies on factors influencing the prescribing choice of the regimen type as a first intensifying therapy after initial metformin are scarce.

Similar to the first line study (Chapter 4), the magnitude and direction of association of patient characteristics at drug intensification with the prescribing choice of ADDs varied by the antidiabetic class, with patient age at drug intensification and HbA1c level showing a significant impact on the majority of studied antidiabetic regimens. Most of the findings are in agreement with drug features and guideline recommendations, reflecting the use of a patient-centred approach in the selection of ADDs at the stage of first drug intensification. Of the studied demographic factors, it was found that elderly patients (>= 65 years old) had a greater likelihood of adding SU than DPP4-I, GLP1-RA, SGLT2-I, insulin, TZD, DPP4-I+SGLT2-I, SGLT2-I+SU, and SU+ insulin to initial metformin monotherapy compared to younger individuals, of which, GLP1-RA showed the lowest likelihood of prescription with an effect size of 0.23[0.17-0.30]. The greater use of SU over the other regimens for elderly patients could be related to the low cost of SU, the availability of more long-term studies on the safety and effectiveness of SU among elderly patients than the newer antidiabetic classes, and the current availability of short-acting agents (e.g., glipizide) with lower risk of hypoglycaemia *(Bajwa et al., 2014, Kim et al., 2012, Yakaryılmaz and Öztürk, 2017)*. That could make clinicians more confident to choose SU for treating older patients with T2DM. Despite the pleiotropic and multisystem effects of GLP1-RA that have been proven to decrease the incidence and progression of some comorbidities, as well as polypharmacy, use in elderly patients *(Karagiannis et al., 2021)*, this study showed that GLP1-RA was the least prescribed ADDs for elderly patients. That observation could be driven by the barrier of using an injectable drug among elderly patients and its impact on patient adherence since the oral form of GLP1-RA became only available in 2020 in Scotland. In addition,

that could be due to the gastrointestinal side effects (nausea, vomiting, diarrhoea) associated with GLP1-RA, which may restrict its prescription for elderly patients as they are more susceptible to ADRs and more likely to have functional and gastrointestinal problems *(Lavan and Gallagher, 2016, Weiss et al., 2022).*

For patient sex, female patients were significantly (statistically) more likely to be intensified with GLP1-RA or insulin than SU after initial metformin, yet less likely to be treated with DPP4-I or TZD as the first intensifying therapy. The lower initiation of SU compared to GLP1-RA and insulin for female patients could be attributed to the earlier findings that type 2 diabetic male patients responded better to SU, and that female patients were more likely to develop SU-associated CVD *(Li et al., 2014, Dennis et al., 2018)*. GLP1-RA was also reported to have a better cardiovascular outcome compared to SU among female patients than male patients *(De Vries et al., 2020, Karagiannis et al., 2021)*. The greater odds of prescribing insulin for female patients despite the higher risk of insulin-induced hypoglycaemia among women could be linked with the previous statement that female patients showed a lesser response to SU compared to male patients, thus warranting the use of insulin *(Arnetz et al., 2014, Dennis et al., 2018)*. On the other hand, the higher likelihood of developing side effects from TZD (e.g., weight gain, fracture, oedema) among female patients relative to male patients could justify the observed impact of patient sex on the choice of TZD as a first intensifying therapy *(Campesi et al., 2017, Joung et al., 2020).*

In general, it is known that patients with a better socioeconomic status tend to get newer more expensive medications compared to their counterparts *(Lublóy, 2014).* In Scotland, all individuals receive care from the NHS; therefore, it was expected that the socioeconomic status measured by urban/rural location and SIMD scores do not impact the prescribing choice of ADDs in Scotland. Nonetheless, it was found that patients living in more deprived areas were more likely to receive cheaper ADDs (e.g., SU) compared to patients living in less deprived areas. The impact of urban/rural locations was more diverse and complex. The findings of this study

relevant to the association of patient age, sex, and socioeconomic status with the prescribing choice of ADDs are in keeping with other evidence from the UK *(Wilkinson et al., 2018a).* The Wilkinson et al. (2018) study was conducted in the UK and investigated the prescribing decision of only SU, DPP4-I, and SGLT2-I between 2000 and 2017. It reported a greater likelihood of adding SU than DPP4-I or SGLT2-I to initial metformin for elderly patients, as well as a lower likelihood of prescribing DPP4-I than SU for female patients, with no significant difference in the prescription of SGLT2-I versus SU among female and male patients *(Wilkinson et al., 2018a).* Additionally, other studies that were based in the USA and Europe showed a consistent impact of patient age and sex on the prescribing choice of particular ADDs, with advancing age and male sex being associated with increased prescriptions of SU *(Ackermann et al., 2017, Heintjes et al., 2017)*, but associated with decreased GLP1-RA prescription *(Ackermann et al., 2017).* However, these studies presented the results as relative risk and adjusted probabilities compared to OR in this study. Furthermore, in Heintjes et al. (2017), only SU, DPP4-I, and TZD in combination with metformin were examined as second-line therapies, where each regimen was compared to any other second-line regimens not to SU as in this study *(Heintjes et al., 2017)*. In contrast, the results of the current analysis were not in line with the findings of a global study that included 38 countries and showed a non-significant impact of patient sex on the prescribing choice of DPP4-I, GLP1-RA, and insulin. It also identified a greater likelihood of prescribing DPP4-I and SGLT2-I in combination with initial metformin for patients aged 65 to 75 years compared to younger individuals *(Nicolucci et al., 2019)*.

The majority of clinical-related factors had a significant association with the prescribing choice of DPP4-I, insulin, SGLT2-I, and TZD, with a lesser effect on the selection of GLP1-RA. It was found that patients with baseline IHD, PVD, higher CCI score (1-4 and >=5 vs. 0), and those with high total cholesterol (200-239 and >= 240 vs. < 200 mg/dl) or very high TG levels (>=500 vs. < 150 mg/dl) were significantly less likely to be treated with DPP4-I over SU as an additional therapy to initial metformin. On the other hand, patients who were using thiazide diuretics, beta-

blockers, angiotensin inhibitors, and CCB, as well as patients with a baseline HbA1c of 7-9%, low eGFR (< 60 ml/min/1.73m^2), and high BMI (25-29.9 and >=30 vs. < 25 kg/m^2) had greater odds of receiving DPP4-I over SU. Although some studies reported that DPP4-I has a neutral to positive effect on cardiovascular outcomes and exerts a more favourable effect on the lipid profile compared to SU *(Eriksson et al., 2016, Monami et al., 2012),* the results of this study relevant to the prescribing choice of DPP4-I over SU as a first intensifying therapy for patients with IHD, PVD, and abnormal lipid profile were not in line with the previous evidence. That could be explained by the results of other studies showing conflicting results on the cardiovascular outcomes of DPP4-I compared to SU *(Fadini et al., 2018, Kim et al., 2019b)*. On the other hand, the association of baseline eGFR and BMI with the prescribing choice of DPP4-I versus SU was in agreement with the known impact of DPP4-I and SU on the body weight and their safety in a situation of reduced kidney function; for example, DPP4-I is known to have a neutral effect on the body weight compared to the weight gain effect of SU, explaining the greater likelihood of prescribing DPP4-I over SU for overweight and obese patients *(Wilding, 2018, Apovian et al., 2019).* In addition, DPP4-I is associated with a lower risk of hypoglycaemia compared to SU, a condition which increasingly occurs with reduced kidney function, hence making DPP4-I a safer option for patients with renal impairment, given providing an appropriate dose based on the agent and degree of impairment *(Eriksson et al., 2016).*

Furthermore, greater odds of adding insulin over SU were noted for patients with baseline HTN, liver disease, CCI score of >=5, larger number of concomitant medications (1-4, >=5), a total cholesterol level of >=240 mg/dl, and a low eGFR value of < 60 ml/min/1.73m^2. The presence of co-existing diseases among patients with T2DM might indicate a longer duration of diabetes and a more severe state of the disease, which eventually require the addition of insulin to achieve better and closer glycaemic control, minimising the risk of hypoglycaemia. That could, in part, explain the positive association of insulin prescription with the presence of HTN, liver disease, reduced kidney function, CCI score, and a number of concomitant

medications. Furthermore, the greater likelihood of prescribing insulin than SU for patients with HTN could be related to the previous report that SU may cause HTN or increase the level of blood pressure, while it has been suggested that insulin induces a slight reduction in blood pressure in the long term *(Heise et al., 1998, Sehra and Sehra, 2015)*. In addition, insulin is considered to be safe for patients with hepatic impairment, it is a preferred option for patients with renal impairment, and it has neutral to favourable effects on the lipid profile. In contrast, SU is not recommended in case of liver disease and should be avoided in severe hepatic impairment; it should also be used with caution for patients with renal impairment because of the high risk of severe hypoglycaemia *(Keidan et al., 2002, Papazafiropoulou A, 2019).* The aforementioned evidence could also justify the observation of greater prescription of insulin relative to SU in combination with initial metformin for patients with T2DM who had liver disease, high total cholesterol (>=240mg/dl), and reduced kidney function (eGFR < 60 ml/min/1.73m^2) at the time of first drug intensification. Consistent with the weight gain effect of insulin *(Apovian et al., 2019),* this study showed a significant negative association of insulin prescription with the baseline BMI (25-29.9 and >=30 vs. < 25 kg/m^2). However, surprisingly, this study showed lower prescription of insulin than SU as a first intensifying therapy to initial metformin for patients with baseline HbA1c of 7-9% and >=9% compared to patients with a baseline HbA1c of <7%, given that insulin is the most effective ADDs in terms of HbA1c reduction. That unexpected result could be related to patients' information about their disease and treatment, expectation, and preference, which unfortunately were unavailable for this study.

Regarding the prescribing choice of SGLT2-I over SU to initial metformin users, greater odds of prescribing SGLT2-I were observed for patients with HF and overweight/obese patients. That is likely due to the known beneficial effects of SGLT2-I on reducing body weight, composite cardiovascular mortality, and HF hospitalisation *(Apovian et al., 2019, Cardoso et al., 2021, Wang et al., 2019).* Likewise, it has been reported that SGLT2-I has partial beneficial effects on the lipid profile, manifested by the reduction of TG level and elevation of HDL, LDL, and total

cholesterol *(Xu et al., 2022)*. That, in turn, could partially explain the negative association of SGLT2-I prescription with a total cholesterol level of >=240 mg/dl. In spite of the evidence on the long-term reno-protective effects of SGLT2-I and its benefit in reducing the progression of renal disease, the incidence of acute kidney disease, and albuminuria *(Yau et al., 2022),* this study identified a lower likelihood of adding SGLT2-I than SU to initial metformin for patients with a low eGFR of < 60 ml/min/1.73m^2. The observed association of reduced kidney function with SGLT2-I prescribing is likely driven by the concern related to the risk of volume depletion and increment in serum creatinine associated with SGLT2-I initiation. The limited efficacy of SGLT2-I in achieving glycaemic control in case of reduced renal function, primarily at eGFR level of < 45 ml/min/1.73m^2, and limited available studies examining the safety of SGLT2-I in patients with CKD could also contribute to the previous finding *(Yau et al., 2022).*

Moreover, it was revealed that IHD, HF, stroke, CCI score (1-2, 3-4, and >=5 vs. 0), number of concomitant medications (>=5 vs. 0), and total cholesterol (200-239 and >= 240 vs. < 200) were negatively associated with TZD prescribing relative to SU as a first intensifying therapy for patients starting on metformin. The prescribing of TZD was; however, positively associated with liver disease, BMI (25–29.9 and >= 30 vs. 25), and HbA1c (7-9 and >= 9 vs. 7). Clinical guidelines have issued a caution statement regarding the use of TZD for patients with CHF or who exhibit symptoms of fluid retention *(Azimova et al., 2014, Nesto et al., 2003)*. As a result, they advised against using TZD for individuals with HF classes III–IV *(Azimova et al., 2014, Nesto et al., 2003).* That could partially explain the lower likelihood of TZD prescribing for patients with HF, discouraging clinicians from prescribing TZD for patients with other CVDs, including IHD, which are major risk factors for HF (Vedin et al., 2017). In contrast, the analysis showed that TZD was preferred over SU as an add-on therapy to initial metformin for patients with baseline liver disease. The observation above could be due to the previous evidence of the usefulness of TZD in certain types of liver disease, opposite to the warning of the hypoglycaemic risk associated with the use of SU, especially for patients with a more severe state of hepatic impairment

(Papazafiropoulou A, 2019, Yen et al., 2022). The effectiveness of TZD versus SU in achieving glycaemic control in combination with metformin was comparable. However, this study found greater odds of prescribing TZD over SU as a first intensifying therapy for patients with baseline HbA1c values of 7-9% and >=9% compared to a value of < 7%. Nonetheless, TZD is associated with a lower risk of hypoglycaemia than SU, which might contribute to the abovementioned observation *(Ceriello et al., 2005).*

Clinical factors relevant to the baseline BMI, HbA1c, and renal function were more often studied in the literature compared to the remaining clinical-related factors. Previous studies that reported on the association of clinical factors with antidiabetic prescribing were in partial agreement with the findings of the current analysis. For instance, consistent with this study, other investigations showed that ADDs with weight neutral to weight loss effect (e.g., GLP1-RA, SGLT2-I, DPP4-I) are more prescribed for overweight/obese patients with T2DM than medications known to have weight gain side effect (e.g., SU) *(Ackermann et al., 2017, Nicolucci et al., 2019, Wilkinson et al., 2018c, Heintjes et al., 2017).* In addition, in line with the findings of this investigation, earlier studies revealed a lower prescription of SGLT2-I and a higher prescription of SU for patients with reduced kidney function *(Nicolucci et al., 2019, Wilkinson et al., 2018c)*. However, studies showed conflicting results regarding the influence of other clinical factors on the prescribing decision to choose ADDs. This discrepancy may be due to variations in the studied population's characteristics, the definition and classification of the covariates, study sample size, and the study period.

Overall, the identified associations of the investigated clinical and non-clinical factors with the prescribing choice of ADDs at the stage of first drug intensification for the initial metformin users could potentially suggest a partial consideration and linkage of certain patient characteristics with drug features to choose an ADD for T2DM management. Of all studied factors, the most appropriate considerations were observed with patient age, baseline BMI, liver disease, HF, and partially, renal

function. On the contrary, there seems to have been inadequate consideration of other factors, most importantly baseline CVD, indicated from the observed non-significant impact of CVDs on prescribing ADDs with known cardioprotective effects (GLP1-RA and SGLT2-I, Table 5.20). Moreover, an unexpected association of the baseline HbA1c with prescribing combination regimen and insulin was found in this study; thus, more investigation of the impact of this factor is still required. The results of renal function associated with the prescribing choice of ADDs reflect a partial consideration of this factor, manifested by the greater prescription of insulin. However, no statistically significant increase in the prescription of medications with renal protective effects was observed, in which a significant decrease was identified with SGLT2-I prescription, with no significant change in GLP1-RA prescribing (Table 5.20). Therefore, further investigation is still needed to assess the prescribing choice of ADDs with renal protective effects across different levels of eGFR. In addition, more efforts should be spent to increase SGLT2-I and GLP1-RA prescribing for patients with T2DM, considering their cardiac and renal benefits. It is essential to improve the awareness of clinicians that the initial increase in serum creatinine associated with SGLT2-I is transient, and the long-term renal benefits should be viewed and considered as a positive effect even for patients with reduced kidney function, given the degree of renal impairment and the frequent monitoring of kidney function *(Yau et al., 2022).* Thereby, it is essential to update clinicians' knowledge about the recent evidence regarding the safety and long-term benefits of newer ADDs (SGLT2-I and GLP1-RA), particularly in the presence of CVD or renal disease.

Compared to what has been discussed with the first cohort of this study (cohort 2-a), overall, less factors were associated with the choice of the regimen type and antidiabetic class at the stage of first drug intensification for patients who were started on SU (cohort 2-b). This could be related to the small sample size of patients who were identified as initial SU and the smaller number of patients per studied antidiabetic regimen at the stage of first intensification. Of the studied factors, living in rural areas with UR rank 7 (versus urban areas with UR rank 1), having liver

disease, having a baseline HbA1c of >=9%, and having a low eGFR of < 60 ml/min/1.73m^2 were positively associated with combination therapy prescription (versus monotherapy) as a first-intensifying therapy to initial SU. On the other hand, only advancing age (>= 65 years vs. < 65 years) had a significant negative association with the addition of combination therapy over monotherapy to initial SU. The greater likelihood of prescribing a combination regimen for patients with an HbA1c value of >= 9% is likely due to the need for more ADDs with increasing level of HbA1c to achieve the targeted glycaemic control. The ADA guideline recommended starting combination therapy for patients who have an HbA1c value that is away from the targeted goal by more than 1.5% *(Sherifali et al., 2010, Hirst et al., 2013, American Diabetes Association, 2021)*; however, there is no definite recommendation on the use of combination therapy based on the level of HbA1c in the SIGN and NICE guidelines. The discrepancy in the significance and direction of association of HbA1c with the prescribing choice of the regimen type between the initial metformin and initial SU users could be related to the variability in the sample size and distribution across different categories of HbA1c (< 7%, 7-<9%, and >=9%: initial SU users: 4.05%, 38.52%, and 52.81% vs. initial metformin users: 2.23%, 47.53%, and 47.13%, respectively). The observed associations of patient age, baseline eGFR, and liver disease were similar to the ones identified with the initial metformin users, and all were explained earlier.

For factors influencing the prescribing choice of the antidiabetic class after initial SU, the most significant impact was seen with prescribing DPP4-I, SGLT2-I, and insulin in comparison to metformin. The lower likelihood of adding SGLT2-I, insulin, and metformin+ insulin relative to metformin monotherapy to initial SU for elderly patients (>= 65 years) were similar to the association observed in the first-line study (Chapter 4). As explained previously, the former negative association could be related to the fear of side effects associated with insulin (particularly hypoglycaemia) and newer ADDs, as well as the adherence barriers associated with injectable medications, in addition to patients' preference and knowledge information about their disease and treatment *(Khunti and Millar-Jones, 2017, Lublóy,*

2014, Yakaryılmaz and Öztürk, 2017). Although SGLT2-I has a similar safety and effectiveness profile among men and women *(Rådholm et al., 2020)*, this study showed a greater likelihood of adding SGLT2-I over metformin to initial SU for female patients compared to male patients. This could be driven by a previous report of a higher incidence of metformin-associated side effects among female patients, which might be attributed to the lower prescription of metformin than SGLT2-I for female patients with T2DM *(Ilias et al., 2022, De Vries et al., 2020).*

The majority of clinical-related factors showed a non-significant influence on the prescribing decision of ADDs as a first intensifying therapy after initial SU, including IHD, HTN, HF, PVD, stroke, CCB, and others. Nevertheless, consistent with the previous findings, it was found that the baseline BMI, HbA1c, and eGFR have been taken into account for making a decision on the prescribing choice of the first intensifying ADDs for patients starting on SU in clinical practice in Scotland. For instance, it was observed that obese patients were significantly more likely to add SGLT2-I over metformin to initial SU, while overweight and obese patients were significantly less likely to be intensified with insulin. The above mentioned observation is mostly explained by the weight change effects of ADDs, in whichSGLT2-I is known to exert weight loss, whereas insulin is associated with weight gain *(Apovian et al., 2019)*. In addition, patients with very high HbA1c (>=9%) had higher odds of adding insulin than metformin for achieving more glycaemic control since insulin is more effective than metformin in reducing HbA1c, and it has been recommended to start insulin for patients with HbA1c value of >=9% *(American Diabetes Association, 2021, Chaudhuri and Dandona, 2011, National Institute of Health and Care Excellence, 2021)*. Likewise, metformin was less likely to be added in combination to initial SU for patients with reduced kidney function, and this could be driven by the higher risk of metformin-induced lactic acidosis in patients with reduced kidney function *(Betônico et al., 2016).*

Lastly, the results of this study relevant to the association of age, sex, HbA1c, BMI, and kidney problems with the selection of first intensifying ADDs for patients who were started on metformin or SU were partially in line with the findings of the

conducted MA (Chapter 2). For example, both showed that older age was significantly associated with higher SU prescription and lower prescribing of SGLT2-I and GLP1-RA, but inconsistent with this study finding, MA showed an overall non-significant result for DPP4-I and insulin. Only GLP1-RA and TZD showed significant associations with patient sex according to the MA, while this study identified significant results with GLP1-RA, TZD, SGLT2-I, DPP4-I, and insulin. Regarding the baseline BMI, the results of MA was comparable to the finding of this study for SU, SGLT2-I, and GLP1-RA. Although that HbA1c in the MA showed only a significant positive association with insulin prescription, this study showed that SU, insulin, and TZD were significantly more likely to be initiated for patients with very high baseline HbA1c value of >=9%.

Similarly, the results of MA showed that patients with kidney problem were more likely to be prescribed DPP4-I and insulin; in addition to that, this study showed a higher prescription of SU and TZD for patients with low baseline eGFR level (< 60 ml/min/1.73m^2). The variability in the findings of this study and MA could be related to the fact that the conducted MA included all studies examined factors influencing prescribing at any stage of treatment; thus, it was not restricted to patients with T2DM who have failed the initial therapy with either metformin or SU as what has been done in this study. It could also be related to the variability in the definition and categorisation of study covariates and the study time interval. Of note, MA was done for only five of the studied factors because of the limited number of studies examining the remaining of the investigated factors in this study; more studies are still required in this area of research.

5.4.5 Strength and limitations

To our knowledge, this study is the first study providing a comprehensive analysis of the prescribing patterns and factors influencing the prescribing choice of ADDs at the stage of first drug intensification in Scotland, not only for patients who started on metformin but also for those starting on SU; the data available on the latter group is scarce even globally. Standardising the initial ADD within each studied

cohort provides a more reliable comparison across different intensifying treatment groups. Moreover, the risk of time-lag bias was reduced by including only the first stage of drug intensification. In addition, the majority of previous studies focused on examining single ADDs prescribing; however, this study provides a substantial summary of the use of combination regimens as well. As mentioned in Chapter 4, section 4.4.4, a key strength of this study is using multiple datasets providing a wide range of high-quality patient-level data, including patient demographic, comorbid conditions, and laboratory data over an 11-year period (2010-2020), and covering all patients with T2DM who were registered with a GP in Scotland, increasing the generalizability of the study findings.

Nevertheless, this study has some limitations similar to those mentioned in the first-line study (Chapter 4, section 4.4.4). For instance, some data relevant to ethnicity, prescriber characteristics, patient opinions, and drug side effects were not available for this study; thus, further studies are required to investigate the prescribing variations that could be driven by factors that were not investigated. Antidiabetic classes which were not frequently prescribed were excluded from the factor analysis because of the complexity of explaining the results, and groups with small sample size mostly produce unreliable results. In addition, despite the substantial data missingness in some included variables, primarily BMI and TG, several approaches were applied to address that, including the LOCF method, multiple imputation, and complete case analysis.

5.4.6 Implications for practice and recommendation

The study findings provide a comprehensive description of the change in the prescribing patterns of ADDs over 11 years, indirectly reflecting the impact of the introduction of newer ADDs on the utilisation of the older classes, providing information to healthcare providers, policymakers, and drug companies. In addition, investigating factors associated with the prescribing decision may reflect the agreement of prescribing decisions with the recent evidence on the safety and extra-glycaemic benefits of ADDs. Through this, the gap in the healthcare process could be highlighted, and then an appropriate action could be implemented to

optimise the process of patient care, where providing an appropriate drug is a crucial part of this process. Improving the process of patient care and providing the most appropriate treatment regimen could eventually result in reducing the progression of the disease and possibly the associated cost, as well as improving patient quality of life by achieving the targeted glycaemic goal with the least side effects of medications.

5.4.7 Conclusion

In conclusion, the prescribing patterns of ADDs for T2DM management are rapidly changing towards using newer agents. The majority of patients who were started on metformin (cohort 2-a) or SU (cohort 2-b) were treated with one additional ADDs after at least three months of the initial therapy. Nevertheless, the use of combination therapy significantly increased over the study period among patients starting on metformin, while no significant change in combination therapy prescribing was identified among the initial SU users. Of the initial metformin users, SU was the most frequently added ADD, followed by DPP4-I and SGLT2-I. On the other hand, metformin was the most commonly added first intensifying therapy to initial SU. Nevertheless, the use of older ADDs has significantly decreased over the study period, while a significant increase was identified in the prescriptions of newer agents for both cohorts (cohort 2-a and cohort 2-b). Interestingly, SGLT2-I has replaced SU as the most common first intensifying therapy to initial metformin since 2019. The results might reflect that newer classes of ADDs do indeed influence the utilisation of the older ones.

Moreover, several factors were identified to be associated with the prescribing choice of the regimen type and antidiabetic class at the stage of first drug intensification, and the results varied by the first-line therapy (metformin versus SU). For both studied cohorts, age, baseline HbA1c, baseline eGFR, and baseline BMI had the most significant impact on the prescribing decision of ADDs, manifested by the number of antidiabetic regimens that had a statistically significant association with the studied factor. Of note, the process of antidiabetic prescribing in clinical

practice was partially consistent with guideline recommendations and the current evidence on the safety and extra-glycaemic benefits of ADDs. For instance, this study showed that the association of cardiovascular and renal disease with the prescribing choice of ADDS was inconsistent with the current evidence and recommendations, manifested by the low utilisation of SGLT2-I and GLP1-RA for patients who had IHD, PVD, HF, low eGFR (< 60 ml/min/1.73m^2) at the time of drug intensification. Since CVD is a major cause of death among patients with T2DM and it is crucial to implement an effective approach to reduce or prevent the progression of the disease, more attention should be given for providing prescribers with continuous educational programs to update their knowledge about the current evidence and guideline recommendations, which in turn would encourage the use of SGLT2-I and GLP1-RA as appropriate and recommended by clinical guidelines. That would positively reflect on the prescribing process and, consequently, clinical outcomes.

6 Chapter 6: General discussion and implication of the findings

6.1 Key findings:

6.1.1 Change in the prescribing patterns of ADDs in Scotland at the stage of drug initiation (2010-2019) and intensification (2010-2020)

It was known from previous utilisation studies conducted in different countries, including the UK, that metformin was the most commonly used first-line therapy for patients newly diagnosed with T2DM, followed by SU *(Montvida et al., 2018, Overbeek et al., 2017, Wilkinson et al., 2018a)*. Likewise, for patients who were started on metformin, SU was the most commonly added ADD as a first intensifying therapy *(Kim et al., 2019a, Montvida et al., 2018, Wilkinson et al., 2018a)*, while metformin was the most frequently added ADD after initial SU *(Geier et al., 2014, Grimes et al., 2015, Moreno Juste et al., 2019)*. Additionally, the use of older antidiabetic groups (SU, TZD, insulin) as both initial and first intensifying therapy decreased over time, and this was accompanied by an increase in the use of newer ADDs (DPP4-I, SGLT2-I, and GLP1-RA), with variability in the selection of particular antidiabetic classes across countries *(Kim et al., 2019a, Montvida et al., 2018, Wilkinson et al., 2018a)*.

However, given that the treatment guideline for T2DM in Scotland (SIGN guideline) has different recommendations compared to the NICE guideline in England *(National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017)*, previous data did not provide information about the utilisation of ADDs as a first-line and subsequent intensifying therapy in Scotland at a national level. Only Wilkinson et al. (2018) showed some data from Scotland *(Wilkinson et al., 2018b),* but this included only a small percent of the population of Scotland since the Clinical Practice Research Datalink (CPRD), which was used in their study, covers around 7% of the UK population and only a few GPs from Scotland are part of the CPRD *(Herrett et al., 2015)*, whereas the Scottish national datasets used in this work cover the entire population of Scotland who were registered with a GP. In addition, little is known globally about the use of the newest antidiabetic class (SGLT2-I) and combination regimens as a first-line and add-on therapy. Besides, most studies

investigating combination regimens did not specify the stage of treatment at which ADDs were prescribed and reported only the overall consumption of combination regimens without studying the prescribing trends over time. Moreover, for prescribing patterns of the first intensifying therapy, some previous studies examined the utilisation of the second-line therapy without determining the initial therapy *(Christensen et al., 2016, Chu et al., 2017, Engler et al., 2020, Ko et al., 2016)*, while others focused only on patients who started on metformin *(Curtis et al., 2018, Dennis et al., 2019, Kim et al., 2019a, Montvida et al., 2018, Sharma et al., 2016, Wilkinson et al., 2018a)* with very few studies investigating the prescribing trends of add-on therapy after initial SU *(Geier et al., 2014, Grimes et al., 2015, Moreno Juste et al., 2019)*.

This project has addressed these gaps by providing comprehensive information on the prescribing trends and drug utilisation of ADDs, including both monotherapy and combination regimens at the stage of both drug initiation and intensification. Despite the fact that the majority of newly diagnosed patients with T2DM are usually started on metformin, it is crucial to study the treatment pathway after the failure of initial non-metformin therapy. Therefore, the first intensification study in this project (Chapter 5) included initial SU users in addition to the initial metformin users since SU was the second most commonly prescribed first-line ADD for drug naïve patients after metformin, as observed in Chapter 4 (metformin: 118737/145909 (81.38%), SU: 10029/145909 (6.87%)).

Chapter 4 showed that the first-line antidiabetic prescribing largely followed SIGN guideline recommendations relevant to the use of metformin as a drug of choice for newly diagnosed patients with T2DM *(The Scottish Intercollegiate Guidelines Network, 2017)*. In this study, metformin was identified as the most commonly used initial therapy for drug naïve patients, followed by SU (Table 4.9, Chapter 4). There was also a change in the prescribing trends of ADDs over time, manifested by a large increase in the prescription of metformin and newer antidiabetic groups (DPP4-I and SGLT2-I) and a significant decline in the use of older ADDs (SU, TZD, and insulin); Table 4.10. This study reported a low utilisation of GLP1-RA as a first-line therapy in Scotland with no significant change in its prescribing pattern over the

study period despite its favourable extra-glycaemic effects comparable to SGLT2-I, and this could be related to the fact that GLP1-RA is assigned as a third or fourth line therapy in the SIGN guideline *(The Scottish Intercollegiate Guidelines Network, 2017).* Furthermore, around 9% of new antidiabetic users were started on combination therapy. Consistent with monotherapy prescriptions, combination regimens, including metformin and SU, were the most commonly prescribed combination regimens for new ADD users (Table 4.15, Chapter 4). Although the prescribing trends of combination regimens, including SGLT2-I or DPP4-I in addition to metformin, had significantly risen over time, the addition of SU, Insulin, and/or TZD has fallen (Table 4.14, Chapter 4). Nevertheless, the most prominent change in the prescription of the first-line ADDs was observed with SGLT2-I, both as a monotherapy and in combination (dual combination with metformin and triple combination with metformin plus SU).

Moreover, as presented in Chapter 5, the initial metformin users who were intensified with monotherapy mostly received SU (48.3%, 22197/45963), followed by DPP4-I (28.3%, 12986/45963) and SGLT2-I (17.1%, 7850/45963), while metformin accounted for around three quarter (75.1%, 2924/3894) of the first intensifying monotherapy added to initial SU, followed by DPP4-I (11.0%, 428/3894) and insulin (8.8%, 342/3894). Of the added combination regimens, DPP4-I-based combination with metformin was the most common combination regimen added to initial SU (41.1%, 44/107). In comparison, DPP4-I with SU shared the highest percentage of combination regimens prescriptions among the initial metformin users (32.5%, 249/767). The prescribing trends of the first intensifying ADDs after initial metformin were found to be similar to those observed in the first-line study (Chapter 4), where a significant rise in the use of SGLT2-I and DPP4-I as monotherapy was observed, yet of the investigated combination regimens, only SGLT2-I based combination (SGLT2-I+DPP4-I, SGLT2-I+SU) showed a significant increment over the study period (Table 5.15, Chapter 5). Notably, in 2019, SGLT2-I surpassed SU as the most common add-on monotherapy to initial metformin (2019: 33.6% vs. 31.7%), and SGLT2-I+SU replaced DPP4-I+SU as the most often used first

intensifying combination therapy for initial-metformin users (2019: 25.5% vs. 23.6%).

On the other hand, only the prescribing patterns of SGLT2-I as add-on therapy to initial SU showed a significant rise over the study period, whereas the addition of metformin, insulin, and TZD significantly decreased. The findings of the prescribing pattern analyses at drug initiation (Chapter 4) and intensification (Chapter 5) indicate that the availability of new antidiabetic classes, particularly SGLT2-I, does indeed influence the utilisation of older ones, including SU, TZD, and insulin in clinical practice in Scotland. Of the new antidiabetic classes with favourable safety and efficacy profiles, SGLT2-I was more utilised than GLP1-RA in clinical practice in Scotland, manifested by the greater and increasing prescription of SGLT2-I compared to GLP1-RA over the entire study period.

6.1.2 Factors associated with the choice of ADDs at drug initiation and stage of first drug intensification

Clinical guidelines have recommended a patient-tailored approach for selecting the optimal ADD for T2DM management. To do so, several factors at different levels (demographic, clinical, socioeconomic, etc.) should be considered while involving patients in deciding the treatment goal and care approach *(American Diabetes Association, 2021, National Institute of Health and Care Excellence, 2021, The Scottish Intercollegiate Guidelines Network, 2017).* However, no clear treatment algorithm around what and how the wide variety of factors should be considered is provided in clinical guidelines, including the SIGN guideline, which creates variability in the degree of factors considered for selecting the optimal ADDs among prescribers. Therefore, it is crucial to explore which factors influence the prescribing decision in clinical practice and to what extent these factors contribute to decision-making.

This thesis first summarised and quantified the evidence from the literature on factors associated with the prescribing choice of ADDs by conducting a SRMA (Chapter 2). The results of the SRMA showed that the magnitude, direction, and significance of the association of the studied factors with the prescribing decisions

varied by the class of ADDs, in which all factors were mapped into four categories: demographic factors, clinical factors, socioeconomic factors, and prescriber-related factors. Of which, age and sex of the demographic factors followed by the baseline HbA1c, BMI, and kidney function of the clinical factors were the most commonly studied in the literature at any stage of treatment (initiation, intensification, or un-specified stage). However, many demographics (ethnicity, educational level), clinical (CVD, microvascular complications, other comorbidities, concomitant medications, etc.), socioeconomic (level of deprivation, working status, etc.), and prescriber (prescriber type or speciality, prescriber age, sex, and duration of experience, etc.) factors were much less frequently reported (Section 2.3.4, Chapter 2).

The pooled estimates of included studies in the MA (Figure 2.3, Chapter 2) revealed that older age was significantly associated with higher odds of receiving SU, yet lower odds of prescribing metformin and newer antidiabetic classes (SGLT2-I and GLP1-RA). In contrast, higher baseline BMI showed opposite significant results, which had a negative association with SU, yet a positive association with metformin, SGLT2-I, and GLP1-RA (Figure 2.4, Chapter 2). Both higher baseline HbA1c and the presence of kidney-related problems were significantly associated with lower metformin prescriptions, but more insulin prescriptions (Figures 2.5 and 2.6, Chapter 2). Additionally, the prescription rate of DPP4-I was found to be positively associated with the presence of kidney disease (Figure 2.6, Chapter 2), yet negatively associated with the baseline HbA1c value (Figure 2.5, Chapter 2). Lastly, female patients were identified to have a greater prescription rate of GLP1-RA, but a lower prescription rate of TZD compared to male patients (Figure 2.2, Chapter 2).

Nevertheless, according to the SRMA, only a few studies investigated the association of each factor with the prescribing choice of the individual antidiabetic class, especially with the newer antidiabetic groups. A variability was also observed across included studies in terms of the stage of treatment, the comparison or reference group, the adjustment for confounders, and the definition or categorisation of the studied variables (Chapter 2). In addition, the SR&MA showed that the majority of studies assessing factors influencing the prescribing choice at

any stage of treatment focused on the use of single ADDs, whereas studies including combination regimens were scarce. Furthermore, similar to the prescribing pattern, some previous studies that examined the predictors of intensifying therapy prescribing have not specified the initial antidiabetic treatment, and this imbalance or heterogeneity in the first-line therapy could potentially affect the reliability and validity of the results relevant to the choice of the second line therapy. Other studies included only patients who were started on metformin to investigate the choice of intensifying therapy, while the prescribing choice of intensifying therapy after initial non-metformin ADD was rarely studied.

Following the results of the SRMA, a retrospective cohort study and regression analyses were conducted using the Scottish national data to examine the association of a wide variety of factors with the prescribing choice of ADDs (monotherapy and combination regimens) among drug naïve patients (Chapter 4) and those who failed the initial therapy, including initial-metformin and initial-SU users (Chapter 5). In line with the findings of the SRMA, the magnitude and significance of the results varied by the class of ADDs at both stages of treatment (initiation and first intensification). Some factors showed a consistent association with the choice of ADDs at both drug initiation and intensification. For instance, patient age at the time of drug prescription was identified as the factor influencing most of the prescribing decisions of ADDs, in which the multivariable regression analysis revealed that older patients (>= 65 years old) had a greater likelihood of receiving SU as first-line therapy and as add-on therapy to initial metformin compared to younger individuals (< 65 years old), yet they were significantly less likely to receive newer antidiabetic classes manifested mainly with GLP1-RA and SGLT2-I (Tables). The results were in line with the findings of the MA (Figure 2.3, Chapter 2) relevant to the association of patient age at the time of drug prescription, as stated earlier. In addition, consistent with the weight change effects of ADDs, metformin was more likely to be prescribed than DPP4-I, insulin, and SU for overweight and obese patients as initial and first intensifying therapy. DPP4-I was also preferred over SU for overweight and obese patients as add-on therapy to

initial metformin. On the contrary, the baseline BMI had a non-significant impact on the use of medications known to cause weight loss (GLP1-RA and SGLT2-I) at the stage of drug initiation. In contrast, overweight and obese patients were significantly more likely to receive GLP1-RA and SGLT2-I over SU as the first intensifying therapy after initial metformin. Obese patients also had greater odds of adding SGLT2-I than metformin to an initial SU. The results relevant to the association of the baseline BMI on the choice of older ADDs (metformin, SU) at drug initiation and intensification (Tables 4.17 and 5.20, chapters 4 and 5) were partially in keeping with the pooled estimate of the MA of BMI data across antidiabetic groups (Figure 2.4, Chapter 2). The results relevant to the newer antidiabetic classes at the stage of first drug intensification (Table 5.20, Chapter 5) were consistent with the findings of the MA (Figure 2.4, Chapter 2); both showed a statistically significant association of the baseline BMI with prescribing newer antidiabetic groups (SGLT2-I, GLP1-RA), yet the results were not statistically significant at drug initiation (Table 4.17, Chapter 4). The variability could be related to the differences in the reference group, severity of the disease, and other methodological differences between this study and those included in the MA.

Furthermore, in accordance with the features of ADDs, a low baseline eGFR (< 60 ml/min/1.73 m^2) was negatively associated with the use of SGLT2-I as a first-line therapy and as an add-on therapy after initial metformin, while positively associated with the use of DPP4-I, insulin, SU, and some combination regimens (e.g., metformin+SU, metformin+TZD, DPP4-I+SU, SU+ insulin, metformin+DPP4-I, metformin+ insulin, and metformin+DPP4-I+SU) at drug initiation and first intensification. Consistent results were observed between the MA of kidney problems (Figure 2.6, section 2.3.4.1) and the data analysis of the baseline eGFR at drug initiation (Table 4.17, Chapter 4) and intensification (Table 5.20, Chapter 5) relevant to the choice of metformin, insulin, and DPP4-I. In accordance with the findings of the MA including HbA1c data (Figure 2.5, Chapter 2), patients with a baseline HbA1c value of >= 9% had greater odds of receiving insulin at drug initiation and first intensification after initial SU. However, they had lower odds of

adding insulin than SU to initial metformin. Although the recent update in clinical guidelines recommended the use of ADDs with cardioprotective effects (SGLT2-I, GLP1-RA) for patients with an established CVD or at a high risk of developing CVD, chapters 4 and 5 showed non-significant associations of the baseline IHD, HF, stroke, and PVD with the selection of SGLT2-I and GLP1-RA as an initial and first intensifying therapy. The results of the SR (Section 2.3.4.2, Chapter 2) also showed that these factors were much less frequently investigated, providing uncertain and heterogenous results. The results of the remaining factors were variable at different stages of treatment. Overall, fewer factors were found to be associated with the choice of antidiabetic class at drug initiation and stage of first intensification for patients who were started on SU, and this could be related to the small number of patients who received SU as initial therapy compared to metformin (chapters 4 and 5).

Lastly, the association of factors with the choice of the regimen type (combination therapy vs. monotherapy) was also investigated. The results varied by the stage of treatment, in which more factors were found to be associated with the choice of the regimen type at the stage of drug initiation compared to intensification (chapters 4 and 5). For example, age, sex, UR areas, baseline CCI score, HbA1c, eGFR, BMI, and lipid profile had a significant association with the choice of regimen type at drug initiation, whereas age, sex, number of concomitant medications, baseline BMI, HbA1c, eGFR, HTN, liver disease, thiazide diuretics, and CCB were significantly associated with the choice of regimen type as a first intensifying therapy after initial metformin. For patients started on SU, only patient age, UR areas, baseline liver disease, HbA1c, and eGFR had a significant association with the regimen type selection at the drug intensification stage.

6.2 Strengths and limitations

One of the main strengths of this project is that the analysed data was obtained from five different datasets containing a wide range of high-quality routinely collected health and health-related data of all patients who were registered with a GP from all Health Boards across Scotland. For instance, the study population was

identified from the SCI-Diabetes database covering over 99.5% of patients with T2DM in Scotland, resulting in a large representative sample of the Scottish diabetic population. In addition, data used in this project covered a long period (from January 2010 to December 2020), including several years after the start of using the newest antidiabetic class (SGLT2-I) in Scotland (2013); thus, a greater proportion of patients using newer antidiabetic classes could be included in this work; hence a more reliable measurement of the potential impact of newer ADDs on the utilisation of the older ones can be attained. Having high-quality data with national coverage of the population of Scotland increases the internal validity or reliability of the study findings and the external validity or generalizability of the results. The linkage of different datasets provided enriched data about patient demographics, clinical conditions, laboratory test results, prescription records, and death, thus providing a comprehensive summary of the prescribing patterns and extensive exploration of the impact of many patient characteristics on the prescribing decision. Furthermore, cohort identification and classification were done based on specific criteria, which were discussed with clinicians to ensure the relevance of the study design with clinical practice. The selection of a 12-month period prior to drug initiation to define new users of ADDs minimises the risk of misclassification of a prevalent user as an incident user.

In addition, the regular constant collection of prescribing data on a monthly basis in Scotland decreases the potential of treatment stage misclassification. A complete case analysis including only cases with complete records into the regression model was also performed as a sensitivity analysis to evaluate the robustness of the regression findings. Furthermore, this project is the first that integrated the results of observational studies assessing the association of multiple factors with prescribing choice of ADDs in all countries by conducting a SRMA to give a better insight toward the prescribing process of ADDs in clinical practice and to identify the gaps in the literature. Moreover, it is the first that comprehensively described the changes in the prescribing patterns and factors influencing the prescribing choice of ADDs for patients with T2DM, at both stages of treatment (initiation and first

intensification), including monotherapy and combination regimens, at a national level in Scotland.

Nevertheless, this project has some limitations that should be taken into account. First, treatment intensification was defined based on the presence of further prescriptions of initial therapy (metformin or SU); thus, there is a possibility of misclassifying intensifying therapy as a switching therapy. However, the definition was used in previous literature and was discussed with a diabetologist and a diabetes specialist pharmacist; therefore, it is unlikely that it has impacted the study findings significantly. Second, less frequently prescribed antidiabetic classes were grouped into 'other' in the prescribing trend analysis, and they were excluded from the factor analysis; thus, no information about factors influencing the prescribing choice of those antidiabetic classes, including alpha-glucosidase inhibitors, meglitinide, and GLP1-RA (for initial-SU users at intensification stage), was provided in this thesis; however, these antidiabetic groups accounted for only very small proportion of patients with T2DM who were treated with ADDs in Scotland. Third, although the level of recording of most variables included in the regression analysis (chapters 4 and 5) was high, resulting in a lower information bias, there is a certain level of missingness in some variables of interest, particularly the baseline BMI and TG. Nevertheless, the missingness was addressed using the LOCF method and multiple imputation.

Furthermore, in the factor analysis, some levels of the studied variables (e.g., SIMD-Q, UR, number of concomitant medications) had a small frequency, especially with antidiabetic classes of small sample size (e.g., GLP1-RA), producing a large effect size and wide confidence intervals; thus, the reliability and accuracy of the results could be potentially influenced. Fourth, it is important to mention that the process of identification and classification of patients into monotherapy and combination therapy users was based on certain rules and assumptions that were set with a diabetologist and a specialised pharmacist, yet the approach could potentially influence the accuracy of the results. Fifth, data on ethnicity, prescriber characteristics other than prescriber type, patient opinion, and experienced side

effects were not available for this study; thus, prescribing variations that could have been driven by these factors were not investigated. Furthermore, the severity state of the disease is an important factor that could influence the prescribing choice of ADDs. Although the time from diagnosis until treatment initiation as a proxy measure for disease severity was not included in the data analysis because of the previous reporting that the date of diabetes diagnosis in the SCI-Diabetes database could be unreliable *(Wild et al., 2016)*, other proxy measures were used, including the baseline HbA1c, comorbid conditions, and renal function. Accordingly, further studies are required to examine the impact of the unmeasured factors on the prescribing decision of ADDs and whether the impact of the currently studied factors would change under the adjustment of the unmeasured ones. This work needs to be followed by qualitative research to determine which factors truly have an impact on the prescribing decision and to explain why and how factors identified in this project are used by prescribers.

6.3 Implications for clinical practice

Findings from this work reflect the familiarity of prescribers with the available options for managing T2DM in clinical practice in Scotland, especially after the introduction of newer antidiabetic classes, how prescribers react to the update in guideline recommendations and the updated evidence of T2DM management, and the utilisation of healthcare resources. In addition, exploring factors that influence the prescribing choice of ADDs in clinical practice could also be used to evaluate the rational use of drugs; thus, an appropriate action could be implemented to optimise the patient care process. For instance, it was observed that there could be a potential low consideration of certain patient conditions, such as cardiovascular and renal diseases, on the use of optimal antidiabetic therapy with cardio and renal protective effects. As a result, more efforts should be spent to assess and improve prescribers' knowledge about the safety and efficacy of newer ADDs to encourage prescribing newer antidiabetic classes when appropriate. Doing that could improve the process of patient care by providing the most appropriate treatment regimens because giving the optimal management for T2DM is pivotal for reducing the

progression of the disease and possibly the associated cost, as well as improving patient quality of life.

6.4 Future research recommendations

As discussed earlier, the findings of this thesis have filled some gaps in the literature relevant to the prescribing patterns and factors associated with the prescribing choice of ADDs at drug initiation and the stage of first intensification. Nevertheless, multiple research questions still need to be answered.

First, increasing the utilisation of newer antidiabetic classes over time could potentially reflect the increasing familiarity of prescribers with the currently available treatment options for T2DM. However, the results of the factor analysis indicated that there seems to have a potential gap in consideration of the recent evidence about the safety and extra-glycaemic benefits, particularly cardioprotective effects, of different antidiabetic classes with the prescribing choice of ADDs. Therefore, further research is required to assess prescriber familiarity and knowledge about the differences in the safety and benefits of older and newer antidiabetic classes, the conditions where newer ADDs are recommended, and their confidence in prescribing new treatments for patients with T2DM. This could be measured quantitively by conducting a cross-sectional study using a pre-structured questionnaire, including questions relevant to the studied topic of interest in addition to the demographic information of prescribers to measure the differences in the knowledge according to prescriber characteristics.

Second, to better understand the identified associations of the studied factors with prescribing choice of ADDs, it is crucial to assess patient and physician preference regarding ADD selection for T2DM management, information which was not available in this thesis. This could be assessed using a discrete choice experiment (DCE), a quantitative method used to assess participant or customer preference for complex multi-attribute products including medications *(Mansfield et al., 2017, Viney et al., 2002).* It is usually performed without directly asking the participants about their preferred options but by asking them to choose an option among multiple

alternative hypothetical scenarios containing a number of attributes related to the benefits and side effects of medications *(Mansfield et al., 2017, Viney et al., 2002)*. This study could be conducted using an online DCE to approach more participants and could include patients with T2DM and prescribers who have experience with prescribing ADDs in Scotland. In addition, patient and prescriber preferences, views, and perceptions can be assessed qualitatively to obtain a deeper understanding of prescribing behaviour; how and why prescribers choose, and patients accept using specific ADDs. Semi-structured interviews could be used for data collection.

Third, understanding factors associated with the prescribing decision is important before conducting outcome research. The renal and cardiovascular benefits of newer antidiabetic classes (SGLT2-I and GLP1-RA) are now the focus of many recent studies since cardiovascular and renal diseases are common complications in T2DM and are associated with morbidity and mortality. Several RCTs showed clinical benefits of SGLT2-i and GLP1-RA compared to placebo in reducing non-fatal MI, non-fatal stroke, HF hospitalization, all-cause mortality, cardiovascular death, and improving renal outcomes *(Marso et al., 2016b, Neal et al., 2017, Zinman et al., 2015).* However, it is challenging for clinicians to infer and apply the results of RCTs into clinical practice because of more diverse patient characteristics in real-world settings compared to RCTs. Therefore, more studies are now being conducted using RWD to build real-world evidence on how the results of cardiovascular outcomes from RCTs can be reflected in clinical practice. Multiple real-world studies such as EMPRISE, OBSERVE-4D, and CVD-REAL were in line with and complemented the evidence from clinical trials *(Birkeland et al., 2017, Ryan et al., 2018)*. Even though limited evidence is available about the renal outcomes of newer ADDs in clinical practice, two recent studies showed that SGLT2-I as a class has renal protective effects at different baseline renal functions compared to the other classes *(Heerspink et al., 2020, Takeuchi et al., 2020)*. In spite of the previous evidence, this work showed that there was a low utilisation of SGLT2-I and GLP1-RA for patients with CVD and renal disease and a non-significant association of the presence of CVD with the choice of SGLT2-I and GLP1-RA in clinical practice; thus, more studies are still

required to support the previous evidence for better guidance of clinical decision making. Previous studies also compared the use of ADDs as monotherapy with a limited focus on the cardiovascular and renal outcomes of combination regimens. Therefore, future research examining the clinical outcomes (cardiovascular and renal events) of the newer ADDs (SGLT2-I, GLP1-RA, TZD) compared to the older ones (metformin, SU, TZD, insulin) as monotherapy and in combination in clinical practice is recommended. This can be answered by conducting a retrospective cohort study using RWD of patients with T2DM who received ADDs in Scotland.

Last, patient adherence to medication is a crucial part of clinical treatment and it is of paramount importance for achieving treatment goals *(Gordon et al., 2018)*. Suboptimal adherence to ADDs was found to be associated with several consequences, including poor glycaemic control *(Gordon et al., 2018, Rwegerera, 2014)*, higher rate of mortality, morbidity, and hospitalization, as well as greater healthcare resources use and costs *(Currie et al., 2012, Egede et al., 2012, DiBonaventura et al., 2014)*. The level of medication adherence varied widely among studies; a SR of 27 studies showed that the prevalence of adherence to ADDs ranged from 38.5 to 93.1% *(Krass et al., 2015)*. Adherence to ADDs is complex and multidimensional and that could be related to multiple factors. These factors are categorized according to the World Health Organisation (WHO) into five categories; healthcare-related factors, social/economic factors, condition-related factors, therapy-related factors, and patient-related factors *(Sabate, 2003)*. It is important to point out that the type of ADD has a significant influence on medication adherence; for instance, being on insulin was associated with a lower adherence compared to the other ADDs and this might be related to the need for injection, fear and pain from needle, and its affordability *(Aminde et al., 2019)*. Among other ADDs, high adherence was observed with DPP4-I monotherapy *(Farr et al., 2014, Gordon et al., 2018, Nishimura et al., 2019)*. On the other hand, for dual therapy, the highest adherence was related to metformin+DPP4-I use *(Gordon et al., 2018, Nishimura et al., 2019)*. However, little is known about the adherence of patients with T2DM with newer ADDs, including SGLT2-I and GLP1-RA, in comparison to the older ones.

Therefore, with the recent recommendations of encouraging the use of newer ADDs, further research assessing patient adherence to the newer antidiabetic classes compared to the older ones is vital as it is fundamental to achieve the desired outcomes.

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8 Appendices

Appendix S.2.1: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	I
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	XVII
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	32
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	32
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	34
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	33
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	33
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	35
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	35
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	35
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	35
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	36-37
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	37
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	37

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	37-44
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	49
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	37-44, 49
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	44-45
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	46, 49
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	46-48
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not relevant
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	49-50
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	49-50
Study characteristics	17	Cite each included study and present its characteristics.	51, 54-63
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	52-53
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured Tables or plots.	54-63,
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	54-63, Appendix S.2.5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	64-81, 95-104
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	82-86
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	83-94
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	86-94
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not Relevant

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	105-118
	23b	Discuss any limitations of the evidence included in the review.	119
	23c	Discuss any limitations of the review processes used.	119
	23d	Discuss implications of the results for practice, policy, and future research.	119
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	32
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	32
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	32
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendix S.2.3

Appendix S.2.2: Systematic review search Strategy

Medline (Ovid)

#	Searches	Results
1	Hypoglycemic Agents/	63688
2	diabetes mellitus/ or diabetes mellitus, type 2/	240539
3	Incretins/	1829
4	Sodium-Glucose Transporter 2 Inhibitors/	1875
5	Dipeptidyl-Peptidase IV Inhibitors/	3736
6	Metformin/	12918
7	Sulfonylurea Compounds/	6144
8	Thiazolidinediones/	11244
9	Insulin/	185565
10	(Type 2 Diabetes Mellitus or Type 2 Diabetes or diabetes mellitus, type 2 or type II diabetes mellitus or Diabetes Mellitus, Adult-Onset or adult-onset diabetes mellitus or Diabetes Mellitus, Non-Insulin-Dependent or Diabetes Mellitus, Type II or Noninsulin-Dependent Diabetes Mellitus or T2DM or NIDDM).ti,ab.	133107
11	(antidiabetic* or antihyperglycemic* or antihyperglycaemic* or antidiabetic drug* or antidiabetic agent* or antihyperglycemic drug* or antihyperglycaemic drug* or antihyperglycemic agent* or antihyperglycaemic agent* or glycemic control drug* or glycaemic control drug* or hypoglycaemic drug* or hypoglycemic drug* or hypoglycemic Agent* or hypoglcaemic agent* or glucose lowering drug* or glucose lowering agent* or type 2 diabetes treatment or Insulin or Metformin or Thiazolidinediones or Dipeptidyl-Peptidase IV Inhibitors or Dipeptidyl-Peptidase 4 Inhibitors or Sodium-Glucose Transporter 2 Inhibitors or Sulfonylurea or GLDs or SU or SGLT2i or DPP4i or TZD).ti,ab.	392565
12	(drug prescri* or prescri* behavio?r or drug utili?ation or practice pattern* or drug selection or treatment choice* or drug choice* or drug initiation or drug addition or intensification or add-on or first intensification or second intensification or third intensification or first line or Drug-naive or initial therapy or drug prescription* or practice patterns, physicians or prescription drugs or choice behavi?r or treatment-decision making or decision making or discrete choice or treatment preference* or "drug use" or "medication use").ti,ab.	321068
13	(factor* influencing or factor* affecting or factor* associated or factor* or patient factor* or prescriber factor* or prescription factor* or social factor* or psychological factor* or patient characteristic* or clinical factor* or predict* or predictor* or determinate or determinant* or determination or facilitate or facilitator* or influence or influencing or indicate or indicator* or barrier* or obstacle or Prescri? indicator* or Patient-care indicators or Diabetes nonspecialist or Diabetes specialist or clinical Indicator*).ti,ab.	6912293
14	Family Practice/ or Practice Patterns, Physicians'/ or Drug Prescriptions/	140893
15	Choice Behavior/ or Decision Making/ or Patient Preference/	127246

16	1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 11	452574
17	2 or 10	286498
18	12 or 14 or 15	534042
19	13 and 16 and 17 and 18	1668
20	limit 19 to (english language and yr="2009 -Current")	**1197**

Embase:

#	Searches	Results
1	"drug use"/ or drug utilization/	131111
2	prescription drug/	9848
3	(drug prescri$ or prescri$ behavio?r or drug utili?ation or practice pattern$1 or drug selection or treatment choice$1 or drug choice$1 or drug initiation or drug addition or intensification or add-on therapy or first intensification or second intensification or third intensification or first line or Drug-naive or initial therapy or drug prescription$1 or practice patterns, physicians or prescription drug$1 or choice behavi?r or treatment-decision making or discrete choice or treatment preference$1 or "drug use" or "medication use").ti,ab.	317682
4	antidiabetic agent/	50247
5	metformin/	61732
6	pioglitazone/	18381
7	incretin/	6237
8	insulin/	355445
9	non insulin dependent diabetes mellitus/	247560
10	(Type 2 Diabetes Mellitus or Type 2 Diabetes or diabetes mellitus, type 2 or type II diabetes mellitus or Diabetes Mellitus, Adult-Onset or adult-onset diabetes mellitus or Diabetes Mellitus, Non-Insulin-Dependent or Diabetes Mellitus, Type II or Noninsulin-Dependent Diabetes Mellitus or T2DM or NIDDM).ti,ab.	205212
11	(antidiabetic$1 or antidiabetic drug$1 or antidiabetic agent$1 or antihyperglycemic drug$1 or antihyperglycaemic drug$1 or antihyperglycemic agent$1 or antihyperglycaemic agent$1 or glycemic control drug$1 or glycaemic control drug$1 or hypoglycaemic drug$1 or hypoglycemic drug$1 or hypoglycemic Agent$1 or hypoglcaemic agent$1 or glucose lowering drug$1 or glucose lowering agent$1 or type 2 diabetes treatment or Insulin or Metformin or Thiazolidinediones or Dipeptidyl-Peptidase IV Inhibitors or Dipeptidyl-Peptidase 4 Inhibitors or Sodium-Glucose Transporter 2 Inhibitors or Sulfonylurea or Glucagon-Like Peptide 1 Receptor Agonists or exenatide or liraglutide or dulaglutide or semaglutide or diabetes Pharmacotherapy or GLDs or GLP1-RA or SU or SGLT2i or DPP4i or TZD).ti,ab.	546583
12	(factor$1 influencing or factor$1 affecting or factor$1 associated or factor$1 or patient factor$1 or prescriber factor$1 or prescription factor$1 or social factor$1 or psychological factor$1 or patient characteristic$1 or clinical factor$1 or predict$ or predictor$1 or determinate or	9040083

	determinant$1 or determination or facilitate or facilitator$1 or influence or influencing or indicate or indicator$1 or barrier$1 or obstacle or Prescri$ indicator$1 or Patient-care indicator$1 or Diabetes nonspecialist or Diabetes specialist or clinical Indicator$1).ti,ab.	
13	patient preference/	17617
14	clinical decision making/ or medical decision making/ or patient decision making/	136032
15	1 or 2 or 3 or 13 or 14	562635
16	9 or 10	288335
17	sulfonylurea/ or sulfonylurea derivative/ or chlorpropamide/ or glibenclamide/ or gliclazide/ or glimepiride/ or glipizide/ or tolbutamide/	65890
18	sodium glucose cotransporter 2 inhibitor/ or oral antidiabetic agent/ or canagliflozin/ or dapagliflozin/ or empagliflozin/ or ertugliflozin/ or ipragliflozin/	27615
19	dipeptidyl peptidase iv inhibitor/ or alogliptin/ or linagliptin/ or saxagliptin/ or sitagliptin/ or vildagliptin/	17799
20	4 or 5 or 6 or 7 or 8 or 11 or 17 or 18 or 19	703805
21	12 and 15 and 16 and 20	2677
22	limit 21 to (english language and yr="2009 -Current")	**2154**

Web of Science:

#	Searches	Results
1	(TS=("Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "diabetes mellitus, type 2" OR "type II diabetes mellitus" OR T2DM)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2009-2020	114,672
2	(TS=(antidiabetic$ OR antihyperglycemic$ OR antihyperglycaemic$ OR "hypoglycaemic drug$" OR "hypoglycemic drug$" OR "hypoglycemic Agent$" OR "hypoglcaemic agent$" OR "glucose lowering drug$" OR "glucose lowering agent$" OR Insulin OR Metformin OR Thiazolidinediones OR "Dipeptidyl-Peptidase IV Inhibitors" OR "Dipeptidyl-Peptidase 4 Inhibitors" OR "Sodium-Glucose Transporter 2 Inhibitors" OR Sulfonylurea OR GLDs OR SU OR SGLT2i OR DPP4i OR TZD OR GLDs)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2009-2020	278,160
3	(TS=("drug prescription" OR "prescri* behavior" OR "prescri* behaviour" OR "drug utilisation" OR "drug utilization" OR "practice pattern$" OR "drug selection" OR "drug initiation" OR "drug addition" OR intensification OR add-on OR first-line OR Drug-naive OR "initial therapy" OR "treatment-decision making")) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2009-2020	117,700

4	(TS=("factor$ influencing" OR "factor$ affecting" OR "factor$ associated" OR "patient factor$" OR "prescriber factor$" OR "prescription factor$" OR "patient characteristic$" OR "clinical factor$" OR predictor$ OR determinant$ OR "clinical Indicator$")) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2009-2020	790,141
5	#4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2009-2020	202

Scopus:

TITLE-ABS-KEY ("drug prescription" OR "drug utilisation" OR "drug utilization" OR "practice pattern" OR "drug selection") AND TITLE-ABS-KEY ("factor$ influencing" OR "factor$ affecting" OR "factor$ associated" OR predictor$ OR determinant$) AND TITLE-ABS-KEY (antidiabetic$ OR antihyperglycemic$ OR antihyperglycaemic$ OR "hypoglycaemic drug$" OR "hypoglycemic drug$" OR "glucose lowering drug$") AND TITLE-ABS-KEY ("Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "diabetes mellitus, type 2" OR "type II diabetes mellitus" OR t2dm) AND (LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011)) AND (LIMIT-TO (LANGUAGE , "English"))

ProQuest:

noft("Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "diabetes mellitus, type 2" OR "type II diabetes mellitus" OR T2DM) AND

noft(antidiabetics OR antihyperglycemics OR antihyperglycaemics OR "hypoglycaemic drugs" OR "hypoglycemic drugs" OR "hypoglycemic Agents" OR "hypoglcaemic agents" OR "glucose lowering drugs" OR "glucose lowering agents" OR Insulin OR Metformin OR Thiazolidinediones OR "Dipeptidyl-Peptidase IV Inhibitors" OR "Dipeptidyl-Peptidase 4 Inhibitors" OR "Sodium-Glucose Transporter 2 Inhibitors" OR Sulfonylurea OR GLDs OR SU OR SGLT2i OR DPP4i OR TZD) AND

noft("drug prescription" OR "prescription behavior" OR "prescribing behavior" OR "prescription behaviour" OR "drug utilisation" OR "drug utilization" OR "practice pattern" OR "drug selection" OR "drug initiation" OR "drug addition" OR intensification OR add-on OR first-line OR Drug-naive OR "initial therapy" OR "practice patterns" OR "treatment-decision making") AND

noft(("factors affecting" OR "factors associated" OR "patient factors" OR "prescriber factors" OR "prescription factors" OR "patient characteristics" OR "clinical factors" OR predictor OR predictors OR determinant OR "factors influencing")) AND la.exact("English").

Appendix S.2.3: Quality assessment Rules

Exposure: receiving antidiabetic drugs. Outcome: Factors influencing the selection

NOS: Cohort studies: Score 0-9

Item	Options in the tool	Star awarded	Star not awarded
Selection (4 points):			
1) Representativeness of the exposed cohort: **The study has to describe the representativeness of cohort and the coverage of the utilized data source**	**a**) truly representative of the average in the community* **b**) somewhat representative of the average in the community* **c**) selected group of users e.g. nurses, volunteers **d**) no description of the derivation of the cohort	Described in the study as representative, Or utilising Population-based database, Or utilising National- diabetes specific registry	Described in the study as non-representative, Or Selected group of users as Insured-based (unless it covers the entire target population), No description about data source and the representativeness of cohort
2) Selection of the Non-Exposed Cohort	**a**) drawn from the same community as the exposed cohort * **b**) drawn from a different source **c**) no description of the non-exposed cohort derivation	If there is comparison group; two or more groups of antidiabetics were compared, then all included groups must be drawn from the same setting/source and over the same time period (give star). If there is no comparison group, then all cohorts must be selected based on uniform inclusion/exclusion criteria (most likely the case; give star)	If there is comparison group, groups of antidiabetics users were not drawn from the same settings/not stated, or over different period
3) Ascertainment of Exposure	**a**) secure record (e.g. surgical records) * **b**) structured interview * **c**) written self-report **d**) no description	Using secure record/ Medical records or pharmacy records	Written self-report/ no description (according to NOS rules)
4) Demonstration That Outcome of Interest Was Not Present at Start of Study	**a**) yes * **b**) no	NA; not applicable since the outcome here is factors so all are present at the start of study; star will be awarded for all studies	
Comparability (2 Points):			

1) Comparability of cohorts on the basis of the design or analysis	**a**) study controls for (select the most important factor) * **b**) study controls for any additional factor * (These criteria could be modified to indicate specific control for a second important factor.)	If study control over the most possible confounders as stated in guidelines (by analysis or exclusion): Age, comorbidities (CVD, CKD), Glycaemic control, BMI, Cost or SES*: if >=3 were controlled then give two stars, if only 1-2 of these were controlled give one star. -For studies stated by physicians controlled over speciality, age, sex, experience **	Not control over the recommended confounders or not state/ not clear which confounders were controlled
Outcome (3 Points):			
1) Assessment of outcome	**a**) independent blind assessment * **b**) record linkage * **c**) self-report **d**) no description	Using record linkage/ health records	Self-report/ no description
2) Was follow-up long enough for outcomes to occur	**a**) yes (select an adequate follow up period for outcome of interest) * **b**) no	NA; not applicable since the outcome here is factors and all are required to be the most recent or at baseline and no follow up is required. Star will be awarded for all studies	
3) Adequacy of follow-up	**a**) complete follow up - all subjects accounted for * **b**) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) * **c**) follow up rate < ____%(select an adequate %) and no description of those lost **d**) no statement	Described missing data and adjusted for missing data.	No statement regarding missing data

Judgment: **Good quality:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. **Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. **Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Adapted NOS: Cross-sectional studies. Score 0-10

Item	Options in the tool	Star awarded	Star not awarded
Selection (5 points):			
1) Representativeness of the sample:	**a**) Truly representative of the average in the target population. * (all subjects or random sampling) **b**) Somewhat representative of the average in the target population. * (non-random sampling) **c**) Selected group of users. **d**) No description of the sampling strategy.	If it was based on random sampling technique	If it was based on non- random sampling technique (as convenient sampling), Selected group of users, or No description of the sampling strategy.
2) Sample size	**a**. Justified and satisfactory (including sample size calculation). * **b**. Not justified.	If the sample size was justified, based on calculation with determination of desired confidence. Adequately powered to detect the difference with desired B=20%, power=80%, alpha=5%	Sample size was not justified
3) Non-respondents	**a**) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory* **b**) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. **c**) No description of the response rate or the characteristics of the responders and the non-responders.	the response rate is satisfactory (>=50%). Or adjusted for low response rate	The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. Or No description of the response rate or the characteristics of the respondents and the non- respondents.
4) Ascertainment of the exposure (risk factor)	**a**) Validated measurement tool. ** b) Non-validated measurement tool, but the tool is available or described* **c**) No description of the measurement tool.	Validated questionnaire or medical records** or non-validated measurement tool, but it is clearly described*	No description of the measurement tool.
Comparability (2 points):			

1) <u>Comparability</u>	**a)** Data/ results adjusted for relevant predictors/risk factors/confounders e.g. age, sex, time since vaccination, etc. ** **b)** Data/results not adjusted for all relevant confounders/risk factors/information not provided.	If study control over the most possible confounders as stated in guidelines (by analysis or exclusion): Age, comorbidities (CVD, CKD), Glycaemic control, BMI, Cost or SES*: if >=3 were controlled then give two stars, if only 2 of these were controlled give one star For studies stated by physicians controlled over speciality, age, sex, experience **	Not control over the recommended confounders or not state which confounders were controlled
Outcome (3 points):			
1) <u>Assessment of outcome</u>	**a)** independent blind assessment** **b)** record linkage** **c)** self-report* **d)** no description	Clinical Record. ** Physician report from medical record. ** Self-report* or physician statement*	no description
2) <u>Statistical test:</u>	If the statistical test used to analyse the data was clearly described and appropriate, and the measurement of the association was presented, including confidence intervals and the probability level*	The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *	The statistical test is not appropriate, not described or incomplete (; as conducting only unadjusted association).

Judgment: "Very good" quality: nine to ten stars. **"Good" quality**: seven to eight stars. **"Satisfactory" quality**: five to six stars. **"Unsatisfactory" quality**: zero to four star

Appendix S.2.4: R syntax of meta-analyses

A- Overall estimate

> full.model <- rma.mv(logOR, Vi, random = list(~ 1 | groupnumb, ~ 1 | study_id), tdist= TRUE, data = Dataset_name, method = 'REML')

To find Anti-log values

> predict (full.model, transf=exp,)

B- Heterogeneity test (overall, between-study, within-study)

> W <- diag(1/Dataset_name$Vi)

> X <- model.matrix(full.model)

> P<- W - W %*% X %*% solve(t(X) %*% W %*% X) %*% t(X) %*% W

> 100 * sum(res$sigma2) / (sum(res$sigma2) + (res$k-res$p)/sum(diag(P))) …. Overall

> 100 * res$sigma2 / (sum(res$sigma2) + (res$k-res$p)/sum(diag(P))) …. level-2 and level-3

C- Model-fitness test:

Level-2:

> model.l2.removed<-rma.mv(logOR, Vi, random = ~ 1 | groupnumb/ study_id, tdist = TRUE, data= Gender, method = "REML", sigma2 = c(NA, 0))

> anova(full.model, model.l2.removed)

Level-3:

> model.l3.removed<-rma.mv(logOR, Vi, random = ~ 1 | groupnumb/ study_id, tdist = TRUE, data = Gender, method = "REML", sigma2 = c(0, NA))

> anova(res, model.l3.removed)

D- Moderator/subgroup analysis:

model.mods<-rma.mv(logOR, Vi, random = ~ 1 | groupnumb/ study_id, tdist = TRUE, data = Dataset_name, method = "REML", mods = ~ variable_name-1)

To find the overall estimate of levels within each variable:

- For antidiabetic groups: Two-level random effect model was utilised

Metformin: > res.metformin2 <- rma (logOR, Vi, subset = (group=="Metformin"), data = dataset_name)

Sulfonylurea: > res.su <- rma (logOR, Vi, subset = (group=="SU"), data = dataset_name)

DPP4-I: > res.DPP4 <- rma (logOR, Vi, subset = (group=="DPP4i"), data = dataset_name)

GLP1-RA: > res.GLP1 <- rma (logOR, Vi, subset = (group=="GLP1-RA"), data = dataset_name)

SGLT2-I: > res.sglt2 <- rma (logOR, Vi, subset = (group=="SGLT2i"), data = dataset_name)

TZD: > res.TZD <- rma (logOR, Vi, subset = (group=="TZD"), data = dataset_name)

Insulin: > res.insulin <- rma (logOR, Vi, subset = (group=="insulin"), data = dataset_name)

- For other examined variables: Three-level meta-analysis was used to measure the overall estimate of each subset

> res <- rma.mv(logOR, Vi, subset = (studied variable name=="subset_id"),random = list(~ 1 | groupnumb, ~ 1 | study_id), tdist= TRUE, data = dataset_name)

E- Publication bias test: In the spirit of Eggers' test; SE of LogOR was used as moderator

test.egger.SE <- rma.mv(logOR,Vi, mod = selogOR, random = list(~ 1 | groupnumb, ~ 1 | study_id), tdist= TRUE, data = Dataset_name, method = 'REML')

F- Outliers and influential cases:

- **Outliers number:**

> Dataset_name$upperci <- Dataset_name $logOR + 1.96 * sqrt(Dataset_name $Vi)

> Dataset_name$lowerci <- Dataset_name $logOR - 1.96 * sqrt(Dataset_name $Vi)

> Dataset_name$outlier <- Dataset_name $upperci < full.model$ci.lb | Dataset_name $lowerci > full.model$ci.ub

> sum(Gender$outlier)

The overall estimate after removing the outliers:

no.outliersmodel <- rma.mv(logOR, Vi, random = list(~ 1 | groupnumb, ~ 1 | study_id), tdist= TRUE, data = dataset_name, method = 'REML')

- **Influential cases: Cook's distance**

X <- cooks.distance(full.model, reestimate = TRUE)

F- Plots:

- **Forest plot: gender was used as an example**

> forest(full.model, annotate = TRUE,addfit = TRUE, slab = paste(Gender$Author, Gender$Year, sep=", "), atransf = exp, xlim = c(-4, 6), cex = 0.9, xlab = "Gender", ylim = c(-2, 113), efac = 0.4, yaxs="i", order = order(Gender$group), rows = c(109:90, 87:76, 73:61, 58:43, 40:31, 28:14, 11:2))

> text(-4, 112, "Author, Year", pos=4)

> text(6, 112, "OR[95%CI]", pos=2)

> res.metformin2 <- rma (logOR, Vi, subset = (group=="Metformin"), data = Gender)

```
> res.su <- rma (logOR, Vi, subset = (group=="SU"), data = Gender)

> res.DPP4 <- rma (logOR, Vi, subset = (group=="DPP4i"), data = Gender)

> res.GLP1 <- rma (logOR, Vi, subset = (group=="GLP1-RA"), data = Gender)

> res.sglt2 <- rma (logOR, Vi, subset = (group=="SGLT2i"), data = Gender)

> res.TZD <- rma (logOR, Vi, subset = (group=="TZD"), data = Gender)

> res.insulin <- rma (logOR, Vi, subset = (group=="insulin"), data = Gender)

> res <-  rma.mv(logOR, Vi, random = list(~ 1 | groupnumb, ~ 1 | study_id), tdist= TRUE, data =
Gender, method = 'REML', mods = ~ group-1)

> text(-4, -1.8, pos=4, cex=0.75, bquote(paste("Test for Subgroup Differences: ",

Q[M], " = ", .(formatC(res$QM, digits=2, format="f")), ", df = ", .(res$p - 1), ", p = ",
.(formatC(res$QMp, digits=2, format="f")))))

> op<- par(cex=0.9, font=4)

> text(-4, c(110, 88, 74, 59, 41, 29, 12), pos=4, c("DPP4i", "GLP1-RA", "insulin", "Metformin",
"SGLT2i", "SU", "TZD"))

> addpoly(res.metformin2, row=42, col = "blue", cex=1, atransf=exp, mlab="")

> addpoly(res.su, row=13, cex=1, col = "blue", atransf=exp, mlab="")

> addpoly(res.sglt2, row=30, cex=1, col = "blue", atransf=exp, mlab="")

> addpoly(res.TZD, row=1, cex=1, col = "blue", atransf=exp, mlab="")

> addpoly(res.DPP4, row=89, cex=1, col = "blue", atransf=exp, mlab="")

> addpoly(res.GLP1, row=75, cex=1, col = "blue", atransf=exp, mlab="")

> addpoly(res.insulin, row=60, cex=1, col = "blue", atransf=exp, mlab="")

> text(-4, 42, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ",
.(formatC(res.metformin2$QE, digits=2, format="f")), ", df = ", .(res.metformin2$k -
res.metformin2$p), ", p = ", .(formatC(res.metformin2$QEp, digits=2, format="f")), "; ", I^2, " = ",
.(formatC(res.metformin2$I2, digits=1, format="f")), "%)")))

> text(-4, 13, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ", .(formatC(res.su$QE,
digits=2, format="f")), ", df = ", .(res.su$k - res.su$p), ", p = ", .(formatC(res.su$QEp, digits=2,
format="f")), "; ", I^2, " = ", .(formatC(res.su$I2, digits=1, format="f")), "%)")))

> text(-4, 30, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ", .(formatC(res.sglt2$QE,
digits=2, format="f")), ", df = ", .(res.sglt2$k - res.sglt2$p), ", p = ", .(formatC(res.sglt2$QEp, digits=2,
format="f")), "; ", I^2, " = ", .(formatC(res.sglt2$I2, digits=1, format="f")), "%)")))

> text(-4, 1, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ", .(formatC(res.TZD$QE,
digits=2, format="f")), ", df = ", .(res.TZD$k - res.TZD$p), ", p = ", .(formatC(res.TZD$QEp, digits=2,
format="f")), "; ", I^2, " = ", .(formatC(res.TZD$I2, digits=1, format="f")), "%)")))
```

> text(-4, 89, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ", .(formatC(res.DPP4$QE, digits=2, format="f")), ", df = ", .(res.DPP4$k - res.DPP4$p), ", p = ", .(formatC(res.DPP4$QEp, digits=2, format="f")), "; ", I^2, " = ", .(formatC(res.DPP4$I2, digits=1, format="f")), "%)")))

> text(-4, 75, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ", .(formatC(res.GLP1$QE, digits=2, format="f")), ", df = ", .(res.GLP1$k - res.GLP1$p), ", p = ", .(formatC(res.GLP1$QEp, digits=2, format="f")), "; ", I^2, " = ", .(formatC(res.GLP1$I2, digits=1, format="f")), "%)")))

> text(-4, 60, pos=4, cex=0.7, bquote(paste("RE Model for Subgroup (Q = ", .(formatC(res.insulin$QE, digits=2, format="f")), ", df = ", .(res.insulin$k - res.insulin$p), ", p = ", .(formatC(res.insulin$QEp, digits=2, format="f")), "; ", I^2, " = ", .(formatC(res.insulin$I2, digits=1, format="f")), "%)")))

- **Funnel plot:**

Funnel (full.model, level=c(90, 95, 99), shade=c("white", "gray55", "gray75"), xlab = "log Odd Ratio")

- **Outliers' distribution as histogram:**

ggplot(data = Gender, aes(x = logOR, colour = outlier, fill = outlier))+

geom_histogram(alpha = .2) +

geom_vline(xintercept = full.model$b[1]) +

theme_bw()

- **Cook's distance values:**

plot(x, type="o", pch=19, xlab="Observed Outcome", ylab="Cook's Distance")

Appendix S.2.5: Quality assessment results

Cohort studies

Author	Selection (4 points)				Comparability (2 points)	Outcome (3 points)			Score/ judgment
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
(Winkelmayer et al. 2010)	*; Cohort is somewhat representative; data were obtained from insurance claims correspond to approximately 90.8% of Austrian population	*; All groups (metformin vs. other OH users) of antidiabetics were drawn from the same source	*; using secure record	*; not applicable as it is not relevant since the outcome here is factors, so all are present at the start of study	*; Multivariable logistic regression was used but they did not state if all of these factors were adjusted: age, sex, SES, hospital stay #, therapeutic classes #, prescriber age, sex, speciality	*; using database record	*; not applicable. not relevant since the outcome is factors and all are required to be the most recent or at baseline; no follow up is required	No statement about missing data and method of dealing with missing data	7/ Good
(Abdelmoneim et al. 2013)	Selected group of users; using insurance database patients with age >=66 years	*; (SU users) drawn from the same community as the exposed cohort (metformin users)	*; using database records	*; NA	**; study controls for age by restricting their cohorts to >=65 years and adjusting in the analysis for sex, comorbidities, and others	*; using database record	*; NA	No statement about missing data	7/ Good

(Brouwer et al. 2012)	Selected group of users (involved in this commercial EH systems)	*; All cohorts exposed (met) and non-exposed (SU, TZD, combination) were derived under the same inclusion and exclusion criteria	*; using database records	*; NA	**; using multinomial regression all of the following confounders were adjusted: age, serum creatinine, HbA1c, BMI, and others	*; using database record	*; NA	No statement about missing data and method of dealing with missing data	7/ Good
(Liu et al. 2017)	*; nationally representative as described; it based on single payer National health insurance	*; All groups of antidiabetics were drawn from the same source	*; using database records	*; NA	**; Controlled by analysis over patient age, the health insurance premium, DCSI, physician's age, sex, specialty, and other	*; using database record	*; NA	*; stated about dealing with missing data	9/Good
(Wang et al. 2013)	selected group of users; only patients who were covered by RAMQ insurance were included	*; all cohort; (metformin) and (non-metformin) were obtained from the same source	*; using database records	*; NA	**; adjusted by analysis over age, cardiovascular, renal disease, and others	*; using database record, Practicality-Conformity questionnaire	*; NA	No description of missing data	7/ Good
(Geier et al. 2014)	Selected group of users only patients enrolled in the DMP-DM2	*; all metformin and SU initiators were derived from the same source	*; pharmacy dispensing records	*; NA	**; Controlled over confounders in the analysis including BMI, age, HbA1c and other	*; using DMP-DM2 records	*; NA	No description of missing data	7/ Good
(Fujihara et al. 2017)	No description about representativeness of the sample	*; All cohorts; BG, DPP4i and SU were derived from the same source	*; electronic medical records	*; NA	**; Adjusted in the analysis over age, BMI, HbA1c, and other	*; electronic medical records	*; NA	*; managed missing data by exclusion	8/ Good
(Desai et al. 2012)	Selected group of users as it included	*; all groups were selected from the	*; pharmacy claims data	*; NA	*; Conducted multivariate logistic	*; pharmacy claims data	*; NA	No description	6/ Good

	only receiving drug benefits	same source based on uniform inclusion/exclusion criteria			regression and controlled over age, SES, and comorbidity but the definition of comorbidity is unclear not specifically include cardiovascular and renal disease			of missing data or the way of dealing with missing data	
(Grimes et al. 2015)	*; somewhat representative as it was based on population-based database free of charge for T2DM patients	*; All Metformin (exposed) and SU (non-exposed) users were derived from the same source	*; Pharmacy claims record	*; NA	*; Adjust in the analysis only for age, sex; no collection for clinical data	*; Pharmacy claims record	*; NA	Not stated about missing data	7/ Good
(Cai et al. 2010)	Special group of patients; only people carrying commercial insurance.	*; All Sitagliptin and non-Sitagliptin users were derived from the same source	*; using claims database records	*; NA	No adjustment over confounders; only unadjusted statistics was conducted	*; using claims database records	*; NA	No description of missing data or the way of dealing with missing data	5/ Poor (as comparability score=0)
(Wilkinson et al. 2018)	*; somewhat representative; databases is broadly representative of the UK population	*; All groups of antidiabetics (SGLT2i, dpp4 I vs. SU users) were drawn from the same source	*; Using secure record	*; NA	**; controlled in the analysis over Age, sex, ethnicity, and SES, glycaemic level, and comorbidities	*; using database record	*; NA	*; described how missing data was managed	9/Good
(Grabner et al. 2015)	selected group of users; as described in the limitations, it was included only	*; canagliflozin and DPP4i users were derived from the same source	*; using medical and pharmacy claims data	*; NA	**; conducted two multivariable logistic regression one including	*; using medical and pharmacy claims data	*; NA	No description of missing data or the	7/ Good

	patients in commercial health plans				microvascular complications, dyslipidaemia, obesity but not include HbA1c and not state if age was included. The second model assessed HbA1C under the control of other factor			way of dealing with missing data	
(Ou et al. 2017)	*; somewhat representative; utilising population-based database, covering 99% of population	*; All cohort of DPP4i users and other antidiabetic drug users were derived from the same source	*; electronic medical records	*; NA	*; Adjusted in the analysis over age and comorbidity	*; electronic medical records	*; NA	Stated about missing data but did not take adequate measure to address them	7/ Good
(Stargardt et al. 2009)	No description on the representativeness of selected sample	*; several countries were included but all exposed and non-exposed groups were derived under the same inclusion and exclusion criteria	*; physician report from clinical records	*; NA	**; Adjusted in the analysis over age, Hba1c, weight, history of macrovascular complication and others	*; physician report from clinical records	*; NA	*; Described the missing values and the way of dealing with missing values	8/ Good
(Zhang et al. 2010)	Selected group: using health insurance database	*; All Sitagliptin and non-Sitagliptin users were derived from the same source	*; electronic medical records	*; NA	**; Adjusted in the analysis for possible confounders including Age, BMI, HbA1c, CRD, CVD-related condition	*; electronic medical records	*; NA	No description of missing data	7/ Good

(Morita et al. 2019)	*Somewhat representative as described in the study despite the sample is convenient but database includes extensive patient specific data from over 100 acute phase hospitals	*All DPP4I and metformin users were selected from the same source, under the same criteria	*Medical administrative records	*; NA	No adjustment over confounders; only unadjusted logistic regression was conducted	*Medical administrative records	*; NA	Stated about missing data but not adjusted over missing data	6/ Poor (as comparability score=0)
(Heintjes. et al. 2017)	*; somewhat representative; based on population-based databases	*; several countries were included but all groups were derived under the same inclusion and exclusion criteria	*; using database records*	*; NA	**; Controlled over the most important factors by analysis as age, comorbidities, HbA1C, BMI	*; using database records*	*; NA	*; stated how missing data was adjusted	9/ Good
(Nicolucci et al. 2019)	Not fully representative globally and for each country for many restrictions as described in the limitations	*; multiple settings were included but all groups were derived from all settings under the same criteria	*; Using Standardized medical report and healthcare records	*; NA	**; Adjusted over multiple factors: Age, BMI, SES, Microvascular and Macrovascular complications, and others	*; Using Standardized medical report and healthcare records	*; NA	*; Described missing data and the method of its adjustment	8/ Good
(Hartmann et al. 2020)	*; somewhat representative; using two diabetes specific registries, covers multiple outpatient clinics	*; all groups were selected from the same source	*; Records of diabetes registry	*; NA	*; conducted multivariate analysis; Models; adjusted for sex, age group, and diabetes duration	*; Records of diabetes registry	*; NA	No description of missing data	7/ Good
(Whyte et al. 2019)	*; Truly representative; based on	*; Antidiabetic groups were not compared to each	*; using database record	*; NA	**; study controlled in the analysis over Age, sex, ethnicity,	*; using database record	*; NA	*; adjusted for missing data	9/ Good

	population databases that are available as free for all residents as described in the study	other, but all groups were selected based on uniform inclusion/exclusion criteria			and SES in the mixed model analysis and in the sensitivity analysis over patient age, sex, Glycaemic control (HbA1c), Comorbidities, etc.				
(Arnold et al. 2018)	Special groups in terms of age, ethnicity and SES as described in this study	*; all groups were selected from the same source	*; using database records	*; NA	**; Adjusted in the analysis over confounders as age, BMI, CAD, CKD, HbA1C and others	*; using database records	*; NA	*; Adjusted for missing data by imputation	8/ Good
(Arnold. et al. 2018)	Special group of patients; patients with T2DM and HF only included	*; all groups were selected from the same source	*; using database records	*; NA	**; adjusted in the analysis over age, CKD, CAD, insurance, and physician specialty, etc	*; using database records	*; NA	Not stated about missing data	7/ Good
(Zaharan et al. 2014)	*; somewhat representative as it only not covered <5% of patients who receives their prescription from different scheme	*; all groups were selected based on uniform inclusion/exclusion criteria	*; Pharmacy claims record	*; NA	*; controlled in the analysis over possible confounders as age, sex, SES (< 3 of pre-stated factors in the decision rules)	*; Pharmacy claims record	*; NA	No description of missing data or method of adjustment	7/ Good
(Zoberi et al. 2017)	not representative to T2DM patients in the USA as database used was limited to an academic medical centre in the Midwest of US	*; Antidiabetic groups were not compared to each other, but all groups were selected based on uniform inclusion/exclusion criteria	*; electronic medical records	*; NA	only unadjusted association was conducted; no control over confounders	*; electronic medical records	*; NA	No description of missing data or ways of dealing with missing data	5/ Poor (as comparability score=0)
(Yu et al. 2017)	No description on the	*; All GLP1-RA and basal insulin users	*; using database	*; NA	**; conducted logistic regression	*; using database	*; NA	Not stated about	7/ Good

	representativeness of studied sample	were obtained from the same source	records		adjusted over age, BMI, HbA1c; not clearly sated	records		missing data	
(Levin et al. 2014)	Special group: (managed care setting) Not representative as described in the study	*; All (3 OHA) and (Insulin, GLP1-RA) were obtained from the same source	*; using healthcare database records	*; NA	Only univariate analysis; no adjustment for possible confounders	*; using healthcare database records	*; NA	Not adjusted missing data	5/ Poor (as comparability score=0)
(Gentile et al. 2018)	*; somewhat representative to the white T2DM patients initiating insulin in Italy as described in the study	*; No comparison group but all cohorts were derived from the same source	*; electronic medical records	*; NA	**; Adjusted in the analysis over age, HbA1C, BMI, kidney function, and others	*; electronic medical records	*; NA	*; stated about missing value and how it was adjusted	9/ Good
(Kostev et al. 2014)	*; somewhat representative according to the description in the reference provided	*; All groups were derived from the same source under the same inclusion/exclusion criteria	*; electronic medical records	*; NA	**; controlled in the analysis over baseline eGFR, age, sex, Charlson Comorbidity Score, and others	*; electronic medical records	*; NA	No description missing data	8/ Good
(Hirsch et al. 2011)	*; somewhat representative; based on Population-based databased	*; All exenatide and non-exenatide users were derived from the same source	*; electronic medical records	*; NA	**; controlled in the analysis including over Age, BMI, HbA1C, Charlson index	*; electronic medical records	*; NA	No adjustment for missing data	8/ Good
(Montvida et al. 2018)	*Generally representative; diabetes prevalence of 7.1% similar to the national diabetes prevalence of 6.7%	*All antidiabetic drug users were obtained from the same data source under the same criteria	*Prescription record	*, NA	Only descriptive analysis; no adjustment over confounders	*Prescription record	*, NA	No description for missing data	6/ Poor (as comparability score=0)
(Katakami et al.	may not be a true	*; all cohort were	*Patient	*, NA	**Adjusted in the	*Patient	*, NA	No	7/Good

2020)	representative due to the limited number of sites and the limited number of patients from each site	derived from the same source	record		analysis over possible confounder as age, HbA1c, renal function, CVD and others	record		description for missing data	
(van den Boom et al. 2020)	*As described in the study; Sampling methods used to select physicians' practices are appropriate for obtaining a representative database	*All insulin and non-insulin users were derived under the same criteria and from the same source	*Patient and prescription records	*, NA	**Adjusted in the analysis for age, sex, practice specialty, health insurance coverage, baseline HbA1c value and comorbidities.	*Patient and prescription records	*, NA	No description for missing data or the way of dealing with missing data	8/Good
Kim et al (Kim et al. 2019)	*; somewhat representative the sample was randomly obtained from National representative data	*; Multiple settings were included but it is controlled in the analysis and all exposed and non-exposed cohorts were derived from all settings	*; using claimed database	*; NA	**; controlled over the confounder in the multivariate model as age, comorbidities (renal and CVD), insurance	*; using claimed database	*; NA	No description of missing data	8/ Good
(Longato et al. 2020)	No description in the study about the generalizability of the database used.	* Both SGLT2-I and GLP1-RA were derived from the same source under the same criteria	*; using claimed database	*; NA	Only descriptive analysis; no adjustment over confounders	*; using claimed database	*; NA	No description of missing data	5/ Poor (as comparability score=0)
(Ackermann et al. 2017)	No description in the study about the generalizability of the database used.	*; all cohort groups were derived from the same source under the same criteria	*; using claimed database	*; NA	**; controlled over the confounder in the multivariate model as age, comorbidities, A1C	*; using claimed database	*; NA	*; stated about missing value and how it was	8/ Good

					insurance, and others			adjusted	
(Korytkowski et al. 2014)	As described in the discussion the small sample size of GLP1-RA made it difficult to draw a conclusion	*; all cohort groups were derived from the same source under the same criteria	*Using electronic medical records	*; NA	Only descriptive analysis; no adjustment over confounders	*Using electronic medical records	*; NA	*; stated about missing value and how it was adjusted	6/ Poor (as comparability score=0)
(Moreno Juste et al. 2019)	As described in the limitation, the generalizability is restricted	*; all cohort groups were derived from the same source under the same criteria	*Using dispensing records	*; NA	Only descriptive analysis; no adjustment over confounders	*Using dispensing records	*; NA	No description of missing data or the way of dealing with missing data	5/ Poor (as comparability score=0)

Cross-sectional studies

Author	Selection (5 points)				Comparability (2 points)	Outcome (3 points)		Score/ judgment
	Representativeness of the exposed cohort	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Adequacy of follow up of cohorts	
(Payk et al. 2015)	*; Somewhat representative as it was based on dataset utilising random probability sampling technique	*; The sample size was not based on calculation but justified and adjusted for sampling error	*; As it was based on survey database so no response rate calculation, but they used sampling weight for survey nonresponse	**; Using database surveys that are subject to quality control	*; Adjusted in the analysis for Age, sex, and other (< 3 of pre-stated factors in the rules)	**; Using database surveys that are subject to quality control	*; The statistical test was appropriate and fully described	9/ Very good
(Saine et al. 2015)	*; somewhat representative as described in the study; analyses have expanded the population by using four different data sources within the USA and UK	*; the sample was based on database	*; As it was based on database so no response rate calculation	**; using database records	**; Controlled over the most important factors by analysis as age, A1C, obesity, comorbidities, and others (>=3 of pre-stated factors in the decision rules)	**; using database records	*; The statistical test was appropriate and fully described	10/ Very good
(Dhanaraj et al. 2013)	No description of sample size representativeness	The sample size was not based on calculation or justified	No description for rate and characteristic of non-respondents	**; based on clearly described tests and tools	No adjustment over confounders	**; based on clearly described tests and tools	*The statistical test is appropriate but incomplete	5/ satisfactory

Appendix S.2.6: The direction and magnitude of association of factors summarised using narrative synthesis

The direction and significance of association of demographic factors with antidiabetic drug's prescription

Number of studies	Ethnicity							Smoking status[a]		Educational level[b]	Diabetes family history
	Asian vs. White	Black vs. White	Mixed vs. White	Other vs. White	Non-White vs. White	Black vs. Other	Non-Hispanic White vs. Hispanic or Black	Current	Former		
Metformin:											
Positive	(Whyte et al. 2019)*	(Whyte et al. 2019)*	(Ackermann et al. 2017)*[c]	(Whyte et al. 2019)*	(Whyte et al. 2019)*,(Ackermann et al. 2017)[d], (Payk et al. 2015) *	-		(Zoberi et al. 2017)	-	-	(Dhanaraj et al. 2013)
Negative	-	-	(Montvida et al. 2018)*		(Ackermann et al. 2017) [d]	(Ackermann et al. 2017)*		(Geier et al. 2014)	(Zoberi et al. 2017)		-
SU:											
Positive	(Whyte et al. 2019)*,(Wilkinson et al. 2018)*	(Whyte et al. 2019)*,(Wilkinson et al. 2018)*, (30)[f]	(Whyte et al. 2019)*,(Wilkinson et al. 2018)[e]	(Whyte et al. 2019)*,(Wilkinson et al. 2018)*[g], (Brouwer et al. 2012)	(Payk et al. 2015)*	(Ackermann et al. 2017)	-	-	(Wilkinson et al. 2018)[m]	-	(Stargardt et al. 2009)
Negative	-	(Brouwer et al. 2012), (30)[f]	(Wilkinson et al. 2018)[e]	-	-	-	(Ackermann et al. 2017)*	(Geier et al. 2014), (Wilkinson et al. 2018)	(Wilkinson et al. 2018)[m]	(Nicolucci et al. 2019)*[n]	(Dhanaraj et al. 2013)*
DPP4-I:											
Positive	(Whyte et al.	(Montvida et al.	(Whyte et al.	(Whyte et al.			(Korytkowski	(Saine et	(Wilkinson	(Nicolucci et	

	2019)*	2018)*[h], (Whyte et al. 2019), (Wilkinson et al. 2018)*	2019), (Wilkinson et al. 2018)	2019)*	-	-	et al. 2014)*	al. 2015)[k]	et al. 2018)	al. 2019)*	-
Negative	(Wilkinson et al. 2018)*	-	-	(Wilkinson et al. 2018)*			-	(Saine et al. 2015)[k], (Wilkinson et al. 2018)	-	-	
TZD:											
Positive		-					(Ackermann et al. 2017)				-
Negative		(Montvida et al. 2018)*					-				(Dhanaraj et al. 2013), (Stargardt et al. 2009)
GLP1-RA:											
Positive	-	(Montvida et al. 2018)*[j]	-	-	(Hirsch et al. 2011)*	-	-	-	-	(Nicolucci et al. 2019)*[n]	
Negative	(Whyte et al. 2019)	(Whyte et al. 2019)*,(Yu et al. 2017)*,(Hirsch et al. 2011)*, (30)*[j]	(Whyte et al. 2019)*	(Whyte et al. 2019)*, (Yu et al. 2017)*, (Hirsch et al. 2011)[a]	-		(Korytkowski et al. 2014)	(Yu et al. 2017)*	(Yu et al. 2017)*	-	
SGLT2-I:											
Positive	-	(Montvida et al. 2018)*[i]	-	-			(Korytkowski et al. 2014)	-	-	(Nicolucci et al. 2019)*	
Negative	(Whyte et al. 2019), (Wilkinson et al. 2018)*	(Whyte et al. 2019)*, (Wilkinson et al. 2018)*, (Montvida et al. 2018)[i]	(Whyte et al. 2019), (Wilkinson et al. 2018)	(Whyte et al. 2019)*, (Wilkinson et al. 2018)			-	(Wilkinson et al. 2018)	(Wilkinson et al. 2018)	-	

Insulin:											
Positive	-	(Yu et al. 2017)*, (Montvida et al. 2018)*[f]	-	(Yu et al. 2017)*	(Zoberi et al. 2017)	-	-	(Zoberi et al. 2017),(Yu et al. 2017)*	(Yu et al. 2017)*	(Nicolucci et al. 2019)[n]	(Dhanaraj et al. 2013)*
Negative	(Whyte et al. 2019)*	(Whyte et al. 2019), (Montvida et al. 2018)*[f]	(Whyte et al. 2019)	(Whyte et al. 2019)	(Korytkowski et al. 2014)*		(Korytkowski et al. 2014)*	-	(Zoberi et al. 2017)*	-	-

*significant association, a; compared to non-smoker, b; No formal education, primary education (1-6 years), or secondary education (7-13 years) versus > 13 years, c; only significant for biguanide vs. SU, d; positive for biguanide vs. TZD, and biguanides vs. combination and negative for biguanide compared to SU, e; positive compared to SGLT2-I and negative compared to DPP4-I, f; positive at initiation stage and negative at first intensification stage, g; only significant compared to DPP4-I, h; only significant at intensification stage, i; positive and significant at intensification stage while negative and non-significant at initiation stage, j; negative at initiation stage and positive at intensification stage, k; positive using THIN database and negative utilising CRPD database, m; positive compared to SGLT2-I and negative compared to DPP4-I, n; non-significant for insulin compared to SU at all levels and GLP1-RA compared to SU at no formal education level.

The direction and significance of association of clinical-related factors with antidiabetic drug prescription

Number of studies	Microvascular complications		Macrovascular complications					Other comorbid conditions		Diabetes duration(g)
	Retinopathy	Neuropathy	CVD[&]	CAD/IHD	Stroke	HF	PVD	Hypertension	Dyslipidaemia	
Metformin:										
Positive	(Abdelmoneim et al. 2013), (Morita et al. 2019)*	(Abdelmoneim et al. 2013), (Morita et al. 2019)	-	(Abdelmoneim et al. 2013)	(Abdelmoneim et al. 2013)	-	-	(Abdelmoneim et al. 2013)*	(Abdelmoneim et al. 2013)*	-
Negative	(Dhanaraj et al. 2013)*, (Zoberi et al. 2017)	(Zoberi et al. 2017), (Dhanaraj et al. 2013)*	(Wang et al. 2013), (Zoberi et al. 2017), (Morita et al. 2019),(Montvida et al. 2018)*,(Katakami et al. 2020)	(Dhanaraj et al. 2013)*	(Zoberi et al. 2017),(Dhanaraj et al. 2013)	(Abdelmoneim et al. 2013)*,(Arnold. et al. 2018)[y]*	(Abdelmoneim et al. 2013)	(Fujihara et al. 2017)*, (Zoberi et al. 2017)	(Zoberi et al. 2017)*	(Geier et al. 2014)*, (Fujihara et al. 2017)*, (Dhanaraj et al. 2013)*
SU:										
Positive	(Wilkinson et al. 2018)[b]	-	(Nicolucci et al. 2019)*[v], (Wilkinson et al. 2018), (Montvida et al. 2018)*,(Katakami et al. 2020) (Kim et al. 2019)	-	-	(Abdelmoneim et al. 2013)*,(Arnold. et al. 2018)[y]* (Kim et al. 2019)	(Abdelmoneim et al. 2013)	(Kim et al. 2019)*, (Fujihara et al. 2017)	-	(Geier et al. 2014)*, (Fujihara et al. 2017)*
Negative	(Wilkinson et al. 2018)c, (Abdelmoneim et al. 2013), (Dhanaraj et al. 2013)*	(Abdelmoneim et al. 2013), (Dhanaraj et al. 2013)*		(Abdelmoneim et al. 2013),(Dhanaraj	(Abdelmoneim et al. 2013),(Dhanaraj		-	(Abdelmoneim et al. 2013)	(Abdelmoneim et al. 2013)*, (Kim et al. 2019)*	(Nicolucci et al. 2019)*[e],(Dhanaraj et al. 2013)*

				et al. 2013)*	et al. 2013)*					
DPP4-I: Positive	(Wilkinson et al. 2018), (Saine et al. 2015)*[a], (Cai et al. 2010)*	(Saine et al. 2015)*d, (Grabner et al. 2015)*	(Saine et al. 2015)[s], (Kim et al. 2019)*,(Zhang et al. 2010), (Morita et al. 2019)*,(Montvida et al. 2018)*[t], (Katakami et al. 2020)	(Ou et al. 2017)*,(Cai et al. 2010)*	(Ou et al. 2017),(Cai et al. 2010)*	(Kim et al. 2019),(Cai et al. 2010)*	(Cai et al. 2010)*,(Saine et al. 2015)[p]	(Saine et al. 2015)*[m], *	(Saine et al. 2015)*,(Zhang et al. 2010)*, (Ou et al. 2017)*	-
Negative	(Grabner et al. 2015)*,(Morita et al. 2019)*	(Cai et al. 2010)*, (Morita et al. 2019)	(Saine et al. 2015)[s], (Montvida et al. 2018)*[t]	-	(Saine et al. 2015)*[r]	(Arnold. et al. 2018)[y]*, (Ou et al. 2017)*[q]	(Saine et al. 2015)[p]	(Saine et al. 2015)*[n], (Zhang et al. 2010), (Grabner et al. 2015)*, (Fujihara et al. 2017) (Ou et al. 2017)*	(Grabner et al. 2015)*	(Fujihara et al. 2017)*
TZD: Positive	(Dhanaraj et al. 2013)	-	(Montvida et al. 2018)[t]	(Arnold et al. 2018)*	-	(Kim et al. 2019)		-	-	-
Negative	-	(Dhanaraj et al. 2013)	(Kim et al. 2019)*,(Montvida et al. 2018)[h],(Katakami et al. 2020) (Stargardt et al.	(Dhanaraj et al. 2013)*	(Dhanaraj et al. 2013)	(Arnold. et al. 2018)[y]*		(Kim et al. 2019)	(Kim et al. 2019)	(Dhanaraj et al. 2013)

			2009)[x]							
GLP1-RA: Positive	-	(Levin et al. 2014)*	(Katakami et al. 2020)	-	-	-	-	(Stargardt et al. 2009)*, (Gentile et al. 2018)	(Yu et al. 2017)*, (Stargardt et al. 2009)*	(Nicolucci et al. 2019), (Hartmann et al. 2020)*f, (Hirsch et al. 2011)*
Negative	(Levin et al. 2014)*, (Longato et al. 2020)	(Longato et al. 2020)*	(Nicolucci et al. 2019)*,(Yu et al. 2017)*,(Montvida et al. 2018), (Longato et al. 2020), (Hartmann et al. 2020)*	(Longato et al. 2020)*, (Levin et al. 2014),(Arnold et al. 2018)*	(Longato et al. 2020)*:	(Longato et al. 2020)*,(Arnold. et al. 2018)[y]*,(Levin et al. 2014)*	(Longato et al. 2020)*, (Levin et al. 2014)*	(Yu et al. 2017)	(Gentile et al. 2018)*	(Longato et al. 2020)*
SGLT2-I: Positive	(Grabner et al. 2015)*, (Longato et al. 2020)	(Grabner et al. 2015)*, (Longato et al. 2020)*	(Longato et al. 2020)*	(Longato et al. 2020)*	(Longato et al. 2020)*	(Longato et al. 2020)*	(Longato et al. 2020)*	(Zhang et al. 2010), (Grabner et al. 2015)*, (Gentile et al. 2018)	(Zhang et al. 2010)*, (Grabner et al. 2015)*,(Gentile et al. 2018)*	(Longato et al. 2020)*
Negative	(Wilkinson et al. 2018)	-	(Nicolucci et al. 2019)*, (Wilkinson et al. 2018), (Kim et al. 2019),(Montvida et al. 2018)[q],(Katakami	(Arnold et al. 2018)*	-	(Arnold. et al. 2018)[y]* ,(Kim et al. 2019)	-	-	-	-

			et al. 2020)							
Insulin: Positive	(71)*,(68)*,(70)* (69)*	(Zoberi et al. 2017)*,(Dhanaraj et al. 2013)*,(Levin et al. 2014)*	(Yu et al. 2017)*,(Zoberi et al. 2017)*,(Hartman et al. 2020), (Montvida et al. 2018)	(Levin et al. 2014)*, (Dhanaraj et al. 2013)*, (Arnold et al. 2018)*	(van den Boom et al. 2020),(Zoberi et al. 2017)*, (Kostev et al. 2014)*[z], (Dhanaraj et al. 2013)	(Arnold. et al. 2018)[y]*, (Levin et al. 2014)*, (Kostev et al. 2014)*[z]	(van den Boom et al. 2020)*, (Levin et al. 2014)*	(Yu et al. 2017), (Levin et al. 2014),(Zoberi et al. 2017)	(Zoberi et al. 2017)* (Yu et al. 2017)*,(Levin et al. 2014)*, (Kostev et al. 2014)[z]*	(Nicolucci et al. 2019)*, (Hartmann et al. 2020)*, (Gentile et al. 2018)*, (Dhanaraj et al. 2013)*
	-	-		-	-	-	-			-
Negative	-		(Katakami et al. 2020),(Nicolucci et al. 2019)	(van den Boom et al. 2020)			-	(Kostev et al. 2014)[z]	-	

SU; Sulfonylurea, DPP4-I; dipeptidyl peptidase 4-Inhibitors, SGLT2-I; sodium glucose transporter-2 inhibitor, GLP1-RA; glucagon like peptide 1 receptor agonist, TZD; thiazolidinedione, CVD; cardiovascular disease, CAD; coronary artery disease, IHD; ischemic heart disease, HF; heart failure, PVD; peripheral vascular disease. *; significant association, a; significant association related to THIN database only, b; SGLT2-I vs. SU, c; DPP4-I vs. SU, d; significant association related to US Medicaire, e; significance only for Insulin compared to SU, f; significance only for >10 years versus < 5 years. g; Nicolucci et al study revealed no association (OR=1) for DPP4-I, SGLT2-I, GLP1-RA compared to SU with diabetes duration, h only significant for metformin versus SU and non-significant for DPP4-I versus SU, m; significant positive for HIRD database, n; significant for CPRD, non-significant for THIN database and no association for US Medicaire, p; positive for HIRD database and negative using CRPD, THIN, and US medicaire databases, q; only significant for patients on dual therapy, r; significant only using CRPD and US medicaire, s; positive for CRPD and negative for the other databases and significant for US medicaire only, t; positive for patients on mono therapy and negative for dual therapy, s; positive at first line and negative at second line, x; predicted probability and its standard error , y; relative risk and 95%CI, z; hazard ratio and 95%CI, v; non-significant for insulin vs. SU, &; two studies showed no association of DPP4-I vs. SU prescription with CVD (Wilkinson et al. 2018, Nicolucci et al. 2019).

The magnitude of association of all studied factors with antidiabetic drug prescribing summarised with narrative synthesis

Assessed factor	Metformin	SU	DPP4-I	SGLT2-I	GLP1-RA	TZD	Insulin
Demographic factors							
Ethnicity:							
Asian to White	(Whyte et al. 2019): 1.29[1.2-1.39]	(Whyte et al. 2019): 1.29[1.2-1.39] (Wilkinson et al. 2018): SGLT2-I, DPP4-I vs. SU	(Whyte et al. 2019): 1.29[1.19-1.39] (Wilkinson et al. 2018): 0.73 [0.59-0.89]	(Whyte et al. 2019): 0.88[0.77-1] (Wilkinson et al. 2018): 0.59[0.40-0.86]	(Whyte et al. 2019): 0.55[0.46-0.65]		(Whyte et al. 2019): 0.67 [0.61-0.74]
Black to White	(Whyte et al. 2019): 1.49[1.29-1.72] (Brouwer et al. 2012)[b]: 2.79 (1.63–4.8), 1.66 [0.81–3.4], 1.59 [0.97–2.61]. (Montvida et al. 2018)*: 0.845[0.834-0.857]	(Whyte et al. 2019): 1.31[1.18-1.44] (Wilkinson et al. 2018): SGLT2-I, DPP4-I vs. SU (Brouwer et al. 2012)[c]: 0.57 (0.3–1.1) (Montvida et al. 2018) *[h]: 1.06[1.04-1.08], 0.99 [0.98-1.01]	(Whyte et al. 2019): 0.99[0.89-1.11] (Wilkinson et al. 2018): 0.64 [0.48-0.85] (Montvida et al. 2018)*[h]: 1.01[0.971-1.051], 1.03[1.014 - 1.053]).	(Whyte et al. 2019): 0.33[0.26-0.42] (Wilkinson et al. 2018): (OR: 0.45[0.24-0.82] (Montvida et al. 2018)*[h]: 0.89[0.77-1.03], 1.516 [1.426 - 1.611]	(Whyte et al. 2019): 0.45[0.36-0.57] (Yu et al. 2017)*:0.601[0.53-0.682] (Hirsch et al. 2011)[a]: 0.45 [0.40-0.51] (Montvida et al. 2018)*[h]: 0.747[0.697-0.801], 1.389 [1.339 - 1.443]	(Montvida et al. 2018)*[h]: 0.89[0.85-0.92], 0.965 [0.942 - 0.989]	(Whyte et al. 2019): 0.98 [0.86-1.11] (Yu et al. 2017)*: GLP1-RA to basal insulin (Montvida et al. 2018)*[h]: 1.46[1.43-1.49], 0.85 [0.84 - 0.871]
Mixed to White	(Whyte et al. 2019): 0.92[0.86-0.98]		(Whyte et al. 2019): 1.08[0.85-1.38] (Wilkinson et al. 2018): 1.01[0.48-2.12]	(Whyte et al. 2019): 0.76[0.5-1.17] (Wilkinson et al. 2018): 0.73[0.15-3.60]			(Whyte et al. 2019): 0.97 [0.73-1.30]
Other to White	(Whyte et al. 2019): 1.5[1.08-2.08] (Brouwer et al. 2012)[d]: 0.93 (0.47–1.85), 1.59 (0.82–3.08), 1.09 (0.68–	(Whyte et al. 2019): 1.38[1.11-1.71] (Wilkinson et al. 2018): SGLT2-I, DPP4-I vs. SU (Whyte et al. 2019): 1.3 [1.04-1.62] (Wilkinson et al.	(Whyte et al. 2019): 1.51 [1.2-1.89] (Wilkinson et al. 2018): 0.66 [0.45-0.97]	(Whyte et al. 2019): 0.62[0.41-0.94] (Wilkinson et al. 2018): 0.52[0.25-1.07]	(Whyte et al. 2019): 0.54[0.33-0.89] (Whyte et al. 2019): 0.44[0.27-0.74]		(Whyte et al. 2019): 0.98 [0.74-1.31] (Yu et al. 2017)*: GLP1-RA to basal insulin

Non-White vs. White	1.73) (Zoberi et al. 2017)*: 1.32 [1.02 - 1.71]	2018): SGLT2-I, DPP4-I vs. SU (Brouwer et al. 2012)[e]: 1.17 (0.54–2.53))			(Yu et al. 2017)*: 0.65[0.57-0.76] (Hirsch et al. 2011)[a]:0.45 [0.37-0.55]		(Zoberi et al. 2017)*: 1.28[0.94-1.76] (Korytkowski et al. 2014)*:0.56[0.43-0.72]
Black to Other		(Payk et al. 2015): 1.23 [1.01–1.50]			(Hirsch et al. 2011)*:2.94[1.18-7.29]		
Non-Hispanic White to Hispanic or Black	(Ackermann et al. 2017)[f]: 0.33 (0.16–0.7], 0.96 [0.42–2.22], 0.68 [0.38–1.23]	(Ackermann et al. 2017)[g]: 2.05 (0.87–4.86)). (Ackermann et al. 2017)*:0.95[0.90-0.99]	(Korytkowski et al. 2014)*: 1.16 [1.09-1.23]	(Korytkowski et al. 2014)*:1.09[0.97-1.23]	(Korytkowski et al. 2014)*:0.91[0.81-1.01]	(Ackermann et al. 2017)*:1.05[0.94-1.18]	(Korytkowski et al. 2014)*: 0.77[0.70-0.85]
Smoking status: Current vs. non-smoker	(Geier et al. 2014): 0.92 (0.80–1.06), (Zoberi et al. 2017)*: 1.063 [0.771-1.467]	(Geier et al. 2014): metformin to SU (Wilkinson et al. 2018): SGLT2-I, DPP4-I to SU (Heintjes. et al. 2017): 1st: 1.20 (1.07-1.34) 1.09 (0.86-1.39) 1.15 (1.06-1.26) 0.95 (0.91-1.00) 2nd: 1.05 (1.01-1.11) 1.02 (1.00-1.05) 1.02 (1.00-1.05) 1.02 (1.01-1.03)	(Saine et al. 2015)c: CPRD (0.93[0.81-1.06]), THIN (1.03[0.93-1.15]). (Wilkinson et al. 2018): 0.99[0.85-1.15] (Heintjes. et al. 2017): 2nd: 0.80 (0.62-1.03) 0.88 (0.72-1.08) 0.90 (0.83-0.97) 0.96 (0.92-1.01)	(Wilkinson et al. 2018): 0.78[0.6-1.01]	(Yu et al. 2017)*: 0.815[0.713-0.931]	(Heintjes. et al. 2017): 2nd: Italy, Netherlands, Spain: 0.95 (0.81-1.11) 0.70 (0.46-1.07) 0.82 (0.71-0.94)	(Zoberi et al. 2017)*: 1.285 [0.883-1.868] (Yu et al. 2017)*: GLP1-RA to basal insulin
Former vs. non-smoker	(Zoberi et al. 2017)*:		(Wilkinson et al.	(Wilkinson et al. 2018): 0.92[0.76-	(Yu et al. 2017)*: 0.887[0.792-0.993]	(Heintjes. et al. 2017): 2nd: Italy, Netherlands, Spain: 1.02 (0.89-1.17)	(Zoberi et al. 2017)*:

	0.764[0.568-1.029]	(Wilkinson et al. 2018): SGLT2-I, DPP4-I to SU (Heintjes. et al. 2017): 1st: 0.96 (0.86-1.07), 0.90 (0.70-1.14), 0.99 (0.93-1.06), 0.91 (0.86-0.96) 2nd: 0.98 (0.94-1.02) 0.99 (0.96-1.01) 1.00 (0.99-1.02) 1.02 (1.01-1.03)	2018): 1.01[0.90-1.12]). (Heintjes. et al. 2017): 2nd: 1.10 (0.89-1.36), 1.13 (0.95-1.34), 0.96 (0.91-1.02), 0.96 (0.92-1.00)	1.11]		0.74 (0.51-1.07) 0.93 (0.81-1.06)	0.998[0.692-1.439] (Yu et al. 2017)*: GLP1-RA to basal insulin
Education: No formal vs. > 13 years Primary (1-6) vs. > 13 Secondary (7-13) vs. > 13	-	All groups compared to SU	(Nicolucci et al. 2019): 0.6[0.38-0.94] (Nicolucci et al. 2019): 0.48[0.39-0.59] (Nicolucci et al. 2019):0.70[0.60-0.82]	(Nicolucci et al. 2019): 0.17[0.05-0.61] (Nicolucci et al. 2019): 0.38[0.26-0.56] (Nicolucci et al. 2019): 0.63[0.48-0.82])	(Nicolucci et al. 2019): 0.35[0.09-1.40] (Nicolucci et al. 2019): 0.32[0.17-0.62] (Nicolucci et al. 2019):0.33[0.20-0.55]	-	(Nicolucci et al. 2019): 0.88[0.4-1.92] (Nicolucci et al. 2019): 0.96[0.62-1.48] (Nicolucci et al. 2019): 0.94[0.65-1.36]
History of diabetes in Family	(Dhanaraj et al. 2013): 1.10 [0.73–1.67]	(Dhanaraj et al. 2013):0.03 [0.03–0.04] (Stargardt et al. 2009): pioglitazone vs. SU	-	-	-	(Dhanaraj et al. 2013):0.75 (0.48–1.17) (Stargardt et al. 2009):0.1340[0.0905], p=0.1389	(Dhanaraj et al. 2013):1.76 [1.18–2.64]
Clinical factors							
Microvascular complications Retinopathy (Yes/No)	(Abdelmoneim et al. 2013):	(Wilkinson et al. 2018):SGLT2-I,	(Wilkinson et al. 2018)f:1.12 [0.99-	(Wilkinson et al. 2018):0.78[0.60-	(Levin et al. 2014)*:	(Dhanaraj et al. 2013): 1.13 [0.93–	(Gentile et al. 2018)g: 1.547

	1.07[0.83-1.37] (Dhanaraj et al. 2013): 0.72 [0.60–0.86] (Zoberi et al. 2017)*: 0.79[0.57-1.08] (Morita et al. 2019):DPP4-I vs. metformin	DPP4-I vs. SU (Abdelmoneim et al. 2013):metformin to SU (Dhanaraj et al. 2013): 0.63 [0.52–0.76]	1.28] (Saine et al. 2015):1.2[1.06-1.35]), 1.11[0.98-1.25], 1.03[1.00-1.06], 1.02[0.91-1.14]) (Cai et al. 2010)*:1.46[1.08-1.98] (Grabner et al. 2015):canagliflozine to DPP4-I (Morita et al. 2019):0.74 [0.7–0.79]	1.01] (Grabner et al. 2015):1.30[1.03-1.64] (Longato et al. 2020)*:1.40[0.89-2.22]	0.73[0.64-0.84] (Longato et al. 2020)*: SGLT2-I to GLP1-RA	1.40]	<0.001, 1.277, p: <0.001 (Zoberi et al. 2017)*:2.93[1.58 – 5.43] (Levin et al. 2014)*: 1.23[1.13 – 1.34] (Dhanaraj et al. 2013): 1.97[1.63–2.40]
Neuropathy (Yes/No)	(Abdelmoneim et al. 2013): 1.15 [0.92-1.44] (Zoberi et al. 2017)*: 0.79[0.57-1.08] (Morita et al. 2019):DPP4-I vs. metformin (Dhanaraj et al. 2013): 0.78[0.51–0.90]	(Abdelmoneim et al. 2013):metformin to SU (Dhanaraj et al. 2013): 0.63 [0.49–0.82]	(Morita et al. 2019): 0.94[0.87– 1.03] (Saine et al. 2015)h:1.11[1.08-1.14], 1.01[0.92-1.11] (Grabner et al. 2015)*: canagliflozine to DPP4-I (Cai et al. 2010)*:1.32[1.12-1.56]	(Grabner et al. 2015)*:1.3[1.01-1.66] (Longato et al. 2020)*:2.34[1.36-4.04]	(Levin et al. 2014):1.42[1.25-1.59] (Longato et al. 2020)*: SGLT2-I to GLP1-RA	(Dhanaraj et al. 2013): 0.98 [0.74-1.31]	(Zoberi et al. 2017)*: 2.41[1.69 –3.41] (Dhanaraj et al. 2013): 1.96 [1.52–2.50] (Levin et al. 2014):1.98[1.82 – 2.16]
Macrovascular complications: CVD	(Wang et al.	(Nicolucci et al.	(Nicolucci et al.	(Nicolucci et al.	(Nicolucci et al.	(Kim et al.	(Nicolucci et al.

	2013):0.78[0.37-1.66] (Zoberi et al. 2017)*: 0.97[0.72-1.31] (Morita et al. 2019): DPP4-I vs. metformin (Montvida et al. 2018):0.56[0.56-0.57] (Katakami et al. 2020): 0.92[0.66-1.28]	2019): SGLT2i or GLP1-RA, insulin, DPP4-I vs. SU (Wilkinson et al. 2018): SGLT2-I, DPP4-I vs. SU (Kim et al. 2019)*: 0.85 [0.67-1.08] (Montvida et al. 2018)[h]: 1.73[1.71-1.76], 1.126 [1.108 -1.144] (Katakami et al. 2020): 1.30[0.85 - 2.01]	2019): 1.00[0.83-1.20] (Wilkinson et al. 2018): 1.00 [0.87-1.16]) (Saine et al. 2015)[j]:1.05[0.9-1.23], 0.97[0.84-1.13], 0.95[0.93-0.97], 0.96[0.88-1.05] (Kim et al. 2019)*:1.28[1.03-1.59] (Zhang et al. 2010):1.10(0.83-1.47) (Morita et al. 2019):2.22 [2.13–2.32] (Montvida et al. 2018)[h]: 1.46[1.42 - 1.49], 0.92 [0.89 - 0.94] (Katakami et al. 2020): 1.18[0.87-1.6]	2019):0.65[0.47-0.91] (Wilkinson et al. 2018): 0.95[0.72-1.27] (Kim et al. 2019)*:0.61[0.35-1.06] (Montvida et al. 2018)[h]: 0.91[0.81-1.02], 0.76 [0.71 - 0.81] (Katakami et al. 2020): 0.70 (0.39-1.27) (Longato et al. 2020)*:1.69[1.55-1.85]	2019): 0.44[0.24-0.79] (Yu et al. 2017)*:0.52[0.47-0.58] (Montvida et al. 2018)[h]: 0.77[0.73 -0.82], 0.591 [0.564 -0.619] (Katakami et al. 2020): 2.1 [0.35 - 13.07] (Longato et al. 2020)*: SGLT2-I to GLPA1-RA (Hartmann et al. 2020): 0.79[0.63, 0.99]	2019)*:0.87[0.53-1.41] (Montvida et al. 2018)[h]:1.06[1.03-1.09], 0.80[0.78-0.83] (Katakami et al. 2020): 0.84[0.45-1.57] (Stargardt et al. 2009)[p]: -0.2517,0.1099	2019):0.94[0.64-1.38] (Yu et al. 2017)*: GLP1-RA vs. basal insulin (Zoberi et al. 2017)*: 2.01[1.44 –2.82] (Montvida et al. 2018)[h]: 1.71 [1.68 -1.74], 1.19[1.16-1.22] (Katakami et al. 2020): 0.29[0.02-4.87] (Hartmann et al. 2020): 1.10 [0.94, 1.28]
CAD or IHD	(Abdelmoneim et al. 2013): 1.01[0.91 -1.11]	(Abdelmoneim et al. 2013): metformin vs. SU (Dhanaraj et al. 2013): 0.59 [0.43–0.83]	(Ou et al. 2017)*[k]:1.22[1.01–1.42], 1.16[1.03 –1.29]	(Longato et al. 2020)*:2.14[1.97-2.33]	(Longato et al. 2020)*: SGLT2-I to GLPA1-RA (Levin et al. 2014)*:0.82[0.60-1.12]	(Dhanaraj et al. 2013):0.58[0.39–0.85]	
Cerebrovascular disease or stroke	(Dhanaraj et al.	(Abdelmoneim et al. 2013):		(Longato et al. 2020)*:1.33[1.12-	(Longato et al. 2020)*: SGLT2-I	(Dhanaraj et al. 2013): 0.86[0.42–	(van den Boom et al. 2020): 0.81[0.49-1.59]

	2013): 0.64[0.46–0.88] (Abdelmoneim et al. 2013): 1.10[0.94-1.28] (Zoberi et al. 2017)*: 0.69[0.42-1.16] (Dhanaraj et al. 2013): 0.68(0.36–1.29 (Abdelmoneim et al. 2013): (0.84[0.75 - 0.95] (Arnold. et al. 2018)[i]: 0.84[0.82-0.86]	metformin vs. SU (Dhanaraj et al. 2013): 0.45[0.23–0.91]	(Cai et al. 2010)*:1.50[1.34-1.69]	1.58]	to GLPA1-RA	1.78]	(Levin et al. 2014)*: 2.59[2.23-3.03] (Dhanaraj et al. 2013): 1.57 [1.14–2.20]
HF		(Abdelmoneim et al. 2013): metformin vs. SU (Arnold. et al. 2018)[i]: 1.04[1.02-1.05] (Kim et al. 2019)*: 0.67[0.41-1.08]	(Saine et al. 2015)[j]: 0.79[0.64-0.98], 0.87[0.72-1.05], 0.9[0.88-0.93], 0.92[0.78-1.09] (Ou et al. 2017)[k]:1.17 [0.94–1.40], 1.01[0.86–1.16] (Cai et al. 2010)*:1.42[1.07-1.88]	(Longato et al. 2020)*:1.31[1.07-1.6] (Arnold. et al. 2018)[i]:0.83[0.78-0.89] (Kim et al. 2019)*:0.69[0.25-1.89]	(Longato et al. 2020)*: SGLT2-I to GLPA1-RA (Arnold. et al. 2018)[i]: 0.90[0.87-0.94] (Levin et al. 2014)*:0.73[0.58-0.90]	(Arnold. et al. 2018)[i]:0.79[0.74-0.83] (Kim et al. 2019)*:1.28[0.59-2.78]	(van den Boom et al. 2020):1.2[0.75-1.92] (Zoberi et al. 2017)*: 2.97[1.76– 5.02] (Kostev et al. 2014)[m]: 1.51 [1.09-2.11] (Dhanaraj et al. 2013): 1.57[0.82–2.9]
PVD		(Abdelmoneim et al. 2013): metformin vs. SU (Abdelmoneim et al. 2013): 0.94[0.80-1.12]	(Arnold. et al. 2018)[i]: 0.92[0.9-0.95] (Kim et al. 2019)*: 1.38 [0.913 -2.09] (Ou et al. 2017)*[k]: 0.85[0.42-1.28], 0.68[0.43– 0.94] (Cai et al. 2010)*:2.29[1.89-2.79] (Saine et al. 2015)[j]:	(Longato et al. 2020)*:1.71[1.36-2.15]	(Longato et al. 2020)*: SGLT2-I to GLPA1-RA (Levin et al. 2014)*:0.84[0.69-1.03]		(Arnold. et al. 2018)[i]: 1.39[1.36-1.42] (Levin et al. 2014)*:2.83[2.56-3.13] (Kostev et al. 2014)[n]:1.52 [1.07-2.16]

			0.88[0.73-1.07], 0.83[0.69-1.00], 0.97[0.94-1.00], 1.06[0.92-1.21] (Cai et al. 2010)*:1.70[1.42-2.04]				(van den Boom et al. 2020):1.94[1.3-2.81] (Levin et al. 2014)*:1.73[1.54 – 1.95]
Comorbid conditions: Hypertension	(Abdelmoneim et al. 2013): 1.10[1.03 – 1.18] (Fujihara et al. 2017): 0.67 [0.50–0.90] (Zoberi et al. 2017)*: 0.91[0.65-1.27]	(Abdelmoneim et al. 2013): metformin to SU (Kim et al. 2019)*: 1.09[0.93-1.278] (Fujihara et al. 2017): metformin, DPP4-I to SU	(Saine et al. 2015)[j]: 0.86[0.75 0.98], 0.88[0.78-1.00], 1.00[0.97-1.03], 1.13[1.07-1.20]) (Kim et al. 2019)*: 0.89[0.77-1.03] (Grabner et al. 2015)*: canagliflozine to DPP4-I (Fujihara et al. 2017): 0.90[0.69–1.18] (Ou et al. 2017)[k]: 0.79[0.61– 0.98], 0.75[0.64 -0.87] (Cai et al. 2010)*: 1.45[1.31-1.6]	(Kim et al. 2019)*: 1.33[0.96-1.84] (Grabner et al. 2015)*: 1.34 [1.19-1.52] (Longato et al. 2020)*: 0.93[0.85-1.02]	(Yu et al. 2017)*:0.96[0.87-1.05] (Levin et al. 2014)*: 1.18[1.1-1.27] (Longato et al. 2020)*: SGLT2-I to GLPA1-RA	(Kim et al. 2019)*: 0.95[0.69-1.31]	(Yu et al. 2017)*: GLP-RA to basal insulin (Levin et al. 2014)*: 1.02[0.0.97-1.07] (Zoberi et al. 2017)*: 1.23[0.81– 1.89] (Kostev et al. 2014)k: 0.85 [0.67-1.11], 0.89 [0.58-1.38]
Dyslipidaemia:	(Abdelmoneim et al. 2013): 1.27[1.18 – 1.36]	(Abdelmoneim et al. 2013): metformin to SU (Kim et al. 2019)*:	(Saine et al. 2015)[j]: 1.19[1.03-1.37], 1.21[1.05-1.39], 1.11[1.08 -1.14], 1.17[1.10-1.24])	(Kim et al. 2019)*: 2.13[1.39 -3.26] (Grabner et al. 2015)*: 1.48[1.23-1.79]	(Yu et al. 2017)*: 1.24[1.14-1.36] (Levin et al.	(Kim et al. 2019)*: 0.96 [0.68-1.36]	(Yu et al. 2017)*:

	(Zoberi et al. 2017)*: 0.75[0.57-0.99]	0.50[0.43-0.59]	(Kim et al. 2019)*: 1.59[1.36 -1.85] (Grabner et al. 2015)*: canagliflozine to DPP4-I (Ou et al. 2017)[k]: 1.04[0.88– 1.99] 1.14[1.04 -1.23]	(Longato et al. 2020)*: 1.26[1.16-1.36]	2014)*: 1.36[1.27-1.46 (Longato et al. 2020)*: SGLT2-I to GLPA1-RA		GLP-RA to basal insulin (Levin et al. 2014)*: 0.81 [0.77-0.85] (Zoberi et al. 2017)*: 1.53[1.08– 2.16] (Kostev et al. 2014)m: 0.65 [0.51-0.82]
Diabetes duration	(Geier et al. 2014): 0.95 [0.94–0.97] (Fujihara et al. 2017): 0.94 [0.92–0.96] (Dhanaraj et al. 2013)r: 0.87 [0.79–0.96]	(Nicolucci et al. 2019): DPP4-I, SGLT2-I, GLP1-RA, insulin to SU (Geier et al. 2014): Metformin to SU (Fujihara et al. 2017): metformin, DPP4-I to SU (Dhanaraj et al. 2013)r: 0.54 [0.42–0.69]	(Nicolucci et al. 2019): 1.00[0.99-1.01] (Fujihara et al. 2017): 0.96 [0.95–0.97]	(Nicolucci et al. 2019): 1.00[0.98-1.01] (Longato et al. 2020)*: 1.50[1.41-1.59]	(Nicolucci et al. 2019): 1.00[0.98-1.02] (Hartmann et al. 2020)n: 1.77 [1.44, 2.18] 1.19 [0.96, 1.46] (Hirsch et al. 2011)q: 1.22[1.09-1.36], 1.38[1.20-1.59] (Longato et al. 2020)*: SGLT2-I to GLPA1-RA	(Dhanaraj et al. 2013)r: 1.17 [0.90–1.50]	(Nicolucci et al. 2019): 1.02[1.01-1.03] (Hartmann et al. 2020)n: 1.30[1.09, 1.55], 1.53[1.28, 1.82 (Gentile et al. 2018)p: 1.363, <0.001 (Dhanaraj et al. 2013)r: 2.62 [2.05–3.36]
Socioeconomic factors							
Patients-related: Deprivation level (IMD)	(Whyte et al. 2019)[q]: 1.18[1.09 - 1.27], 1.13[1.05 - 1.22], 1.04[0.97 - 1.11],	(Whyte et al. 2019)[q]: 1.04[0.97 - 1.10], 1.06[0.99 - 1.12], 1.03[0.97 - 1.09],	(Whyte et al. 2019)[q]: 1.13[1.05-1.21], 1.12[1.05 - 1.20], 1.14[1.07-1.22],	(Whyte et al. 2019)[q]: 1.07[0.96-1.20], 1.01[0.90 - 1.13], 0.96[0.85 - 1.08],	(Whyte et al. 2019)[q]: 0.89[0.79-1.00], 0.88[0.78 - 1.00], 1.00[0.89 - 1.12],		(Whyte et al. 2019)[q]: 1.02[0.94 - 1.10], 1.03[0.95 - 1.12], 0.97[0.89 - 1.05],

	1.02[0.95 - 1.09]	0.98[0.92 – 1.02] (Wilkinson et al. 2018)[r]: DPP4-I, SGLT2-I vs. SU	1.10[1.03– 1.17] (Wilkinson et al. 2018)[r]: 0.95[0.80-1.12], 0.95[0.80-1.12], 0.79[0.67-0.93], 0.99[0.84-1.18]	1.12 [1.00– 1.25] (Wilkinson et al. 2018)[r]: 0.98[0.73-1.30], 1.02[0.76-1.33], 0.61[0.46-0.81], 0.59[0.44-0.80]	1.02 [0.91 – 1.14]		1.01[0.94 – 1.10]
Income level	(Desai et al. 2012):1.05[1.04–1.05] (Liu et al. 2017)[s]:1.30[1.18-1.44]						
Employment status: Employed vs. non-employed		(Nicolucci et al. 2019): DPP4-I, SGLT2-I, GLP1-RA, insulin vs. SU	(Nicolucci et al. 2019): 1.08[0.92-1.27]	(Nicolucci et al. 2019): 1.51[1.14 -1.99]	(Nicolucci et al. 2019): 1.74 [1.07 -2.81]		(Nicolucci et al. 2019): 0.97[0.7-1.35]
Having insurance (No/Yes)		(Nicolucci et al. 2019): DPP4-I, SGLT2-I, GLP1-RA, insulin vs. SU	(Nicolucci et al. 2019): 0.55[0.46-0.67]	(Nicolucci et al. 2019): 0.61[0.42-0.88]	(Nicolucci et al. 2019): 1.38[0.64-2.98]	(Kim et al. 2019)*[v]: 1.69[0.74-3.88]	(Nicolucci et al. 2019): 0.82[0.51-1.32]
Types of insurance	(Desai et al. 2012)[t]: 1.04 [1.02–1.07], 1.36[1.32-1.49], 0.74 [0.72-0.77]	(Kim et al. 2019)*[v]: 0.79[0.57-1.07]	(Kim et al. 2019)*[v]: 1.03[0.77-1.39]	(Kim et al. 2019)*[v]: 1.71[0.75-3.90]	(Hirsch et al. 2011)[x]: 0.47 [0.38-0.57], 0.41 [0.39-0.44], 0.21 [0.13-0.34]		
Area of living	(Liu et al. 2017)[y]: 1.23[1.13-1.34], 1.23[1.14-1.33],	(Payk et al. 2015)[w]: 1.09 [0.89–1.32]					

Rural vs. Urban	1.65[1.27-2.15], 1.68[1.43-1.96], 1.62[1.39-1.89], 1.06[0.99-1.13] (Moreno Juste et al. 2019)*:1.02[0.87-1.19]	(Moreno Juste et al. 2019)*:1.08[0.87-1.35]	(Moreno Juste et al. 2019)*:0.60[0.31-1.18]		
Medical facility-related Institution: -Local hospital, primary clinic, community hospital vs. medical centres -General hospital, tertiary hospital vs. clinic	(Liu et al. 2017): 1.30[1.20-1.41], 1.45[1.35-1.56], 1.02[0.95-1.10]	(Kim et al. 2019)*:0.35 [0.26-0.47], 0.30[0.19-0.46]	(Kim et al. 2019)*: 2.09[1.67-2.63], 2.11[1.55-2.87]	(Kim et al. 2019)*:1.43[0.95-2.16]	(Kim et al. 2019)*:0.76[0.46-1.24]
Ownership	(Liu et al. 2017)[z]: 1.16[1.09-1.24], 0.87[0.81-0.94].				
Prescriber-related factors					
Age	(Winkelmayer et al. 2010)[$]: 0.94[0.81 -1.08], 0.89[0.77-1.03], 0.77 [0.66-0.89] (Liu et al. 2017)[£]: 1.65[1.50-1.80], 1.82[1.66-1.99],				

	1.81[1.64-2.00]						
Sex(F:M)	(Liu et al. 2017)[^]:1.37[1.26-1.49] (Winkelmayer et al. 2010): 1.02[0.97-1.09] (Wang et al. 2013): 1.37[1.26-1.49]						
Speciality:							
Endocrinologist	(Liu et al. 2017)[E]:1.87[1.72-2.03], 2.03[1.84-2.25], 2.09[1.92-2.27], 215[1.98-2.32])	(Ackermann et al. 2017)*:0.85 [0.80 -0.90]	(Grabner et al. 2015)*: SGLT2-I vs. DPP4-I (Nicolucci et al. 2019): 3.77[3.11-4.58] (Ackermann et al. 2017)*:1.08 [1.01 - 1.15]	(Nicolucci et al. 2019): 6.00[4.32-8.35] (Ackermann et al. 2017)*:0.83 [0.72 -0.95] (Grabner et al. 2015)*:0.20[0.18–0.23]	(Nicolucci et al. 2019):5.97[3.47-10.27] (Ackermann et al. 2017)*:1.53[1.39 -1.68] (Yu et al. 2017)*:1.39[1.24-1.55]	(Ackermann et al. 2017)*:0.62 [0.53 - 0.73]	(van den Boom et al. 2020):2.71[1.81-4.06] (Kostev et al. 2014)[m]:1.94 [1.14-3.32] (Nicolucci et al. 2019):1.51[1.02-2.23] (Ackermann et al. 2017)*:1.33[1.20-1.46]
Internal medicine vs. General practitioner (GP) or family medicine	(Winkelmayer et al. 2010):1.34 [1.24-1.46]	(Ackermann et al. 2017)*:1.05[1.02 - 1.09] (Payk. et al. 2015): 0.99 [0.77–1.28] (Kim et al. 2019)*:0.42[0.34-0.53]	(Kim et al. 2019)*:2.01[1.64-2.47] (Nicolucci et al. 2019): 2.35[1.86-2.98] (Ackermann et al. 2017)*:1.03 [0.99 - 1.06]	(Nicolucci et al. 2019): 1.19 [0.73 - 1.93] (Kim et al. 2019)*:1.74[0.96-3.16] (Ackermann et al. 2017)*:0.92 [0.86 -0.99]	(Ackermann et al. 2017)*:1.03[0.97 -1.09] (Nicolucci et al. 2019):1.73 [0.83 - 3.41]	(Ackermann et al. 2017)*:0.75 [0.69 - 0.81] (Kim et al. 2019)*:0.81[0.52-1.28]	(Yu et al. 2017)*: GLP1-RA vs. basal insulin (Ackermann et al. 2017)*:1.00[0.94 -1.06] (Nicolucci et al. 2019):0.69 [0.42 - 1.13]
Other vs. GP	(Winkelmayer et	(Payk. et al. 2015): 0.81 [0.51–1.27]	(Nicolucci et al. 2019): 7.80[4.78-12.74]	(Nicolucci et al. 2019): 13.16[5.98-28.97]	(Nicolucci et al. 2019): 12.52[3.10-50.55]	(Stargardt et al. 2009): GP vs. specialists: estimates,	

	al. 2010):1.25 [0.98-1.60]		SE:-0.2848 0.0982	
				(Nicolucci et al. 2019): 0.33[0.06-1.75]
Practice experience	(Wang et al. 2013):1.00[0.96-1.05]	(Stargardt et al. 2009):Pioglitazone vs. SU	(Stargardt et al. 2009): estimates, SE: - 0.0099[0.0075]	

*: based on calculated OR, a: Represents Hazard ratio and 95%CI, b; the values represent the probability ratio for White versus Black association with biguanide versus SU, biguanide versus TZD, and biguanides versus combination therapy respectively, c; the value represent the probability ratio for White versus Black association with SU versus combination therapy, d; the values represent the probability ratio for White versus Other association with biguanide versus SU, biguanide versus TZD, and biguanides versus combination therapy respectively, e; the value represent the probability ratio for White versus Other association with SU versus combination therapy, f; the values represent the probability ratio for Black versus Other association with biguanide versus SU, biguanide versus TZD, and biguanides versus combination therapy respectively, g; the value represent the probability ratio for Black versus Other association with SU versus combination therapy, h, the outcome was evaluated at initiation and first intensification stages respectively, I; adjusted relative risk with 95%CI, j; results from 4 databases: CPRD, THIN, US medicaire, and HIRD databases respectively, k; OR for patients already on monotherapy or dual therapy respectively, m; Hazard ratio for patients started on metformin, n; Hazard ratio for patients started on SU, p; predicted probability with its standard error, q; Italy, Netherlands, UK, and Spain respectively, SU; Sulfonylurea, DPP4-I; dipeptidyl peptidase 4-Inhibitors, SGLT2-I; sodium glucose transporter-2 inhibitor, GLP1-RA; glucagon like peptide 1 receptor agonist, TZD; thiazolidinedione, CVD; cardiovascular disease, CAD; coronary artery disease, IHD; ischemic heart disease, HF; heart failure, PVD; peripheral vascular disease.

Appendix S.3.1: BNF codes of all medications of interest

Medications of interest	BNF code
Antidiabetic groups	0601
Biguanide	0601022
Sulfonylurea	0601021
Other antidiabetics*	0601023
Insulin	060101
Rapid/Short-acting insulin	0601011
Intermediate/Long-acting insulin	0601012
Loop diuretic	020202
Thiazide diuretic	020201
Beta-blockers	0204
Angiotensin drugs	0205051, 0205052
Calcium channel blocker	020602
Other anti-hypertensive drugs	020501, 020502, 020203, 020204
Antiarrhythmic drugs	0203
Nitrates	020601
Lipid-lowering drugs	0212
Antiplatelet	0209
Antipsychotic drugs	040201

Appendix S.3.2: ICD 10 codes of all investigated comorbid conditions and complications

Comorbidity	ICD-10 code
Hypertension:	I10, I10X, I11, I110, I1100, I1101, I1109, I119, I12, I120, I129, I13, I130, I1300, I1301, I1309, I131, I132, I1320, I1321, I1329, I139
Hyperlipidaemia	E780, E781, E782, E784, E785
Angina pectoris	I20, I200, I2000, I2001, I2002, I2009, I201, I208, I209
Myocardial infarction (MI):	I21, I210, I2100, I2101, I2109, I211, I2110, I2111, I2119, I212, I2120, I2121, I2129, I213, I2130, I2131, I2139, I214, I2140, I2141, I2149, I219, I2190, I2191, I2199, I22, I220, I2200, I2201, I2209, I221, I2210, I2211, I2219, I228, I2280, I2281, I2289, I229, I2290, I2291, I2299, I23, I230, I231, I232, I233, I234, I235, I236, I238
Other ischemic heart diseases (IHD)	I24, I240, I241, I248, I249, I25, I250, I251, I252, I253, I254, I255, I2550, I2551, I2559, I256, I258, I259
Heart failure (HF)	I50, I500, I5000, I5001, I5009, I501, I5010, I5011, I5019, I509, I5090, I5091, I5099
Stroke:	
Haemorrhagic	I60, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I61, I610, I611, I612, I613, I614, I615, I616, I618, I619, I62, I620, I621, I629
Ischemic (infarction)	I63, I630, I631, I632, I633, I634, I635, I636, I638, I639
Not specified	I64, I64X
Liver disease	K70 – K77
Obesity	E66, E660, E661, E662, E668, E669
Retinal disease	H35.0 – H35.9
Neuropathy disease	
Peripheral vascular disease (PVD)	I70, I700, I7000, I7001, I701, I7010, I7011, I702, I7020, I7021, I708, I7080, I7081, I709, I7090, I7091, I71, I710, I711, I712, I713, I714, I715, I716, I718, I719, I72, I720, I721, I722, I723, I724, I725, I726, I728, I729, I73, I730, I731, I738, I739, I74, I740, I741, I742, I743, I744, I745, I748, I749

Appendix S.3.3: Notifications of PBPP application approvals (application number:1920-0280)

Stage 1 of approval: Feb/2021

Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP)
phs.PBPP@phs.scot
https://www.informationgovernance.scot.nhs.uk/pbpphsc/

NHS SCOTLAND

Dr Amanj Kurdi,
University of Strathclyde,
Strathclyde Institute of Pharmacy and Biomedical Sciences,
161 Cathedral Street,
Glasgow. G4 0RE

Date: 11th February 2021
Our Ref: 1920-0280

Dear Dr Kurdi,

Re application: Utilisation Trend and Clinical Outcomes of Antidiabetics in Type II Diabetes Patients in Scotland over the Period of 2010-2019: a multi-studies project
Version: v2

Thank you for your application for consideration by the Public Benefit and Privacy Panel for Health and Social Care. Your application has undergone proportionate governance review and has been approved.

This approval is given to process data as specified in the approved version of the application, and is limited to this. Approval is valid for the period specified in your application until 31st October 2023. You are required to notify the Panel Manager, via your eDRIS coordinator, of any proposed changes to your proposal, e.g. purpose or method of processing, data or data variables being processed, study cohorts, individuals accessing and processing data, timescales, technology/infrastructure.

On conclusion of your proposal, as part of NHS Scotland Governance and monitoring we will require you to complete an End of Project reporting form to demonstrate that you have complied with the obligations outlined e.g. data destruction or submission of references for publications of findings.

I would take this opportunity to remind you of the declaration you have made in your application form committing you to undertakings in respect of information governance, confidentiality and data protection. It is the responsibility of the applicant and their organisation to ensure that their study complies with current legislation at all times during the study.

Requests for access to NHS Scotland data as part of this approved application must be supported by providing a copy of your approval letter and approved application to the relevant local board contacts and/or data providers.

Please note that summary information about your application and its approval, including the title and nature of your proposal, will be published on the panel website (https://www.informationgovernance.scot.nhs.uk/pbpphsc/).
Please note that our email address has changed and the previous addresses are no longer in use.

I hope that your proposal progresses well.

Yours sincerely,

Dr Marian Aldhous

Panel Manager
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: phs.PBPP@phs.scot

Stage 2 of approval: in April/2021

Public Benefit and Privacy Panel for Health and Social Care
phs.pbpp@phs.scot
www.informationgovernance.scot.nhs.uk

NHS SCOTLAND

Dr Amanj Kurdi,
University of Strathclyde,
Strathclyde Institute of Pharmacy and Biomedical Sciences,
161 Cathedral Street,
Glasgow. G4 0RE

Date: 29th Aprul 2021
Our Ref: 1920-0280

Dear Dr Kurdi,

Re application: **Utilisation Trend and Clinical Outcomes of Antidiabetics in Type II Diabetes Patients in Scotland over the Period of 2010-2021: a multi-studies project.**
Version: v3

Further to your approval issued by the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) on 9th December 2020, I am writing to confirm that we accept the amendments to the proposal notified on 19th April 2021.

The approved amendments are:

- Extend the end date for approved variables data to 28th February 2021.
- Extend the cohort inclusion date to the end of 2019 (31st December 2019).

Please note that any conditions attached to your original approval remain in place and you should continue to comply with those conditions outlined in the approval letter. It is the responsibility of the applicant and their organisation to ensure that their study complies with current legislation at all times during the study.

This approval is given to process data until 31st October 2023 and is limited to this.

Requests for access to NHS Scotland data as part of this approved application should be supported by providing a copy of your approval letter and approved application to the relevant local board contacts/data providers.

I would take this opportunity to remind you of the declaration you have made in your application committing you to undertakings in respect of information governance, confidentiality and data protection.

Yours sincerely,

Phil Dalgleish
Panel Manager
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: phs.pbpp@phs.scot

Cc: Professor Robin Plevin, Main contact for Lead Organisation

Stage 3 of approval: March/2022

Public Benefit and Privacy Panel for Health and Social Care
phs.pbpp@phs.scot
www.informationgovernance.scot.nhs.uk

NHS SCOTLAND

Dr Amanj Kurdi,
University of Strathclyde,
Strathclyde Institute of Pharmacy and Biomedical Sciences,
161 Cathedral Street,
Glasgow. G4 0RE

Date: 3rd March 2022
Our Ref: 1920-0280

Dear Dr Kurdi,

Re application: **Utilisation Trend and Clinical Outcomes of Antidiabetics in Type II Diabetes Patients in Scotland over the Period of 2010-2019: a multi-studies project**
Version: v4.1

Further to your approval issued by the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) on 12th February 2021, I am writing to confirm that we accept the amendment(s) to the proposal received by the HSC-PBPP on 11th February 2022.

The approved amendments are:

- Add SCI-Diabetes variables.
- Change of Main Lead for the Organisation.

Please provide the complete information governance evidence for Section 1.3.9. You have only provided partial evidence. The HSC-PBPP Guidance for Applicants Appendix A table 4 states

MRC

- 'Research, GDPR and Confidentiality – what you really need to know' online module

A series of 10 bite-sized e-learning modules accompanied by supplementary resources and a quiz.

We ask that applicants go through all the modules and pass the quiz. Each module has a dotted box next to it. As each module is completed, a tick will appear automatically when the module has been completed. Please print out a screen shot of the ticked boxes showing that each module has been completed and send it to the Research Coordinator, together with the certificate showing that you have passed the quiz.

Please note, you did not provide an updated HSC-PBPP Amendment Request Form for the change of Main Lead for the Organisation however the HSC-PBPP will accept the brief explanation contained within the clarifications provided. In future, all changes must be explained and justified on the HSC-PBPP Amendment Request Form and the HSC-PBPP Application Form updated accordingly.

Please note that any conditions attached to your original approval remain in place and you should continue to comply with those conditions outlined in the approval letter. It is the responsibility of the applicant and their organisation to ensure that their study always complies with current legislation during the study.

This approval is given to process data, as specified in the approved application form version specified in this letter, until

Appendix S.3.4: Information governance certificate

This is to certify that:

Fatema Mahmoud

Passed

Research, GDPR and confidentiality Quiz

Date / Time	Student Score	Passing Score	Result
March 16, 2020 2:12 pm	88.88	70	Pass

Appendix S.3.5: Departmental ethical approval

STRATHCLYDE INSTITUTE OF PHARMACY & BIOMEDICAL SCIENCES

Dr Amanj Kurdi
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
Glasgow

25th January 2021

Dear Amanj,

Ethical review of research project "Utilisation Trend and Clinical Outcomes of Antidiabetics in Type II Diabetes Patients in Scotland over the Period of 2010-2019: a multi-studies project"

I can confirm that, due to the nature of research project, the information that is being collected and the method by which it is being collected, the project does not require approval through the University's ethics review process.

Regards,

Dr Christopher Prior
Convenor, Departmental Ethics Committee
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
116 Cathedral Street
Glasgow
G4 0NR

(44) 141 548 2459
c.b.prior@strath.ac.uk

Appendix S.3.6: Privacy Impact Assessment (PIA) Screening Questions

Q1. Will the project involve the collection of new information about individuals?

No, all data will be used are already collected in routine care.

Q2. Will the project compel individuals to provide information about themselves?

No, no individuals will be contacted at all.

Q3. Will information about individuals be disclosed to organisations or people who have not previously had routine access to the information?

No, this study is a research project will be undertaken at the University of Strathclyde. So, only University of Strathclyde researchers will be allowed to access data.

Q4. Are you using information about individuals for a purpose it is not currently used for, or in a way it is not currently used?

No, it is only used for health research purposes and in Scotland electronic data are usually accessed using anonymised extracts through record linkage by accredited Safe Havens.

Q5. Does the project involve you using new technology which might be perceived as being privacy intrusive? For example, the use of biometrics or facial recognition.

No. Data will be accessed electronically, using a secure server accessed remotely which take into consideration all privacy and security issues.

Q6. Will the project result in you making decisions or taking action against individuals in ways which can have a significant impact on them?

No. since individuals are not identifiable, no decision or actions will directly affect them.

Q7. Is the information about individuals of a kind particularly likely to raise privacy concerns or expectations? For example, health records, criminal records or other information that people would consider to be particularly private.

No. No personal data will be identifiable; this project will use electronic anonymised health records. Only approved researchers who underwent information governance training, using a secure accredited Safe Haven will be accessed to health data.

Q8. Will the project require you to contact individuals in ways which they may find intrusive?

No. No individuals will be contacted at all.

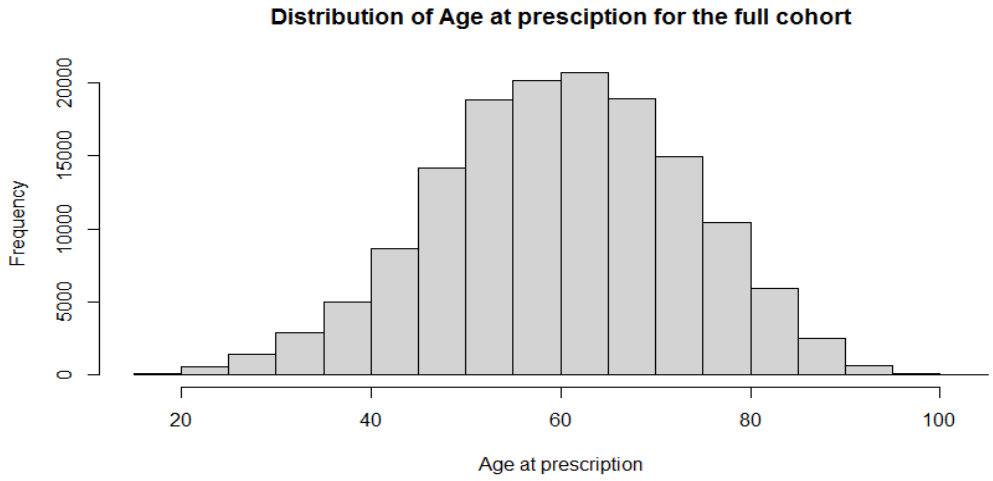
Q9. Will the project involve processing or releasing personal or sensitive personal data? (As defined by the Data Protection Act/GDPR).

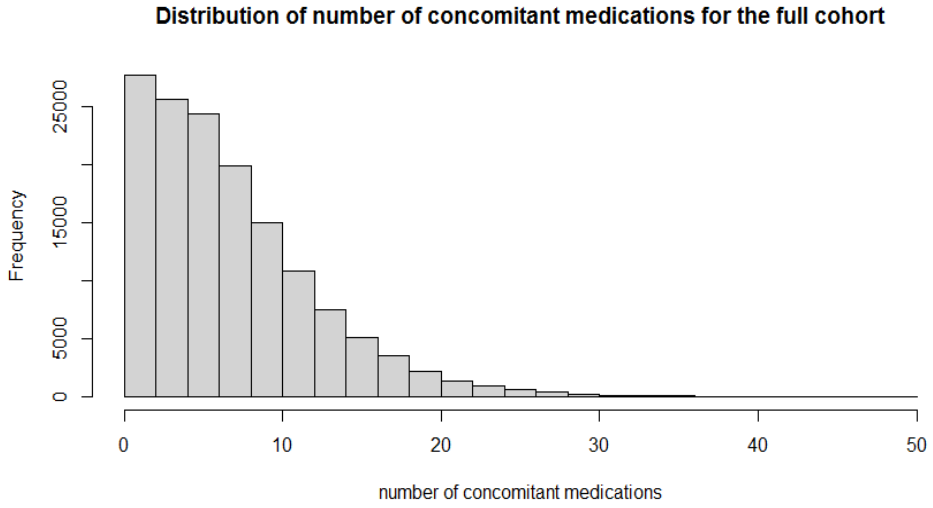
No. All data will be anonymised and will not process a sensitive data.

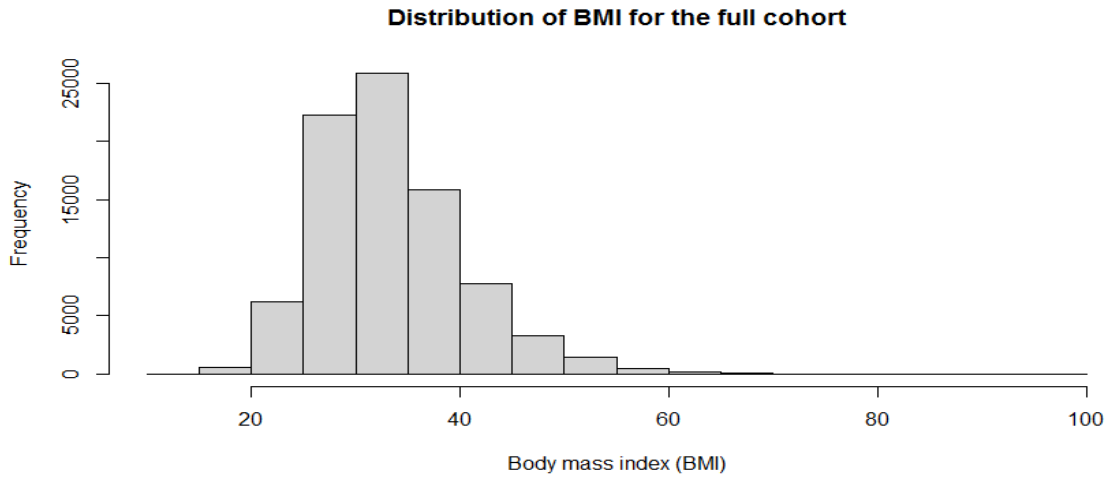
Q10. Will the project use or develop IT which is not University managed or provided via Information Services?

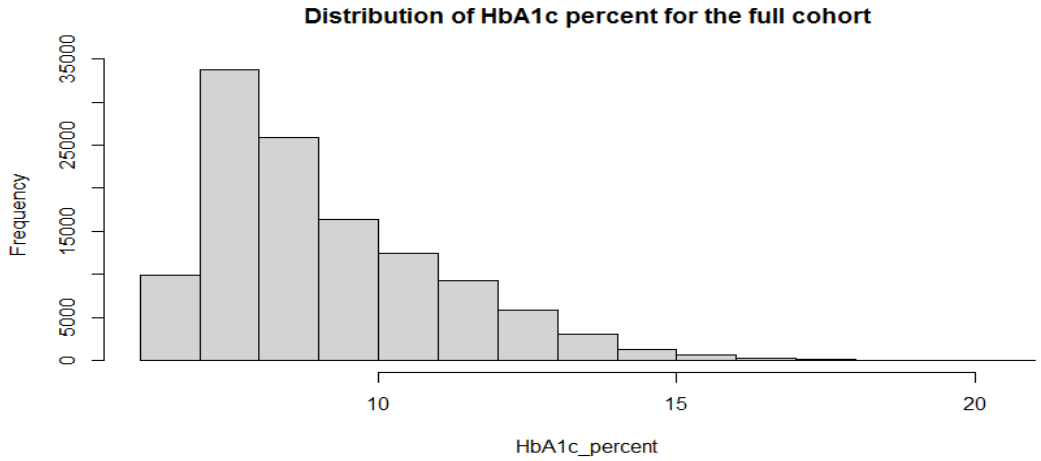
No. this project will use a secured IT environment (accredited safe haven) provided by Information Services.

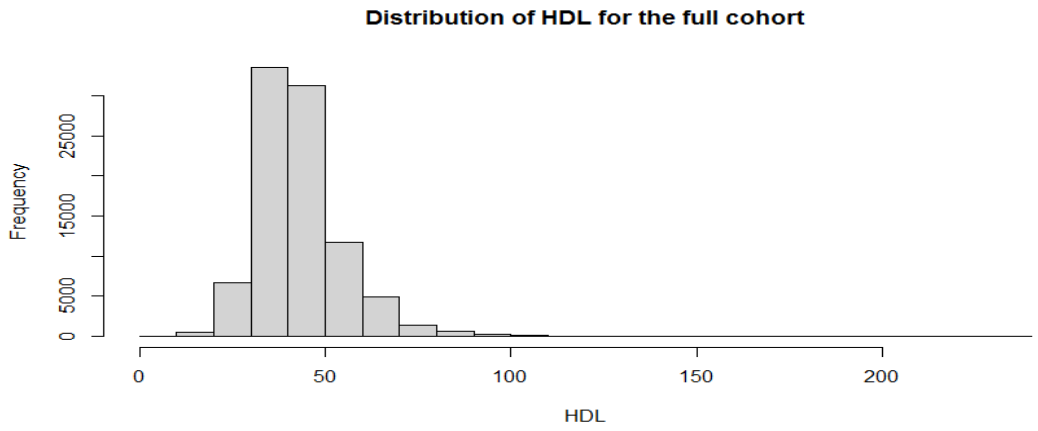
Appendix S.4.1: Normality test of continuous variables

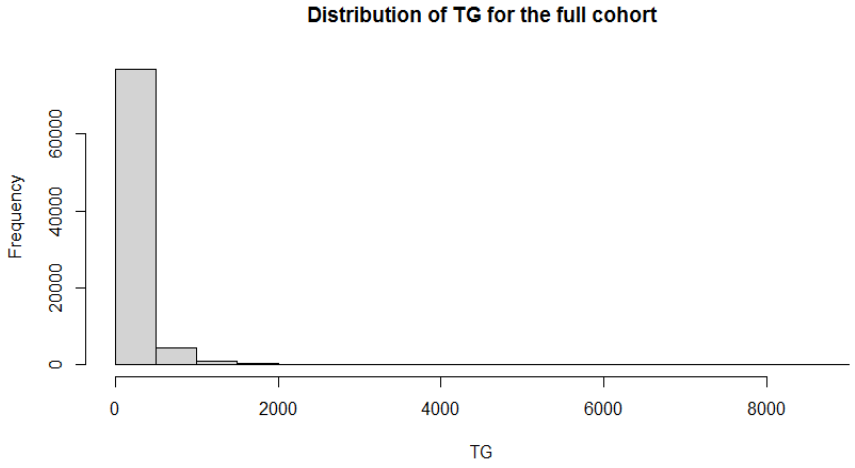


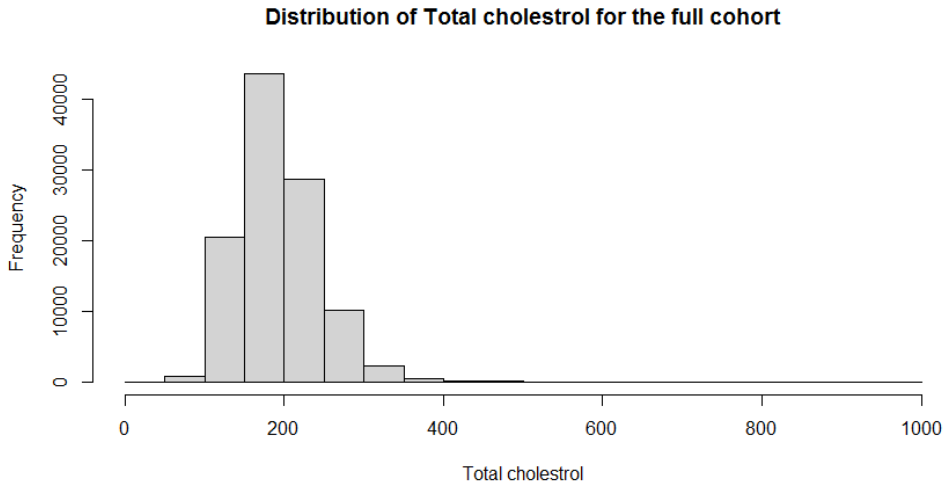


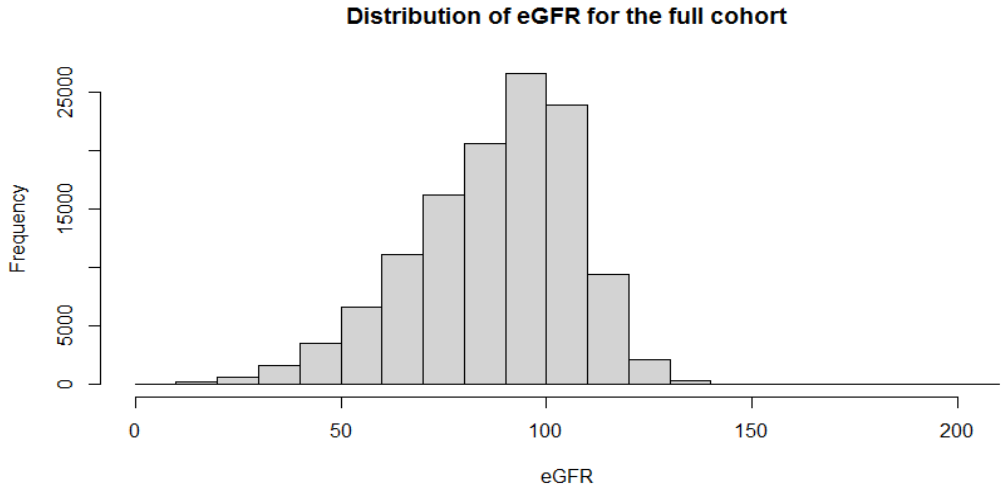

Distribution of BMI for the full cohort
Frequency
0
5000
15000
25000
20
40
60
80
100
Body mass index (BMI)


Distribution of HbA1c percent for the full cohort
Frequency
0
5000
15000
25000
35000
10
15
20
HbA1c_percent


Distribution of HDL for the full cohort
Frequency
0
5000
15000
25000
0
50
100
150
200
HDL


Distribution of TG for the full cohort
Frequency
0
20000
40000
60000
0
2000
4000
6000
8000
TG


Distribution of Total cholestrol for the full cohort
Frequency
0
10000
20000
30000
40000
0
200
400
600
800
1000
Total cholestrol


Distribution of eGFR for the full cohort
Frequency
0
5000
15000
25000
0
50
100
150
200
eGFR

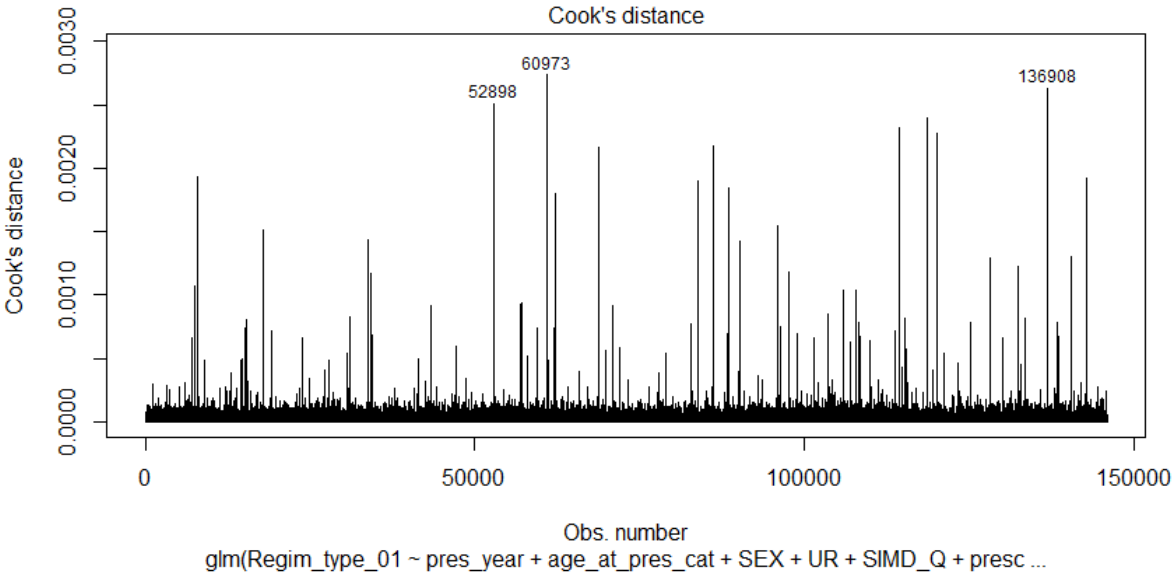
Appendix S.4.2: Regression assumptions test results

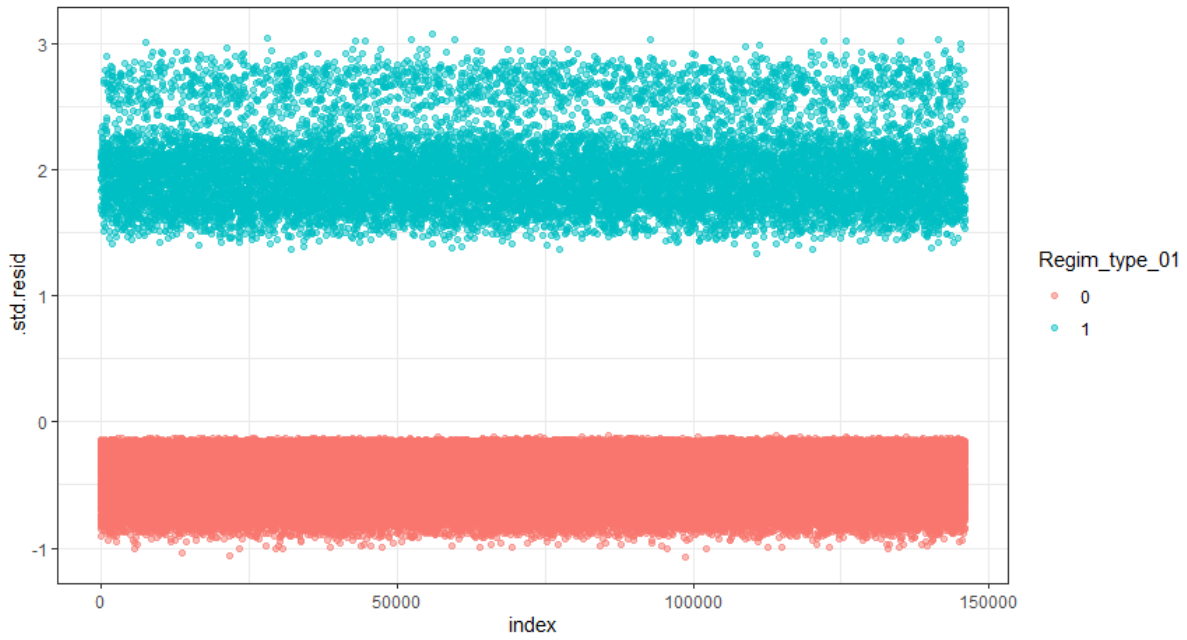
- Little test:

statistic	df	p.value	missing.patterns
9719.029	507	0	92

A- By regimen type

- Assumption:
  - Influential effect:





- Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	sqr(GVIF^(1/(2*Df))
pres_year	1.067201	1	1.033054	1.067201
age_at_pres_cat	1.388899	1	1.178516	1.388899
SEX	1.127028	1	1.061616	1.127028
UR	1.977452	8	1.043534	1.088963
SIMD_Q	1.94282	5	1.068669	1.142054
prescriber_type2	1.022117	1	1.010998	1.022117
ALL_IHD	1.403416	1	1.184658	1.403416
HTN	1.341109	1	1.158063	1.341109
HF	1.41725	1	1.190483	1.41725
stroke	1.053058	1	1.026186	1.053058
PVD	1.063136	1	1.031085	1.063136
liver_disease	1.22241	1	1.105627	1.22241
Lipid_drugs	1.32696	1	1.151937	1.32696
antipsycotic	1.038852	1	1.019241	1.038852
Thiazide_diuretics	1.170317	1	1.081812	1.170317
Beta_blocker	1.305722	1	1.142682	1.305722
Angiotensin_inhibitors	1.354437	1	1.163803	1.354437
CCB	1.17296	1	1.083033	1.17296
polypharmacy_3levels	1.673644	2	1.137407	1.293694
BMI_Cat	1.199625	5	1.018368	1.037072
A1C_3months_cat	1.555479	3	1.076409	1.158657
HDL_Cat	4.290705	4	1.199682	1.439237
TG_Cat	3.480825	3	1.231063	1.515517
TCholesterol_Cat	5.086679	3	1.311412	1.719801
eGFR_cat	2.362879	5	1.089793	1.187649
CCI_score_QUAN_cat	1.935357	3	1.116332	1.246198

- Model fitness:
  - **LRT:**

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 145851 80686

2 145908 90102 -57 -9415.5 **< 2.2e-16 *****

-Full model compared to the intercept model: Analysis of Deviance Table

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 145851 80686

2 145908 90102 -57 -9415.5 < 2.2e-16 ***

  - **Goodness of fit test**

X-squared = 137531, df = 140625, p-value = 1

- **PR2**

llh llhNull G2 McFadden r2ML r2CU

-4.034311e+04 -4.505084e+04 9.415453e+03 1.044981e-01 6.249166e-02 1.356392e-01

- **Hoslem test**

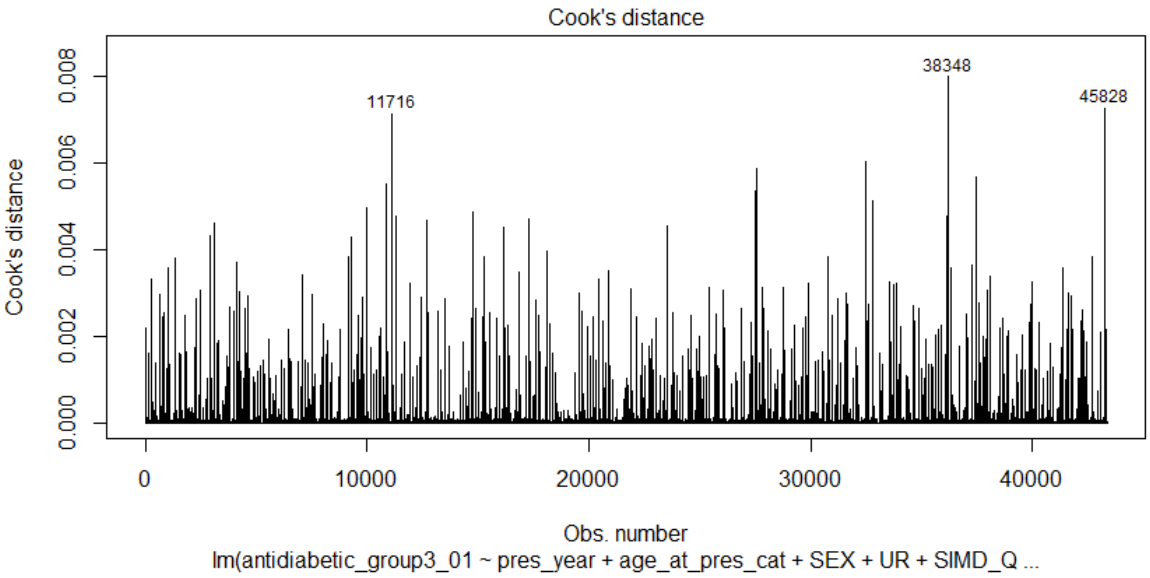
X-squared = 11.028, df = 8, p-value = 0.2001

B- By antidiabetic class: drop other_mono, other_comb

❖ monotherapy vs. metformin

➢ Assumption:

- Influential effect:



- Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	sqr(GVIF^(1/(2*Df))
pres_year	1.045019	9	1.002449	1.004905
age_at_pres_cat	1.317366	1	1.147766	1.317366
SEX	1.163126	1	1.078483	1.163126
UR	1.230448	7	1.014923	1.030069
SIMD_Q	1.214484	4	1.024587	1.049779
prescriber_type2	1.029729	1	1.014756	1.029729
ALL_IHD	1.403644	1	1.184755	1.403644
HTN	1.306647	1	1.143087	1.306647
HF	1.366195	1	1.168843	1.366195
stroke	1.034686	1	1.017195	1.034686
PVD	1.052887	1	1.026103	1.052887
liver_disease	1.18778	1	1.089853	1.18778
Lipid_drugs	1.275127	1	1.129215	1.275127
antipsycotic	1.031026	1	1.015394	1.031026
Thiazide_diuretics	1.158569	1	1.076368	1.158569
Beta_blocker	1.308203	1	1.143767	1.308203

Angiotensin_inhibitors	1.27733	1	1.13019	1.27733
CCB	1.145034	1	1.070063	1.145034
polypharmacy_3levels	1.50058	2	1.106789	1.224982
BMI_Cat	1.125416	2	1.029979	1.060856
A1C_3months_cat	1.090766	2	1.021958	1.044397
HDL_Cat	1.248424	2	1.057038	1.117329
TG_Cat	1.318282	2	1.071524	1.148164
TCholesterol_Cat	1.342984	2	1.076509	1.158872
eGFR_cat	1.125117	1	1.060715	1.125117
CCI_score_QUAN_cat	1.718655	3	1.094456	1.197833

- Model fitness:
  - **LRT:**

Resid. df Resid. Dev Test Df LR stat. Pr(Chi)

1 260124 28030.33

2 259818 23220.33 1 vs. 2 306 4810.001 0

Full model to the intercept model: Likelihood ratio tests of Multinomial Models

Resid. df Resid. Dev Test Df LR stat. Pr(Chi)

1 259962 24168.65

2 259818 23220.33 1 vs. 2 144 948.3209 0

  - **Goodness of fit:**

X-squared = 1007.6, df = 12, p-value < 2.2e-16

  - **PR2**

llh llhNull G2 McFadden r2ML r2CU

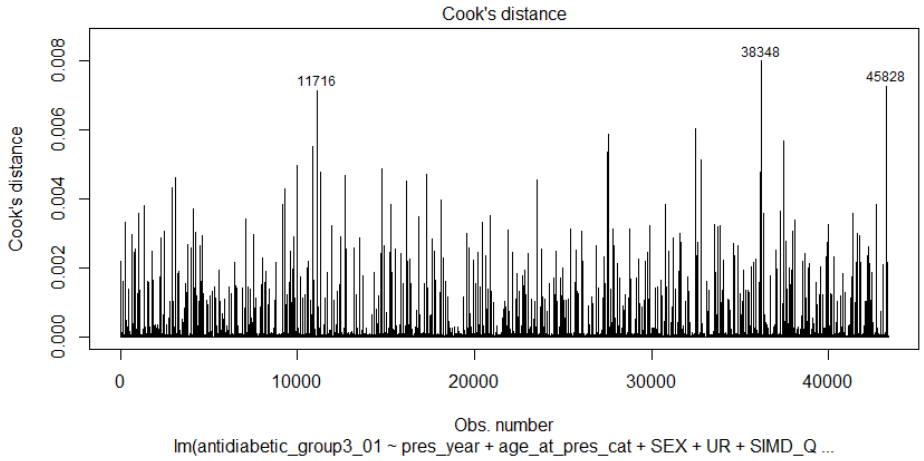
-1.161016e+04 -1.401516e+04 4.810001e+03 1.715999e-01 1.050116e-01 2.205479e-01

  - **Hoslem test**

X-squared = 72.455, df = 48, p-value = 0.01283

- combination vs. metformin

- Assumption:
  - Influential effect:



- Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	SQR(GVIF^(1/(2*Df))
pres_year	1.045446	9	1.002472	1.00495
age_at_pres_cat	1.302779	1	1.141393	1.302779
SEX	1.164321	1	1.079037	1.164321
UR	1.230436	7	1.014922	1.030067
SIMD_Q	1.215764	4	1.024722	1.050056
prescriber_type2	1.0291	1	1.014446	1.0291
ALL_IHD	1.404626	1	1.185169	1.404626
HTN	1.301782	1	1.140956	1.301782
HF	1.334403	1	1.155164	1.334403
stroke	1.034468	1	1.017088	1.034468
PVD	1.050629	1	1.025002	1.050629
liver_disease	1.183145	1	1.087725	1.183145
Lipid_drugs	1.278064	1	1.130515	1.278064
antipsycotic	1.03058	1	1.015175	1.03058
Thiazide_diuretics	1.163683	1	1.078742	1.163683
Beta_blocker	1.312325	1	1.145568	1.312325
Angiotensin_inhibitors	1.280362	1	1.131531	1.280362
CCB	1.147903	1	1.071402	1.147903
polypharmacy_3levels	1.500234	2	1.106725	1.224841
BMI_Cat	1.109445	2	1.026305	1.053302
A1C_3months_cat	1.091706	2	1.022178	1.044847
HDL_Cat	1.245297	2	1.056375	1.115929
TG_Cat	1.318826	2	1.071635	1.148401
TCholesterol_Cat	1.341045	2	1.07612	1.158035
eGFR_cat	1.09666	1	1.047215	1.09666
CCI_score_QUAN_cat	1.667817	3	1.088992	1.185904

- Model fitness:
  - **LRT:**

Resid. df	Resid. Dev	Test	Df	LR stat.	Pr(Chi)
1	554411	23133.18			
2	554099	23293.19	1 vs. 2	312	-160.0072	1

Full model to the intercept model: Likelihood ratio tests of Multinomial Models

Resid. df	Resid. Dev	Test	Df	LR stat.	Pr(Chi)
1	554762	25641.54			
2	554099	23293.19	1 vs. 2	663	2348.352	0

  - **Goodness of fit:**

X-squared = 3009.8, df = 39, p-value < 2.2e-16

  - **PR2**

llh	llhNull	G2	McFadden	r2ML	r2CU
-1.164659e+04	-1.282077e+04	2.348352e+03	9.158389e-02	5.354207e-02	1.185456e-01

  - **Hoslem test**

X-squared = 244.73, df = 104, p-value = 2.329e-13

Appendix S.4.3: R script at the stage of drug initiation

#A- prescribing trend

#1- monotherapy vs. combination over study period: total sample size = 145,909

```
combination_initiation_allYears_full$Regim_type <- 'Combination'

Monotherapy_initiation_allYears_full$Regim_type <- 'Monotherapy'

MONO <- Monotherapy_initiation_allYears_full[, c(1, 6, 19)]

COMB <- combination_initiation_allYears_full[, c(1, 6, 18)]

MONO_COMB <- rbind(MONO, COMB)

MONO_COMB$pres_year <- as.factor(MONO_COMB$pres_year)
```

#A- Frequency/percentage

```
MONO_COMB_Freq <- Table1(~ Regim_type | factor(pres_year), data = MONO_COMB, overall= 'Total')
```

#B- Absolute/relative change: calculate it in Excel using the original frequency Table without percentage

```
tab <- Table(MONO_COMB$pres_year, MONO_COMB$Regim_type)

tab <- as.data.frame(tab)

colnames(tab) <- c('Prescription_Year', 'Regimen_Type', 'Frequency')
```

#Ctrend test: CALCULATE P-VALE AND ADD IT TO HE FREQUENCY TABLE

```
tab <- Table(MONO_COMB$pres_year, MONO_COMB$Regim_type)

Pvalue <- CochranArmitageTest(tab)
```

#Frequency plot

```
tab <- tab %>% group_by(Prescription_Year) %>% mutate(percentage= round(Patients_Number/sum(Patients_Number)*100, 2))

MONO_COMB_plot_percent <- ggplot(tab, aes(Prescription_Year, percentage, group= Regimen_Type, colour= Regimen_Type)) + geom_line() + geom_point(size= 4, shape = 19, fill= 'white') + theme(text = element_text(size = 16)) + ylab('% of patients') + xlab('Calendar year') +theme_light()
```

##- MONOTHERAPY

#A-summary Tables for frequency and %:

```
Monotherapy_initiation_allYears_full$antidiabetic_group3 <- Monotherapy_initiation_allYears_full$antidiabetic_group2

Monotherapy_initiation_allYears_full$antidiabetic_group3[Monotherapy_initiation_allYears_full$antidiabetic_group2 %in% c('alpha-glucosidase-inhibitor', 'meglitinide')] <- 'Other'
```

Monotherapy_full_Freq_group3 <- Table1(~ antidiabetic_group3 | factor(pres_year), data = Monotherapy_initiation_allYears_full, overall= 'Total')

#Approved name summary:

Monotherapy_full_Freq_agent3 <- Table1(~ approved_name3 | factor(pres_year), data = Monotherapy_initiation_allYears_full, overall= 'Total')

#Summarise agents per group (to find percentage of each agents per each group)

#Ex. DPP4-I

DPP4I <-
Monotherapy_initiation_allYears_full[Monotherapy_initiation_allYears_full$antidiabetic_group3 == 'DPP4-I',]

Monotherapy_full_DPP4I <- Table1(~ approved_name3 | factor(pres_year), data = DPP4I, overall= 'Total')

#B- relative and absolute change: calculate it in Excel using the original frequency Table without percentage

tab <- Table(Monotherapy_initiation_allYears_full$pres_year,
Monotherapy_initiation_allYears_full$antidiabetic_group3)

tab <- as.data.frame(tab)

colnames(tab) <- c('Prescription_Year', 'antidiabetic_group', 'Frequency')

#c- trend test: each class versus the other classes

##cochrane_armitage test

#ex. biguanide vs. others

biguanide_others <- Monotherapy_initiation_allYears_full

biguanide_others$group_test <- biguanide_others$antidiabetic_group3

biguanide_others$group_test[biguanide_others$group_test %in% c('DPP4-I', 'GLP1-RA', 'MULTIPLE INSULIN REGIMEN', 'Other', 'SGLT2-I', 'SINGLE INSULIN REGIMEN', 'SU', 'TZD')] <- 'Other-groups'

biguanide_trend_test <- Table(biguanide_others$pres_year, biguanide_others$group_test)

biguanide_trend_test <- CochranArmitageTest(biguanide_trend_test)

#3- plot:

#antidiabetic group

#1- metformin vs. others

Monotherapy_initiation_allYears_full$antidiabetic_group_plot <-
Monotherapy_initiation_allYears_full$antidiabetic_group2

Monotherapy_initiation_allYears_full$antidiabetic_group_plot[Monotherapy_initiation_allYears_full$antidiabetic_group_plot %in% c('alpha-glucosidase-inhibitor', 'DPP4-I', 'GLP1-RA', 'insulin', 'meglitinide', 'SGLT2-I', 'SU', 'TZD')] <- 'Other_groups'

```
Table_antidiabeticgroup_plot <- Table(Monotherapy_initiation_allYears_full$pres_year,
Monotherapy_initiation_allYears_full$antidiabetic_group_plot)

Table_antidiabeticgroup_plot <- as.data.frame(Table_antidiabeticgroup_plot)

colnames(Table_antidiabeticgroup_plot) <- c('Prescription_Year', 'Antidiabetic_group',
'Patients_Number')

Table_antidiabeticgroup_plot <- Table_antidiabeticgroup_plot %>% group_by(Prescription_Year)
%>% mutate(percentage_of_patients= round(Patients_Number/sum(Patients_Number)*100, 2))

Monotherapy_full_met_others_plot <- ggplot(Table_antidiabeticgroup_plot, aes(Prescription_Year,
percentage_of_patients, group= Antidiabetic_group, colour= Antidiabetic_group)) + geom_line() +
geom_point(size= 4, shape = 19, fill= 'white') +theme_light()

Monotherapy_full_met_others_plot <- Monotherapy_full_met_others_plot + theme(text =
element_text(size = 16))

Monotherapy_full_met_others_plot <- Monotherapy_full_met_others_plot + ylab('% of patients') +
xlab('Calendar year')
```

#2- plot to display the distribution of all groups other than metformin

```
Other_groups_plot_subset <-
Monotherapy_initiation_allYears_full[Monotherapy_initiation_allYears_full$antidiabetic_group_plot
== 'Other_groups', ]
```

#antidiabetic group:

```
Other_groups_antidiabeticgroup3 <- Table(Other_groups_plot_subset$pres_year,
Other_groups_plot_subset$antidiabetic_group3)

Other_groups_antidiabeticgroup3 <- as.data.frame(Other_groups_antidiabeticgroup3)

colnames(Other_groups_antidiabeticgroup3) <- c('Prescription_Year', 'Antidiabetic_group',
'Patients_Number')

Other_groups_antidiabeticgroup3 <- Other_groups_antidiabeticgroup3 %>%
group_by(Prescription_Year) %>% mutate(percentage_of_patients =
round(Patients_Number/sum(Patients_Number)*100, 2))

Other_groups_full_group3_Freq_plot <- ggplot(Other_groups_antidiabeticgroup3,
aes(Prescription_Year, percentage_of_patients, group= Antidiabetic_group, colour=
Antidiabetic_group)) + geom_line() + geom_point(size= 4, shape = 19, fill= 'white') + theme(text =
element_text(size = 16)) + ylab('% of patients') + xlab('Calendar year') +theme_light()
```

#plots for agents within each group:

```
#ex. SU

su_monotherapy <-
Monotherapy_initiation_allYears_full[Monotherapy_initiation_allYears_full$antidiabetic_group ==
'SU', ]

Table(su_monotherapy$approved_name3)
```

```
su_monotherapy_agents <- Table(su_monotherapy$pres_year, su_monotherapy$approved_name3)

su_monotherapy_agents <- as.data.frame(su_monotherapy_agents)

colnames(su_monotherapy_agents) <- c('Prescription_Year', 'Agents', 'Patients_Number')

su_monotherapy_agents <- su_monotherapy_agents %>% group_by(Prescription_Year) %>%
mutate(percentage= round(Patients_Number/sum(Patients_Number)*100, 2))

su_monotherapy_agents_plot_percent <- ggplot(su_monotherapy_agents, aes(Prescription_Year,
percentage, group= Agents, colour= Agents)) + geom_line() + geom_point(size= 4, shape = 19, fill=
'white') + theme(text = element_text(size = 16)) + ylab('% of patients') + xlab('Calendar year')
+theme_light()
```

###2- Combination:

##1- Dual therapy:

#A-summary Tables for frequency and %

```
Combination_dualtherapy_allYears$combination_group3 <-
Combination_dualtherapy_allYears$combination_group2

Combination_dualtherapy_Freq_group3 <- Table1(~ combination_group3 | factor(pres_year), data =
Combination_dualtherapy_allYears, overall= 'Total')

Combination_dualtherapy_allYears$combination_group3[Combination_dualtherapy_allYears$combi
nation_group3 %in% c('alpha-glucosidase-inhibitor+biguanide', 'alpha-glucosidase-inhibitor+insulin',
'alpha-glucosidase-inhibitor+SU', 'biguanide+meglitinide', 'DPP4-I+insulin', 'DPP4-I+meglitinide',
'DPP4-I+SGLT2-I', 'DPP4-I+TZD', 'GLP1-RA+insulin', 'GLP1-RA+SGLT2-I', 'GLP1-RA+SU',
'meglitinide+insulin', 'SGLT2-I+insulin', 'SGLT2-I+SU', 'SU+TZD', 'TZD+insulin')] <- 'Other'
```

#Summarise antidiabetic groups:

```
Combination_dualtherapy_Freq_group3 <- Table1(~ combination_group3 | factor(pres_year), data =
Combination_dualtherapy_allYears, overall= 'Total')
```

#Approved name summary:

```
Combination_Dual_Freq_agent_group3 <- Table1(~ combination_type3 | factor(pres_year), data =
Combination_dualtherapy_allYears, overall= 'Total')
```

#Summarise agents per group

```
#ex. biguanide+DPP4-I

biguanide_DPP4I <-
Combination_dualtherapy_allYears[Combination_dualtherapy_allYears$combination_group3 ==
'biguanide+DPP4-I', ]

Combination_Dual_biguanide_DPP4I <- Table1(~ combination_type3 | factor(pres_year), data =
biguanide_DPP4I, overall= 'Total')
```

#B- absolute and relative change: calculate in Excel

```
tab <- Table(Combination_dualtherapy_allYears$pres_year,
Combination_dualtherapy_allYears$combination_group3)
```

```
tab <- as.data.frame(tab)

colnames(tab) <- c('Prescription_Year', 'combination_group', 'Frequency')
```

#C- trend test: each regimen versus all other dual regimens

```
#ex. biguanide+DPP4-I vs. others

biguanide_DPP4I_others <- Combination_dualtherapy_allYears

biguanide_DPP4I_others$group_test <- biguanide_DPP4I_others$combination_group3

biguanide_DPP4I_others$group_test[biguanide_DPP4I_others$group_test %in% c('biguanide+GLP1-RA', 'biguanide+insulin', 'biguanide+SGLT2-I', 'biguanide+SU', 'biguanide+TZD', 'DPP4-I+SU', 'Other', 'SU+insulin')] <- 'Other-groups'

biguanide_DPP4I_trend_test <- Table(biguanide_DPP4I_others$pres_year, biguanide_DPP4I_others$group_test)

biguanide_DPP4I_trend_test <- CochranArmitageTest(biguanide_DPP4I_trend_test)
```

#D- Frequency plot

```
tab_comb_dual <- Table(Combination_dualtherapy_allYears$pres_year, Combination_dualtherapy_allYears$combination_group3)

tab_comb_dual <- as.data.frame(tab_comb_dual)

colnames(tab_comb_dual) <- c('Prescription_Year', 'Combination_group', 'Patients_Number')

tab_comb_dual <- tab_comb_dual %>% group_by(Prescription_Year) %>% mutate(percentage= round(Patients_Number/sum(Patients_Number)*100, 2))

comb_dual_plot_percent <- ggplot(tab_comb_dual, aes(Prescription_Year, percentage, group= Combination_group, colour= Combination_group)) + geom_line() + geom_point(size= 4, shape = 19, fill= 'white') + theme(text = element_text(size = 16)) + ylab('% of patients') + xlab('Calendar year')+ theme_light()
```

##2- more than two drugs:

#A- frequency and percentage:

```
Combination_morethantwo_Freq_group3 <- Table1(~ combination_group3 | factor(pres_year), data = Combination_morethantwo_allYears, overall= 'Total')

Combination_morethantwo_Freq_group3
```

#Approved name summary:

```
Combination_morethantwo_Freq_agent_group3 <- Table1(~ combination_type3 | factor(pres_year), data = Combination_morethantwo_allYears, overall= 'Total')
```

#Summarise agents per group

```
#ex. biguanide+DPP4-I+SU
```

```
biguanide_DPP4I_SU <-
Combination_morethantwo_allYears[Combination_morethantwo_allYears$combination_group3 ==
'biguanide+DPP4-I+SU', ]

Combination_MORETHANTWO_biguanide_DPP4I_SU <- Table1(~ combination_type3 |
factor(pres_year), data = biguanide_DPP4I_SU, overall= 'Total')
```

#B- absolute and relative change: calculate in Excel

```
tab <- Table(Combination_morethantwo_allYears$pres_year,
Combination_morethantwo_allYears$combination_group3)

tab <- as.data.frame(tab)

colnames(tab) <- c('Prescription_Year', 'combination_group', 'Frequency')
```

#C- trend test: each regimen compared to the remaining triple or more

```
#ex. biguanide+DPP4-I+insulin vs. others

biguanide_DPP4Iinsulin_others <- Combination_morethantwo_allYears

biguanide_DPP4Iinsulin_others$group_test <- biguanide_DPP4Iinsulin_others$combination_group3

biguanide_DPP4Iinsulin_others$group_test[biguanide_DPP4Iinsulin_others$group_test %in%
c('biguanide+DPP4-I+SGLT2-I', 'biguanide+DPP4-I+SU', 'biguanide+GLP1-RA+insulin',
'biguanide+GLP1-RA+SU', 'biguanide+SGLT2-I+insulin', 'biguanide+SGLT2-I+SU',
'biguanide+SU+insulin', 'biguanide+SU+TZD', 'Other')] <- 'Other-groups'

biguanide_DPP4I_insulin_trend_test <- Table(biguanide_DPP4Iinsulin_others$pres_year,
biguanide_DPP4Iinsulin_others$group_test)

biguanide_DPP4I_insulin_trend_test <- CochranArmitageTest(biguanide_DPP4I_insulin_trend_test)
```

#D- Frequency plot

```
tab_comb_morethantwo <- Table(Combination_morethantwo_allYears$pres_year,
Combination_morethantwo_allYears$combination_group3)

tab_comb_morethantwo <- as.data.frame(tab_comb_morethantwo)

colnames(tab_comb_morethantwo) <- c('Prescription_Year', 'Combination_group',
'Patients_Number')

tab_comb_morethantwo <- tab_comb_morethantwo %>% group_by(Prescription_Year) %>%
mutate(percentage= round(Patients_Number/sum(Patients_Number)*100, 2))

comb_morethantwo_plot_percent <- ggplot(tab_comb_morethantwo, aes(Prescription_Year,
percentage, group= Combination_group, colour= Combination_group)) + geom_line() +
geom_point(size= 4, shape = 19, fill= 'white') + theme(text = element_text(size = 16)) + ylab('% of
patients') + xlab('Calendar year')+ theme_light()

######################
```

###B- summary statistics

#change NA to unknown for categorical variables with missing data to calculate the % of each level out of the total 145,909 (without excluding the missing obs)

#ex. UR variable

```
MONO_COMB2$UR <- as.character(MONO_COMB2$UR)

MONO_COMB2$UR[is.na(MONO_COMB2$UR)] <- 'unknown'
```

#1- Full cohort and by regimen type

###summary for all variables:

#as overall and by regimen type: Mono vs. combination

#categorical variables:

```
summary_statis_byRegimen_Cat_allvars <- MONO_COMB2 %>% select(SEX, age_at_pres_cat, UR, SIMD_Q, prescriber_type2,ALL_IHD, HTN, HF, stroke, PVD, liver_disease, diabetic_retinopathy, retinal_disease, diabetic_neuropathy, neuropathy_disease, CCI_score_QUAN_cat, Lipid_drugs, antipsycotic, Thiazide_diuretics, Beta_blocker, Angiotensin_inhibitors, CCB, polypharmacy_3levels, BMI_Cat, A1C_3months_cat, HDL_Cat, TCholesterol_Cat, TG_Cat, eGFR_cat, Regim_type) %>% tbl_summary(by=Regim_type, statistic =  list(all_continuous() ~ '{mean} ({sd})', all_categorical() ~ '{p}% ({n}/{N})'), digits = list(all_categorical() ~ c(2, 0, 0))) %>% add_overall() %>% add_p(test = list(all_categorical() ~ 'chisq.test')) %>% bold_labels()

summary_statis_byRegimen_Cat_allvars <- summary_statis_byRegimen_Cat_allvars %>% gtsummary::as_tibble()
```

#continous variable:

```
summary_statis_byRegimen_othercontinousvar <- MONO_COMB2 %>% select(age_at_presc, num_of_ConcoMed, BMI, A1C_3months, A1C_3months_percent, HDL_mgdl, TG_mgdl, Tcholestrol_mgdl, Creatinine_mgdl, eGFR, Regim_type) %>% tbl_summary(by=Regim_type, statistic = list(all_continuous() ~ '{median} ({p25}, {p75})', all_categorical() ~ '{p} %({n}/{N})'), digits = list(all_categorical() ~ c(2)))%>% add_overall() %>% add_p(test = list(all_continuous() ~ 'wilcox.test', all_categorical() ~ 'chisq.test')) %>% bold_labels()

summary_statis_byRegimen_othercontinousvar <- summary_statis_byRegimen_othercontinousvar %>% gtsummary::as_tibble()
```

#2- Monotherapy

```
mono_summary_regimentypedetailed <- MONO_COMB2[MONO_COMB2$Regim_type== 'Monotherapy', ]
```

####summary statistics by antidiabetic group

#categorical variables:

```
summary_statis_monoClass_Cat_allvars <- mono_summary_regimentypedetailed %>% select(SEX, age_at_pres_cat, UR, SIMD_Q, prescriber_type2,ALL_IHD, HTN, HF, stroke, PVD, liver_disease, diabetic_retinopathy, retinal_disease, diabetic_neuropathy, neuropathy_disease, CCI_score_QUAN_cat, Lipid_drugs, antipsycotic, Thiazide_diuretics, Beta_blocker, Angiotensin_inhibitors, CCB, polypharmacy_3levels, BMI_Cat, A1C_3months_cat, HDL_Cat,
```

```
TCholesterol_Cat, TG_Cat, eGFR_cat, antidiabetic_group3) %>%
tbl_summary(by=antidiabetic_group3, statistic =  list(all_continuous() ~ '{mean} ({sd})',
all_categorical() ~ '{p}% ({n}/{N})'), digits = list(all_categorical() ~ c(2, 0, 0))) %>% add_p(test =
list(all_categorical() ~ 'fisher.test'), test.args = all_categorical() ~ list(simulate.p.value=TRUE)) %>%
bold_labels()

summary_statis_monoClass_Cat_allvars <- summary_statis_monoClass_Cat_allvars %>%
gtsummary::as_tibble()
```

 # continuous variable:

```
summary_statis_monoClass_othercontinousvar <- mono_summary_regimentypedetailed %>%
select(age_at_presc, num_of_ConcoMed, BMI, A1C_3months, A1C_3months_percent, HDL_mgdl,
TG_mgdl, Tcholestrol_mgdl, Creatinine_mgdl, eGFR, antidiabetic_group3) %>%
tbl_summary(by=antidiabetic_group3, statistic =  list(all_continuous() ~ '{median} ({p25}, {p75})',
all_categorical() ~ '{p} %({n}/{N})'), digits = list(all_categorical() ~ c(2))) %>% add_p(test =
list(all_continuous() ~ 'kruskal.test', all_categorical() ~ 'chisq.test')) %>% bold_labels()

summary_statis_monoClass_othercontinousvar <- summary_statis_monoClass_othercontinousvar
%>% gtsummary::as_tibble()
```

#3- Combination:

```
comb_summary_regimentypedetailed <- MONO_COMB2[MONO_COMB2$Regim_type==
'Combination', ]
```

#categorical variables:

```
summary_statis_byCOMBRegimen_Cat_allvars <- comb_summary_regimentypedetailed %>%
select(SEX, age_at_pres_cat, UR, SIMD_Q, prescriber_type2,ALL_IHD, HTN, HF, stroke, PVD,
liver_disease, diabetic_retinopathy, retinal_disease, diabetic_neuropathy, neuropathy_disease,
CCI_score_QUAN_cat, Lipid_drugs, antipsycotic, Thiazide_diuretics, Beta_blocker,
Angiotensin_inhibitors, CCB, polypharmacy_3levels, BMI_Cat, A1C_3months_cat, HDL_Cat,
TCholesterol_Cat, TG_Cat, eGFR_cat, Regimen_type_detailed) %>%
tbl_summary(by=Regimen_type_detailed, statistic =  list(all_continuous() ~ '{mean} ({sd})',
all_categorical() ~ '{p}% ({n}/{N})'), digits = list(all_categorical() ~ c(2, 0, 0))) %>% add_p(test =
list(all_categorical() ~ 'chisq.test')) %>% bold_labels()

summary_statis_byCOMBRegimen_Cat_allvars <- summary_statis_byCOMBRegimen_Cat_allvars
%>% gtsummary::as_tibble()
```

#continous variable:

```
summary_statis_byCOMBRegimen_othercontinousvar <- comb_summary_regimentypedetailed %>%
select(age_at_presc, num_of_ConcoMed, BMI, A1C_3months, A1C_3months_percent, HDL_mgdl,
TG_mgdl, Tcholestrol_mgdl, Creatinine_mgdl, eGFR, Regimen_type_detailed) %>%
tbl_summary(by=Regimen_type_detailed, statistic =  list(all_continuous() ~ '{median} ({p25}, {p75})',
all_categorical() ~ '{p} %({n}/{N})'), digits = list(all_categorical() ~ c(2))) %>% add_p(test =
list(all_continuous() ~ 'wilcox.test', all_categorical() ~ 'chisq.test')) %>% bold_labels()

summary_statis_byCOMBRegimen_othercontinousvar <-
summary_statis_byCOMBRegimen_othercontinousvar %>% gtsummary::as_tibble()
```

####summary statistics by antidiabetic group:

#categorical variables:

summary_statis_COMBClass_Cat_allvars <- comb_summary_regimentypedetailed %>% select(SEX, age_at_pres_cat, UR, SIMD_Q, prescriber_type2,ALL_IHD, HTN, HF, stroke, PVD, liver_disease, diabetic_retinopathy, retinal_disease, diabetic_neuropathy, neuropathy_disease, CCI_score_QUAN_cat, Lipid_drugs, antipsycotic, Thiazide_diuretics, Beta_blocker, Angiotensin_inhibitors, CCB, polypharmacy_3levels, BMI_Cat, A1C_3months_cat, HDL_Cat, TCholesterol_Cat, TG_Cat, eGFR_cat, antidiabetic_group3) %>% tbl_summary(by=antidiabetic_group3, statistic = list(all_continuous() ~ '{mean} ({sd})', all_categorical() ~ '{p}% ({n}/{N})'), digits = list(all_categorical() ~ c(2, 0, 0))) %>% add_p(test = list(all_categorical() ~ 'fisher.test'), test.args = all_categorical() ~ list(simulate.p.value=TRUE)) %>% bold_labels()

summary_statis_COMBClass_Cat_allvars <- summary_statis_COMBClass_Cat_allvars %>% gtsummary::as_tibble()

 # continuous variable:

summary_statis_COMBClass_othercontinousvar <- comb_summary_regimentypedetailed %>% select(age_at_presc, num_of_ConcoMed, BMI, A1C_3months, A1C_3months_percent, HDL_mgdl, TG_mgdl, Tcholestrol_mgdl, Creatinine_mgdl, eGFR, antidiabetic_group3) %>% tbl_summary(by=antidiabetic_group3, statistic = list(all_continuous() ~ '{median} ({p25}, {p75})', all_categorical() ~ '{p} %({n}/{N})'), digits = list(all_categorical() ~ c(2))) %>% add_p(test = list(all_continuous() ~ 'kruskal.test', all_categorical() ~ 'chisq.test')) %>% bold_labels()

summary_statis_COMBClass_othercontinousvar <- summary_statis_COMBClass_othercontinousvar %>% gtsummary::as_tibble()

#######

#NORMALITY TESTS:

#assess normality distribution of continuous variables:

#ex. age_at_presc

set.seed(100)

normality_age_hist <- hist(MONO_COMB$age_at_presc, main = 'Distribution of Age at presciption for the full cohort', xlab = 'Age at prescription')

normality_age_QQ <- qqnorm(MONO_COMB$age_at_presc, main = 'Distribution of Age at presciption for the full cohort', xlab = 'Age at prescription')

set.seed(100)

AGE_RNORM <- rnorm(MONO_COMB$age_at_presc)

normality_test_AGE_fullcohort <- ks.test(AGE_RNORM, 'pnorm')

##############################

#REGRESSION

#A- Original cohort: MONO_COMB (missing data was considered a separate level: 'unknown')

#littile test for MCAR testing

littile_test <- mcar_test(MONO_COMB_littiletest)

#logistic regression for the entire cohort

#recode NA as unknown

MONO_COMB_NAasunknown <- MONO_COMB

MONO_COMB_NAasunknown <- MONO_COMB_NAasunknown[, c(1:3, 5:7, 9, 11, 16:18, 21, 25, 38, 40:43, 47, 50, 51:54, 58, 60, 74, 77, 80, 83, 86, 95, 112, 114:118)] ##take only categorical variable

#ex. UR

MONO_COMB_NAasunknown$UR <- as.character(MONO_COMB_NAasunknown$UR)

MONO_COMB_NAasunknown$UR[is.na(MONO_COMB_NAasunknown$UR)] <- 'unknown'

MONO_COMB_NAasunknown[sapply(MONO_COMB_NAasunknown, is.character)] <- lapply(MONO_COMB_NAasunknown[sapply(MONO_COMB_NAasunknown, is.character)], as.factor) #CHANGE THE CHARCHTER VARIABLE BACK TO FACTOR

#1- by regimen_type as an outcome variable

#Recode regimen type to 0, 1

MONO_COMB_NAasunknown$Regim_type_01 <- if_else((MONO_COMB_NAasunknown$Regim_type == 'Combination'), '1', '0') #to be able to do log reg we need the outcome to be as 01: combination =1 and monotherapy =0

MONO_COMB_NAasunknown$Regim_type_01 <- as.factor(MONO_COMB_NAasunknown$Regim_type_01)

###check for logistic regression assumptions:

#influential cases:

str(MONO_COMB_NAasunknown)

LOG_REG_fullcohort_byregimen_model1 <- glm(Regim_type_01 ~ pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, data = MONO_COMB_NAasunknown, family = binomial)

plot(LOG_REG_fullcohort_byregimen_model1, which = 4, id.n = 3)

influence <- broom::augment(LOG_REG_fullcohort_byregimen_model1) %>% mutate(index = 1:n())

x <- influence %>% top_n(3, .cooksd)

ggplot(influence, aes(index, .std.resid)) + geom_point(aes(color= Regim_type_01), alpha=0.5) + theme_bw()

x <- influence %>% filter(abs(.std.resid) > 3)

#check for multicollinearity: none has vif value of > 5

```
VIF(LOG_REG_fullcohort_byregimen_model1)

multicollinearity <- as.data.frame(VIF(LOG_REG_fullcohort_byregimen_model1))
```

#Apply log reg for regimen type for the entire cohort

#a- univariate regression:

```
str(MONO_COMB_NAasunknown)

explanatory_vars <- c('pres_year', 'age_at_pres_cat', 'SEX', 'UR', 'SIMD_Q', 'prescriber_type2',
'ALL_IHD', 'HTN', 'HF', 'stroke', 'PVD',  'liver_disease', 'retinal_disease', 'neuropathy_disease',
'Lipid_drugs', 'antipsycotic', 'Thiazide_diuretics', 'Beta_blocker', 'Angiotensin_inhibitors', 'CCB',
'polypharmacy_3levels',  'BMI_Cat', 'A1C_3months_cat', 'HDL_Cat', 'TG_Cat', 'TCholesterol_Cat',
'eGFR_cat', 'CCI_score_QUAN_cat')

explanatory_vars %>% str_c('Regim_type_01 ~', .)

LOG_REG_fullcohort_byregimen_univariate_allVARs <- MONO_COMB_NAasunknown %>%
dplyr::select(all_of(explanatory_vars), Regim_type_01) %>% tbl_uvregression(method = glm,
y=Regim_type_01, method.args = list(family= 'binomial'), exponentiate = TRUE)  %>% add_global_p()

LOG_REG_fullcohort_byregimen_univariate_allVARs <-
LOG_REG_fullcohort_byregimen_univariate_allVARs %>% gtsummary::as_tibble()
```

#b- multivariate including all variables

```
LOG_REG_fullcohort_byregimen_multivariate_allVARs <- glm(Regim_type_01 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = MONO_COMB_NAasunknown, family = binomial)

summary(LOG_REG_fullcohort_byregimen_multivariate_allVARs)

LOG_REG_fullcohort_byregimen_multivariate_allVARs <-
LOG_REG_fullcohort_byregimen_multivariate_allVARs %>% tbl_regression(exponentiate = TRUE,
conf.int = TRUE) %>% add_global_p()

LOG_REG_fullcohort_byregimen_multivariate_allVARs <-
LOG_REG_fullcohort_byregimen_multivariate_allVARs %>% gtsummary::as_tibble()
```

##assess the goodness of fit of the multivariate model:

```
fitness_model1 <- glm(Regim_type_01 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = MONO_COMB_NAasunknown, family = binomial)

fitness_model2 <- glm(Regim_type_01 ~ 1, data = MONO_COMB_NAasunknown, family = binomial)
```

```
fitness_model2 <- glm(Regim_type_01 ~
pres_year+age_at_pres_cat+SEX+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_
Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, data = MONO_COMB_NAasunknown, family
= binomial)
```

#a-liklihood ratio test (lmtest pachkage)

```
anova(fitness_model1, fitness_model2, test = 'Chisq')

LRT_fitness <- lrtest(fitness_model1, fitness_model2)
```

#b-test the goodness of fit

```
chisq.test(MONO_COMB_NAasunknown$Regim_type, predict(fitness_model1))
```

#c-pseud R2 by McFadden's R2:pscl package

```
PseudoR2(fitness_model1, which = c('CoxSnell', 'Nagelkerke', 'McFadden'))

pR2_fitness <- pR2(fitness_model1)
```

#d- Hosmer lemeshow test

```
Hosleme_fitness <- hoslem.test(fitness_model1$y, fitted(fitness_model1), g=10)
```

#test the significance of each parameter in the model overall p-value across txt:

```
#ex. pres-year

lrtest(fitness_model1, 'pres_year')
```

#2- by the antidiabetic group as an outcome variable

```
#multinomial logistic regression: biguanide as ref group

#drop patients on othe_mono and other_comb

MONO_COMB_NAasunknown2 <- MONO_COMB_NAasunknown

MONO_COMB_NAasunknown2 <-
MONO_COMB_NAasunknown2[!(MONO_COMB_NAasunknown2$antidiabetic_group3 %in%
c('Other_mono', 'Other_comb')), ]

MONO_COMB_NAasunknown2$antidiabetic_group3 <-
as.factor(MONO_COMB_NAasunknown2$antidiabetic_group3)

MONO_COMB_NAasunknown2$antidiabetic_group3 <-
factor(MONO_COMB_NAasunknown2$antidiabetic_group3)

MONO_COMB_NAasunknown2$antidiabetic_group3 <-
relevel(MONO_COMB_NAasunknown2$antidiabetic_group3, ref = 'biguanide')

str(MONO_COMB_NAasunknown2)

#ex: age_at_pres_cat: applied to all studied variables
```

```
multinom_age_uni <- multinom(antidiabetic_group3 ~ age_at_pres_cat, data =
MONO_COMB_NAasunknown2)

multinom_age_uni <- multinom_age_uni %>% tbl_regression(exponentiate = TRUE, conf.int = TRUE)
%>% add_global_p()

multinom_age_uni <- multinom_age_uni %>% gtsummary::as_tibble()
```

##B- MULTIVARIATE MULTINOMIAL

#mono vs. biguanide

```
mono_vs._met <- MONO_COMB_NAasunknown2[MONO_COMB_NAasunknown2$Regim_type ==
'Monotherapy', ]

mono_vs._met$antidiabetic_group3 <- factor(mono_vs._met$antidiabetic_group3)

multinomial_intensification_class_MULTIvariate <- multinom(antidiabetic_group3 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = mono_vs._met)

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% tbl_regression(exponentiate = TRUE, conf.int = TRUE) %>% add_global_p()

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% gtsummary::as_tibble()
```

#comb vs. biguanide

```
comb_vs._met <- MONO_COMB_NAasunknown2[(MONO_COMB_NAasunknown2$Regim_type ==
'Combination' | MONO_COMB_NAasunknown2$antidiabetic_group3 == 'biguanide'), ]

comb_vs._met$antidiabetic_group3 <- factor(comb_vs._met$antidiabetic_group3)

multinomial_intensification_class_MULTIvariate <- multinom(antidiabetic_group3 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = comb_vs._met)

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% tbl_regression(exponentiate = TRUE, conf.int = TRUE) %>% add_global_p()

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% gtsummary::as_tibble()
```

#p value per var per antidiabetic class

```
#ex: DPP4-I

p_value <- MONO_COMB_NAasunknown2[MONO_COMB_NAasunknown2$antidiabetic_group3
%in% c('DPP4-I', 'biguanide'), ]
```

```
p_value$antidiabetic_group3_01 <- if_else((p_value$antidiabetic_group3 == 'biguanide'), '0', '1') #to be able to do log reg we need the outcome to be as 01: combination =1 and monotherapy =0

p_value$antidiabetic_group3_01 <- as.factor(p_value$antidiabetic_group3_01)

explanatory_vars <- c('polypharmacy_3levels', 'HDL_Cat')

explanatory_vars %>% str_c('antidiabetic_group3_01 ~', .)

p_value <- p_value %>% dplyr::select(all_of(explanatory_vars), antidiabetic_group3_01) %>% tbl_uvregression(method = glm, y=antidiabetic_group3_01, method.args = list(family= 'binomial'), exponentiate = TRUE)  %>% add_global_p()

p_value <- p_value %>% gtsummary::as_tibble()
```

#Multivariate

```
p_value <- mono_vs._met[mono_vs._met$antidiabetic_group3 %in% c('DPP4-I', 'biguanide'), ]

p_value$antidiabetic_group3_01 <- if_else((p_value$antidiabetic_group3 == 'biguanide'), '0', '1') #to be able to do log reg we need the outcome to be as 01: combination =1 and monotherapy =0

p_value$antidiabetic_group3_01 <- as.factor(p_value$antidiabetic_group3_01)

p_value <- glm(antidiabetic_group3_01 ~ pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_6months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, data = p_value, family = binomial)

p_value <- p_value %>% tbl_regression(exponentiate = TRUE, conf.int = TRUE) %>% add_global_p()

p_value <- p_value %>% gtsummary::as_tibble()

################################
```

#2- complete case regression

```
MONO_COMB_noNA <- MONO_COMB

MONO_COMB_noNA <- MONO_COMB_noNA[, c(1:3, 5:7, 9, 11, 16:18, 21, 25, 38, 40:43, 47, 50:54, 58, 60, 77, 80, 83, 86, 95, 112, 114)] ##take only categorical variable

MONO_COMB_noNA <- drop_na(MONO_COMB_noNA)

MONO_COMB_noNA[sapply(MONO_COMB_noNA, is.character)] <- lapply(MONO_COMB_noNA[sapply(MONO_COMB_noNA, is.character)], as.factor) #CHANGE THE CHARCHTER VARIABLE BACK TO FACTOR
```

#1- by regimen_type as an outcome variable

```
#Recode regimen type to 0, 1

MONO_COMB_noNA$Regim_type_01 <- if_else((MONO_COMB_noNA$Regim_type == 'Combination'), '1', '0') #to be able to do log reg we need the outcome to be as 01: combination =1 and monotherapy =0

MONO_COMB_noNA$Regim_type_01 <- as.factor(MONO_COMB_noNA$Regim_type_01)
```

```
MONO_COMB_noNA$pres_year <- as.factor(MONO_COMB_noNA$pres_year)

#multivariate including all variables

LOG_REG_fullcohort_byregimen_multivariate_allVARs <- glm(Regim_type_01 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = MONO_COMB_noNA, family = binomial)

summary(LOG_REG_fullcohort_byregimen_multivariate_allVARs)

LOG_REG_fullcohort_byregimen_multivariate_allVARs <-
LOG_REG_fullcohort_byregimen_multivariate_allVARs %>% tbl_regression(exponentiate = TRUE,
conf.int = TRUE) %>% add_global_p()

LOG_REG_fullcohort_byregimen_multivariate_allVARs <-
LOG_REG_fullcohort_byregimen_multivariate_allVARs %>% gtsummary::as_tibble()

#2- by antidiabetic class

MONO_COMB_noNA2 <- MONO_COMB_noNA

Table(MONO_COMB_noNA2$antidiabetic_group3)

MONO_COMB_noNA2 <- MONO_COMB_noNA2[!(MONO_COMB_noNA2$antidiabetic_group3 %in%
c('Other_mono', 'Other_comb')), ]

MONO_COMB_noNA2$antidiabetic_group3 <-
as.factor(MONO_COMB_noNA2$antidiabetic_group3)

MONO_COMB_noNA2$antidiabetic_group3 <- factor(MONO_COMB_noNA2$antidiabetic_group3)

MONO_COMB_noNA2$antidiabetic_group3 <- relevel(MONO_COMB_noNA2$antidiabetic_group3,
ref = 'biguanide')

MONO_COMB_noNA2$pres_year <- as.factor(MONO_COMB_noNA2$pres_year)

#mono vs. biguanide

mono_vs._met <- MONO_COMB_noNA2[MONO_COMB_noNA2$Regim_type == 'Monotherapy', ]

mono_vs._met$antidiabetic_group3 <- factor(mono_vs._met$antidiabetic_group3)

multinomial_intensification_class_MULTIvariate <- multinom(antidiabetic_group3 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = mono_vs._met)

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% tbl_regression(exponentiate = TRUE, conf.int = TRUE) %>% add_global_p()

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% gtsummary::as_tibble()

#comb vs. biguanide
```

```
comb_vs._met <- MONO_COMB_noNA2[(MONO_COMB_noNA2$Regim_type == 'Combination' |
MONO_COMB_noNA2$antidiabetic_group3 == 'biguanide'), ]

comb_vs._met$antidiabetic_group3 <- factor(comb_vs._met$antidiabetic_group3)

multinomial_intensification_class_MULTIvariate <- multinom(antidiabetic_group3 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, data = comb_vs._met)

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% tbl_regression(exponentiate = TRUE, conf.int = TRUE) %>% add_global_p()

multinomial_intensification_class_MULTIvariate <- multinomial_intensification_class_MULTIvariate
%>% gtsummary::as_tibble()

############################
```

#C- regression of imputed dataset: MONO_COMB_reg

```
MONO_COMB_imputated <- MONO_COMB_reg[, c(1:7, 9:11, 13:55, 58:60, 75:86, 92:95, 112)]
```

#2- summary for missing data PERCENTAGE: range from 0 to 45%

```
(sum(is.na(MONO_COMB_imputated))/prod(dim(MONO_COMB_imputated)))*100

mean(is.na(MONO_COMB_imputated))*100

mean(is.na(MONO_COMB_imputated$SIMD_Q))*100 #0.039%

mean(is.na(MONO_COMB_imputated$UR))*100 #0.053%

mean(is.na(MONO_COMB_imputated$BMI))*100 #32.16937%

mean(is.na(MONO_COMB_imputated$A1C_3months_percent))*100 #18.679%

mean(is.na(MONO_COMB_imputated$HDL_mgdl))*100 #27.97497%

mean(is.na(MONO_COMB_imputated$TG_mgdl))*100 #34.81211%

mean(is.na(MONO_COMB_imputated$Tcholestrol_mgdl))*100 #16.9263%

mean(is.na(MONO_COMB_imputated$Creatinine_mgdl))*100 #9.876704%

mean(is.na(MONO_COMB_imputated$eGFR))*100 #9.876704%
```

#PERCENTAGE OF PATIENTS WITH NA in at least one variable: 108387/145909*100:

```
missing_atleast_onevariable <- MONO_COMB_imputated[(is.na(MONO_COMB_imputated$SIMD_Q)
| is.na(MONO_COMB_imputated$UR) | is.na(MONO_COMB_imputated$BMI) |
is.na(MONO_COMB_imputated$A1C_3months_percent) |
is.na(MONO_COMB_imputated$HDL_mgdl) | is.na(MONO_COMB_imputated$TG_mgdl) |
is.na(MONO_COMB_imputated$Tcholestrol_mgdl) |
is.na(MONO_COMB_imputated$Creatinine_mgdl) | is.na(MONO_COMB_imputated$eGFR)), ]

missing_atleast_onevariable <- (87790/145909)*100
```

missing_atleast_onevariable #60.17%

#3- assess missing data pattern: mice package

MONO_COMB_imputated2 <- MONO_COMB_imputated[, c(1:4, 6:8, 10, 14:16, 19:21, 23, 24, 26:29, 36, 39, 41, 43:55, 58, 61, 64, 67, 71, 73, 75)]

missingness_pattern <- md.pattern(MONO_COMB_imputated2, plot = TRUE) ##WE HAVE A TOTAL OF 96 DIFFERENT PATTERN WITHTOTAL OF 205,047 MISSING CELLS

missingness_pattern <- md.pairs(MONO_COMB_imputated2)

influx_outflux <- flux(MONO_COMB_imputated2)[, c(1:3)]

FULX_PLOT <- fluxplot(MONO_COMB_imputated2)

#4- do multiple imputation

MONO_COMB_imputated2_m5 <- mice(MONO_COMB_imputated2, maxit = 0)

meth <- trial$method

PredM <- trial$predictorMatrix

PredM[, 'ID'] <- 0

set.seed(100)

MONO_COMB_imputated2_m5 <- mice(MONO_COMB_imputated2, method = meth, predictorMatrix = PredM, maxit = 10)

MONO_COMB_imputated2_m5_complete <- complete(MONO_COMB_imputated2_m5, action = 'long', include = TRUE)

#RECODE continuous variables:

#HbA1c

MONO_COMB_imputated2_m5_complete$A1C_3months_cat <- MONO_COMB_imputated2_m5_complete$A1C_3months_percent

MONO_COMB_imputated2_m5_complete$A1C_3months_cat[(MONO_COMB_imputated2_m5_complete$A1C_3months_percent < 7.0)] <- '0'

MONO_COMB_imputated2_m5_complete$A1C_3months_cat[(MONO_COMB_imputated2_m5_complete$A1C_3months_percent >= 7.0 &
MONO_COMB_imputated2_m5_complete$A1C_3months_percent < 9.0)] <- '1'

MONO_COMB_imputated2_m5_complete$A1C_3months_cat[(MONO_COMB_imputated2_m5_complete$A1C_3months_percent >= 9.0)] <- '2'

#BMI

MONO_COMB_imputated2_m5_complete$BMI_Cat <- MONO_COMB_imputated2_m5_complete$BMI

```
MONO_COMB_imputated2_m5_complete$BMI_Cat[(MONO_COMB_imputated2_m5_complete$BMI <= 24.9)] <- '0' #UNDERWEIGHT

MONO_COMB_imputated2_m5_complete$BMI_Cat[(MONO_COMB_imputated2_m5_complete$BMI >= 25.0 & MONO_COMB_imputated2_m5_complete$BMI <= 29.9)] <- '1' #OVERWEIGHT

MONO_COMB_imputated2_m5_complete$BMI_Cat[(MONO_COMB_imputated2_m5_complete$BMI >= 30.0)] <- '2' #OBESE
```

#eGFR

```
Table(MONO_COMB_imputated2_m5_complete$eGFR_cat)

MONO_COMB_imputated2_m5_complete$eGFR_cat <-
MONO_COMB_imputated2_m5_complete$eGFR

MONO_COMB_imputated2_m5_complete$eGFR_cat[(MONO_COMB_imputated2_m5_complete$eGFR >= 60)] <- '0'

MONO_COMB_imputated2_m5_complete$eGFR_cat[(MONO_COMB_imputated2_m5_complete$eGFR < 60)] <- '1'
```

#HDL

```
MONO_COMB_imputated2_m5_complete$HDL_Cat <-
MONO_COMB_imputated2_m5_complete$HDL_mgdl

MONO_COMB_imputated2_m5_complete$HDL_Cat[(MONO_COMB_imputated2_m5_complete$HDL_mgdl < 40 & MONO_COMB_imputated2_m5_complete$SEX == '1') |
(MONO_COMB_imputated2_m5_complete$HDL_mgdl < 50 &
MONO_COMB_imputated2_m5_complete$SEX == '2')] <- '0' ##low hdl

MONO_COMB_imputated2_m5_complete$HDL_Cat[(MONO_COMB_imputated2_m5_complete$HDL_mgdl >= 40 & MONO_COMB_imputated2_m5_complete$HDL_mgdl < 60 &
MONO_COMB_imputated2_m5_complete$SEX == '1') |
(MONO_COMB_imputated2_m5_complete$HDL_mgdl >= 50 &
MONO_COMB_imputated2_m5_complete$HDL_mgdl < 60 &
MONO_COMB_imputated2_m5_complete$SEX == '2')] <- '1' ##medium hdl

MONO_COMB_imputated2_m5_complete$HDL_Cat[(MONO_COMB_imputated2_m5_complete$HDL_mgdl >= 60)] <- '2' ##high hdl
```

#TG

```
MONO_COMB_imputated2_m5_complete$TG_Cat <-
MONO_COMB_imputated2_m5_complete$TG_mgdl

MONO_COMB_imputated2_m5_complete$TG_Cat[(MONO_COMB_imputated2_m5_complete$TG_mgdl < 150 )] <- '0' ##normal tg

MONO_COMB_imputated2_m5_complete$TG_Cat[(MONO_COMB_imputated2_m5_complete$TG_mgdl >= 150 & MONO_COMB_imputated2_m5_complete$TG_mgdl <= 499)] <- '1' ##mild-moderate HTG
```

```
MONO_COMB_imputated2_m5_complete$TG_Cat[(MONO_COMB_imputated2_m5_complete$TG_
mgdl >= 500)] <- '2' ## SEVER HTG


#TC

MONO_COMB_imputated2_m5_complete$TCholesterol_Cat <-
MONO_COMB_imputated2_m5_complete$Tcholestrol_mgdl

MONO_COMB_imputated2_m5_complete$TCholesterol_Cat[(MONO_COMB_imputated2_m5_comp
lete$Tcholestrol_mgdl < 200 )] <- '0' ##desirable

MONO_COMB_imputated2_m5_complete$TCholesterol_Cat[(MONO_COMB_imputated2_m5_comp
lete$Tcholestrol_mgdl >= 200 & MONO_COMB_imputated2_m5_complete$Tcholestrol_mgdl <=
239)] <- '1' ##borderline high

MONO_COMB_imputated2_m5_complete$TCholesterol_Cat[(MONO_COMB_imputated2_m5_comp
lete$Tcholestrol_mgdl >= 240)] <- '2' #hight


#change type of variable

MONO_COMB_imputated2_m5_complete[sapply(MONO_COMB_imputated2_m5_complete,
is.character)] <-
lapply(MONO_COMB_imputated2_m5_complete[sapply(MONO_COMB_imputated2_m5_complete,
is.character)], as.factor) #CHANGE THE CHARCHTER VARIABLE BACK TO FACTOR

#recode regimen type to 0, 1

MONO_COMB_imputated2_m5_complete$Regim_type_01 <-
if_else((MONO_COMB_imputated2_m5_complete$Regim_type == 'Combination'), '1', '0') #to be
able to do log reg we need the outcome to be as 01: combination =1 and monotherapy =0

MONO_COMB_imputated2_m5_complete$Regim_type_01 <-
as.factor(MONO_COMB_imputated2_m5_complete$Regim_type_01)

MONO_COMB_imputated2_m5_complete$antidiabetic_group3 <-
as.character(MONO_COMB_imputated2_m5_complete$antidiabetic_group3)

MONO_COMB_imputated2_m5_complete_dropped_Other <-
MONO_COMB_imputated2_m5_complete[!(MONO_COMB_imputated2_m5_complete$antidiabetic
_group3 %in% c('Other_comb', 'Other_mono')), ]

MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 <-
factor(MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3)

MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 <-
as.factor(MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3)

MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 <-
relevel(MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3, ref =
'biguanide')
```

```
MONO_COMB_imputated2_m5_complete_dropped_Other$pres_year <-
factor(MONO_COMB_imputated2_m5_complete_dropped_Other$pres_year)

MONO_COMB_imputated2_m5_complete_dropped_Other$pres_year <-
as.factor(MONO_COMB_imputated2_m5_complete_dropped_Other$pres_year)
```

#Logistic regression: pooling of results

#1- by regimen_type as an outcome variable

```
#convert MONO_COMB_imputated2_m5_complete to as.mids class

MONO_COMB_imputated2_m5_complete2 <- as.mids(MONO_COMB_imputated2_m5_complete)

is.mids(MONO_COMB_imputated2_m5_complete2)

identical(complete(MONO_COMB_imputated2_m5_complete2, action = 'long', include= TRUE),
MONO_COMB_imputated2_m5_complete)
```

#multivariate including all variables

```
LOG_REG_imputed_byregimen_multivariate <- with(data =
MONO_COMB_imputated2_m5_complete2, exp=glm(Regim_type_01 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, family = binomial))

LOG_REG_imputed_byregimen_multivariate <-
summary(pool(LOG_REG_imputed_byregimen_multivariate), method= 'rubin1987')
```

#global p-value

```
#ex1:

test <- with(data = MONO_COMB_imputated2_m5_complete2, exp=glm(Regim_type_01 ~
age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+
Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharma
cy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_Q
UAN_cat, family = binomial))

p_imputed1_multi <- pool.compare(LOG_REG_imputed_byregimen_multivariate, test, method =
'wald')$pvalue

#ex2:

test <- with(data = MONO_COMB_imputated2_m5_complete2, exp=glm(Regim_type_01 ~
pres_year+age_at_pres_cat+SEX+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_di
sease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polyp
harmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_sc
ore_QUAN_cat, family = binomial))

p_imputed2_multi <- pool.compare(LOG_REG_imputed_byregimen_multivariate, test, method =
'wald')$pvalue
```

#2- by antidiabetic group as an outcome variable:

```
#convert MONO_COMB_imputated2_m5_complete_dropped_Other to as.mids class

MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 <-
as.factor(MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3)

MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 <-
relevel(MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3, ref =
'biguanide')
```

#1- mono vs. met

```
mono <-
MONO_COMB_imputated2_m5_complete_dropped_Other[MONO_COMB_imputated2_m5_comple
te_dropped_Other$Regim_type == 'Monotherapy', ]

mono$antidiabetic_group3 <- factor(mono$antidiabetic_group3)

mono$antidiabetic_group3 <- as.factor(mono$antidiabetic_group3)

MONO_COMB_imputated2_m5_complete2_class <- as.mids(mono)

is.mids(MONO_COMB_imputated2_m5_complete2_class)

identical(complete(MONO_COMB_imputated2_m5_complete2_class, action = 'long', include=
TRUE), MONO_COMB_imputated2_m5_complete_dropped_Other)
```

#multivariate including all variables

```
LOG_REG_imputed_byclass_multivariate <- with(data =
MONO_COMB_imputated2_m5_complete2_class, exp=multinom(antidiabetic_group3 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+live
r_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+p
olypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+C
CI_score_QUAN_cat, model=T))

LOG_REG_imputed_byclass_multivariate <-
summary(pool(LOG_REG_imputed_byclass_multivariate))
```

#p value per var per antidiabetic class

```
#ex. GLP1-RA

subset <-
MONO_COMB_imputated2_m5_complete_dropped_Other[MONO_COMB_imputated2_m5_comple
te_dropped_Other$antidiabetic_group3 %in% c('GLP1-RA', 'biguanide'), ]

subset$antidiabetic_group3 <- factor(subset$antidiabetic_group3)

subset$antidiabetic_group3_01 <- if_else((subset$antidiabetic_group3 == 'biguanide'), '0', '1')

subset$antidiabetic_group3_01 <- as.factor(subset$antidiabetic_group3_01)

subset <- as.mids(subset)

##UR
```

```
P_value_multi <- with(data = subset, exp=glm(antidiabetic_group3_01 ~ pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, family = binomial))

test <- with(data = subset, exp=glm(antidiabetic_group3_01 ~ pres_year+age_at_pres_cat+SEX+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, family = binomial))

p_ur2_multi <- pool.compare(P_value_multi, test, method = 'wald')$pvalue
```

#2- comb vs. met

```
comb <- MONO_COMB_imputated2_m5_complete_dropped_Other[(MONO_COMB_imputated2_m5_complete_dropped_Other$Regim_type == 'Combination' | MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 == 'biguanide'), ]

comb$antidiabetic_group3 <- factor(comb$antidiabetic_group3)

comb$antidiabetic_group3 <- as.factor(comb$antidiabetic_group3)

MONO_COMB_imputated2_m5_complete2_class <- as.mids(comb)

is.mids(MONO_COMB_imputated2_m5_complete2_class)

identical(complete(MONO_COMB_imputated2_m5_complete2_class, action = 'long', include= TRUE), MONO_COMB_imputated2_m5_complete_dropped_Other)
```

#multivariate including all variables

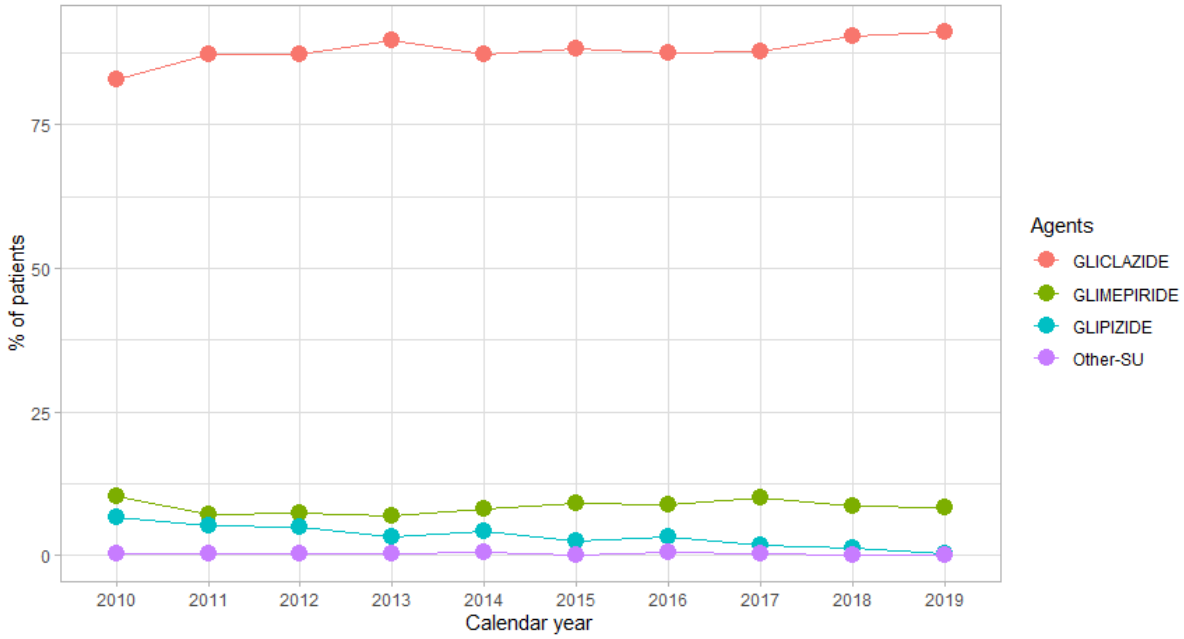
```
LOG_REG_imputed_byclass_multivariate <- with(data = MONO_COMB_imputated2_m5_complete2_class, exp=multinom(antidiabetic_group3 ~ pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, model=T))

LOG_REG_imputed_byclass_multivariate <- summary(pool(LOG_REG_imputed_byclass_multivariate))
```

#p value per var per antidiabetic class

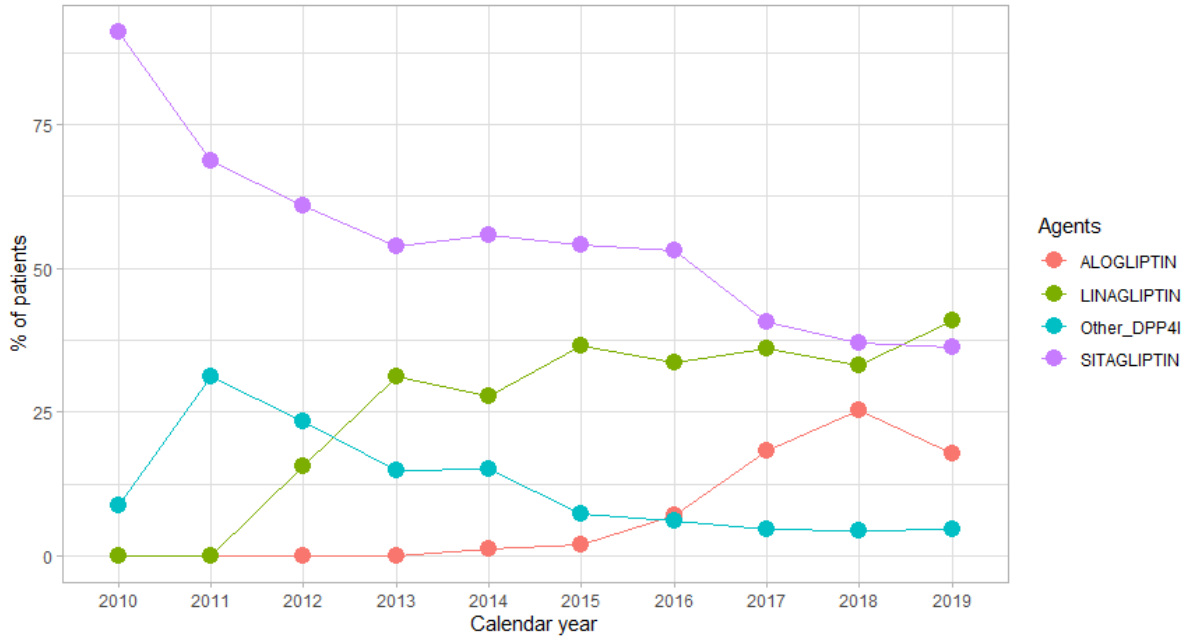
```
#ex. DPP4-I+SU

subset <- MONO_COMB_imputated2_m5_complete_dropped_Other[MONO_COMB_imputated2_m5_complete_dropped_Other$antidiabetic_group3 %in% c('DPP4-I+SU', 'biguanide'), ]

subset$antidiabetic_group3 <- factor(subset$antidiabetic_group3)

subset$antidiabetic_group3_01 <- if_else((subset$antidiabetic_group3 == 'biguanide'), '0', '1')
```

```
subset$antidiabetic_group3_01 <- as.factor(subset$antidiabetic_group3_01)

subset <- as.mids(subset)


##UR

P_value_multi <- with(data = subset, exp=glm(antidiabetic_group3_01 ~
pres_year+age_at_pres_cat+SEX+UR+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, family = binomial))

test <- with(data = subset, exp=glm(antidiabetic_group3_01 ~
pres_year+age_at_pres_cat+SEX+SIMD_Q+prescriber_type2+ALL_IHD+HTN+HF+stroke+PVD+liver_disease+Lipid_drugs+antipsycotic+Thiazide_diuretics+Beta_blocker+Angiotensin_inhibitors+CCB+polypharmacy_3levels+BMI_Cat+A1C_3months_cat+HDL_Cat+TG_Cat+TCholesterol_Cat+eGFR_cat+CCI_score_QUAN_cat, family = binomial))

p_UR_multi_comb <- pool.compare(P_value_multi, test, method = 'wald')$pvalue
```

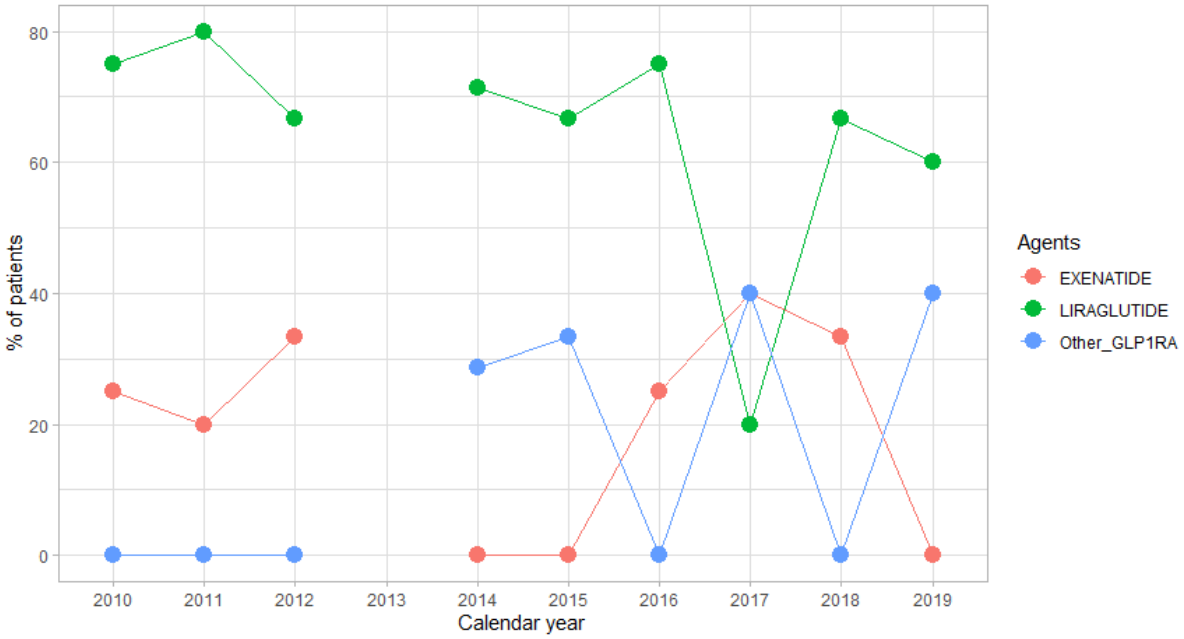
Appendix S.4.4: Prescribing trends of the individual agents within each class of ADDs prescribed as initial monotherapy



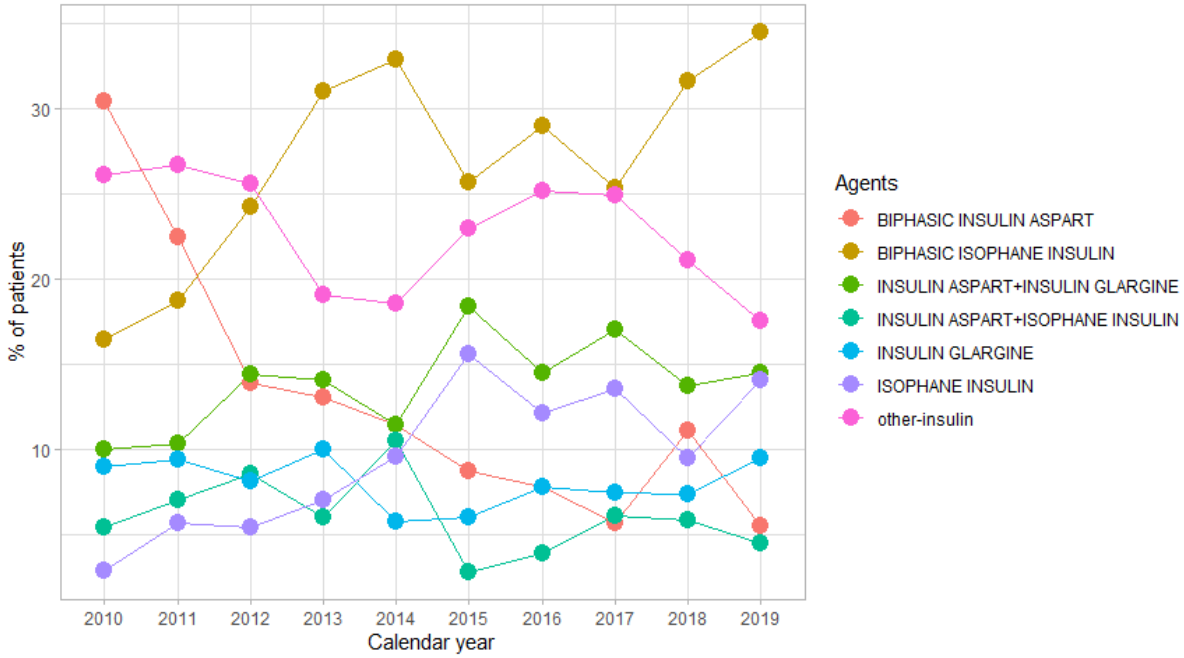
Line chart distribution of agents within sulfonylurea group over study period



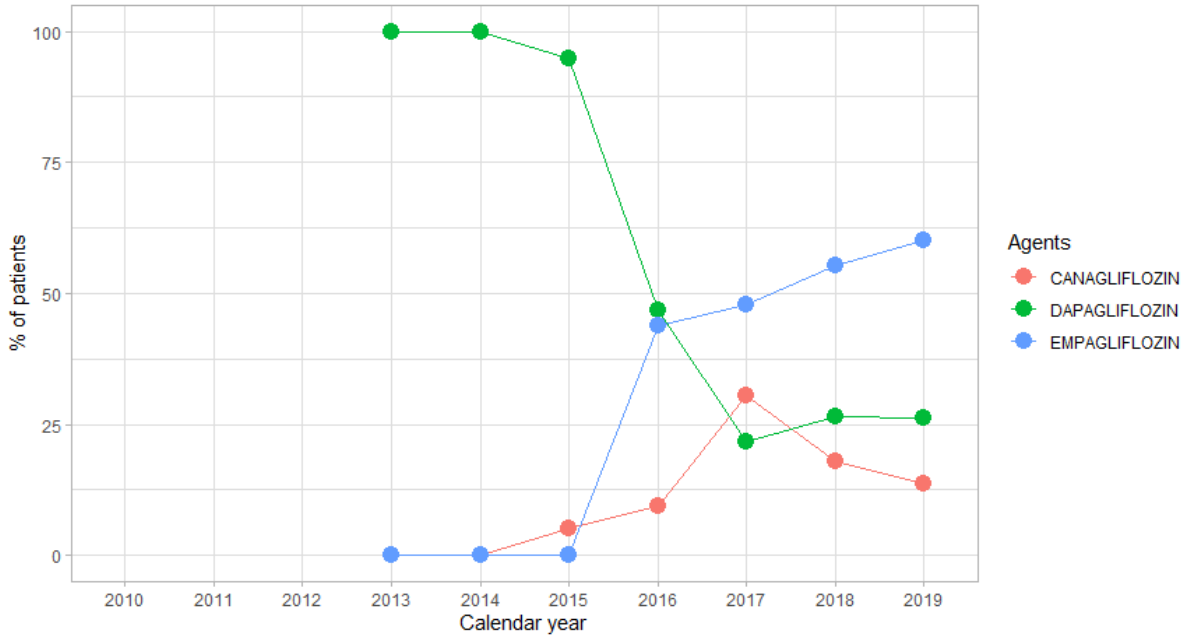
Line chart distribution of agents within dipeptidyl peptidase 4 inhibitor group over study period



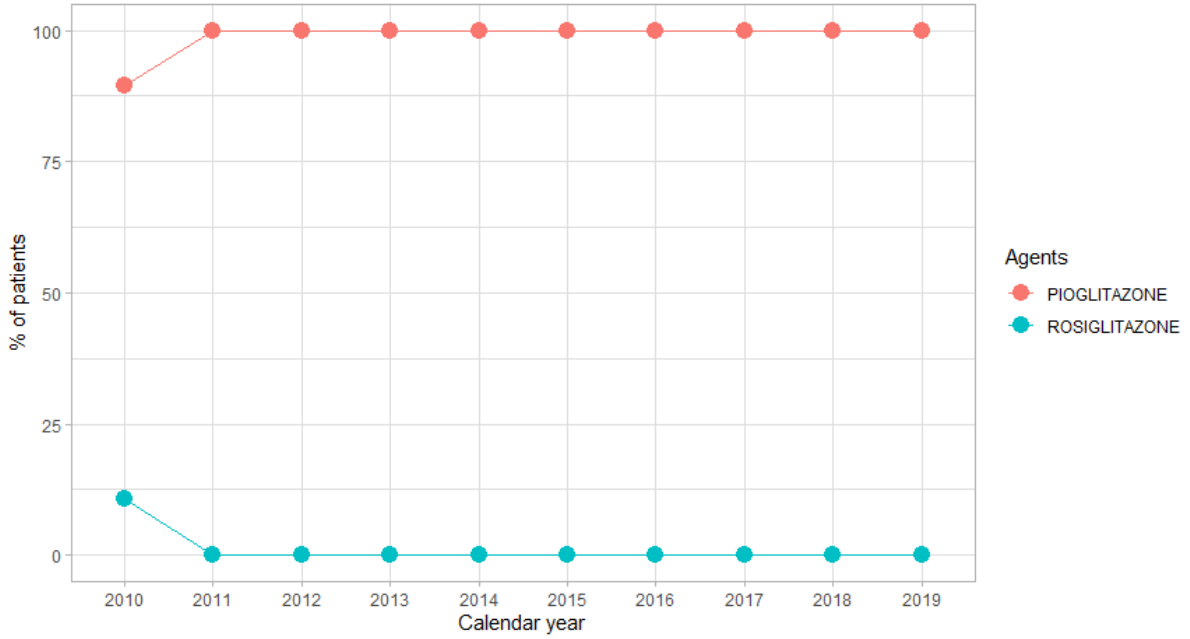
Line chart distribution of agents within glucagon like peptide receptor agonist group over study period



Line chart distribution of agents within insulin group over study period



Line chart distribution of agents within sodium glucose transporter inhibitor group over study period



Line chart distribution of agents within thiazolidinedione group over study period

Frequency and percentage of the most commonly prescribed agents within each class of antidiabetic drugs over study period

1- Biguanide	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N= 12600)	**(N= 11372)**	**(N= 12070)**	**(N= 12190)**	**(N= 10732)**	**(N= 12249)**	**(N= 11775)**	**(N= 11666)**	**(N= 11591)**	**(N= 12492)**	**(N= 118737)**
Metformin HCL	12600 (100%)	11372 (100%)	12070 (100%)	12190 (100%)	10732 (100%)	12249 (100%)	11775 (100%)	11666 (100%)	11591 (100%)	12492 (100%)	118737 (100%)
2- DPP4-I	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=34)	**(N=48)**	**(N=64)**	**(N=80)**	**(N=79)**	**(N=96)**	**(N=113)**	**(N=125)**	**(N=154)**	**(N=151)**	**(N=944)**
Other-DPP4-I	3 (8.8%)	15 (31.3%)	15 (23.4%)	12 (15.0%)	13 (16.5%)	9 (9.4%)	15 (13.3%)	29 (23.2%)	46 (29.9%)	34 (22.5%)	191 (20.2%)
SITAGLIPTIN	31 (91.2%)	33 (68.8%)	39 (60.9%)	43 (53.8%)	44 (55.7%)	52 (54.2%)	60 (53.1%)	51 (40.8%)	57 (37.0%)	55 (36.4%)	465 (49.3%)
LINAGLIPTIN	0 (0%)	0 (0%)	10 (15.6%)	25 (31.3%)	22 (27.8%)	35 (36.5%)	38 (33.6%)	45 (36.0%)	51 (33.1%)	62 (41.1%)	288 (30.5%)
3- GLP1-RA[a]	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	*****	**(N=5)**	*****	**(N=0)**	**(N=7)**	**(N=6)**	*****	**(N=5)**	*****	**(N=5)**	**(N=42)**
EXENATIDE											7 (16.7%)
LIRAGLUTIDE											27 (64.3%)
Other GLP1-RA											8 (19.0%)
4- insulin	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=280)	(N=214)	(N=223)	(N=200)	(N=210)	(N=218)	(N=207)	(N=229)	(N=190)	(N=200)	(N=2171)
BIPHASIC INSULIN ASPART	85 (30.4%)	48 (22.4%)	31 (13.9%)	26 (13.0%)	24 (11.4%)	19 (8.7%)	16 (7.7%)	13 (5.7%)	21 (11.1%)	11 (5.5%)	294 (13.5%)
BIPHASIC ISOPHANE INSULIN	46 (16.4%)	40 (18.7%)	54 (24.2%)	62 (31.0%)	69 (32.9%)	56 (25.7%)	60 (29.0%)	58 (25.3%)	60 (31.6%)	69 (34.5%)	574 (26.4%)
INSULIN ASPART+INSULIN GLARGINE	28 (10.0%)	22 (10.3%)	32 (14.3%)	28 (14.0%)	24 (11.4%)	40 (18.3%)	30 (14.5%)	39 (17.0%)	26 (13.7%)	29 (14.5%)	298 (13.7%)
INSULIN ASPART+ISOPHANE INSULIN	15 (5.4%)	15 (7.0%)	19 (8.5%)	12 (6.0%)	22 (10.5%)	6 (2.8%)	8 (3.9%)	14 (6.1%)	11 (5.8%)	9 (4.5%)	131 (6.0%)
INSULIN GLARGINE	25 (8.9%)	20 (9.3%)	18 (8.1%)	20 (10.0%)	12 (5.7%)	13 (6.0%)	16 (7.7%)	17 (7.4%)	14 (7.4%)	19 (9.5%)	174 (8.0%)
ISOPHANE INSULIN	8 (2.9%)	12 (5.6%)	12 (5.4%)	14 (7.0%)	20	34	25	31	18	28	202 (9.3%)

					(9.5%)	(15.6%)	(12.1%)	(13.5%)	(9.5%)	(14.0%)	
other-insulin	73 (26.1%)	57 (26.6%)	57 (25.6%)	38 (19.0%)	39 (18.6%)	50 (22.9%)	52 (25.1%)	57 (24.9%)	40 (21.1%)	35 (17.5%)	498 (22.9%)
5- SGLT2-I	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=0)	**(N=0)**	**(N=0)**	*****	*****	**(N=19)**	**(N=32)**	**(N=46)**	**(N=83)**	**(N=118)**	**(N=303)**
Other-SGLT2-I	0 (0%)	0 (0%)	0 (0%)	*	*	19 (100%)	18 (56.3%)	24 (52.2%)	37 (44.6%)	47 (39.8%)	150 (49.5%)
EMPAGLIFLOZIN	0 (0%)	0 (0%)	0 (0%)	*	*	0 (0%)	14 (43.8%)	22 (47.8%)	46 (55.4%)	71 (60.2%)	153 (50.5%)
6- SU	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=1467)	**(N=1317)**	**(N=1206)**	**(N=1109)**	**(N=903)**	**(N=955)**	**(N=837)**	**(N=750)**	**(N=733)**	**(N=752)**	**(N=10029)**
GLICLAZIDE	1216 (82.9%)	1150 (87.3%)	1051 (87.1%)	994 (89.6%)	788 (87.3%)	843 (88.3%)	733 (87.6%)	658 (87.7%)	662 (90.3%)	686 (91.2%)	8781 (87.6%)
GLIMEPIRIDE	151 (10.3%)	95 (7.2%)	90 (7.5%)	76 (6.9%)	72 (8.0%)	87 (9.1%)	73 (8.7%)	76 (10.1%)	62 (8.5%)	63 (8.4%)	845 (8.4%)
GLIPIZIDE	*	*	60 (5.0%)	*	37 (4.1%)	*	26 (3.1%)	*	9 (1.2%)	*	372 (3.7%)
Other-SU	*	*	5 (0.4%)	*	6 (0.7%)	*	5 (0.6%)	*	0 (0%)	*	31 (0.3%)
7- TZD	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=47)	**(N=29)**	**(N=10)**	**(N=8)**	*****	**(N=6)**	**(N=7)**	**(N=6)**	**(N=6)**	*****	**(N=127)**
PIOGLITAZONE	42 (89.4%)	29 (100%)	10 (100%)	8 (100%)	*	6 (100%)	7 (100%)	6 (100%)	6 (100%)	*	122 (96.1%)
ROSIGLITAZONE											5 (3.9%)

a; most values per calendar year are less than 5, * values remove either they are less than 5 or to not reveal values of less than 5

Appendix S.4.5: Prescribing trend of the individual agents within each class of ADDs prescribed as initial combination therapy

Dual therapy

1- biguanide+DPP4-I	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=55)	**(N=69)**	**(N=58)**	**(N=54)**	**(N=99)**	**(N=121)**	**(N=141)**	**(N=151)**	**(N=143)**	**(N=151)**	**(N=1042)**
METFORMIN HYDROCHLORIDE SAXAGLIPTIN	6 (10.9%)	14 (20.3%)	*	*	7 (7.1%)	*	*	6 (4.0%)	5 (3.5%)	0 (0%)	80 (7.7%)
METFORMIN HYDROCHLORIDE SITAGLIPTIN	45 (81.8%)	52 (75.4%)	47 (81.0%)	39 (72.2%)	73 (73.7%)	79 (65.3%)	83 (58.9%)	83 (55.0%)	60 (42.0%)	78 (51.7%)	639 (61.3%)
LINAGLIPTIN METFORMIN HYDROCHLORIDE	0 (0%)	0 (0%)	*	*	15 (15.2%)	17 (14.0%)	27 (19.1%)	26 (17.2%)	26 (18.2%)	18 (11.9%)	137 (13.1%)
ALOGLIPTIN METFORMIN HYDROCHLORIDE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	*	*	30 (19.9%)	47 (32.9%)	47 (31.1%)	141 (13.5%)
2- biguanide+GLP1-RA	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=17)	**(N=14)**	**(N=11)**	*****	*****	*****	*****	*****	**(N=12)**	**(N=13)**	**(N=97)**
LIRAGLUTIDE METFORMIN HYDROCHLORIDE	10 (58.8%)	11 (78.6%)	5 (45.5%)	*	*	*	*	*	5 (41.7%)	6 (46.2%)	48 (49.5%)
3- biguanide+ insulin	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=130)	**(N=107)**	**(N=133)**	**(N=110)**	**(N=147)**	**(N=164)**	**(N=147)**	**(N=131)**	**(N=129)**	**(N=134)**	**(N=1332)**
BIPHASIC INSULIN ASPART METFORMIN HYDROCHLORIDE	40 (30.8%)	30 (28.0%)	26 (19.5%)	13 (11.8%)	18 (12.2%)	15 (9.1%)	13 (8.8%)	13 (9.9%)	9 (7.0%)	9 (6.7%)	186 (14.0%)
BIPHASIC ISOPHANE INSULIN METFORMIN HYDROCHLORIDE	24 (18.5%)	26 (24.3%)	31 (23.3%)	35 (31.8%)	47 (32.0%)	58 (35.4%)	40 (27.2%)	37 (28.2%)	34 (26.4%)	41 (30.6%)	373 (28.0%)
INSULIN ASPART INSULIN GLARGINE METFORMIN HYDROCHLORIDE	15 (11.5%)	7 (6.5%)	16 (12.0%)	17 (15.5%)	17 (11.6%)	20 (12.2%)	24 (16.3%)	14 (10.7%)	17 (13.2%)	21 (15.7%)	168 (12.6%)
INSULIN GLARGINE METFORMIN HYDROCHLORIDE	18 (13.8%)	13 (12.1%)	5 (3.8%)	7 (6.4%)	16 (10.9%)	9 (5.5%)	21 (14.3%)	13 (9.9%)	12 (9.3%)	15 (11.2%)	129 (9.7%)
ISOPHANE INSULIN METFORMIN HYDROCHLORIDE	8 (6.2%)	*	18 (13.5%)	*	14 (9.5%)	18 (11.0%)	18 (12.2%)	15 (11.5%)	18 (14.0%)	17 (12.7%)	137 (10.3%)
Other-MET+insulin	25 (19.2%)	*	37 (27.8%)	*	35 (23.8%)	44 (26.8%)	31 (21.1%)	39 (29.8%)	39 (30.2%)	31 (23.1%)	339 (25.5%)
4- biguanide+SGLT2-I	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=0)	**(N=0)**	**(N=0)**	*****	*****	**(N=28)**	**(N=54)**	**(N=84)**	**(N=110)**	**(N=167)**	**(N=454)**

DAPAGLIFLOZIN METFORMIN HYDROCHLORIDE	0 (0%)	0 (0%)	0 (0%)	*	*	21 (75.0%)	25 (46.3%)	27 (32.1%)	33 (30.0%)	49 (29.3%)	165 (36.3%)
CANAGLIFLOZIN METFORMIN HYDROCHLORIDE	0 (0%)	0 (0%)	0 (0%)	*	*	*	14 (25.9%)	9 (10.7%)	21 (19.1%)	18 (10.8%)	65 (14.3%)
EMPAGLIFLOZIN METFORMIN HYDROCHLORIDE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	*	*	15 (27.8%)	48 (57.1%)	56 (50.9%)	100 (59.9%)	224 (49.3%)
5- biguanide+ SU	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=893)	**(N=735)**	**(N=825)**	**(N=874)**	**(N=828)**	**(N=772)**	**(N=912)**	**(N=838)**	**(N=876)**	**(N=855)**	**(N=8408)**
GLICLAZIDE METFORMIN HYDROCHLORIDE	765 (85.7%)	632 (86.0%)	724 (87.8%)	779 (89.1%)	742 (89.6%)	702 (90.9%)	817 (89.6%)	757 (90.3%)	796 (90.9%)	788 (92.2%)	7502 (89.2%)
GLIMEPIRIDE METFORMIN HYDROCHLORIDE	73 (8.2%)	65 (8.8%)	62 (7.5%)	51 (5.8%)	53 (6.4%)	56 (7.3%)	59 (6.5%)	67 (8.0%)	60 (6.8%)	53 (6.2%)	599 (7.1%)
GLIPIZIDE METFORMIN HYDROCHLORIDE	46 (5.2%)	33 (4.5%)	34 (4.1%)	37 (4.2%)	29 (3.5%)	13 (1.7%)	29 (3.2%)	12 (1.4%)	11 (1.3%)	12 (1.4%)	256 (3.0%)
6- biguanide+ TZD	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=71)	**(N=52)**	**(N=20)**	**(N=17)**	**(N=14)**	**(N=18)**	**(N=8)**	**(N=16)**	**(N=10)**	**(N=7)**	**(N=233)**
METFORMIN HYDROCHLORIDE PIOGLITAZONE	51 (71.8%)	52 (100%)	20 (100%)	17 (100%)	14 (100%)	18 (100%)	8 (100%)	16 (100%)	10 (100%)	7 (100%)	213 (91.4%)
METFORMIN HYDROCHLORIDE ROSIGLITAZONE	20 (28.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (8.6%)
7- SU+ DPP4-I	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=9)	*****	**(N=10)**	*****	**(N=14)**	**(N=16)**	**(N=18)**	**(N=31)**	**(N=20)**	**(N=19)**	**(N=158)**
GLICLAZIDE SITAGLIPTIN	7 (77.8%)	*	6 (60.0%)	*	9 (64.3%)	7 (43.8%)	8 (44.4%)	16 (51.6%)	10 (50.0%)	10 (52.6%)	81 (51.3%)
8- SU + insulin	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
	(N=39)	**(N=32)**	**(N=37)**	**(N=31)**	**(N=35)**	**(N=45)**	**(N=40)**	**(N=25)**	**(N=39)**	**(N=24)**	**(N=347)**
GLICLAZIDE INSULIN GLARGINE	11 (28.2%)	10 (31.3%)	11 (29.7%)	9 (29.0%)	5 (14.3%)	5 (11.1%)	7 (17.5%)	5 (20.0%)	5 (12.8%)	9 (37.5%)	77 (22.2%)
GLICLAZIDE ISOPHANE INSULIN	*	*	9 (24.3%)	10 (32.3%)	13 (37.1%)	21 (46.7%)	12 (30.0%)	9 (36.0%)	16 (41.0%)	9 (37.5%)	109 (31.4%)
Other-SU+insulin	*	*	17 (45.9%)	12 (38.7%)	17 (48.6%)	19 (42.2%)	21 (52.5%)	11 (44.0%)	18 (46.2%)	6 (25.0%)	161 (46.4%)

Triple or more therapy:

Frequency and percentage of the most frequently prescribed more than two combination antidiabetic agents over study period (2010-2019) at stage of initiation

1- biguanide+DPP4-I+SU	**Total (N=370)**
GLICLAZIDE METFORMIN HYDROCHLORIDE SITAGLIPTIN	208 (56.2%)
GLIMEPIRIDE METFORMIN HYDROCHLORIDE SITAGLIPTIN	37 (10.0%)
GLICLAZIDE LINAGLIPTIN METFORMIN HYDROCHLORIDE	50 (13.5%)
2- biguanide+GLP1-RA+SU	**Total (N=81)**
EXENATIDE GLICLAZIDE METFORMIN HYDROCHLORIDE	21 (25.9%)
GLICLAZIDE LIRAGLUTIDE METFORMIN HYDROCHLORIDE	43 (53.1%)
3- biguanide+SGLT2-I+SU	**Total (N=93)**
DAPAGLIFLOZIN GLICLAZIDE METFORMIN HYDROCHLORIDE	32 (34.4%)
EMPAGLIFLOZIN GLICLAZIDE METFORMIN HYDROCHLORIDE	37 (39.8%)
4- biguanide+ SU+ insulin	**Total (N=246)**
BIPHASIC INSULIN ASPART GLICLAZIDE METFORMIN HYDROCHLORIDE	9 (3.7%)
GLICLAZIDE INSULIN GLARGINE METFORMIN HYDROCHLORIDE	62 (25.2%)
GLICLAZIDE ISOPHANE INSULIN METFORMIN HYDROCHLORIDE	83 (33.7%)
GLICLAZIDE INSULIN ASPART INSULIN GLARGINE METFORMIN HYDROCHLORIDE	10 (4.1%)
BIPHASIC ISOPHANE INSULIN GLICLAZIDE METFORMIN HYDROCHLORIDE	26 (10.6%)
5- biguanide+ SU+ TZD	**Total (N=132)**
GLICLAZIDE METFORMIN HYDROCHLORIDE PIOGLITAZONE	95 (72.0%)
GLIMEPIRIDE METFORMIN HYDROCHLORIDE PIOGLITAZONE	20 (15.2%)
6- Other	**Total (N=364)**
INSULIN GLARGINE METFORMIN HYDROCHLORIDE SITAGLIPTIN	12 (3.3%)
DAPAGLIFLOZIN METFORMIN HYDROCHLORIDE SITAGLIPTIN	11 (3.0%)
EMPAGLIFLOZIN METFORMIN HYDROCHLORIDE SITAGLIPTIN	13 (3.6%)

Appendix S.4.6: Univariable multinomial logistic regression analyses results at drug initiation

Monotherapy groups

Studied factor	DPP4-I	GLP1-RA	insulin	SGLT2-I	SU	TZD
1- Demographic factors						
Age at prescription	<0.001	0.002	0.8	<0.001	<0.001	0.001
>= 65 vs. < 65 years	3.48[3.04, 4.00]	0.31[0.13, 0.70]	0.99[0.90, 1.08]	0.56[0.43, 0.72]	2[1.92, 2.08]	1.77[1.25, 2.51]
SEX	<0.001	0.049	0.012	0.042	0.041	0.002
F vs. M	1.68[1.47, 1.91]	1.84[1.00, 3.38]	1.12[1.02, 1.21]	1.26[1.01, 1.59]	1.04[1.00, 1.09]	1.75[1.23, 2.48]
2- Socioeconomic factors						
UR	0.013	0.04	0.5	0.13	<0.001	0.039
2 vs. 1	1.18[1.02, 1.38]	1.06[0.45, 2.50]	0.96[0.87, 1.07]	1.01[0.76, 1.34]	0.92[0.87, 0.96]	1.66[1.04, 2.65]
3 vs. 1	1.13[0.89, 1.45]	0.89[0.21, 3.86]	0.98[0.84, 1.16]	0.97[0.62, 1.54]	0.99[0.92, 1.07]	1.45[0.71, 2.97]
4 vs. 1	1.1[0.71, 1.69]	3.25[0.75, 14.1]	0.93[0.69, 1.25]	2.2[1.26, 3.84]	1.16[1.02, 1.32]	1.87[0.62, 5.59]
5 vs. 1	2[1.28, 3.11]	2.94[0.39, 22.0]	1.11[0.77, 1.60]	0.8[0.24, 2.64]	1.16[0.97, 1.37]	0.07[0.00, 104]
6 vs. 1	1.16[0.93, 1.45]	3.15[1.29, 7.69]	1.04[0.90, 1.21]	1.54[1.09, 2.20]	0.99[0.93, 1.07]	2.53[1.44, 4.42]
7 vs. 1	0.67[0.42, 1.06]	0.99[0.12, 8.21]	1.02[0.80, 1.30]	1.02[0.52, 2.00]	1.08[0.96, 1.20]	2.32[0.98, 5.52]
8 vs. 1	0.8[0.51, 1.26]	5.43[1.78, 16.5]	0.87[0.66, 1.14]	0.82[0.38, 1.79]	0.84[0.74, 0.96]	1.03[0.28, 3.73]
Unknown vs. 1	0.07[0.00, 7,141]	0.77[0.00, inf]	3.53[1.22, 10.2]	0.22[0.00, inf]	1.07[0.43, 2.62]	0.52[0.00, inf]
SIMD_Q	0.4	0.3	0.2	0.02	<0.001	0.8
2 vs. 1	0.46[0.36, 0.58]	34.5[7.16, 167]	1.12[0.99, 1.25]	1.08[0.79, 1.48]	1.03[0.97, 1.09]	3.94[2.45, 6.34]
3 vs. 1	1.33[1.11, 1.60]	15.6[3.12, 78.3]	0.83[0.73, 0.95]	0.7[0.49, 1.02]	1.01[0.95, 1.07]	2.51[1.50, 4.22]
4 vs. 1	0.96[0.77, 1.18]	74.1[15.5, 355]	0.91[0.79, 1.04]	1.24[0.89, 1.72]	1.19[1.11, 1.26]	1.66[0.92, 2.98]
5 vs. 1	1.11[0.89, 1.39]	1.53[0.14, 16.5]	1.15[1.00, 1.33]	0.26[0.14, 0.50]	1.3[1.22, 1.39]	5.81[3.57, 9.48]
Unknown vs. 1	2.34[0.25, 22.0]	0.86[0.00, inf]	3.62[1.13, 11.6]	0.39[0.00, 3,561]	0.69[0.19, 2.44]	0.64[0.00, inf]
3- Prescriber-related factors						
Prescriber type	0.8	0.2	<0.001	0.046	0.002	0.8
Non-GP vs. GP	1.03[0.80, 1.32]	0.39[0.06, 2.47]	0.19[0.13, 0.27]	1.5[1.03, 2.19]	0.87[0.80, 0.95]	0.92[0.45, 1.89]

4- Clinical-related factors						
IHD	<0.001	0.1	0.016	<0.001	<0.001	0.4
Yes vs. No	2.35[2.02, 2.73]	0.38[0.09, 1.55]	1.17[1.04, 1.33]	1.77[1.33, 2.35]	1.61[1.52, 1.70]	0.76[0.42, 1.38]
HTN	<0.001	>0.9	<0.001	0.081	<0.001	0.6
Yes vs. No	2.41[2.11, 2.77]	1.01[0.45, 2.26]	1.29[1.16, 1.43]	1.29[0.98, 1.70]	1.61[1.54, 1.69]	1.11[0.71, 1.73]
HF	<0.001	0.5	<0.001	<0.001	<0.001	0.8
Yes vs. No	5.01[4.12, 6.08]	1.41[0.30, 6.69]	2.53[2.13, 3.00]	2.81[1.84, 4.29]	3.15[2.91, 3.41]	0.97[0.33, 2.84]
Stroke	<0.001	0.14	<0.001	0.5	<0.001	>0.9
Yes vs. No	2.6[1.99, 3.39]	0[0.00, inf]	1.68[1.36, 2.09]	0.79[0.35, 1.77]	1.91[1.73, 2.11]	0.93[0.29, 2.95]
PVD						
Yes vs. No	2.16[1.59, 2.93]	0[0.00, 0.00]	2.22[1.82, 2.71]	1.68[0.92, 3.06]	2.22[2.01, 2.45]	1.07[0.34, 3.35]
Liver disease	0.001	0.8	<0.001	0.7	<0.001	0.4
Yes vs. No	1.87[1.33, 2.64]	0.54[0.03, 10.1]	5.22[4.49, 6.06]	0.84[0.35, 2.03]	2.7[2.45, 2.98]	1.89[0.75, 4.78]
CCI score	<0.001	0.3	<0.001	0.007	<0.001	0.08
1-2 vs. 0	2.78[2.39, 3.23]	0.54[0.17, 1.66]	1.96[1.75, 2.18]	1.55[1.16, 2.06]	2.19[2.08, 2.31]	1.6[1.03, 2.49]
3-4 vs. 0	5.38[4.34, 6.67]	2.83[0.95, 8.38]	4.59[3.95, 5.33]	1.92[1.14, 3.24]	4.66[4.32, 5.02]	2.15[1.00, 4.63]
>= 5 vs. 0	5.23[3.96, 6.90]	0[0.00, inf]	8.67[7.48, 10.0]	1.45[0.66, 3.16]	6.09[5.58, 6.66]	1.81[0.61, 5.36]
Antihyperlipidemic drugs	0.005	<0.001	<0.001	0.002	<0.001	<0.001
Yes vs. No	1.21[1.06, 1.38]	0.3[0.16, 0.57]	0.34[0.31, 0.37]	0.7[0.56, 0.88]	0.74[0.71, 0.77]	1.98[1.33, 2.96]
Antipsychotic	0.6	0.11	<0.001	0.6	<0.001	0.6
Yes vs. No	1.09[0.76, 1.56]	0.05[0.00, 108]	1.51[1.23, 1.86]	1.21[0.67, 2.22]	1.21[1.09, 1.35]	1.33[0.55, 3.24]
Thiazide diuretics	>0.9	0.6	<0.001	0.005	<0.001	0.8
Yes vs. No	1[0.85, 1.19]	0.79[0.33, 1.88]	0.51[0.44, 0.59]	0.62[0.44, 0.89]	0.83[0.78, 0.88]	1.05[0.67, 1.66]
Beta-blockers	<0.001	0.8	0.011	0.014	<0.001	0.017
Yes vs. No	2.14[1.88, 2.44]	1.1[0.55, 2.18]	0.88[0.79, 0.97]	1.37[1.07, 1.75]	1.23[1.18, 1.29]	1.58[1.09, 2.29]
Angiotensin inhibitors	<0.001	0.088	<0.001	0.3	<0.001	0.043
Yes vs. No	1.46[1.28, 1.66]	0.57[0.30, 1.11]	0.48[0.44, 0.53]	1.12[0.89, 1.40]	0.81[0.78, 0.85]	1.43[1.01, 2.03]
CCB	0.042	0.5	<0.001	0.02	<0.001	0.001
Yes vs. No	1.17[1.01, 1.35]	0.8[0.37, 1.70]	0.56[0.49, 0.63]	0.72[0.53, 0.96]	0.92[0.88, 0.97]	1.87[1.30, 2.68]
Number of concomitant medications	<0.001	0.007	0.5	0.4	<0.001	0.2
1-4 vs. 0	1.08[0.66, 1.75]	0.21[0.08, 0.54]	1.09[0.86, 1.38]	1.01[0.54, 1.89]	0.87[0.77, 0.97]	1.42[0.44, 4.61]
>= 5 vs. 0	2.78[1.74, 4.44]	0.21[0.09, 0.50]	1.13[0.90, 1.42]	1.2[0.65, 2.20]	1.31[1.18, 1.47]	1.95[0.62, 6.15]

BMI	<0.001	0.01	<0.001	<0.001	<0.001	>0.9
25-29.9 vs. <=24.9	0.49[0.37, 0.65]	185[0.00, inf]	0.26[0.22, 0.31]	0.79[0.38, 1.66]	0.26[0.24, 0.29]	0.82[0.31, 2.22]
>= 30 vs. <=24.9	0.41[0.32, 0.54]	1478[0.00, inf]	0.13[0.11, 0.16]	1.7[0.87, 3.33]	0.11[0.10, 0.11]	0.86[0.34, 2.15]
Unknown vs. <= 24.9	0.47[0.36, 0.60]	1309[0.00, inf]	0.53[0.46, 0.61]	0.78[0.39, 1.55]	0.3[0.28, 0.32]	0.91[0.36, 2.29]
HbA1c	0.007	<0.001	<0.001	0.082	<0.001	0.003
7- <9% vs. < 7%	1.57[1.13, 2.18]	0.23[0.08, 0.69]	0.38[0.29, 0.49]	0.75[0.49, 1.16]	1.16[1.03, 1.32]	1.07[0.49, 2.35]
>=9% vs. < 7%	1.31[0.93, 1.83]	0.18[0.05, 0.62]	1.87[1.48, 2.38]	0.79[0.50, 1.23]	2.65[2.34, 3.00]	0.71[0.31, 1.63]
Unknown vs. < 7%	1.4[0.98, 2.00]	1.8[0.69, 4.75]	5.82[4.59, 7.38]	0.52[0.31, 0.89]	4.1[3.62, 4.65]	1.85[0.82, 4.18]
eGFR	<0.001	<0.001	<0.001	0.079	<0.001	<0.001
< 60 vs. >= 60	11.2[9.73, 12.9]	1.68[0.42, 6.70]	4.69[4.16, 5.30]	0.76[0.45, 1.27]	5.01[4.75, 5.29]	11.4[7.60, 17.2]
Unknown vs. < 60	1.67[1.37, 2.04]	6.61[3.46, 12.6]	4.52[4.11, 4.97]	0.68[0.46, 0.99]	1.86[1.76, 1.97]	4.16[2.70, 6.42]
HDL	<0.001	0.003	<0.001	0.001	<0.001	0.077
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.98[0.82, 1.17]	4.45[2.02, 9.79]	0.88[0.75, 1.05]	1.31[0.99, 1.72]	1[0.94, 1.06]	1.4[0.92, 2.12]
>= 60 vs. <40 (M) or <50 (F)	1.39[1.07, 1.81]	0.54[0.04, 6.55]	1.47[1.16, 1.87]	0.31[0.13, 0.75]	1.63[1.49, 1.78]	1.95[1.06, 3.56]
Unknown vs. <40 (M) or <50 (F)	1.21[1.04, 1.40]	3.53[1.63, 7.65]	4.19[3.74, 4.69]	0.87[0.66, 1.15]	1.79[1.70, 1.88]	0.92[0.60, 1.40]
TG	<0.001	0.009	<0.001	0.2	<0.001	<0.001
150-499 vs. < 150	0.87[0.72, 1.05]	0.92[0.32, 2.70]	0.66[0.55, 0.78]	0.89[0.66, 1.21]	0.83[0.78, 0.88]	1.09[0.58, 2.03]
>= 500 vs. < 150	0.44[0.27, 0.74]	0[0.00, inf]	2.02[1.57, 2.59]	0.47[0.20, 1.09]	1.11[0.99, 1.26]	1.39[0.46, 4.22]
Unknown vs. < 150	1.06[0.89, 1.26]	2.36[0.91, 6.13]	3.13[2.72, 3.62]	0.81[0.60, 1.11]	1.45[1.37, 1.53]	2.37[1.34, 4.20]
Total cholesterol	<0.001	<0.001	<0.001	0.7	<0.001	0.065
200-239 vs. < 200	0.77[0.63, 0.94]	1.61[0.78, 3.34]	1[0.84, 1.20]	1.45[1.08, 1.96]	0.93[0.87, 0.99]	1.17[0.73, 1.87]
>=240 vs. < 200	0.78[0.62, 0.97]	2.11[1.00, 4.43]	1.5[1.26, 1.78]	1.08[0.74, 1.57]	1.06[0.99, 1.14]	1.4[0.85, 2.30]
Unknown vs. < 200	1.17[1.01, 1.37]	2.55[1.40, 4.63]	5.95[5.35, 6.62]	1.08[0.80, 1.47]	1.99[1.90, 2.08]	1.14[0.74, 1.75]

Dual therapy groups

Studied factor	biguanide+DPP4-I	biguanide+GLP1-RA	biguanide+ insulin	biguanide+SGLT2-I	biguanide+ SU	biguanide+ TZD	DPP4-I+SU	SU+ insulin
5- Demographic factors								
Age at prescription	<0.001	<0.001	<0.001	<0.001	<0.001	0.1	<0.001	0.012
>= 65 vs. < 65 years	0.72[0.63, 0.83]	0.31[0.18, 0.54]	0.6[0.53, 0.68]	0.47[0.37, 0.58]	0.78[0.74, 0.82]	0.81[0.62, 1.06]	2.67[1.93, 3.67]	1.32[1.07, 1.63]
SEX	0.2	0.2	<0.001	0.6	<0.001	0.6	0.044	0.3
F vs. M	0.93[0.82, 1.05]	1.29[0.87, 1.93]	1.36[1.22, 1.51]	1.06[0.88, 1.27]	0.85[0.82, 0.89]	0.93[0.72, 1.21]	1.38[1.01, 1.88]	0.9[0.73, 1.12]
6- Socioeconomic factors								
UR	0.5	<0.001	0.4	0.088	<0.001	0.001	<0.001	0.7
2 vs. 1	1.06[0.91, 1.22]	0.58[0.32, 1.05]	0.87[0.76, 0.99]	0.82[0.66, 1.03]	0.9[0.85, 0.95]	1.47[1.04, 2.07]	0.83[0.56, 1.24]	1.1[0.86, 1.41]
3 vs. 1	0.96[0.75, 1.22]	1.33[0.64, 2.79]	0.87[0.70, 1.07]	0.79[0.54, 1.15]	0.97[0.89, 1.06]	1.55[0.93, 2.58]	2.13[1.33, 3.41]	0.79[0.50, 1.24]
4 vs. 1	1.19[0.80, 1.76]	2.19[0.79, 6.07]	0.96[0.67, 1.37]	1.23[0.71, 2.12]	1[0.86, 1.16]	0.97[0.33, 2.84]	0.59[0.15, 2.39]	0.64[0.26, 1.56]
5 vs. 1	1.77[1.14, 2.73]	2[0.49, 8.22]	1.15[0.73, 1.79]	1.88[1.03, 3.44]	0.79[0.63, 0.98]	3.13[1.34, 7.27]	0.04[0.00, 49.0]	1.57[0.71, 3.45]
6 vs. 1	1.11[0.90, 1.37]	1.33[0.68, 2.63]	0.86[0.71, 1.04]	0.86[0.62, 1.20]	0.91[0.84, 0.98]	2.06[1.34, 3.17]	0.98[0.55, 1.73]	1.07[0.75, 1.54]
7 vs. 1	1.18[0.84, 1.64]	4.96[2.58, 9.51]	0.84[0.61, 1.17]	1.25[0.79, 1.99]	1.15[1.02, 1.29]	2.52[1.37, 4.64]	1.61[0.76, 3.42]	0.9[0.47, 1.72]
8 vs. 1	0.98[0.67, 1.44]	4.63[2.32, 9.24]	1.1[0.81, 1.49]	1.22[0.74, 2.00]	0.83[0.72, 0.95]	2.47[1.30, 4.69]	2.42[1.25, 4.71]	1.11[0.60, 2.05]
Unknown vs. 1	0.06[0.00, 6,250]	0.51[0.00, 505,196]	1.48[0.21, 10.6]	0.13[0.00, 11,091]	0.24[0.03, 1.73]	13.5[1.83, 100]	0.37[0.00, 75,802]	0.18[0.00, 17,250]
SIMD_Q	0.6	0.1	0.001	0.1	0.086	0.018	0.8	0.6
2 vs. 1	0.95[0.79, 1.14]	0.66[0.32, 1.37]	0.82[0.70, 0.96]	0.77[0.60, 0.99]	1.06[0.99, 1.13]	1.24[0.86, 1.79]	1.9[1.26, 2.86]	1.02[0.73, 1.44]
3 vs. 1	1.11[0.92, 1.33]	2.14[1.22, 3.76]	1.1[0.95, 1.28]	0.84[0.65, 1.09]	0.98[0.91, 1.04]	1.73[1.21, 2.46]	1.14[0.71, 1.83]	1.15[0.82, 1.62]
4 vs. 1	0.86[0.70, 1.06]	6.91[4.22, 11.3]	0.66[0.55, 0.80]	0.72[0.54, 0.96]	1.02[0.96, 1.10]	1.37[0.93, 2.03]	2.3[1.51, 3.52]	1.04[0.72, 1.51]

5 vs. 1	1.16[0.94, 1.43]	0.12[0.02, 0.80]	0.91[0.76, 1.09]	0.63[0.45, 0.88]	1.02[0.94, 1.10]	1.2[0.77, 1.86]	0.28[0.11, 0.71]	0.83[0.54, 1.29]
Unknown vs. 1	0.15[0.00, 658]	0.7[0.00, 726,840]	1.67[0.22, 12.6]	0.16[0.00, 5,389]	0.07[0.00, 4.30]	7.58[0.59, 96.8]	0.52[0.00, 67,489]	0.39[0.00, 6,544]
7- Prescriber-related factors								
Prescriber type	0.021	<0.001	<0.001	0.9	<0.001	<0.001	0.015	<0.001
Non-GP vs. GP	0.73[0.55, 0.97]	0[0.00, 6,253]	0.21[0.13, 0.32]	0.97[0.67, 1.40]	0.62[0.55, 0.69]	0.24[0.09, 0.64]	0.35[0.13, 0.96]	0.32[0.16, 0.65]
8- Clinical-related factors								
IHD	<0.001	0.054	0.8	0.4	0.9	0.002	0.003	0.002
Yes vs. No	0.65[0.52, 0.81]	0.46[0.20, 1.06]	0.99[0.83, 1.16]	1.12[0.85, 1.47]	1[0.93, 1.07]	0.46[0.26, 0.79]	1.89[1.29, 2.77]	1.56[1.18, 2.05]
HTN	<0.001	0.004	>0.9	0.071	0.6	0.7	0.002	<0.001
Yes vs. No	0.64[0.53, 0.78]	0.37[0.17, 0.80]	1[0.87, 1.15]	0.79[0.60, 1.03]	1.02[0.96, 1.08]	0.93[0.65, 1.32]	1.83[1.29, 2.60]	1.79[1.41, 2.27]
HF	0.8	0.6	0.006	>0.9	<0.001	0.3	<0.001	<0.001
Yes vs. No	0.94[0.65, 1.38]	0.67[0.16, 2.86]	1.48[1.13, 1.94]	1[0.57, 1.74]	1.49[1.33, 1.67]	0.58[0.21, 1.58]	5.52[3.51, 8.69]	3.62[2.52, 5.19]
Stroke	0.9	0.3	0.3	0.3	<0.001	0.2	<0.001	<0.001
Yes vs. No	1.03[0.70, 1.52]	0.41[0.06, 2.91]	1.17[0.85, 1.62]	1.35[0.81, 2.25]	1.28[1.12, 1.45]	0.5[0.16, 1.58]	4.38[2.61, 7.36]	2.5[1.61, 3.90]
PVD								
Yes vs. No	0.77[0.49, 1.24]	1.38[0.43, 4.40]	1.09[0.76, 1.54]	0.79[0.39, 1.59]	1.3[1.14, 1.49]	0.59[0.19, 1.82]	2.96[1.56, 5.63]	3.57[2.39, 5.33]
Liver disease	0.4	0.2	<0.001	0.5	<0.001	0.4	0.054	<0.001
Yes vs. No	0.8[0.49, 1.31]	1.94[0.68, 5.53]	2.04[1.54, 2.69]	0.78[0.37, 1.66]	1.63[1.44, 1.86]	0.67[0.22, 2.06]	2.34[1.10, 4.98]	8.05[5.93, 10.9]
CCI score	0.009	0.13	<0.001	0.7	<0.001	0.052	<0.001	<0.001
1-2 vs. 0	0.73[0.60, 0.89]	0.97[0.55, 1.71]	1.2[1.04, 1.40]	0.91[0.69, 1.20]	1.2[1.13, 1.28]	0.64[0.41, 0.98]	2.01[1.36, 2.96]	3.75[2.90, 4.86]
3-4 vs. 0	1.14[0.81, 1.59]	1.27[0.45, 3.57]	1.69[1.30, 2.19]	1.3[0.80, 2.11]	1.57[1.40, 1.75]	0.43[0.14, 1.30]	5.01[3.02, 8.33]	9.23[6.66, 12.8]
>= 5 vs. 0	0.95[0.58, 1.54]	0[0.00, inf]	2.36[1.76, 3.16]	0.93[0.44, 1.97]	1.97[1.73, 2.25]	0.85[0.30, 2.43]	5.95[3.26, 10.9]	18.6[13.6, 25.4]
Antihyperlipidemic	<0.001	<0.001	<0.001	<0.001	<0.001	0.3	0.007	<0.001

drugs								
Yes vs. No	0.77[0.68, 0.87]	0.51[0.34, 0.76]	0.35[0.31, 0.39]	0.67[0.56, 0.81]	0.55[0.53, 0.58]	1.14[0.87, 1.49]	0.65[0.48, 0.89]	0.51[0.41, 0.63]
Antipsychotic	0.8	>0.9	0.054	0.7	0.015	0.2	0.7	0.008
Yes vs. No	0.95[0.66, 1.37]	1.03[0.33, 3.23]	1.32[1.00, 1.74]	1.09[0.65, 1.83]	1.17[1.03, 1.32]	1.59[0.87, 2.92]	0.85[0.32, 2.27]	1.95[1.24, 3.06]
Thiazide diuretics	0.003	0.1	<0.001	<0.001	<0.001	0.15	0.011	0.077
Yes vs. No	0.77[0.65, 0.92]	0.61[0.33, 1.14]	0.56[0.47, 0.66]	0.51[0.38, 0.70]	0.75[0.70, 0.80]	1.27[0.93, 1.74]	0.54[0.32, 0.90]	0.77[0.56, 1.04]
Beta blocker	0.037	0.4	<0.001	0.8	<0.001	0.007	0.026	0.047
Yes vs. No	0.86[0.74, 0.99]	0.8[0.49, 1.31]	0.78[0.68, 0.89]	0.98[0.79, 1.21]	0.88[0.83, 0.93]	0.64[0.46, 0.90]	1.47[1.05, 2.05]	1.27[1.01, 1.60]
Angiotensin inhibitors	0.5	>0.9	<0.001	0.039	<0.001	0.15	0.4	0.017
Yes vs. No	1.05[0.93, 1.18]	1.02[0.69, 1.53]	0.54[0.48, 0.60]	0.82[0.68, 0.99]	0.68[0.65, 0.71]	1.21[0.93, 1.56]	0.87[0.64, 1.20]	0.77[0.62, 0.96]
CCB	0.14	0.9	<0.001	<0.001	<0.001	0.7	0.8	0.2
Yes vs. No	0.9[0.77, 1.04]	0.96[0.60, 1.55]	0.59[0.51, 0.68]	0.62[0.48, 0.80]	0.71[0.67, 0.75]	1.07[0.80, 1.44]	1.04[0.72, 1.50]	0.85[0.66, 1.11]
Number of concomitant medications	<0.001	0.004	<0.001	<0.001	<0.001	<0.001	0.6	<0.001
1-4 vs. 0	0.64[0.50, 0.81]	0.29[0.15, 0.57]	0.96[0.74, 1.25]	0.58[0.40, 0.83]	0.68[0.62, 0.75]	0.94[0.54, 1.64]	0.96[0.41, 2.24]	0.69[0.36, 1.32]
>= 5 vs. 0	0.46[0.36, 0.58]	0.31[0.16, 0.57]	0.77[0.59, 0.99]	0.45[0.32, 0.64]	0.6[0.55, 0.66]	0.53[0.30, 0.92]	1.14[0.50, 2.61]	1.62[0.89, 2.96]
BMI	<0.001	0.001	<0.001	0.009	<0.001	0.03	<0.001	<0.001
25-29.9 vs. <=24.9	0.93[0.66, 1.30]	1546[0.00, inf]	0.74[0.53, 1.03]	1.25[0.61, 2.54]	0.61[0.55, 0.69]	0.69[0.29, 1.62]	0.26[0.13, 0.49]	0.22[0.15, 0.34]
>= 30 vs. <=24.9	0.66[0.48, 0.91]	4656[0.00, inf]	0.7[0.51, 0.95]	1.85[0.95, 3.62]	0.46[0.41, 0.51]	1.17[0.54, 2.51]	0.21[0.12, 0.37]	0.1[0.07, 0.14]
Unknown vs. <= 24.9	1.03[0.75, 1.41]	4083[0.00, inf]	1.42[1.05, 1.91]	1.9[0.97, 3.71]	0.91[0.82, 1.01]	1.33[0.62, 2.86]	0.41[0.24, 0.69]	0.38[0.28, 0.52]
HbA1c	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
7-9% vs. < 7%	0.53[0.38, 0.73]	0.47[0.13, 1.68]	0.36[0.27, 0.49]	0.73[0.42, 1.27]	0.85[0.71, 1.03]	0.79[0.39, 1.61]	0.77[0.30, 1.97]	0.96[0.34, 2.72]

>=9% vs. < 7%	1.52[1.11, 2.07]	1.84[0.56, 6.02]	1.53[1.15, 2.02]	2.67[1.58, 4.51]	6.71[5.60, 8.02]	1.15[0.57, 2.32]	2.53[1.02, 6.27]	6.01[2.22, 16.2]
Unknown vs. < 7%	3.73[2.74, 5.08]	6.8[2.12, 21.8]	4.63[3.51, 6.10]	3.35[1.96, 5.72]	8.59[7.16, 10.3]	4.8[2.43, 9.47]	4.08[1.63, 10.2]	17.4[6.47, 47.0]
eGFR	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
< 60 vs. >= 60	1.84[1.45, 2.32]	0.47[0.10, 2.15]	2.87[2.38, 3.46]	0.28[0.14, 0.60]	1.64[1.51, 1.78]	1.92[1.16, 3.16]	13.1[9.20, 18.7]	6.71[5.19, 8.68]
Unknown vs. < 60	4.14[3.64, 4.71]	5.96[3.99, 8.92]	5.64[5.03, 6.32]	2.32[1.89, 2.85]	2.08[1.97, 2.19]	4.71[3.59, 6.17]	3.57[2.37, 5.39]	2.91[2.24, 3.77]
HDL	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1[0.82, 1.23]	0.82[0.40, 1.69]	0.67[0.54, 0.83]	0.76[0.58, 1.0]	0.79[0.73, 0.84]	1.43[0.98, 2.08]	0.82[0.47, 1.44]	0.61[0.39, 0.94]
>= 60 vs. <40 (M) or <50 (F)	1.11[0.79, 1.56]	0.42[0.07, 2.41]	0.59[0.39, 0.89]	0.81[0.50, 1.30]	0.78[0.69, 0.88]	0.82[0.38, 1.80]	0.88[0.33, 2.31]	3.93[2.70, 5.74]
Unknown vs. <40 (M) or <50 (F)	2.66[2.29, 3.09]	2.6[1.57, 4.29]	3.39[2.96, 3.87]	1.37[1.12, 1.69]	1.85[1.76, 1.95]	2.16[1.58, 2.96]	2.75[1.87, 4.05]	3.33[2.56, 4.33]
TG	<0.001	<0.001	<0.001	0.004	<0.001	<0.001	<0.001	<0.001
150-499 vs. < 150	0.92[0.74, 1.13]	1.85[0.69, 4.92]	0.89[0.70, 1.12]	1.09[0.82, 1.46]	1.24[1.14, 1.34]	0.96[0.60, 1.55]	0.92[0.52, 1.65]	0.94[0.61, 1.44]
>= 500 vs. < 150	1.23[0.83, 1.81]	4.86[1.41, 16.8]	3.03[2.22, 4.13]	1.05[0.59, 1.87]	2.86[2.55, 3.21]	1.75[0.82, 3.76]	1.43[0.53, 3.88]	1.57[0.77, 3.20]
Unknown vs. < 150	2.17[1.80, 2.63]	5.86[2.36, 14.5]	3.95[3.23, 4.83]	1.49[1.13, 1.96]	2.38[2.21, 2.56]	2.57[1.68, 3.93]	2.63[1.57, 4.39]	3.43[2.36, 4.99]
Total cholesterol	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
200-239 vs. < 200	1.04[0.85, 1.29]	1.62[0.91, 2.86]	0.64[0.50, 0.82]	0.88[0.64, 1.21]	1.27[1.18, 1.36]	0.89[0.56, 1.39]	0.64[0.35, 1.19]	1.39[0.93, 2.06]
>=240 vs. < 200	1.22[0.97, 1.52]	1.03[0.49, 2.19]	1.18[0.94, 1.48]	1.1[0.78, 1.53]	1.93[1.80, 2.07]	1.11[0.69, 1.78]	0.8[0.42, 1.53]	1.42[0.91, 2.21]
Unknown vs. < 200	3.24[2.81, 3.73]	2.85[1.80, 4.50]	5.45[4.78, 6.21]	2.18[1.75, 2.71]	2.83[2.68, 2.99]	3.28[2.46, 4.37]	3.3[2.34, 4.66]	5.56[4.24, 7.29]

Triple or more antidiabetic groups

Studied factor	biguanide+DPP4-I+SU	biguanide+GLP1-RA+SU	biguanide+SGLT2-I+SU	biguanide+ SU +insulin	biguanide+ SU+TZD
5- Demographic factors					
Age at prescription	>0.9	0.09	0.024	<0.001	0.2
>= 65 vs. < 65 years	1[0.81, 1.23]	0.67[0.42, 1.08]	0.38[0.23, 0.64]	0.74[0.57, 0.97]	1.29[0.91, 1.81]
SEX	0.022	0.7	<0.001	0.031	0.091
F vs. M	0.78[0.63, 0.97]	1.1[0.71, 1.71]	0.62[0.40, 0.97]	0.63[0.48, 0.82]	0.74[0.52, 1.05]
6- Socioeconomic factors					
UR	<0.001	<0.001	0.042	0.001	0.028
2 vs. 1	0.82[0.62, 1.08]	2.17[1.15, 4.08]	0.78[0.44, 1.39]	0.74[0.55, 1.00]	0.63[0.41, 0.98]
3 vs. 1	0.94[0.61, 1.45]	1.86[0.73, 4.72]	1.62[0.78, 3.36]	0.87[0.54, 1.41]	1.12[0.62, 2.04]
4 vs. 1	1.19[0.60, 2.37]	4.24[1.41, 12.8]	1.72[0.52, 5.71]	1.05[0.48, 2.29]	0.88[0.28, 2.84]
5 vs. 1	1.61[0.72, 3.59]	4.11[0.96, 17.5]	2.17[0.51, 9.17]	1.1[0.39, 3.09]	0.04[0.00, 47.5]
6 vs. 1	2.03[1.50, 2.74]	1.49[0.59, 3.76]	2.14[1.15, 3.97]	0.88[0.57, 1.36]	1.19[0.69, 2.03]
7 vs. 1	2.64[1.74, 4.02]	6.95[3.03, 16.0]	2.18[0.85, 5.56]	1.04[0.53, 2.03]	1.07[0.43, 2.67]
8 vs. 1	2.82[1.84, 4.32]	2.38[0.67, 8.41]	3.77[1.72, 8.29]	1.6[0.90, 2.86]	2.46[1.26, 4.79]
Unknown vs. 1	6.89[0.98, 48.6]	0.7[0.00, 13,992,763]	28.3[3.74, 214]	15[3.55, 63.8]	0.37[0.00, 84,606]
SIMD_Q	<0.001	0.7	0.035	0.3	0.8
2 vs. 1	0.84[0.59, 1.20]	3.09[0.89, 10.7]	3.05[1.51, 6.14]	1.43[0.99, 2.06]	2.09[1.11, 3.95]
3 vs. 1	1.3[0.94, 1.81]	35.5[12.0, 105]	10.5[5.57, 19.8]	0.96[0.63, 1.47]	2.9[1.57, 5.38]
4 vs. 1	1.72[1.24, 2.37]	23.9[7.96, 71.7]	4.8[2.40, 9.58]	1.08[0.70, 1.66]	1.96[0.98, 3.91]
5 vs. 1	0.87[0.56, 1.33]	8.37[2.55, 27.5]	15.6[8.24, 29.5]	1.66[1.10, 2.50]	4.07[2.17, 7.65]
Unknown vs. 1	0.42[0.00, 4,831]	0.74[0.00, inf]	10.8[0.09, 1,311]	0.43[0.00, 23,935]	0.69[0.00, 7,066,868]
7- Prescriber-related factors					
Prescriber type	<0.001	0.015	<0.001	0.039	0.004
Non-GP vs. GP	0.26[0.12, 0.56]	0.17[0.02, 1.23]	0.29[0.07, 1.21]	0.18[0.06, 0.54]	0.21[0.05, 0.86]
8- Clinical-related factors					
IHD	<0.001	0.077	0.4	0.009	<0.001
Yes vs. No	0.48[0.31, 0.73]	0.48[0.19, 1.19]	0.34[0.13, 0.91]	1.17[0.82, 1.69]	0.3[0.13, 0.72]
HTN	<0.001	0.061	0.3	0.08	<0.001
Yes vs. No	0.47[0.33, 0.67]	0.53[0.25, 1.10]	0.57[0.30, 1.10]	1.2[0.88, 1.63]	0.27[0.13, 0.58]

HF	0.9	0.8	0.081	0.2	0.087
Yes vs. No	1.03[0.56, 1.88]	0.76[0.17, 3.37]	0.34[0.04, 2.67]	1.76[0.98, 3.15]	0.25[0.03, 1.89]
Stroke	0.12	0.043	0.002	0.3	0.13
Yes vs. No	0.54[0.22, 1.29]	0[0.00, inf]	0.42[0.06, 3.05]	2.53[1.50, 4.27]	0.3[0.04, 2.13]
PVD					
Yes vs. No	0.48[0.18, 1.28]	0.44[0.05, 3.98]	0.48[0.07, 3.43]	1.67[0.86, 3.25]	0.66[0.16, 2.71]
Liver disease	0.2	0.8	<0.001	0.9	0.3
Yes vs. No	0.54[0.20, 1.46]	1.36[0.35, 5.31]	1.29[0.35, 4.76]	3.08[1.80, 5.27]	0.38[0.05, 2.74]
CCI score	<0.001	0.021	<0.001	0.002	<0.001
1-2 vs. 0	0.43[0.29, 0.65]	0.18[0.05, 0.66]	0.44[0.20, 0.98]	2.18[1.62, 2.95]	0.24[0.10, 0.58]
3-4 vs. 0	0.69[0.34, 1.39]	1.22[0.40, 3.68]	0[0.00, 47,572,865]	3.52[2.20, 5.64]	0.52[0.14, 1.91]
>= 5 vs. 0	0.3[0.07, 1.20]	1.28[0.31, 5.27]	0[0.00, inf]	3.87[2.16, 6.92]	0.41[0.06, 2.83]
Antihyperlipidemic drugs	0.2	0.054	<0.001	0.04	0.11
Yes vs. No	1.15[0.93, 1.42]	0.65[0.42, 1.01]	0.65[0.43, 0.98]	0.57[0.44, 0.73]	1.33[0.93, 1.92]
Antipsychotic	0.7	0.15	0.12	>0.9	0.07
Yes vs. No	0.89[0.47, 1.67]	2.04[0.81, 5.12]	1.02[0.32, 3.32]	1.64[0.92, 2.94]	0.26[0.04, 1.76]
Thiazide diuretics	<0.001	0.8	0.7	0.006	0.2
Yes vs. No	0.58[0.42, 0.80]	1.08[0.62, 1.89]	0.39[0.18, 0.84]	0.93[0.66, 1.30]	0.75[0.46, 1.24]
Beta blocker	0.031	0.002	0.2	0.2	0.004
Yes vs. No	0.76[0.59, 0.98]	0.39[0.20, 0.78]	0.69[0.41, 1.17]	0.83[0.61, 1.13]	0.52[0.32, 0.85]
Angiotensin inhibitors	0.12	0.3	0.057	>0.9	0.051
Yes vs. No	1.18[0.96, 1.44]	1.25[0.81, 1.94]	1.01[0.67, 1.53]	0.78[0.60, 1.01]	1.41[1.00, 1.98]
CCB	0.6	0.6	0.056	0.5	0.061
Yes vs. No	0.93[0.72, 1.19]	0.88[0.52, 1.50]	0.88[0.54, 1.45]	0.73[0.53, 1.02]	0.64[0.40, 1.02]
Number of concomitant medications	<0.001	0.3	0.4	<0.001	<0.001
1-4 vs. 0	0.82[0.55, 1.22]	0.78[0.30, 2.00]	0.49[0.25, 0.95]	0.66[0.37, 1.17]	0.85[0.45, 1.61]
>= 5 vs. 0	0.37[0.25, 0.56]	0.58[0.23, 1.47]	0.23[0.12, 0.45]	0.73[0.42, 1.26]	0.27[0.14, 0.53]
BMI	<0.001	0.11	<0.001	0.037	0.024
25-29.9 vs. <=24.9	0.59[0.37, 0.93]	1.8[0.23, 14.3]	1.84[0.42, 8.03]	0.72[0.39, 1.35]	0.96[0.36, 2.55]
>= 30 vs. <=24.9	0.34[0.22, 0.53]	2.5[0.34, 18.1]	1.1[0.26, 4.65]	0.39[0.21, 0.71]	0.64[0.25, 1.63]
Unknown vs. <= 24.9	0.62[0.41, 0.94]	3.58[0.50, 25.7]	2.12[0.51, 8.75]	0.88[0.49, 1.55]	1.17[0.47, 2.91]
HbA1c	<0.001	<0.001	<0.001	<0.001	<0.001

7-9% vs. < 7%	0.45[0.26, 0.77]	0.47[0.13, 1.68]	0.55[0.16, 1.94]	0.69[0.27, 1.79]	0.31[0.14, 0.68]
>=9% vs. < 7%	0.66[0.39, 1.13]	1.36[0.41, 4.54]	1.72[0.52, 5.65]	4.38[1.79, 10.7]	0.44[0.20, 0.95]
Unknown vs. < 7%	5.31[3.24, 8.69]	5.75[1.78, 18.5]	6.27[1.95, 20.1]	7.14[2.90, 17.6]	3.44[1.73, 6.86]
eGFR	<0.001	<0.001	<0.001	<0.001	<0.001
< 60 vs. >= 60	2.2[1.41, 3.43]	1.34[0.43, 4.15]	1.14[0.42, 3.07]	2.74[1.83, 4.08]	2.01[0.95, 4.25]
Unknown vs. < 60	9.43[7.60, 11.7]	8.3[5.27, 13.1]	5.59[3.73, 8.39]	3.22[2.43, 4.26]	8.59[6.01, 12.3]
HDL	<0.001	<0.001	<0.001	<0.001	<0.001
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1[0.69, 1.47]	0.54[0.24, 1.22]	0.56[0.27, 1.19]	0.66[0.41, 1.07]	0.7[0.37, 1.34]
>= 60 vs. <40 (M) or <50 (F)	1.33[0.75, 2.38]	0.39[0.07, 2.25]	0.59[0.15, 2.30]	0.63[0.25, 1.54]	0.17[0.02, 1.69]
Unknown vs. <40 (M) or <50 (F)	3.88[2.97, 5.06]	2.5[1.53, 4.08]	2.17[1.35, 3.46]	3.06[2.25, 4.14]	3.47[2.30, 5.23]
TG	<0.001	<0.001	<0.001	<0.001	<0.001
150-499 vs. < 150	0.91[0.59, 1.40]	0.86[0.34, 2.15]	0.63[0.31, 1.25]	1.26[0.73, 2.16]	0.49[0.25, 0.95]
>= 500 vs. < 150	2.04[1.07, 3.90]	2.78[0.81, 9.49]	2.43[0.98, 6.03]	3.25[1.56, 6.74]	0[0.00, inf]
Unknown vs. < 150	3.74[2.58, 5.43]	3.56[1.62, 7.81]	1.66[0.92, 2.98]	4.06[2.50, 6.61]	2.5[1.49, 4.18]
Total cholesterol	<0.001	<0.001	<0.001	<0.001	<0.001
200-239 vs. < 200	0.54[0.34, 0.87]	0.17[0.02, 1.35]	0.75[0.28, 2.00]	1.04[0.66, 1.65]	0.12[0.03, 0.56]
>=240 vs. < 200	0.7[0.43, 1.14]	0.43[0.09, 2.08]	5.37[2.95, 9.76]	1.27[0.78, 2.07]	2.12[1.25, 3.60]
Unknown vs. < 200	4.48[3.54, 5.66]	5.46[3.02, 9.86]	4.74[2.74, 8.21]	4.26[3.16, 5.73]	3.91[2.64, 5.78]

Appendix S.4.7: Complete case multivariable regression analyses results at drug initiation

Regimen type

Studied factor	OR[95%CI]	Overall p-value
Age at prescription		
>= 65 vs. < 65 years	0.69[0.62, 0.76]	<0.001
Sex		
F vs. M	0.97[0.89, 1.06]	0.6
UR		<0.001
2 vs. 1	0.97[0.88, 1.07]	
3 vs. 1	1[0.85, 1.18]	
4 vs. 1	1.05[0.80, 1.36]	
5 vs. 1	1.15[0.73, 1.73]	
6 vs. 1	0.98[0.85, 1.14]	
7 vs. 1	1.68[1.36, 2.06]	
8 vs. 1	1.32[0.99, 1.73]	
SCOTTISH INDEX OF MULTIPLE DEPRIVATION-QUANTILE		0.13
2 vs. 1	0.97[0.87, 1.08]	
3 vs. 1	0.86[0.75, 0.98]	
4 vs. 1	0.95[0.83, 1.08]	
5 vs. 1	0.89[0.77, 1.02]	
Prescriber type		
Non-GP vs. GP	0.76[0.65, 0.89]	<0.001
IHD		
Yes vs. No	1[0.86, 1.16]	>0.9
HTN		
Yes vs. No	1.03[0.91, 1.16]	0.7
HF		
Yes vs. No	1.19[0.92, 1.53]	0.2
Stroke		
Yes vs. No	1.01[0.76, 1.32]	>0.9
PVD		
Yes vs. No	1.35[1.03, 1.73]	0.028
Liver disease		
Yes vs. No	1.06[0.80, 1.38]	0.7
CCI-score		0.3
1-2 vs. 0	0.96[0.84, 1.10]	
3-4 vs. 0	1.04[0.80, 1.34]	
>= 5 vs. 0	1.26[0.94, 1.67]	
Antihyperlipidemic drugs		<0.001
Yes vs. No	0.75[0.69, 0.83]	
Antipsychotic		0.4
Yes vs. No	1.09[0.87, 1.36]	

Thiazide diuretics		0.9
Yes vs. No	0.99[0.87, 1.12]	
Beta-blockers		0.7
Yes vs. No	1.02[0.91, 1.14]	
Angiotensin inhibitors		0.4
Yes vs. No	0.96[0.87, 1.06]	
CCB		0.005
Yes vs. No	0.85[0.76, 0.95]	
Number of concomitant medications		0.08
1-4 vs. 0	1.07[0.89, 1.31]	
>= 5 vs. 0	1.19[0.97, 1.47]	
BMI (kg/m^2)		<0.001
25-29.9	0.8[0.69, 0.93]	
>= 30	0.67[0.58, 0.77]	
HbA1c (%)		<0.001
7-9 vs. < 7	0.63[0.52, 0.78]	
>= 9 vs. < 7	2.74[2.27, 3.33]	
eGFR:		
< 60 vs. >= 60 ml/min/1.73m^2	1.66[1.42, 1.93]	<0.001
HDL (mg/dl)		0.002
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.85[0.77, 0.93]	
>= 60 vs. <40 (M) or <50 (F)	0.99[0.84, 1.17]	
TG (mg/dl)		<0.001
150-499 vs. < 150	0.96[0.87, 1.06]	
>= 500 vs. < 150	1.36[1.14, 1.61]	
Total cholesterol (mg/dl)		0.058
200-239 vs. < 200	0.88[0.79, 0.98]	
>=240 vs. < 200	0.96[0.85, 1.08]	

Antidiabetic class: Monotherapy groups

Studied factor	DPP4-I	GLP1-RA	insulin	SGLT2-I	SU	TZD
Age at prescription						
>= 65 vs. < 65 years	1.41[1.05, 1.88]	0.25[0.02, 2.51]	0.48[0.34, 0.66]	0.4[0.25, 0.64]	1.12[1.01, 1.25]	0.65[0.26, 1.61]
SEX						
F vs. M	1.37[1.07, 1.75]	2.79[0.48, 16.2]	0.73[0.54, 0.97]	1.52[1.04, 2.21]	0.95[0.86, 1.04]	1.83[0.81, 4.14]
UR						
2 vs. 1	0.91[0.69, 1.21]	0.53[0.08, 3.36]	1.13[0.84, 1.53]	1.22[0.80, 1.88]	1[0.90, 1.11]	0.86[0.33, 2.20]
3 vs. 1	1.36[0.91, 2.03]	0.02[0.00, 3,340]	1.05[0.64, 1.72]	0.93[0.43, 2.02]	0.99[0.83, 1.17]	1.94[0.58, 6.57]
4 vs. 1	1.31[0.70, 2.46]	5.77[0.47, 70.5]	0.62[0.22, 1.77]	0.79[0.19, 3.34]	1.24[0.95, 1.62]	0.06[0.00, 979]
5 vs. 1	0.82[0.25, 2.67]	0.39[0.00, 4,101]	0.03[0.00, 355]	0.78[0.10, 5.81]	0.65[0.39, 1.09]	0.09[0.00, 1,199]
6 vs. 1	1.03[0.68, 1.57]	0.01[0.00, 15,915]	1.09[0.68, 1.74]	1.64[0.93, 2.89]	1.02[0.87, 1.20]	2.5[0.80, 7.80]
7 vs. 1	0.98[0.49, 2.00]	0.19[0.00, 3,259]	0.76[0.30, 1.95]	0.91[0.27, 3.01]	1.29[1.01, 1.64]	3.66[0.73, 18.3]
8 vs. 1	0.85[0.36, 1.99]	3.74[0.21, 66.9]	1.41[0.62, 3.23]	0.76[0.18, 3.24]	0.8[0.57, 1.12]	0.07[0.00, 1,027]
SIMD_Q						
2 vs. 1	1.36[0.98, 1.88]	1.5[0.09, 24.5]	1.28[0.89, 1.86]	0.96[0.59, 1.58]	1.07[0.94, 1.21]	0.88[0.33, 2.33]
3 vs. 1	1.15[0.79, 1.65]	0[0.00, inf]	0.89[0.57, 1.39]	0.9[0.51, 1.59]	1.02[0.89, 1.17]	0.34[0.09, 1.34]
4 vs. 1	1.01[0.68, 1.51]	8.62[0.70, 106]	1.07[0.68, 1.67]	1.7[1.02, 2.81]	1.19[1.03, 1.37]	0.94[0.32, 2.79]
5 vs. 1	1.33[0.90, 1.96]	7.82[0.64, 95.4]	2.07[1.41, 3.05]	0.57[0.26, 1.25]	1.13[0.98, 1.30]	0.69[0.18, 2.63]
Prescriber type						
Non-GP vs. GP	1.27[0.85, 1.89]	1.8[0.18, 17.9]	0.13[0.04, 0.41]	1.23[0.73, 2.08]	1.17[1.01, 1.37]	0.84[0.20, 3.59]
IHD						
Yes vs. No	0.97[0.70, 1.34]	0.49[0.03, 7.34]	1.29[0.84, 1.98]	2.07[1.19, 3.59]	0.88[0.76, 1.01]	0.23[0.03, 1.76]
HTN						
Yes vs. No	1.01[0.76, 1.34]	9.73[1.43, 66.1]	1.22[0.84, 1.76]	0.94[0.57, 1.56]	1.15[1.02, 1.30]	0.67[0.23, 1.95]
HF						
Yes vs. No	1.26[0.80, 1.99]	0.28[0.00, 66,499]	0.74[0.39, 1.40]	2.87[1.22, 6.75]	1.01[0.81, 1.27]	0.04[0.00, 719]
Stroke						
Yes vs. No	1.4[0.85, 2.33]	0.33[0.00, 31,743]	1.16[0.55, 2.45]	0.92[0.28, 2.98]	0.94[0.72, 1.22]	1.74[0.22, 13.8]
PVD						
Yes vs. No	0.88[0.47, 1.61]	0.5[0.00, 3,085,995]	1.68[0.86, 3.27]	1.87[0.73, 4.82]	1.21[0.95, 1.55]	0.08[0.00, 1,355]
Liver disease						

Yes vs. No	0.9[0.45, 1.78]	0.21[0.00, 58,775]	1.06[0.59, 1.92]	0.64[0.15, 2.83]	1.27[0.99, 1.62]	6.59[1.63, 26.6]
CCI score						
1-2 vs. 0	1.5[1.11, 2.02]	1.39[0.12, 16.6]	1.49[1.01, 2.19]	0.98[0.57, 1.70]	1.43[1.26, 1.62]	1.82[0.69, 4.79]
3-4 vs. 0	1.92[1.16, 3.19]	0.24[0.00, inf]	3.11[1.73, 5.57]	1.3[0.49, 3.49]	2.3[1.85, 2.86]	3.33[0.66, 16.7]
>= 5 vs. 0	2.57[1.49, 4.45]	0.51[0.00, inf]	9.2[5.58, 15.2]	0.02[0.00, 489]	2.95[2.33, 3.73]	0.07[0.00, 1,655]
Antihyperlipidemic drugs						
Yes vs. No	0.74[0.56, 0.98]	0.18[0.03, 1.15]	0.34[0.25, 0.45]	0.69[0.45, 1.03]	0.63[0.57, 0.69]	0.9[0.38, 2.11]
Antipsychotic						
Yes vs. No	0.79[0.34, 1.80]	0.21[0.00, 4,566]	0.84[0.40, 1.78]	0.55[0.17, 1.77]	1.01[0.77, 1.32]	3.44[0.96, 12.4]
Thiazide diuretics						
Yes vs. No	0.7[0.50, 0.96]	0.8[0.07, 8.60]	0.49[0.30, 0.80]	0.85[0.47, 1.55]	0.84[0.74, 0.95]	1.27[0.52, 3.10]
Beta blocker						
Yes vs. No	1.49[1.14, 1.94]	5.24[0.87, 31.7]	0.95[0.67, 1.36]	0.93[0.57, 1.50]	1.03[0.92, 1.16]	0.98[0.42, 2.31]
Angiotensin inhibitors						
Yes vs. No	0.92[0.71, 1.18]	0.46[0.07, 3.05]	0.75[0.55, 1.02]	0.96[0.64, 1.44]	0.92[0.84, 1.02]	0.47[0.21, 1.07]
CCB						
Yes vs. No	1.02[0.79, 1.33]	0[0.00, inf]	1.16[0.82, 1.63]	0.81[0.50, 1.29]	0.88[0.79, 0.98]	1.84[0.82, 4.15]
Number of concomitant medications						
1-4 vs. 0	1.15[0.46, 2.89]	1.28[0.02, 81.2]	4.61[1.77, 12.0]	0.64[0.27, 1.49]	1.22[0.96, 1.56]	4.28[0.02, 876]
>= 5 vs. 0	1.56[0.62, 3.92]	0.5[0.01, 42.8]	5.65[2.13, 14.9]	1.19[0.51, 2.79]	1.67[1.30, 2.15]	5.17[0.03, 1,060]
BMI						
25-29.9 vs. <=24.9	0.58[0.39, 0.86]	0[0.00, inf]	0.33[0.23, 0.47]	0.97[0.33, 2.81]	0.27[0.24, 0.30]	1[0.21, 4.71]
>= 30 vs. <=24.9	0.52[0.36, 0.76]	7.93[0.01, 6,360]	0.16[0.11, 0.23]	1.53[0.56, 4.16]	0.11[0.10, 0.13]	0.71[0.16, 3.13]
HbA1c						
7-9% vs. < 7%	1.28[0.80, 2.05]	0.21[0.03, 1.46]	0.39[0.23, 0.67]	0.86[0.46, 1.61]	1.17[0.94, 1.47]	2.49[0.34, 18.1]
>=9% vs. < 7%	1.25[0.76, 2.05]	0.08[0.01, 1.06]	1.52[0.92, 2.50]	1.14[0.60, 2.17]	2.85[2.28, 3.56]	1.33[0.17, 10.6]
eGFR						
< 60 vs. >= 60	8.31[6.36, 10.9]	0.11[0.00, 16,269]	7.47[5.19, 10.7]	0.9[0.35, 2.30]	4.42[3.91, 4.99]	14.2[5.86, 34.4]
HDL						
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.95[0.73, 1.24]	2.46[0.46, 13.2]	0.83[0.61, 1.12]	1.43[0.98, 2.08]	0.98[0.89, 1.08]	0.52[0.19, 1.43]
>= 60 vs. <40 (M) or <50 (F)	0.99[0.67, 1.47]	0.05[0.00, 204,940]	1.39[0.90, 2.13]	0.34[0.10, 1.10]	1.16[1.00, 1.35]	1.6[0.54, 4.74]

TG						
150-499 vs. < 150	0.78[0.60, 1.01]	1.07[0.19, 5.96]	0.75[0.55, 1.02]	0.99[0.65, 1.50]	1.01[0.91, 1.12]	1.55[0.62, 3.86]
>= 500 vs. < 150	0.56[0.26, 1.20]	0.1[0.00, 122,503]	1.49[0.90, 2.48]	0.69[0.27, 1.78]	1.29[1.05, 1.58]	2.19[0.38, 12.5]
Total cholesterol						
200-239 vs. < 200	0.87[0.63, 1.22]	0[0.00, 121,572,711]	1.4[1.01, 1.95]	1.2[0.78, 1.86]	0.96[0.86, 1.08]	0.66[0.23, 1.85]
>=240 vs. < 200	1.06[0.71, 1.58]	0.66[0.06, 6.78]	1.44[0.99, 2.11]	1.2[0.70, 2.05]	1.04[0.90, 1.19]	0.75[0.23, 2.44]

dual therapy regimens

Studied factor	biguanide+DPP4-I	biguanide+GLP1-RA	biguanide+ insulin	biguanide+SGLT2-I	biguanide+ SU	biguanide+ TZD	DPP4-I+SU	SU+ insulin
Age at prescription								
>= 65 vs. < 65 years	**0.55[0.39, 0.78]**	0.81[0.20, 3.38]	0.88[0.61, 1.26]	**0.55[0.36, 0.84]**	**0.73[0.64, 0.83]**	**0.46[0.22, 0.97]**	0.67[0.23, 1.99]	**0.25[0.10, 0.61]**
SEX								
F vs. M	1.05[0.78, 1.42]	3.18[0.97, 10.3]	1.01[0.74, 1.39]	**1.46[1.02, 2.08]**	0.95[0.85, 1.07]	0.53[0.26, 1.05]	1.95[0.79, 4.83]	1.16[0.57, 2.37]
UR								
2 vs. 1	0.93[0.68, 1.28]	1.23[0.24, 6.30]	0.87[0.62, 1.24]	0.81[0.54, 1.21]	1[0.89, 1.13]	1.77[0.79, 3.96]	0.71[0.24, 2.11]	1.88[0.85, 4.13]
3 vs. 1	0.65[0.34, 1.21]	2.2[0.20, 24.5]	1.16[0.68, 2.00]	1.07[0.56, 2.06]	0.95[0.78, 1.16]	0.71[0.15, 3.47]	1.65[0.39, 6.97]	1.62[0.45, 5.90]
4 vs. 1	0.92[0.35, 2.38]	13.2[1.95, 88.8]	1.66[0.77, 3.55]	0.99[0.30, 3.22]	1[0.72, 1.40]	1.32[0.16, 11.1]	0[0.00, inf]	0[0.00, inf]
5 vs. 1	1.78[0.62, 5.10]	0.11[0.00, inf]	0.71[0.10, 5.36]	1.77[0.43, 7.23]	0.92[0.53, 1.60]	4.04[0.45, 36.5]	0.04[0.00, inf]	4.37[0.44, 43.0]
6 vs. 1	1.18[0.74, 1.89]	2.72[0.33, 22.4]	1.11[0.65, 1.88]	1.08[0.58, 2.00]	0.86[0.71, 1.04]	2.61[0.96, 7.12]	0.89[0.16, 5.09]	0.7[0.13, 3.68]
7 vs. 1	0.96[0.40, 2.31]	**27.5[4.71, 161]**	1.27[0.56, 2.87]	1.84[0.76, 4.41]	**1.67[1.30, 2.15]**	**4.21[1.21, 14.6]**	4.02[0.71, 22.7]	3.05[0.60, 15.4]
8 vs. 1	0.47[0.10, 2.10]	6.91[0.31, 152]	1.59[0.61, 4.15]	**2.6[1.01, 6.74]**	0.95[0.65, 1.40]	**4.7[1.14, 19.3]**	**9.03[1.81, 44.9]**	0[0.00, inf]
SIMD_Q								
2 vs. 1	0.98[0.68, 1.42]	0.31[0.05, 1.80]	0.72[0.49, 1.06]	1[0.66, 1.53]	1.03[0.90, 1.19]	1.52[0.56, 4.09]	0.41[0.11, 1.50]	0.68[0.27, 1.73]

3 vs. 1	0.78[0.50, 1.21]	0.95[0.23, 3.87]	**0.51[0.32, 0.82]**	**0.46[0.25, 0.82]**	0.98[0.83, 1.14]	1.84[0.69, 4.94]	0.43[0.11, 1.63]	0.55[0.18, 1.73]
4 vs. 1	0.73[0.46, 1.16]	0[0.00, inf]	0.72[0.45, 1.14]	0.69[0.40, 1.20]	1.11[0.95, 1.31]	0.94[0.29, 3.02]	0.52[0.14, 1.91]	1.34[0.53, 3.42]
5 vs. 1	1[0.65, 1.56]	1.22[0.21, 6.97]	0.65[0.39, 1.08]	0.56[0.30, 1.05]	0.98[0.83, 1.17]	**3.02[1.12, 8.18]**	0.53[0.13, 2.25]	0.51[0.13, 1.98]
Prescriber type								
Non-GP vs. GP	1.05[0.65, 1.70]	0[0.00, 0.00]	**0.38[0.17, 0.85]**	0.99[0.57, 1.72]	0.84[0.70, 1.02]	0.21[0.03, 1.58]	0.97[0.20, 4.72]	0.36[0.07, 1.78]
IHD								
Yes vs. No	0.75[0.44, 1.27]	0.91[0.09, 8.74]	**1.73[1.10, 2.72]**	0.78[0.42, 1.43]	1.11[0.93, 1.33]	0.62[0.17, 2.21]	0.44[0.07, 2.75]	1.14[0.40, 3.26]
HTN								
Yes vs. No	0.74[0.48, 1.16]	0.44[0.06, 3.03]	1.12[0.74, 1.68]	1.01[0.61, 1.67]	1.16[1.00, 1.35]	1.54[0.68, 3.47]	1.27[0.40, 4.03]	1.14[0.46, 2.85]
HF								
Yes vs. No	1.51[0.65, 3.50]	0[0.00, inf]	0.72[0.32, 1.63]	0.98[0.35, 2.78]	**1.43[1.06, 1.92]**	0[0.00, inf]	0.71[0.06, 8.99]	0.71[0.16, 3.18]
Stroke								
Yes vs. No	0.59[0.18, 1.99]	0.01[0.00, inf]	1.5[0.69, 3.24]	1.2[0.44, 3.30]	1.04[0.74, 1.45]	0[0.00, inf]	2.6[0.46, 14.6]	0.78[0.09, 6.52]
PVD								
Yes vs. No	1.85[0.82, 4.18]	0.01[0.00, inf]	1.21[0.53, 2.79]	0.41[0.06, 2.89]	1.36[1.00, 1.86]	0[0.00, inf]	3.93[0.73, 21.3]	2.32[0.57, 9.49]
Liver disease								
Yes vs. No	0.91[0.33, 2.51]	0[0.00, inf]	**2.1[1.04, 4.24]**	0.36[0.08, 1.55]	1.13[0.81, 1.58]	0[0.00, inf]	0[0.00, inf]	0.85[0.17, 4.40]
CCI score								
1-2 vs. 0	1.02[0.64, 1.61]	1.01[0.18, 5.72]	1.2[0.78, 1.84]	1.11[0.66, 1.88]	1[0.85, 1.18]	0.34[0.07, 1.63]	1.85[0.58, 5.84]	1.19[0.46, 3.13]
3-4 vs. 0	1.4[0.58, 3.37]	8.47[0.76, 94.4]	1.28[0.58, 2.82]	2.52[0.99, 6.39]	1.13[0.82, 1.56]	**5.76[1.23, 27.0]**	4.32[0.62, 30.1]	1.88[0.44, 8.06]
>= 5 vs. 0	1.42[0.49, 4.10]	0.05[0.00, inf]	1.69[0.70, 4.07]	1.17[0.28, 4.86]	**1.48[1.04, 2.10]**	0.01[0.00, inf]	0.01[0.00, inf]	**7.21[1.97, 26.4]**
Antihyperlipidemic drugs								

Yes vs. No	0.93[0.68, 1.28]	0.62[0.19, 1.95]	**0.46[0.33, 0.64]**	0.96[0.65, 1.41]	**0.67[0.60, 0.75]**	1.28[0.61, 2.69]	0.68[0.27, 1.71]	0.53[0.25, 1.11]
Antipsychotic								
Yes vs. No	1.3[0.63, 2.65]	**5.76[1.36, 24.3]**	1.39[0.67, 2.88]	1.15[0.50, 2.66]	1.02[0.77, 1.34]	2.08[0.48, 9.05]	1.66[0.19, 14.6]	0.55[0.07, 4.66]
Thiazide diuretics								
Yes vs. No	1.05[0.70, 1.58]	0[0.00, inf]	0.77[0.48, 1.23]	0.94[0.54, 1.65]	1[0.86, 1.17]	**2.07[1.04, 4.12]**	1.25[0.39, 3.98]	1.69[0.69, 4.16]
Beta blocker								
Yes vs. No	1.18[0.82, 1.70]	0.42[0.07, 2.69]	1.13[0.77, 1.65]	1.42[0.91, 2.21]	1.01[0.88, 1.16]	0.82[0.38, 1.76]	1.07[0.35, 3.27]	1.74[0.77, 3.91]
Angiotensin inhibitors								
Yes vs. No	1.1[0.80, 1.51]	**3.89[1.21, 12.5]**	0.99[0.71, 1.39]	1.06[0.72, 1.57]	**0.83[0.74, 0.94]**	0.9[0.46, 1.76]	0.67[0.25, 1.75]	1.23[0.56, 2.71]
CCB								
Yes vs. No	0.81[0.56, 1.17]	0.5[0.09, 2.71]	0.77[0.52, 1.15]	**0.37[0.21, 0.66]**	0.89[0.78, 1.02]	1.04[0.52, 2.06]	2.1[0.80, 5.52]	0.62[0.24, 1.61]
Number of concomitant medications								
1-4 vs. 0	0.87[0.44, 1.70]	12.8[0.00, 329,263]	1.17[0.58, 2.37]	0.83[0.38, 1.80]	1.13[0.89, 1.43]	0.46[0.11, 1.86]	2.49[0.17, 36.1]	2.61[0.18, 38.2]
>= 5 vs. 0	0.94[0.46, 1.90]	26.6[0.00, 690,093]	1.06[0.50, 2.21]	0.91[0.41, 2.06]	**1.4[1.09, 1.79]**	0.48[0.11, 2.15]	0.87[0.05, 14.6]	4.82[0.33, 71.2]
BMI								
25-29.9 vs. <=24.9	1.5[0.78, 2.87]	5.41[0.01, 4,934]	0.72[0.41, 1.26]	1.4[0.54, 3.64]	**0.62[0.51, 0.74]**	3.34[0.18, 60.7]	**0.21[0.06, 0.79]**	**0.17[0.08, 0.39]**
>= 30 vs. <=24.9	1.05[0.55, 1.98]	6.8[0.01, 5,769]	0.65[0.38, 1.11]	1.57[0.63, 3.92]	**0.46[0.39, 0.55]**	5.56[0.32, 96.5]	**0.23[0.07, 0.70]**	**0.04[0.02, 0.11]**
HbA1c								
7-9% vs. < 7%	**0.55[0.33, 0.93]**	35.2[0.00, inf]	0.57[0.29, 1.11]	1.13[0.48, 2.66]	0.6[0.45, 0.80]	0.67[0.23, 1.94]	0.69[0.12, 3.84]	0.49[0.09, 2.65]
>=9% vs. < 7%	1.36[0.82, 2.28]	274[0.00, inf]	**2.3[1.22, 4.34]**	**4.15[1.81, 9.50]**	**4.09[3.13, 5.34]**	0.72[0.23, 2.20]	1.73[0.33, 9.19]	2.57[0.53, 12.4]
eGFR								

< 60 vs. >= 60	**2.37[1.43, 3.91]**	0.49[0.01, 18.1]	**3.5[2.26, 5.43]**	0.15[0.02, 1.10]	**1.87[1.54, 2.27]**	**5.03[2.12, 11.9]**	**7.54[2.48, 22.9]**	**12.4[5.18, 29.9]**
HDL								
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.23[0.90, 1.67]	0.92[0.25, 3.44]	**0.64[0.45, 0.91]**	0.73[0.49, 1.09]	**0.85[0.76, 0.96]**	1.59[0.83, 3.02]	1.27[0.50, 3.24]	**0.29[0.11, 0.80]**
>= 60 vs. <40 (M) or <50 (F)	1.56[0.95, 2.57]	0.84[0.07, 9.86]	0.64[0.33, 1.25]	1.18[0.63, 2.23]	1.06[0.87, 1.29]	2.11[0.71, 6.25]	0.2[0.01, 2.95]	0.93[0.32, 2.66]
TG								
150-499 vs. < 150	0.91[0.66, 1.25]	1.71[0.36, 8.17]	0.78[0.56, 1.10]	0.91[0.62, 1.35]	1.01[0.89, 1.14]	1.37[0.69, 2.73]	1.03[0.37, 2.91]	0.76[0.31, 1.83]
>= 500 vs. < 150	0.93[0.49, 1.80]	5.11[0.63, 41.4]	1.72[0.97, 3.04]	0.45[0.17, 1.22]	**1.45[1.18, 1.79]**	1.31[0.26, 6.68]	**5.56[1.16, 26.6]**	1.07[0.29, 3.89]
Total cholesterol								
200-239 vs. < 200	0.92[0.65, 1.31]	0.6[0.14, 2.58]	**0.61[0.40, 0.91]**	0.63[0.40, 1.00]	0.97[0.85, 1.10]	0.85[0.41, 1.76]	1.07[0.38, 3.00]	1.25[0.42, 3.67]
>=240 vs. < 200	0.91[0.60, 1.38]	1.02[0.25, 4.10]	**0.6[0.37, 0.95]**	0.63[0.37, 1.09]	1.09[0.94, 1.26]	0.32[0.09, 1.18]	0.57[0.15, 2.23]	**5.03[1.99, 12.7]**

Triple therapy regimens

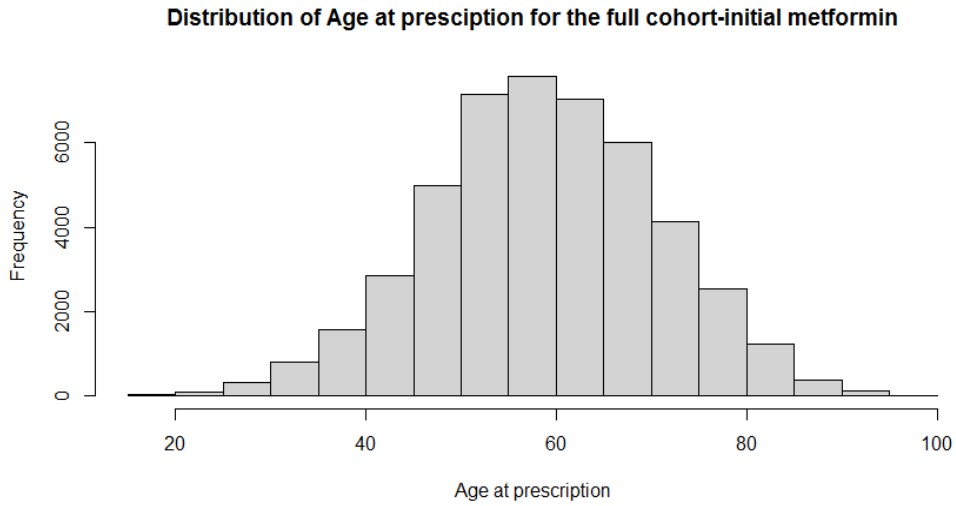
Studied factor	biguanide+DPP4-I+SU	biguanide+GLP1-RA+SU	biguanide+SGLT2-I+SU	biguanide+ SU +insulin	biguanide+ SU+TZD
Age at prescription					
>= 65 vs. < 65 years	**0.41[0.20, 0.85]**	**0[0.00, 0.10]**	0.36[0.05, 2.43]	0.63[0.27, 1.47]	2.17[0.59, 8.06]
SEX					
F vs. M	0.57[0.31, 1.06]	5.91[0.79, 44.4]	0.74[0.16, 3.36]	0.58[0.26, 1.28]	1.01[0.29, 3.53]
UR					
2 vs. 1	0.75[0.39, 1.46]	6.71[0.25, 181]	0[0.00, 0.00]	1.25[0.53, 2.93]	0.87[0.18, 4.31]
3 vs. 1	1.41[0.56, 3.52]	**154[2.28, 10,410]**	0.59[0.06, 5.61]	**3.16[1.15, 8.69]**	4.83[0.94, 24.8]
4 vs. 1	1.63[0.38, 6.88]	**468[5.11, 42,852]**	0[0.00, 0.00]	0[0.00, inf]	4[0.34, 47.0]
5 vs. 1	0.01[0.00, inf]	**0.13[0.13, 0.14]**	**34.8[2.79, 433]**	0.04[0.00, inf]	0.09[0.00, inf]
6 vs. 1	1.18[0.48, 2.87]	**109[2.23, 5,381]**	1.28[0.25, 6.70]	0.86[0.21, 3.49]	3.16[0.41, 24.3]
7 vs. 1	**3.1[1.12, 8.57]**	**3575[30.5, 418,488]**	0.8[0.03, 19.5]	2.54[0.50, 12.9]	0[0.00, inf]
8 vs. 1	1.66[0.38, 7.31]	0[0.00, 0.00]	0.26[0.00, 19.7]	2.03[0.22, 19.0]	11.1[0.71, 173]
SIMD_Q					
2 vs. 1	0.74[0.33, 1.63]	0.11[0.01, 1.08]	3.88[0.24, 63.9]	0.91[0.35, 2.38]	0.61[0.17, 2.21]
3 vs. 1	1.1[0.51, 2.35]	**0.01[0.00, 0.27]**	5.87[0.35, 98.7]	0.35[0.08, 1.49]	0.15[0.02, 1.13]
4 vs. 1	0.97[0.43, 2.18]	**0[0.00, 0.55]**	9.31[0.57, 151]	1.89[0.74, 4.81]	0[0.00, 1,963]
5 vs. 1	0.82[0.33, 2.00]	0[0.00, 13.3]	1.34[0.05, 38.6]	0.67[0.19, 2.37]	0.06[0.00, 2.09]
Prescriber type					
Non-GP vs. GP	0.42[0.10, 1.72]	1.78[0.08, 40.4]	0.23[0.01, 7.02]	0.32[0.04, 2.31]	0[0.00, 0.00]
IHD					
Yes vs. No	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, 0.00]	1.77[0.57, 5.48]	0[0.00, 0.00]
HTN					
Yes vs. No	0.25[0.05, 1.25]	0[0.00, 0.00]	0[0.00, inf]	1.49[0.58, 3.82]	0[0.00, inf]
HF					
Yes vs. No	0[0.00, inf]	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, inf]	0[0.00, 0.00]
Stroke					
Yes vs. No	0[0.00, inf]	0.01[0.00, inf]	0.01[0.00, inf]	2.05[0.47, 8.94]	0.01[0.00, inf]
PVD					
Yes vs. No	0[0.00, inf]	**0.02[0.02, 0.02]**	**705[12.3, 40,584]**	0[0.00, inf]	0.01[0.00, inf]
Liver disease					

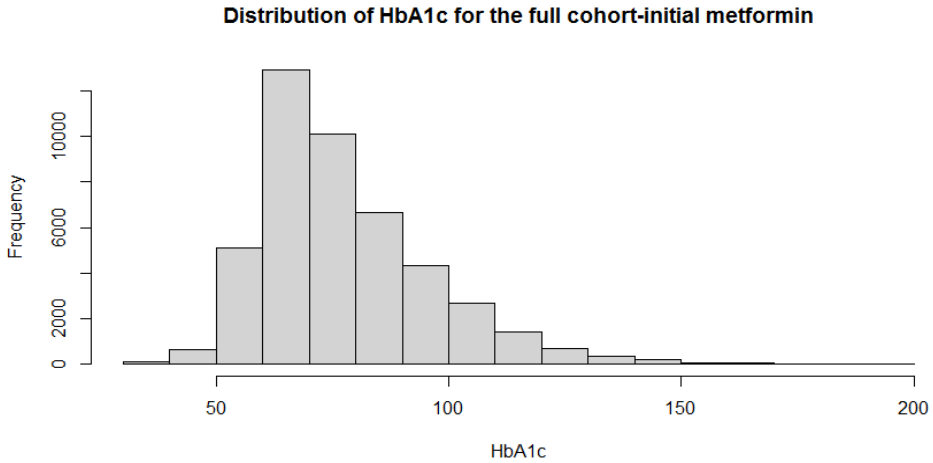
Yes vs. No	0[0.00, inf]	**>1000[306, inf]**	**6617[5.74, inf]**	2[0.34, 11.9]	**0.01[0.00, 0.01]**
CCI score					
1-2 vs. 0	0.64[0.19, 2.12]	0[0.00, 0.00]	0.01[0.00, 6.35]	0.75[0.23, 2.39]	NA
3-4 vs. 0	0[0.00, inf]	21.2[0.04, 10,681]	0[0.00, 6.05]	2.17[0.36, 13.2]	0.01[0.00, inf]
>= 5 vs. 0	0.01[0.00, inf]	0[0.00, inf]	0[0.00, 9.45]	1.57[0.18, 13.7]	0[0.00, 0.00]
Antihyperlipidemic drugs					
Yes vs. No	1.36[0.75, 2.47]	NA	1.46[0.34, 6.28]	0.8[0.37, 1.75]	0.32[0.09, 1.19]
Antipsychotic					
Yes vs. No	1.86[0.58, 5.94]	**6282[57.6, inf]**	0[0.00, inf]	0.81[0.10, 6.37]	0[0.00, inf]
Thiazide diuretics					
Yes vs. No	0.57[0.22, 1.45]	18.4[0.44, 767]	0[0.00, inf]	**2.66[1.09, 6.48]**	0.6[0.10, 3.62]
Beta blocker					
Yes vs. No	0.76[0.35, 1.67]	0[0.00, 0.00]	0.85[0.05, 14.3]	0.33[0.11, 1.00]	1.21[0.24, 6.23]
Angiotensin inhibitors					
Yes vs. No	1.29[0.72, 2.30]	7.29[0.11, 491]	1.71[0.34, 8.53]	0.71[0.31, 1.60]	1.64[0.47, 5.69]
CCB					
Yes vs. No	0.93[0.46, 1.86]	5.37[0.18, 161]	0[0.00, 0.00]	0.79[0.32, 1.92]	0.86[0.18, 4.10]
Number of concomitant medications					
1-4 vs. 0	0.89[0.27, 2.88]	**0[0.00, 0.15]**	0.34[0.06, 2.10]	0.57[0.14, 2.30]	4.17[0.13, 131]
>= 5 vs. 0	0.68[0.19, 2.42]	**0[0.00, 0.00]**	0.18[0.02, 1.82]	0.92[0.22, 3.90]	1.66[0.04, 63.8]
BMI					
25-29.9 vs. <=24.9	0.6[0.23, 1.59]	375[0.09, inf]	44.5[0.21, 9,227]	0.81[0.22, 2.93]	0.36[0.04, 2.90]
>= 30 vs. <=24.9	0.41[0.16, 1.04]	352[0.07, inf]	14.8[0.07, 2,927]	0.48[0.13, 1.68]	0.37[0.05, 2.54]
HbA1c					
7-9% vs. < 7%	0.53[0.22, 1.24]	0.26[0.01, 5.56]	0.6[0.03, 10.4]	2.87[0.10, 85.7]	0.5[0.07, 3.54]
>=9% vs. < 7%	0.65[0.27, 1.57]	2.17[0.12, 38.6]	4.01[0.26, 61.1]	13.8[0.49, 394]	1.24[0.18, 8.34]
eGFR					
< 60 vs. >= 60	**5.79[2.42, 13.9]**	**6837[79.6, 587,211]**	11.6[0.53, 251]	2.04[0.55, 7.59]	1.47[0.15, 14.5]
HDL					
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.6[0.33, 1.09]	1.15[0.18, 7.38]	0.89[0.19, 4.12]	0.53[0.23, 1.23]	1.06[0.31, 3.61]
>= 60 vs. <40 (M) or <50 (F)	0.22[0.03, 1.59]	13.6[0.36, 506]	2.98[0.49, 18.3]	0.69[0.15, 3.25]	0[0.00, 0.00]

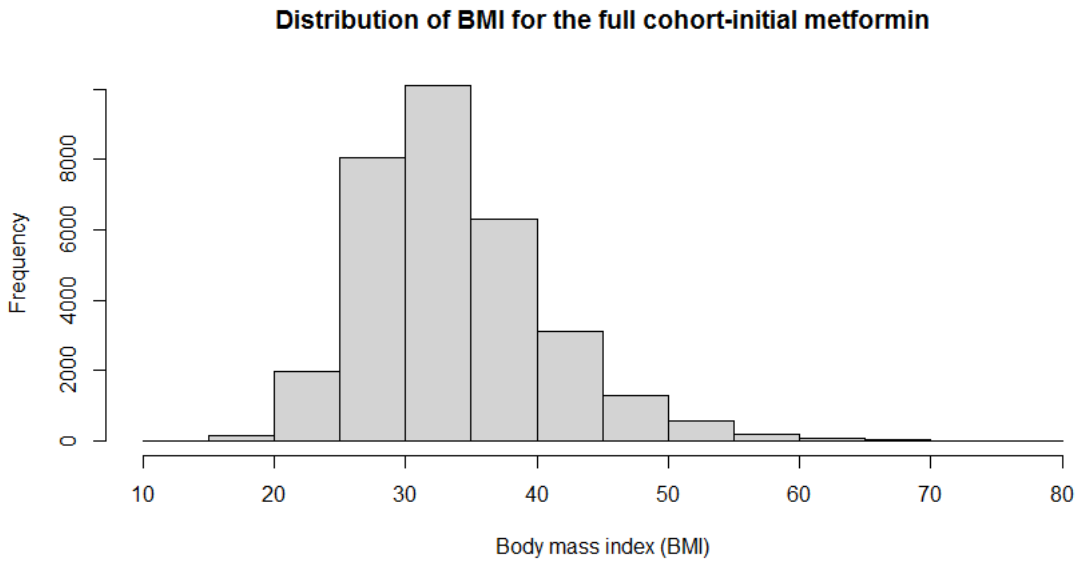
TG					
150-499 vs. < 150	1.31[0.69, 2.50]	0.54[0.07, 4.11]	0[0.00, 90,891]	1.23[0.51, 2.96]	0.59[0.18, 1.97]
>= 500 vs. < 150	2.36[0.82, 6.81]	11[0.29, 417]	0.13[0.01, 1.98]	2.08[0.53, 8.08]	0[0.00, 0.00]
Total cholesterol					
200-239 vs. < 200	0.61[0.31, 1.20]	0.12[0.01, 1.38]	1.71[0.39, 7.41]	0.33[0.11, 1.05]	0.57[0.13, 2.53]
>=240 vs. < 200	**0.31[0.11, 0.82]**	**0.02[0.00, 0.98]**	2.05[0.29, 14.3]	0.8[0.30, 2.11]	0[0.00, 0.00]

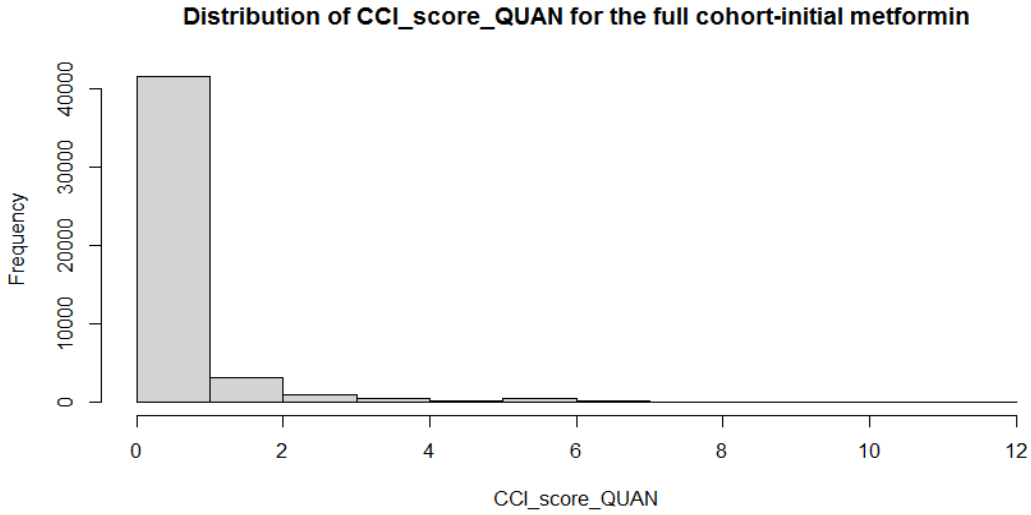
Appendix S.5.1: Normality tests of continuous variables at the stage of drug intensification

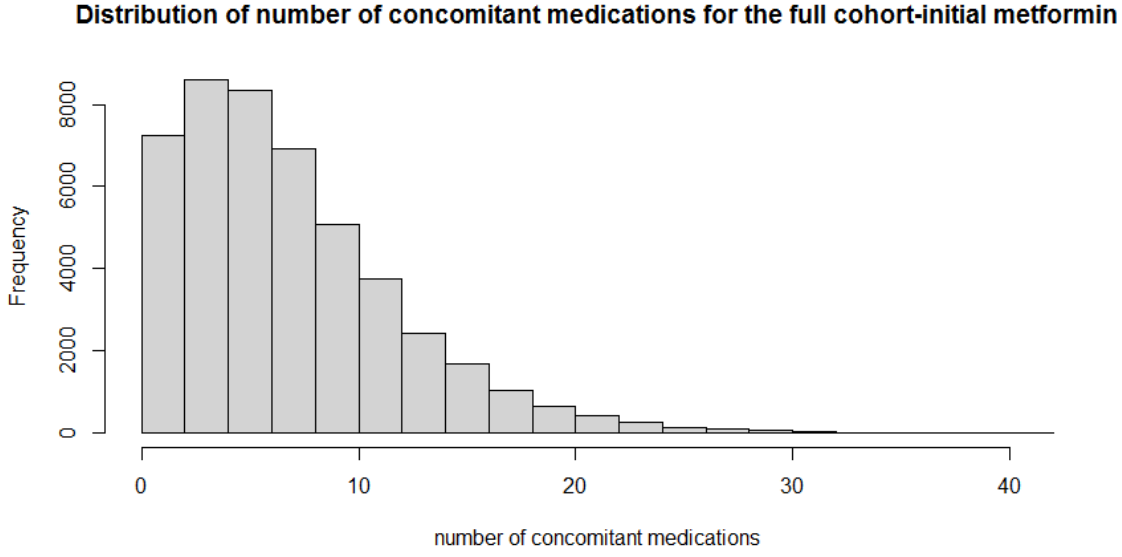
Normality tests:

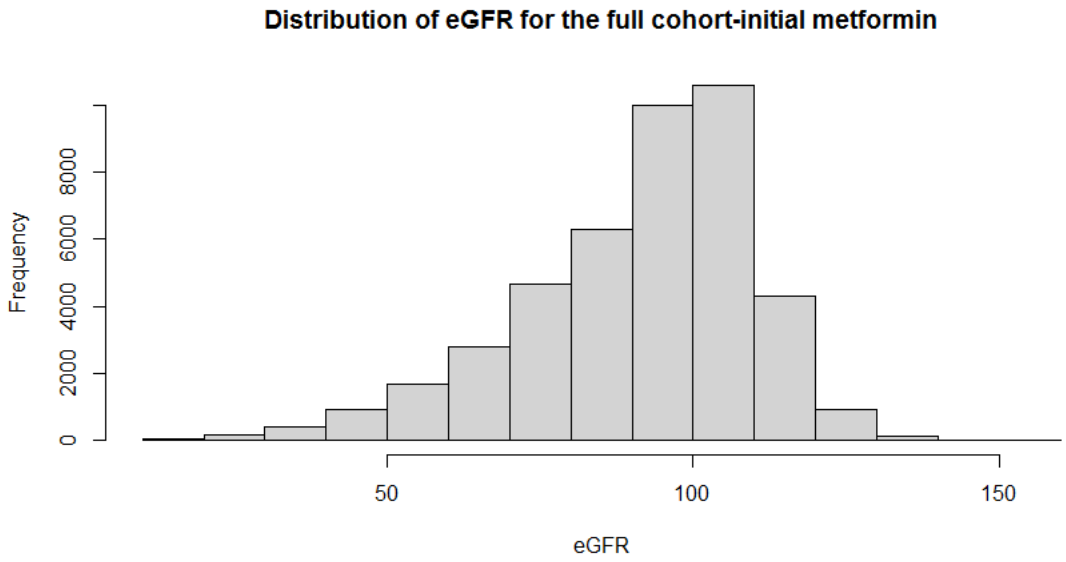


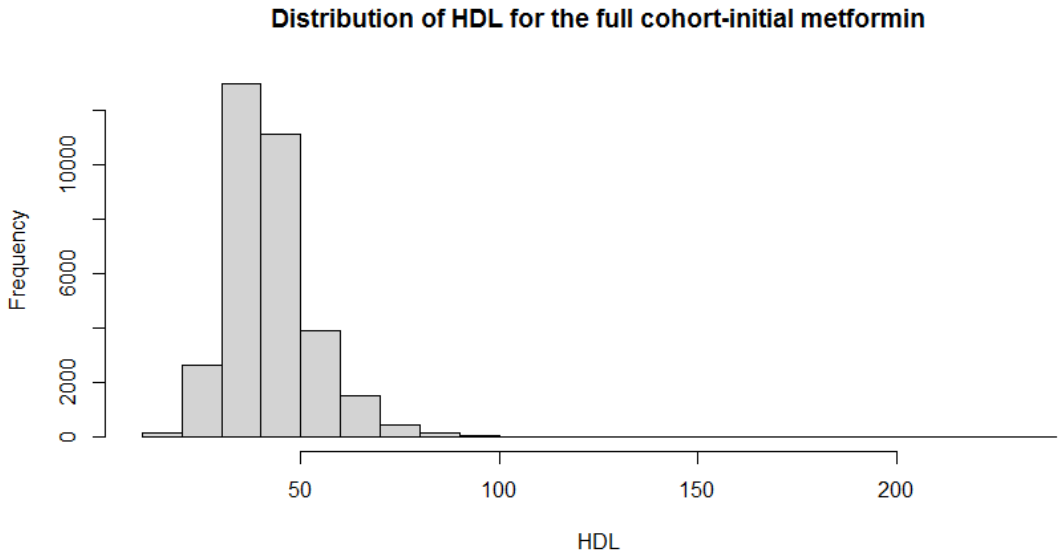


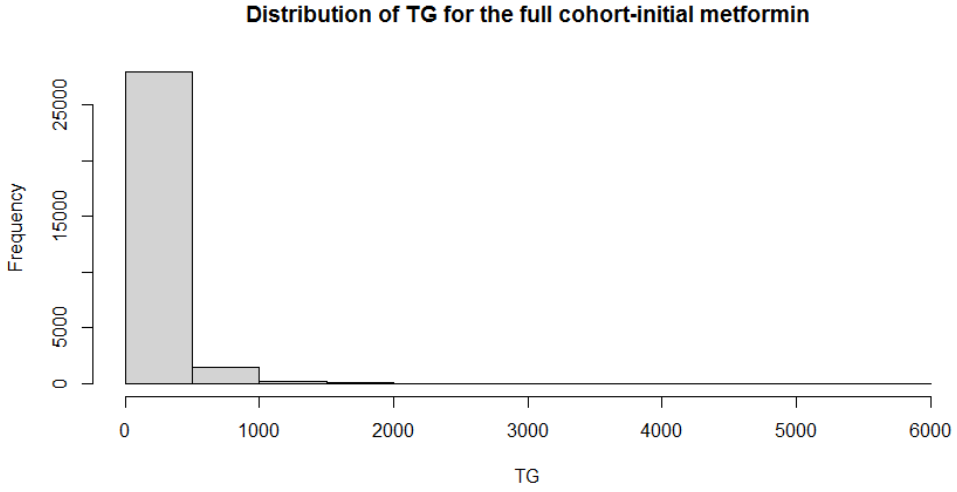

Distribution of BMI for the full cohort-initial metformin
Frequency
0
2000
4000
6000
8000
10
20
30
40
50
60
70
80
Body mass index (BMI)

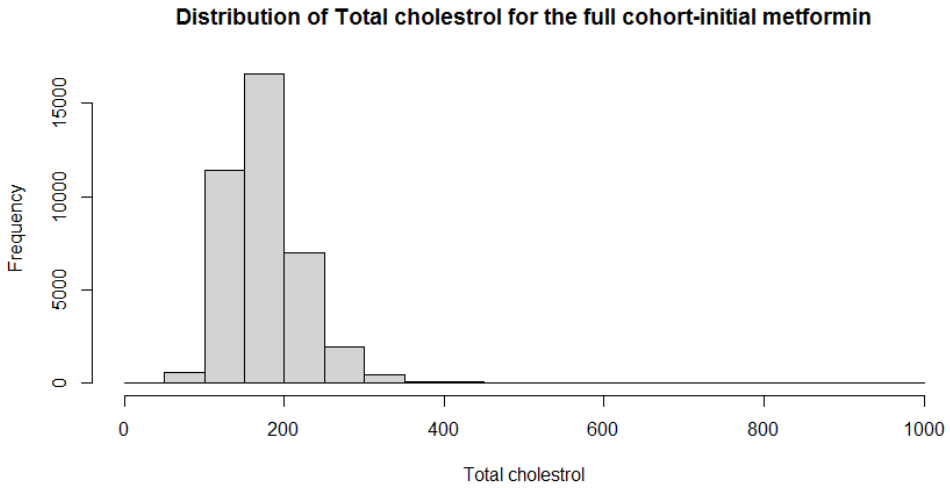

Distribution of CCI_score_QUAN for the full cohort-initial metformin
Frequency
0
10000
20000
30000
40000
0
2
4
6
8
10
12
CCI_score_QUAN


Distribution of number of concomitant medications for the full cohort-initial metformin
Frequency
0
2000
4000
6000
8000
0
10
20
30
40
number of concomitant medications


Distribution of eGFR for the full cohort-initial metformin
Frequency
0
2000
4000
6000
8000
50
100
150
eGFR


Distribution of HDL for the full cohort-initial metformin
Frequency
0
2000
6000
10000
50
100
150
200
HDL


Distribution of TG for the full cohort-initial metformin
Frequency
0
5000
15000
25000
0
1000
2000
3000
4000
5000
6000
TG



- KRUSKALIS WALLIS TETS

Continuous variable	KS-test for normality
Age	D = 0.0045922, p-value = 0.2779
Number of concomitant medications	D = 0.0065838, p-value = 0.0348
BMI	D = 0.0075658, p-value = 0.009499
HbA1c-6months-percent	D = 0.0067854, p-value = 0.02705
HDL	D = 0.0071893, p-value = 0.01596
TG	D = 0.0096506, p-value = 0.0003317
Total cholesterol	D = 0.006885, p-value = 0.02382
eGFR	D = 0.0080279, p-value = 0.004844
CCI score	D = 0.0074352, p-value = 0.01141

Appendix S.5.2: Regression assumption tests at drug intensification

❖ Initial metformin users (cohort 2-a)

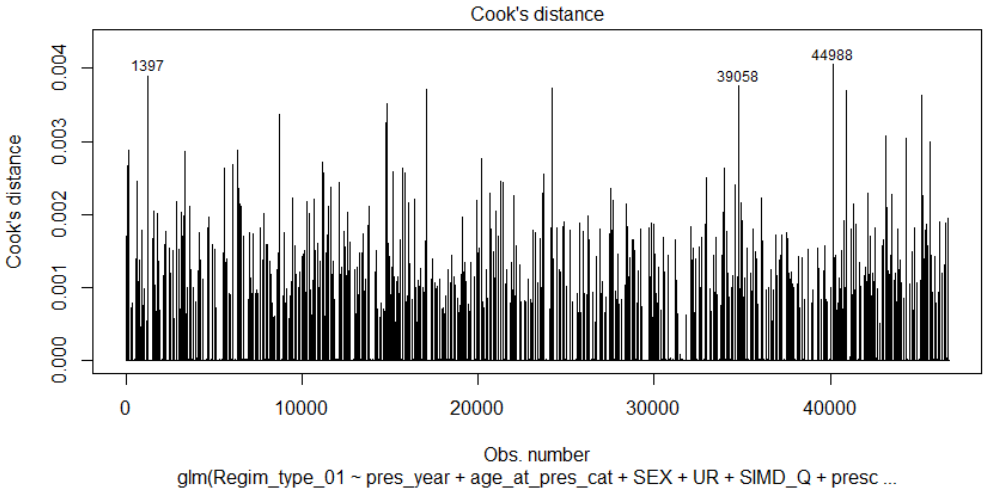
➢ Little test:

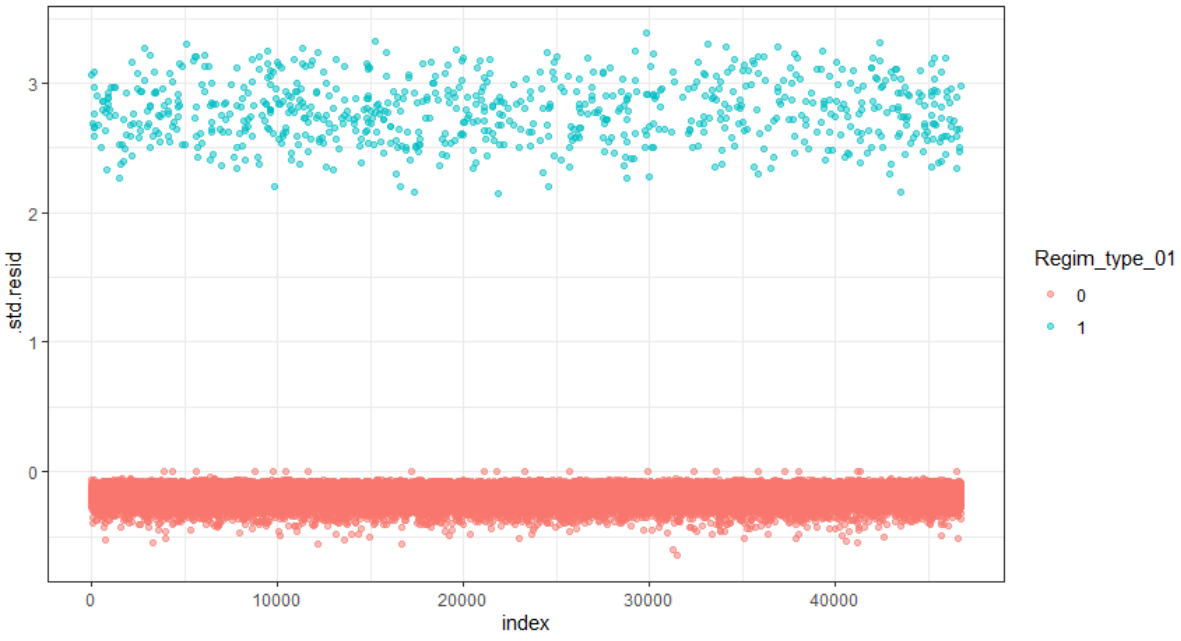
statistic	df	p.value	missing.patterns
2297.449	381	0	64

A- By regimen type

➢ Assumption:

- Influential effect:





Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	sqr(GVIF^(1/(2*Df))
pres_year	1.332071	10	1.01444	1.029088
age_at_pres_cat	1.287598	1	1.134724	1.287598
SEX	1.121102	1	1.058821	1.121102
UR	1.305571	8	1.016805	1.033892
SIMD_Q	1.257432	5	1.023172	1.04688
prescriber_type2	1.02768	1	1.013745	1.02768
ALL_IHD	1.37094	1	1.170871	1.37094
HTN	1.326038	1	1.151537	1.326038
HF	1.396	1	1.181525	1.396
stroke	1.044014	1	1.02177	1.044014
PVD	1.04805	1	1.023743	1.04805
liver_disease	1.240606	1	1.113825	1.240606
Lipid_drugs	1.357328	1	1.165044	1.357328
antipsycotic	1.037989	1	1.018817	1.037989
Thiazide_diuretics	1.142957	1	1.069092	1.142957
Beta_blocker	1.451421	1	1.204749	1.451421
Angiotensin_inhibitors	1.321388	1	1.149516	1.321388
CCB	1.33155	1	1.153928	1.33155
polypharmacy_3levels	1.28674	2	1.065057	1.134346
BMI_Cat	1.216898	3	1.033259	1.067623
A1C_6months_cat	1.327615	3	1.048364	1.099067
HDL_Cat	3.954848	3	1.257539	1.581406
TG_Cat	3.138918	3	1.210031	1.464176
TCholesterol_Cat	4.317137	3	1.276045	1.628291
eGFR_cat	1.625986	2	1.129222	1.275142
CCI_score_QUAN_cat	1.742197	3	1.09694	1.203277

- Model fitness:
  - **LRT:**

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 46669 7480.7

2 46681 7511.3 -12 -30.627 0.002245 **

-Full model compared to the intercept model: Analysis of Deviance Table

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 46669 7480.7

2 46729 7825.6 -60 -344.88 < 2.2e-16 ***

  - **Goodness of fit test**

X-squared = 45634, df = 45459, p-value = 0.2808

- **PR2**

llh llhNull G2 McFadden r2ML r2CU

-3.740334e+03 -3.912776e+03 3.448849e+02 4.407164e-02 7.353206e-03 4.768858e-02

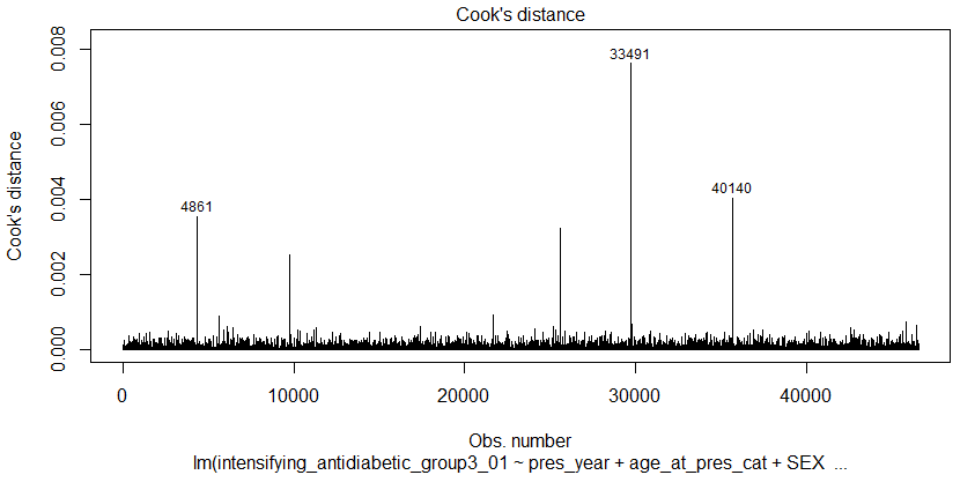
- **Hoslem test**

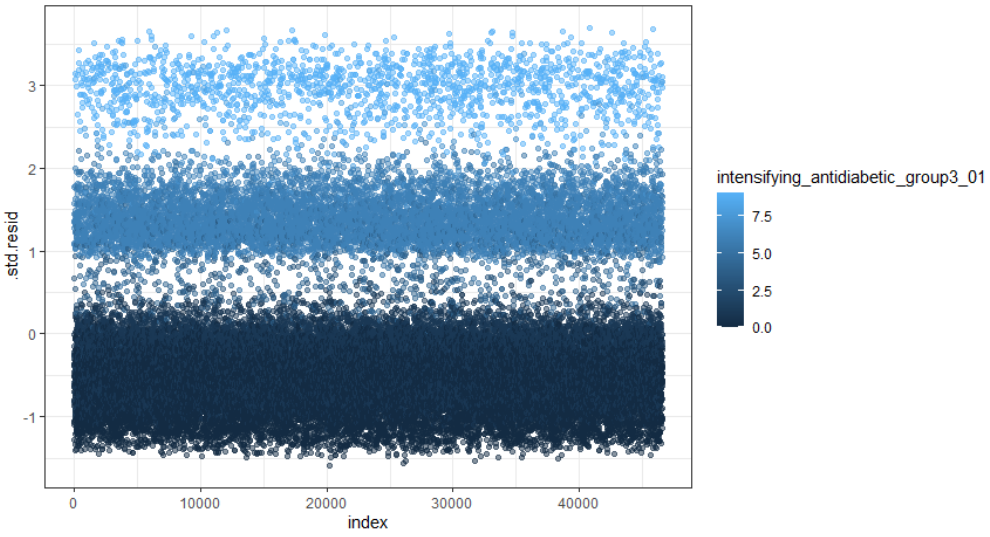
X-squared = 15.926, df = 8, p-value = 0.04345

B- By antidiabetic class: drop other_mono, other_comb

➢ Assumption:

- Influential effect:





Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	sqr(GVIF^(1/(2*Df))
pres_year	1.256393	10	1.011478	1.023087
age_at_pres_cat	1.236766	1	1.1121	1.236766
SEX	1.127085	1	1.061643	1.127085
UR	1.331303	8	1.018046	1.036417

SIMD_Q	1.282743	5	1.025213	1.051061
prescriber_type2	1.026937	1	1.013379	1.026937
ALL_IHD	1.342537	1	1.158679	1.342537
HTN	1.280869	1	1.131755	1.280869
HF	1.301614	1	1.140883	1.301614
stroke	1.037016	1	1.01834	1.037016
PVD	1.043734	1	1.021633	1.043734
liver_disease	1.177296	1	1.085033	1.177296
Lipid_drugs	1.325655	1	1.151371	1.325655
antipsycotic	1.027756	1	1.013783	1.027756
Thiazide_diuretics	1.18536	1	1.088742	1.18536
Beta_blocker	1.499373	1	1.224489	1.499373
Angiotensin_inhibitors	1.324225	1	1.15075	1.324225
CCB	1.416622	1	1.190219	1.416622
polypharmacy_3levels	1.384632	2	1.08476	1.176704
BMI_Cat	1.174571	3	1.02718	1.055099
A1C_6months_cat	1.213383	3	1.032761	1.066594
HDL_Cat	3.058141	3	1.204785	1.451507
TG_Cat	2.50179	3	1.165132	1.357533
TCholesterol_Cat	3.305899	3	1.220529	1.489692
eGFR_cat	1.523549	2	1.111	1.234321
CCI_score_QUAN_cat	1.590459	3	1.080406	1.167278

- Model fitness:
  - **LRT:**

Resid. df Resid. Dev Test Df LR stat. Pr(Chi)

1 418626 107920.1

2 418392 107505.3 1 vs. 2 234 414.7586 3.167355e-12

Full model to the intercept model: Likelihood ratio tests of Multinomial Models

Resid. df Resid. Dev Test Df LR stat. Pr(Chi)

1 418932 122843.4

2 418392 107505.3 1 vs. 2 540 15338.1 0

  - **Goodness of fit:**

X-squared = 7915.3, df = 36, p-value < 2.2e-16

  - **PR2**

llh llhNull G2 McFadden r2ML r2CU

-5.375267e+04 -6.142172e+04 1.533810e+04 1.248590e-01 2.807199e-01 3.023148e-01

  - **Hoslem test**

X-squared = 254.54, df = 72, p-value < 2.2e-16

❖ **Initial SU cohort (cohort 2-b):**

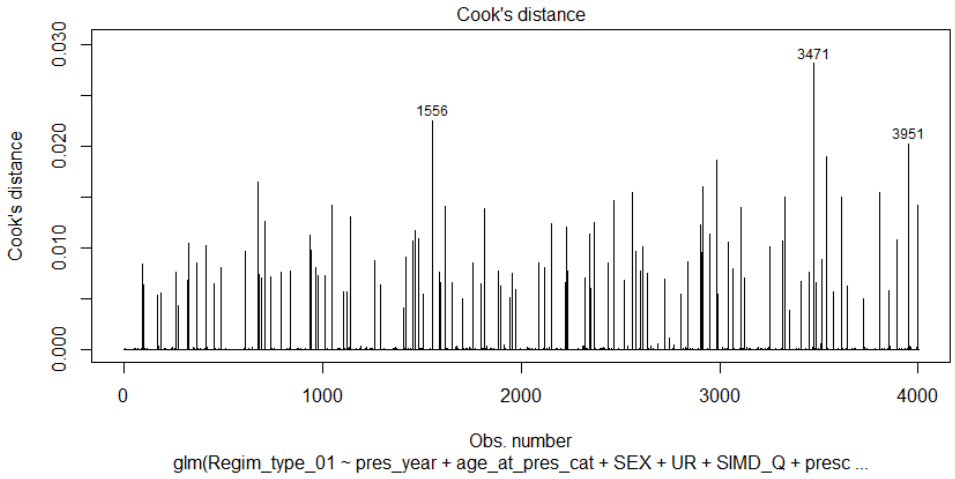
➢ Little test:

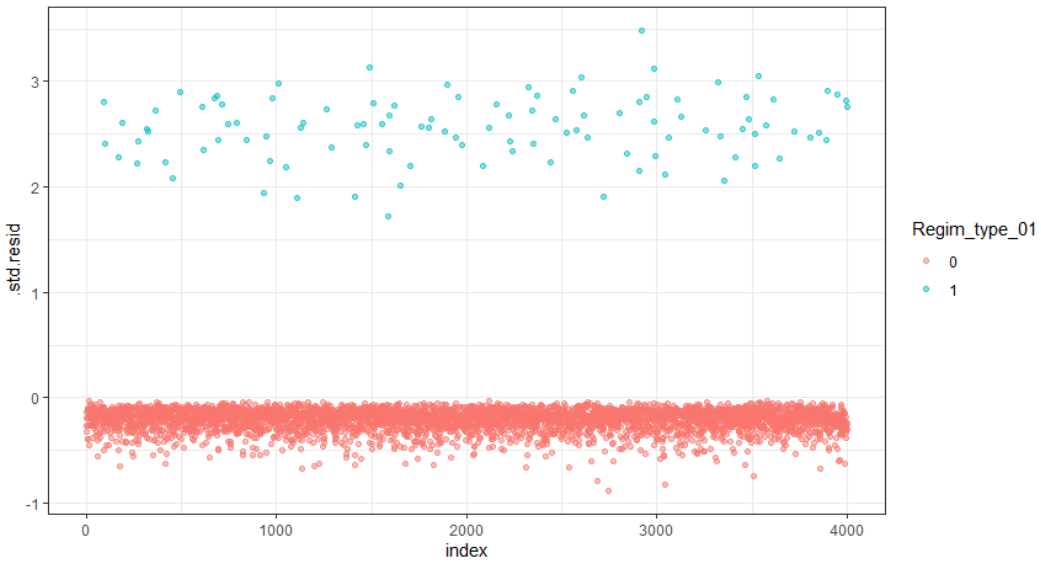
statistic	df	p.value	missing.patterns
366.9587	220	1.87E-09	37

A- By regimen type

➢ Assumption:

- Influential effect:





- Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	sqr(GVIF^(1/(2*Df))
pres_year	1.380243	10	1.016244	1.032751
age_at_pres_cat	1.407519	1	1.186389	1.407519
SEX	1.150699	1	1.072706	1.150699
UR	1.551964	8	1.027851	1.056477
SIMD_Q	1.360703	4	1.039251	1.080042
prescriber_type2	1.05162	1	1.025485	1.05162
ALL_IHD	1.343512	1	1.1591	1.343512
HTN	1.348012	1	1.161039	1.348012
HF	1.384995	1	1.176858	1.384995
stroke	1.076004	1	1.037306	1.076004
PVD	1.097469	1	1.047602	1.097469
liver_disease	1.56636	1	1.251543	1.56636
Lipid_drugs	1.357297	1	1.165031	1.357297
antipsycotic	1.043312	1	1.021427	1.043312
Thiazide_diuretics	1.060946	1	1.030023	1.060946
Beta_blocker	1.560824	1	1.249329	1.560824
Angiotensin_inhibitors	1.284364	1	1.133298	1.284364
CCB	1.231007	1	1.109507	1.231007
polypharmacy_3levels	1.531932	2	1.112525	1.237712
BMI_Cat	1.278581	3	1.041809	1.085366
A1C_6months_cat	1.202666	3	1.031235	1.063445
HDL_Cat	3.357315	3	1.223673	1.497375
TG_Cat	2.881416	3	1.192892	1.422991
TCholesterol_Cat	3.293307	3	1.219753	1.487798
eGFR_cat	1.803659	2	1.15888	1.343004
CCI_score_QUAN_cat	2.272299	3	1.146597	1.314685

➢ Model fitness:

- **LRT:**

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 3941 901.67

2 3965 926.37 -24 -24.691 0.4227

-Full model compared to the intercept model: Analysis of Deviance Table

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 3941 901.67

2 4000 986.11 -59 -84.433 0.0166 *

- **Goodness of fit test**

X-squared = 4001, df = 3999, p-value = 0.4881

- **PR2**

llh	llhNull	G2	McFadden	r2ML	r2CU
-450.83730497	-493.05367773	84.43274553	0.08562227	0.02088180	0.09559450

- **Hoslem test**

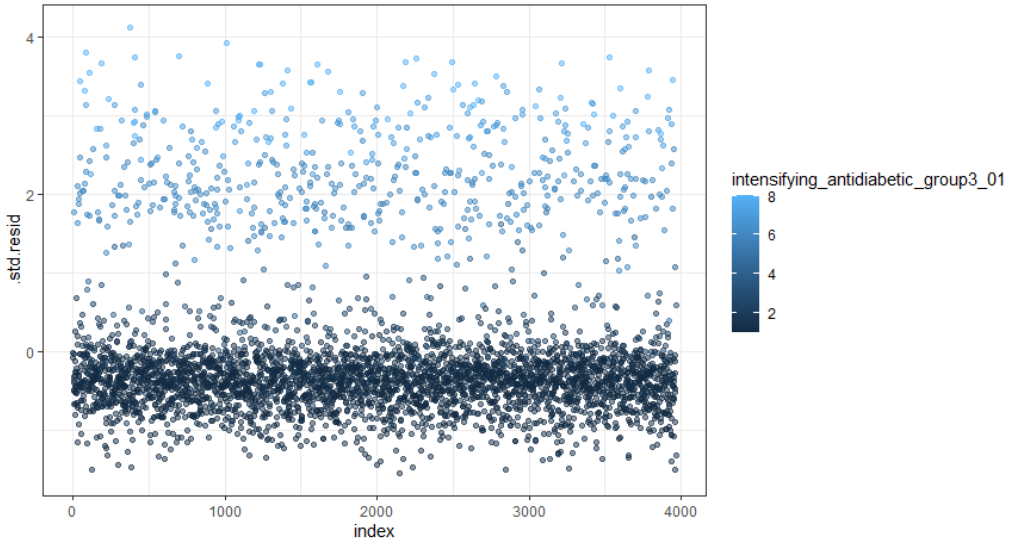
X-squared = 4.8154, df = 8, p-value = 0.7771

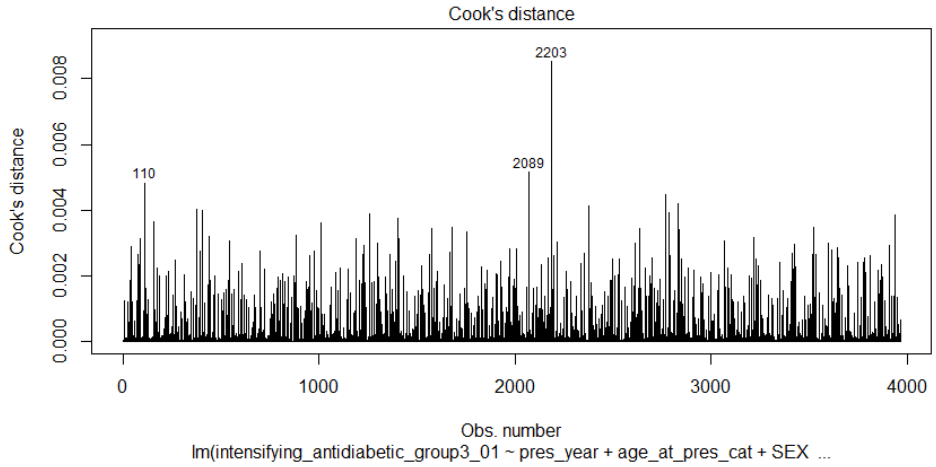
B- By antidiabetic class:

❖ **drop other_mono, other_comb**

➢ Assumption:

- Influential effect:





- Multicollinearity:

	GVIF	Df	GVIF^(1/(2*Df))	SQR(GVIF^(1/(2*Df))
pres_year	1.264404	10	1.011799	1.023737
age_at_pres_cat	1.310129	1	1.144609	1.310129
SEX	1.153759	1	1.074132	1.153759
UR	1.415691	8	1.021964	1.04441
SIMD_Q	1.282926	4	1.031633	1.064266
prescriber_type2	1.053688	1	1.026493	1.053688
ALL_IHD	1.365371	1	1.168491	1.365371
HTN	1.338214	1	1.156812	1.338214
HF	1.404094	1	1.184945	1.404094
stroke	1.06414	1	1.031572	1.06414
PVD	1.080624	1	1.03953	1.080624
liver_disease	1.297475	1	1.139068	1.297475
Lipid_drugs	1.303032	1	1.141504	1.303032
antipsycotic	1.029359	1	1.014573	1.029359
Thiazide_diuretics	1.155204	1	1.074804	1.155204
Beta_blocker	1.5575	1	1.247998	1.5575
Angiotensin_inhibitors	1.312115	1	1.145476	1.312115
CCB	1.367541	1	1.169419	1.367541
polypharmacy_3levels	1.529784	2	1.112135	1.236844
BMI_Cat	1.254915	3	1.03857	1.078627
A1C_6months_cat	1.289157	3	1.04324	1.08835
HDL_Cat	3.422795	3	1.227619	1.507048
TG_Cat	2.917092	3	1.195341	1.428839
TCholesterol_Cat	3.722258	3	1.2449	1.549776
eGFR_cat	1.699863	2	1.141835	1.303788
CCI_score_QUAN_cat	1.923344	3	1.115174	1.243614

Model fitness:

- **LRT:**

Resid. df Resid. Dev Test Df LR stat. Pr(Chi)

1 27503 6401.463

2 27335 6177.767 1 vs. 2 168 223.6954 0.002626616

Full model to the intercept model: Likelihood ratio tests of Multinomial Models

Resid. df Resid. Dev Test Df LR stat. Pr(Chi)

1 27748 7561.365

2 27335 6177.767 1 vs. 2 413 1383.597 0

- **Goodness of fit:**

X-squared = 952.17, df = 42, p-value < 2.2e-16

- **PR2**

llh llhNull G2 McFadden r2ML r2CU

-3088.8835668 -3780.6822806 1383.5974276 0.1829825 0.2945735 0.3459552

- **Hoslem test**

X-squared = 65.749, df = 56, p-value = 0.175

Appendix S.5.3: Univariable multinomial logistic regression analyses results at drug intensification of initial-metformin cohort.

Univariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to SU) for initial-metformin cohort (N=46549)

Studied factor	DPP4-I	GLP1-RA	Insulin	SGLT2-I	TZD	DPP4-I+SGLT2-I	DPP4-I+SU	SGLT2-I+SU	SU+ Insulin	
1- Demographic factors										
Age at prescription	0.9	<0.001	<0.001	<0.001	<0.001	0.017	>0.9	<0.001	0.071	
>= 65 vs. < 65 years	1[0.95, 1.04]	**0.21[0.16, 0.27]**	**0.66[0.56, 0.77]**	**0.5[0.47, 0.53]**	**0.74[0.66, 0.83]**	**0.59[0.37, 0.92]**	1[0.78, 1.30]	**0.41[0.26, 0.64]**	1.38[0.98, 1.95]	
SEX	0.3	<0.001	<0.001	0.4	<0.001	0.8	0.016	0.12	0.6	**<0.001**
F vs. M	0.98[0.93, 1.02]	**1.72[1.45, 2.04]**	**2.34[2.03, 2.70]**	0.98[0.93, 1.03]	**0.75[0.67, 0.84]**	1.05[0.70, 1.57]	**1.36[1.06, 1.75]**	1.33[0.93, 1.89]	1.11[0.78, 1.58]	
2- Socioeconomic factors										
UR	<0.001	0.005	0.3	<0.001	<0.001	0.3	0.8	0.094	0.05	
2 vs. 1	**1.34[1.27, 1.41]**	0.85[0.70, 1.03]	1.05[0.89, 1.23]	0.99[0.93, 1.06]	**3.56[3.06, 4.15]**	1.05[0.67, 1.65]	1.04[0.77, 1.41]	0.91[0.61, 1.37]	1.02[0.66, 1.55]	
3 vs. 1	**1.14[1.05, 1.23]**	**0.61[0.43, 0.88]**	0.85[0.64, 1.12]	**0.74[0.67, 0.82]**	**2.89[2.35, 3.56]**	0.42[0.15, 1.18]	1.2[0.76, 1.88]	0.89[0.46, 1.73]	1.01[0.52, 1.98]	
4 vs. 1	0.87[0.75, 1.02]	1.11[0.68, 1.81]	0.97[0.62, 1.52]	**0.76[0.64, 0.91]**	**1.86[1.27, 2.74]**	0[0.00, 0.00]	0.81[0.33, 2.02]	1.93[0.87, 4.29]	0[0.00, inf]	
5 vs. 1	**1.26[1.03, 1.53]**	1.29[0.68, 2.46]	0.49[0.20, 1.19]	**1.25[1.01, 1.55]**	0.38[0.12, 1.19]	0.76[0.10, 5.58]	0.69[0.17, 2.81]	0.59[0.08, 4.24]	0[0.00, 0.00]	
6 vs. 1	1.08[1.00, 1.17]	**0.66[0.48, 0.91]**	0.84[0.65, 1.08]	**0.84[0.77, 0.93]**	**2.97[2.45, 3.60]**	0.82[0.40, 1.66]	1.04[0.68, 1.61]	0.57[0.28, 1.16]	1.6[0.95, 2.69]	
7 vs. 1	1.01[0.89, 1.14]	0.8[0.49, 1.30]	1.07[0.74, 1.55]	**0.85[0.73, 0.98]**	1.17[0.78, 1.76]	1.03[0.36, 2.93]	0.95[0.46, 1.97]	0.6[0.19, 1.94]	1.87[0.88, 3.99]	

8 vs. 1	**1.23[1.07, 1.40]**	**1.56[1.04, 2.35]**	1.08[0.71, 1.64]	1.01[0.87, 1.19]	**2.31[1.64, 3.26]**	1[0.30, 3.29]	**1.85[1.01, 3.41]**	0[0.00, 8,253]	0.88[0.27, 2.89]	
Unknown vs. 1	1.96[0.63, 6.08]	0[0.00, inf]	4.42[0.53, 36.7]	0.89[0.18, 4.43]	0[0.00, inf]	0.02[0.00, inf]	0.01[0.00, inf]	0.01[0.00, inf]	0.02[0.00, inf]	
SIMD_Q	<0.001	0.001	0.01	<0.001	0.015	0.7	0.7	0.2	0.4	
2 vs. 1	**0.9[0.84, 0.95]**	0.91[0.73, 1.13]	0.88[0.73, 1.06]	**0.85[0.79, 0.92]**	1.15[0.99, 1.33]	0.91[0.54, 1.53]	0.84[0.60, 1.20]	0.98[0.63, 1.53]	0.81[0.48, 1.38]	
3 vs. 1	**0.93[0.87, 0.99]**	0.79[0.62, 1.01]	**0.76[0.62, 0.93]**	**0.85[0.79, 0.92]**	**1.25[1.07, 1.45]**	0.59[0.31, 1.11]	0.95[0.67, 1.36]	0.64[0.37, 1.09]	1.39[0.86, 2.26]	
4 vs. 1	**0.9[0.84, 0.96]**	**0.6[0.46, 0.80]**	**0.77[0.62, 0.96]**	**0.87[0.80, 0.94]**	1.12[0.95, 1.33]	0.77[0.42, 1.43]	0.74[0.49, 1.12]	0.55[0.30, 1.00]	1.25[0.74, 2.11]	
5 vs. 1	**0.87[0.81, 0.94]**	**0.61[0.44, 0.84]**	**0.66[0.51, 0.85]**	**0.91[0.83, 0.99]**	**1.34[1.13, 1.60]**	0.85[0.44, 1.66]	0.96[0.63, 1.46]	0.64[0.34, 1.23]	1.03[0.56, 1.91]	
Unknown vs. 1	0.63[0.12, 3.27]	0[0.00, 0.00]	0[0.00, 0.00]	0.51[0.06, 4.37]	0[0.00, 0.00]	0.01[0.01, 0.01]	0[0.00, 0.00]	0[0.00, 0.00]	0.01[0.01, 0.01]	
3- Prescriber-related factors										
Prescriber type	<0.001	0.6	<0.001	<0.001	0.4	0.046	0.6	0.8	0.5	**<0.001**
Non-GP vs. GP	**1.47[1.35, 1.59]**	0.91[0.62, 1.31]	**0.29[0.18, 0.49]**	**1.77[1.61, 1.94]**	0.91[0.73, 1.15]	**2.02[1.08, 3.79]**	0.88[0.50, 1.54]	1.1[0.54, 2.25]	0.77[0.34, 1.75]	
4- Clinical-related factors										
IHD	<0.001	<0.001	0.2	<0.001	<0.001	0.1	0.4	0.2	0.2	**<0.001**
Yes vs. No	**0.88[0.83, 0.94]**	**0.5[0.37, 0.68]**	0.87[0.71, 1.07]	**0.82[0.76, 0.89]**	**0.45[0.37, 0.55]**	1.53[0.94, 2.51]	0.85[0.58, 1.24]	1.37[0.87, 2.16]	1.36[0.87, 2.11]	
HTN	0.017	0.049	0.11	<0.001	<0.001	>0.9	0.2	0.4	<0.001	**<0.001**
Yes vs. No	**0.94[0.89, 0.99]**	0.81[0.65, 1.00]	1.14[0.97, 1.35]	**0.8[0.75, 0.85]**	**0.69[0.59, 0.79]**	1.03[0.64, 1.67]	1.2[0.90, 1.61]	1.21[0.80, 1.82]	**2.16[1.51, 3.08]**	
HF	<0.001	0.4	0.12	<0.001	<0.001	0.7	0.083	0.028	0.2	**<0.001**
Yes vs. No	**0.77[0.68, 0.87]**	0.81[0.50, 1.31]	1.31[0.95, 1.81]	**0.66[0.57, 0.77]**	**0.12[0.06, 0.25]**	0.81[0.26, 2.57]	1.65[0.98, 2.80]	**2.26[1.18, 4.32]**	1.69[0.82, 3.46]	
Stroke	0.2	0.007	0.14	<0.001	0.002	0.7	0.4	0.4	0.8	**<0.001**
Yes vs. No	0.91[0.80,	**0.38[0.17,**	0.71[0.43,	**0.72[0.60,**	**0.54[0.35,**	0.74[0.18,	1.33[0.68,	1.49[0.61,	0.84[0.27, 2.64]	

	1.05]	**0.86]**	1.16]	**0.86]**	**0.82]**	3.01]	2.60]	3.66]		
PVD	<0.001	0.059	0.6	<0.001	<0.001	0.2	>0.9	0.4	0.018	< **0.001**
Yes vs. No	**0.79[0.69, 0.91]**	0.56[0.29, 1.08]	1.11[0.74, 1.65]	**0.61[0.51, 0.74]**	**0.5[0.32, 0.76]**	0.35[0.05, 2.52]	0.99[0.46, 2.10]	0.56[0.14, 2.26]	**2.53[1.28, 5.01]**	
Liver disease	<0.001	0.4	<0.001	0.3	0.003	0.2	0.2	0.018	<0.001	<**0.001**
Yes vs. No	**0.77[0.67, 0.88]**	0.78[0.45, 1.35]	**1.92[1.41, 2.61]**	0.91[0.78, 1.07]	**0.58[0.40, 0.86]**	0.34[0.05, 2.41]	1.5[0.82, 2.77]	**2.55[1.29, 5.05]**	**3.31[1.82, 6.03]**	
CCI score	<0.001	0.2	<0.001	<0.001	<0.001	0.5	0.11	0.006	<0.001	<**0.001**
1-2 vs. 0	**0.88[0.83, 0.93]**	0.79[0.61, 1.02]	**1.32[1.10, 1.58]**	**0.75[0.70, 0.81]**	**0.48[0.40, 0.58]**	0.69[0.37, 1.29]	1.31[0.94, 1.81]	**1.67[1.09, 2.56]**	**1.95[1.28, 2.96]**	
3-4 vs. 0	**0.73[0.63, 0.83]**	0.79[0.47, 1.33]	**1.58[1.13, 2.21]**	**0.69[0.59, 0.81]**	**0.21[0.12, 0.38]**	0.59[0.14, 2.39]	**1.86[1.08, 3.23]**	**2.24[1.08, 4.64]**	**2.74[1.37, 5.48]**	
>= 5 vs. 0	**0.58[0.48, 0.71]**	0.71[0.34, 1.51]	**3.51[2.54, 4.84]**	**0.53[0.41, 0.68]**	**0.27[0.14, 0.55]**	0.56[0.08, 4.06]	1.02[0.38, 2.77]	0[0.00, inf]	**5.86[3.01, 11.4]**	
Antihyperlipidemic drugs	0.3	<0.001	<0.001	<0.001	0.12	>0.9	0.12	0.029	<0.001	<**0.001**
Yes vs. No	1.02[0.98, 1.08]	**0.48[0.40, 0.56]**	**0.26[0.23, 0.30]**	**0.63[0.59, 0.66]**	1.1[0.97, 1.23]	1.02[0.65, 1.59]	0.81[0.62, 1.05]	**0.66[0.46, 0.95]**	**0.53[0.37, 0.75]**	
Antipsychotic	0.021	0.081	0.2	<0.001	0.003	0.9	0.078	0.095	0.12	<**0.001**
Yes vs. No	**0.86[0.76, 0.98]**	1.45[0.98, 2.14]	1.3[0.92, 1.82]	**0.71[0.61, 0.84]**	**0.61[0.42, 0.87]**	0.9[0.28, 2.84]	1.69[0.98, 2.92]	1.96[0.95, 4.03]	1.86[0.91, 3.83]	
Thiazide diuretics	0.15	0.3	<0.001	<0.001	0.014	0.073	>0.9	0.3	0.4	<**0.001**
Yes vs. No	1.06[0.98, 1.15]	0.83[0.59, 1.18]	**0.51[0.36, 0.74]**	**0.63[0.56, 0.71]**	**1.26[1.05, 1.52]**	0.39[0.12, 1.26]	1[0.62, 1.61]	0.65[0.29, 1.49]	0.69[0.32, 1.51]	
Beta blocker	<0.001	0.11	0.071	<0.001	<0.001	0.3	0.1	>0.9	0.5	<**0.001**
Yes vs. No	**0.9[0.85, 0.95]**	0.83[0.65, 1.05]	0.84[0.69, 1.02]	**0.71[0.66, 0.77]**	**0.68[0.58, 0.79]**	1.29[0.79, 2.11]	0.74[0.51, 1.07]	1.02[0.64, 1.64]	0.86[0.53, 1.40]	
Angiotensin inhibitors	0.046	0.6	<0.001	0.6	0.5	0.9	0.12	0.5	0.4	<**0.001**
Yes vs. No	1.06[1.00, 1.11]	1.06[0.86, 1.30]	**0.49[0.39, 0.61]**	0.98[0.92, 1.05]	1.04[0.92, 1.19]	0.96[0.58, 1.59]	1.26[0.94, 1.69]	1.17[0.77, 1.78]	0.81[0.51, 1.28]	

CCB	0.032	0.007	<0.001	0.5	0.8	0.4	0.024	0.087	0.7	**<0.001**
Yes vs. No	**1.06[1.01, 1.12]**	**0.73[0.57, 0.93]**	**0.54[0.43, 0.68]**	0.98[0.91, 1.04]	0.99[0.86, 1.13]	0.78[0.44, 1.37]	**0.66[0.45, 0.96]**	0.64[0.37, 1.09]	1.12[0.72, 1.73]	
Number of concomitant medications	<0.001	0.4	0.3	<0.001	<0.001	0.067	0.002	<0.001	0.055	**<0.001**
1-4 vs. 0	**1.25[1.07, 1.48]**	0.89[0.51, 1.54]	0.92[0.58, 1.46]	0.84[0.72, 1.00]	**1.63[1.09, 2.42]**	117[0.00, inf]	**0.4[0.20, 0.82]**	102[0.00, inf]	2.03[0.27, 15.2]	
>= 5 vs. 0	1.15[0.98, 1.35]	0.8[0.46, 1.37]	0.82[0.52, 1.30]	**0.66[0.56, 0.78]**	0.99[0.67, 1.47]	156[0.00, inf]	0.64[0.33, 1.26]	210[0.00, inf]	3.12[0.43, 22.8]	
BMI	<0.001	<0.001	<0.001	<0.001	<0.001	0.07	0.091	0.042	<0.001	**<0.001**
25-29.9 vs. <=24.9	**1.42[1.26, 1.59]**	**3597[1,963, 6,592]**	**0.43[0.32, 0.58]**	**1.89[1.59, 2.24]**	**1.68[1.24, 2.27]**	2.12[0.48, 9.35]	0.71[0.38, 1.33]	0.45[0.18, 1.11]	**0.51[0.28, 0.94]**	
>= 30 vs. <=24.9	**1.77[1.59, 1.98]**	**109432[87,953, 136,157]**	**0.45[0.35, 0.59]**	**3.42[2.91, 4.01]**	**1.76[1.32, 2.35]**	3.46[0.84, 14.2]	0.95[0.54, 1.66]	1.02[0.49, 2.15]	**0.22[0.12, 0.40]**	
Unknown vs. <= 24.9	**1.31[1.17, 1.47]**	**44923[35,402, 57,006]**	**0.71[0.55, 0.91]**	**1.66[1.41, 1.96]**	**1.52[1.13, 2.03]**	2.39[0.57, 10.0]	1.16[0.66, 2.03]	0.83[0.39, 1.78]	**0.52[0.30, 0.90]**	
HbA1c	<0.001	0.063	<0.001	<0.001	<0.001	0.09	<0.001	<0.001	<0.001	**<0.001**
7- < 9% vs. < 7%	**1.73[1.47, 2.04]**	**0.57[0.37, 0.90]**	**0.08[0.07, 0.10]**	**1.5[1.24, 1.83]**	**2.17[1.38, 3.41]**	2.75[0.38, 20.0]	**0.44[0.22, 0.89]**	1.65[0.23, 12.2]	0.12[0.05, 0.27]	
>=9% vs. < 7%	1.03[0.88, 1.21]	**0.54[0.34, 0.83]**	**0.11[0.09, 0.14]**	1.2[0.99, 1.46]	1.4[0.89, 2.20]	1.69[0.23, 12.4]	0.68[0.35, 1.35]	3.58[0.50, 25.8]	0.51[0.25, 1.06]	
Unknown vs. < 7%	**0.62[0.50, 0.77]**	**0.47[0.25, 0.88]**	**0.45[0.34, 0.59]**	**0.61[0.47, 0.80]**	0.66[0.36, 1.21]	2.87[0.33, 24.7]	1.33[0.61, 2.94]	4.57[0.57, 36.7]	0.64[0.25, 1.68]	
eGFR	0.8	0.054	<0.001	<0.001	0.002	0.14	0.001	0.047	<0.001	**<0.001**
< 60 vs. >= 60	1.03[0.94, 1.11]	0.75[0.52, 1.09]	**1.93[1.55, 2.40]**	**0.18[0.15, 0.22]**	**0.67[0.53, 0.85]**	0.4[0.13, 1.26]	**1.87[1.27, 2.76]**	0.33[0.10, 1.03]	**3.1[2.00, 4.78]**	
Unknown vs. < 60	1[0.92, 1.08]	1.28[0.97, 1.69]	**2.1[1.72, 2.56]**	**0.84[0.76, 0.93]**	1.01[0.84, 1.22]	0.7[0.31, 1.61]	**1.65[1.12, 2.43]**	1.25[0.70, 2.23]	0.52[0.21, 1.29]	
HDL	<0.001	0.002	<0.001	<0.001	<0.001	0.064	0.2	0.047	0.013	**<0.001**
40-59 (M) or 50-59 (F) vs. <40 (M) or	1.05[1.00, 1.11]	**0.74[0.59, 0.93]**	0.84[0.68, 1.04]	1[0.94, 1.07]	**1.22[1.07, 1.38]**	**0.49[0.27, 0.89]**	0.96[0.68, 1.35]	0.68[0.43, 1.08]	0.86[0.51, 1.45]	

<50 (F)										
>= 60 vs. <40 (M) or <50 (F)	0.97[0.88, 1.07]	**0.47[0.28, 0.79]**	1.28[0.93, 1.77]	**0.77[0.68, 0.87]**	0.89[0.69, 1.14]	0.46[0.14, 1.48]	1.01[0.55, 1.84]	0.6[0.24, 1.48]	1.43[0.67, 3.05]	
Unknown vs. <40 (M) or <50 (F)	**0.86[0.82, 0.91]**	0.83[0.68, 1.01]	**1.89[1.61, 2.22]**	**0.81[0.76, 0.86]**	**0.8[0.70, 0.91]**	0.78[0.50, 1.23]	1.31[0.98, 1.75]	**0.56[0.36, 0.88]**	**1.71[1.16, 2.54]**	
TG	<0.001	0.011	<0.001	<0.001	<0.001	0.9	0.043	<0.001	0.003	**<0.001**
150-499 vs. < 150	0.97[0.91, 1.03]	**1.32[1.04, 1.69]**	**0.79[0.63, 0.98]**	**1.12[1.04, 1.20]**	0.98[0.84, 1.15]	0.97[0.56, 1.71]	1.25[0.85, 1.86]	**2.44[1.32, 4.52]**	0.73[0.43, 1.25]	
>= 500 vs. < 150	**0.65[0.57, 0.74]**	**1.62[1.08, 2.43]**	**1.44[1.01, 2.04]**	0.98[0.85, 1.12]	0.78[0.56, 1.09]	0.72[0.21, 2.44]	**1.91[1.04, 3.52]**	**5.03[2.32, 10.9]**	1.18[0.48, 2.91]	
Unknown vs. < 150	1[0.94, 1.06]	1.04[0.81, 1.35]	**1.71[1.40, 2.09]**	**0.89[0.82, 0.96]**	**1.67[1.43, 1.94]**	1.09[0.62, 1.92]	**1.59[1.08, 2.35]**	1.42[0.73, 2.75]	1.55[0.96, 2.52]	
Total cholesterol	<0.001	<0.001	<0.001	<0.001	<0.001	0.3	<0.001	0.11	0.004	**< 0.001**
200-239 vs. < 200	**0.88[0.82, 0.94]**	**1.81[1.44, 2.28]**	**1.48[1.18, 1.86]**	**1.12[1.03, 1.21]**	0.9[0.77, 1.06]	0.85[0.43, 1.67]	**1.49[1.03, 2.17]**	**1.77[1.09, 2.86]**	0.97[0.53, 1.76]	
>=240 vs. < 200	**0.65[0.60, 0.72]**	**1.85[1.42, 2.42]**	**1.53[1.18, 1.99]**	**0.85[0.76, 0.93]**	**0.72[0.59, 0.89]**	0.78[0.33, 1.81]	**1.66[1.09, 2.53]**	1.52[0.84, 2.77]	1.25[0.66, 2.37]	
Unknown vs. < 200	**0.85[0.80, 0.90]**	**1.27[1.02, 1.59]**	**3.08[2.63, 3.60]**	**0.92[0.86, 0.99]**	**0.71[0.62, 0.83]**	1.47[0.92, 2.34]	**1.8[1.33, 2.43]**	1.33[0.84, 2.10]	**2.08[1.40, 3.07]**	

DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors. UR; urban-rural, SIMD-Q; Scottish index of multiple deprivation-Quantile, GP; General practitioner, IHD; ischemic heart disease, HTN; hypertension, HF; heart failure, PVD; peripheral vascular disease, CCI; Charlson comorbidity index, CCB; calcium channel blocker, BMI; body mass index, eGFR; estimated glomerular filtration rate, HDL; high density lipoprotein, TG; triglyceride.

Appendix S.5.4: Complete case analysis regression results of the initial metformin cohort

Multivariable logistic regression of factors influencing prescribing of antidiabetic regimen (Combination therapy vs. monotherapy) type

Studied factor	OR[95%CI]	Overall p value
Age at prescription		0.031
>= 65 vs. < 65 years	0.72[0.53, 0.97]	
Sex		0.2
F vs. M	1.19[0.92, 1.54]	
UR		0.5
2 vs. 1	0.8[0.60, 1.06]	
3 vs. 1	0.93[0.56, 1.48]	
4 vs. 1	1.36[0.63, 2.59]	
5 vs. 1	0.36[0.02, 1.64]	
6 vs. 1	1.19[0.77, 1.79]	
7 vs. 1	1[0.44, 1.97]	
8 vs. 1	1.04[0.40, 2.26]	
SCOTTISH INDEX OF MULTIPLE DEPRIVATION-QUANTILE		0.7
2 vs. 1	0.85[0.61, 1.18]	
3 vs. 1	0.92[0.64, 1.32]	
4 vs. 1	0.77[0.50, 1.15]	
5 vs. 1	0.9[0.58, 1.37]	
Prescriber type		0.2
Non-GP vs. GP	1.32[0.84, 1.98]	
IHD		0.5
Yes vs. No	0.88[0.58, 1.29]	
HTN		
Yes vs. No	1.08[0.78, 1.50]	0.6
HF		
Yes vs. No	1.27[0.66, 2.32]	0.5
Stroke		
Yes vs. No	1.18[0.55, 2.22]	0.6
PVD		
Yes vs. No	1.18[0.55, 2.24]	0.6
Liver disease		
Yes vs. No	1.39[0.76, 2.42]	0.3
CCI-score		0.5
1-2 vs. 0	1.12[0.78, 1.59]	
3-4 vs. 0	1.6[0.83, 2.96]	
>= 5 vs. 0	1.53[0.61, 3.28]	
Antihyperlipidemic drugs		0.6
Yes vs. No	1.1[0.81, 1.50]	
Antipsychotic		0.7

Yes vs. No	0.9[0.46, 1.61]	
Thiazide diuretics		
Yes vs. No	0.79[0.45, 1.31]	0.4
Beta-blockers		
Yes vs. No	0.82[0.55, 1.21]	0.3
Angiotensin inhibitors		
Yes vs. No	0.88[0.62, 1.23]	0.5
CCB		
Yes vs. No	0.58[0.38, 0.87]	0.008
Number of concomitant medications		<0.001
1-4 vs. 0	1.52[0.55, 6.33]	
>= 5 vs. 0	2.94[1.06, 12.2]	
BMI (kg/m^2)		0.2
25-29.9	0.67[0.42, 1.10]	
>= 30	0.64[0.42, 1.02]	
HbA1c (%)		<0.001
7- <9 vs. < 7	0.5[0.26, 1.14]	
>= 9 vs. < 7	0.9[0.46, 2.02]	
eGFR:		
< 60 vs. >= 60 $ml/min/1.73m^2$	1.84[1.17, 2.82]	0.01
HDL (mg/dl)		0.2
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.77[0.57, 1.03]	
>= 60 vs. <40 (M) or <50 (F)	0.84[0.49, 1.36]	
TG (mg/dl)		0.7
150-499 vs. < 150	1.06[0.79, 1.45]	
>= 500 vs. < 150	1.24[0.72, 2.08]	
Total cholesterol (mg/dl)		0.3
200-239 vs. < 200	1.26[0.90, 1.74]	
>=240 vs. < 200	1.26[0.82, 1.89]	

Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class (compared to SU)

Studied factors	DPP4-I	GLP1-RA	Insulin	SGLT2-I	TZD	DPP4-I+SGLT2-I	DPP4-I+SU	SGLT2-I+SU	SU+ insulin
Age at prescription									
>= 65 vs. < 65 years	0.95[0.88, 1.03]	**0.28[0.19, 0.42]**	0.81[0.59, 1.10]	0.52[0.47, 0.58]	0.96[0.78, 1.19]	0.77[0.46, 1.29]	0.72[0.45, 1.14]	0.64[0.37, 1.11]	0.76[0.44, 1.32]
SEX									
F vs. M	**0.92[0.85, 0.99]**	1.28[0.99, 1.65]	1.59[1.21, 2.08]	0.98[0.89, 1.08]	**0.77[0.63, 0.94]**	1.12[0.70, 1.78]	1.14[0.76, 1.69]	1.29[0.81, 2.07]	1.07[0.65, 1.77]
UR									
2 vs. 1	**1.3[1.20, 1.41]**	0.96[0.73, 1.27]	1.35[1.01, 1.81]	**1.13[1.02, 1.25]**	**3.13[2.43, 4.03]**	1.33[0.80, 2.22]	0.74[0.47, 1.17]	1.02[0.61, 1.71]	0.84[0.48, 1.46]
3 vs. 1	0.97[0.84, 1.11]	0.86[0.53, 1.39]	1.14[0.70, 1.88]	0.84[0.71, 1.00]	**2.57[1.79, 3.69]**	0.73[0.26, 2.08]	1.2[0.62, 2.32]	1.14[0.50, 2.58]	0.74[0.28, 1.97]
4 vs. 1	1.02[0.81, 1.29]	0.93[0.42, 2.09]	0.94[0.38, 2.29]	0.89[0.66, 1.19]	**2.55[1.42, 4.57]**	0.56[0.07, 4.54]	0.48[0.09, 2.47]	2.65[0.99, 7.09]	0.48[0.06, 3.80]
5 vs. 1	1.31[0.90, 1.91]	**2.72[1.09, 6.78]**	**0.6[0.09, 3.93]**	**2.52[1.68, 3.77]**	0.48[0.06, 3.85]	0.85[0.04, 20.4]	0.43[0.02, 12.3]	2.5[0.44, 14.2]	0.68[0.03, 14.8]
6 vs. 1	1.1[0.97, 1.25]	0.78[0.49, 1.24]	1.11[0.70, 1.76]	0.94[0.80, 1.10]	**3.36[2.43, 4.65]**	1.74[0.83, 3.64]	1.19[0.63, 2.24]	0.79[0.31, 1.99]	1.16[0.54, 2.49]
7 vs. 1	0.91[0.74, 1.12]	1.09[0.56, 2.12]	1.1[0.52, 2.34]	**0.76[0.58, 0.98]**	1.71[0.95, 3.08]	1.4[0.42, 4.68]	1.16[0.43, 3.13]	0.36[0.04, 3.22]	1.21[0.37, 3.97]
8 vs. 1	1.02[0.79, 1.32]	1.24[0.56, 2.78]	1.59[0.70, 3.61]	1.12[0.84, 1.51]	**2.13[1.04, 4.35]**	1.25[0.26, 6.10]	0.97[0.25, 3.66]	0.42[0.03, 5.92]	1.02[0.22, 4.77]
SIMD_Q									
2 vs. 1	**0.87[0.79, 0.95]**	1[0.73, 1.36]	0.88[0.63, 1.23]	**0.87[0.77, 0.98]**	0.89[0.69, 1.15]	0.84[0.47, 1.51]	0.59[0.35, 1.01]	1.09[0.63, 1.92]	0.87[0.44, 1.71]
3 vs. 1	**0.88[0.79, 0.98]**	0.97[0.67, 1.39]	0.76[0.51, 1.13]	0.9[0.79, 1.03]	1.01[0.76, 1.33]	0.65[0.32, 1.33]	0.88[0.51, 1.50]	0.63[0.30, 1.33]	1.22[0.61, 2.43]
4 vs. 1	**0.84[0.75, 0.93]**	0.81[0.54, 1.21]	0.93[0.63, 1.38]	**0.86[0.75, 0.99]**	0.85[0.63, 1.15]	0.63[0.30, 1.33]	0.56[0.29, 1.06]	0.76[0.36, 1.62]	1.02[0.48, 2.19]

5 vs. 1	**0.83[0.74, 0.94]**	0.88[0.57, 1.37]	0.72[0.45, 1.15]	0.93[0.80, 1.08]	0.93[0.67, 1.28]	1[0.49, 2.03]	0.66[0.34, 1.29]	0.87[0.40, 1.91]	1.14[0.52, 2.52]
Prescriber type									
Non-GP vs. GP	**1.35[1.18, 1.53]**	0.81[0.49, 1.33]	**0.32[0.14, 0.73]**	1.14[0.97, 1.33]	0.74[0.50, 1.11]	1.28[0.60, 2.72]	0.68[0.27, 1.76]	1.46[0.70, 3.06]	1.09[0.43, 2.76]
IHD									
Yes vs. No	0.99[0.88, 1.11]	0.87[0.55, 1.38]	1.2[0.79, 1.82]	1.07[0.93, 1.25]	**0.54[0.36, 0.81]**	1.33[0.68, 2.59]	0.66[0.34, 1.29]	0.63[0.28, 1.42]	0.94[0.45, 1.97]
HTN									
Yes vs. No	**0.89[0.80, 0.98]**	0.85[0.59, 1.22]	1.28[0.90, 1.81]	**0.83[0.73, 0.94]**	1.22[0.94, 1.60]	0.88[0.48, 1.62]	1.02[0.61, 1.71]	0.75[0.40, 1.44]	1.32[0.71, 2.43]
HF									
Yes vs. No	1.06[0.84, 1.33]	1.76[0.82, 3.77]	0.63[0.30, 1.30]	1.12[0.83, 1.52]	0.45[0.15, 1.33]	1.2[0.32, 4.42]	0.61[0.18, 2.05]	2.49[0.76, 8.15]	1.15[0.36, 3.63]
Stroke									
Yes vs. No	1.02[0.82, 1.28]	0.94[0.35, 2.53]	0.55[0.20, 1.51]	0.81[0.60, 1.10]	0.66[0.31, 1.43]	0.87[0.20, 3.73]	1.45[0.55, 3.87]	0.81[0.16, 4.14]	0.78[0.18, 3.35]
PVD									
Yes vs. No	0.83[0.65, 1.05]	0.68[0.22, 2.12]	1.44[0.74, 2.82]	0.97[0.71, 1.32]	0.3[0.09, 0.96]	0.39[0.05, 3.00]	1.12[0.37, 3.40]	1.34[0.35, 5.21]	1.74[0.60, 5.05]
Liver disease									
Yes vs. No	1.09[0.86, 1.38]	1.27[0.60, 2.69]	1.37[0.76, 2.47]	1.29[0.98, 1.70]	1.45[0.74, 2.86]	0.79[0.17, 3.65]	1.41[0.55, 3.61]	1.95[0.66, 5.77]	1.81[0.64, 5.06]
CCI score									
1-2 vs. 0	**0.79[0.71, 0.89]**	0.79[0.53, 1.18]	1.14[0.79, 1.65]	**0.67[0.58, 0.77]**	**0.65[0.46, 0.93]**	0.64[0.31, 1.32]	0.99[0.56, 1.74]	0.84[0.43, 1.66]	1.17[0.60, 2.25]
3-4 vs. 0	**0.66[0.50, 0.86]**	0.64[0.25, 1.64]	**2.06[1.10, 3.86]**	**0.64[0.46, 0.89]**	0.51[0.19, 1.32]	1[0.25, 3.99]	1.61[0.58, 4.43]	0.82[0.21, 3.14]	1.27[0.37, 4.33]
>= 5 vs. 0	**0.66[0.47, 0.93]**	0.95[0.30, 2.99]	**2.29[1.10, 4.77]**	**0.5[0.32, 0.79]**	0.54[0.17, 1.72]	0.95[0.16, 5.60]	1.77[0.53, 5.91]	0.21[0.01, 5.20]	1.63[0.39, 6.71]
Antihyperlipidemic drugs									

Yes vs. No	1.05[0.96, 1.15]	0.78[0.59, 1.03]	**0.52[0.39, 0.68]**	1.09[0.98, 1.21]	0.97[0.78, 1.22]	1.4[0.78, 2.49]	1.21[0.74, 1.97]	0.9[0.53, 1.54]	1.18[0.65, 2.14]
Antipsychotic									
Yes vs. No	0.87[0.71, 1.07]	0.97[0.55, 1.72]	1.13[0.61, 2.11]	**0.66[0.51, 0.86]**	0.68[0.35, 1.31]	0.59[0.15, 2.33]	0.48[0.13, 1.71]	1.41[0.58, 3.44]	1.17[0.37, 3.64]
Thiazide diuretics									
Yes vs. No	1.09[0.94, 1.26]	1.16[0.70, 1.93]	**0.48[0.26, 0.90]**	1[0.82, 1.23]	1.34[0.96, 1.87]	0.9[0.35, 2.30]	0.94[0.43, 2.04]	1.26[0.49, 3.21]	0.57[0.19, 1.74]
Beta-blockers									
Yes vs. No	0.99[0.88, 1.12]	1.27[0.86, 1.87]	0.64[0.42, 0.97]	0.97[0.84, 1.13]	0.8[0.57, 1.11]	0.81[0.40, 1.64]	0.93[0.50, 1.72]	1.36[0.68, 2.71]	0.73[0.35, 1.53]
Angiotensin inhibitors									
Yes vs. No	1.08[0.98, 1.19]	1.28[0.93, 1.77]	**0.51[0.34, 0.75]**	**1.14[1.01, 1.29]**	0.9[0.70, 1.16]	0.97[0.53, 1.79]	1.06[0.63, 1.78]	1.01[0.52, 1.94]	0.68[0.35, 1.34]
CCB									
Yes vs. No	1.05[0.94, 1.16]	0.81[0.54, 1.22]	**0.52[0.34, 0.80]**	1.12[0.98, 1.28]	1.06[0.81, 1.39]	0.5[0.23, 1.10]	0.75[0.40, 1.38]	1.04[0.51, 2.10]	0.51[0.23, 1.13]
Number of concomitant medications									
1-4 vs. 0	**1.53[1.17, 2.00]**	1.77[0.69, 4.51]	2.45[0.96, 6.23]	1[0.76, 1.31]	1.55[0.80, 2.97]	1.43[0.18, 11.1]	0.84[0.23, 3.09]	3.14[0.25, 40.3]	2.27[0.24, 21.8]
>= 5 vs. 0	**1.53[1.17, 2.01]**	1.8[0.70, 4.63]	2.17[0.84, 5.61]	0.98[0.74, 1.29]	1.16[0.60, 2.27]	2.55[0.33, 19.7]	1.1[0.30, 4.08]	4.85[0.38, 62.1]	3.04[0.31, 29.4]
BMI									
25-29.9 vs. <=24.9	**1.37[1.17, 1.60]**	2.38[0.35, 16.3]	**0.48[0.32, 0.71]**	**1.8[1.44, 2.25]**	1.28[0.85, 1.94]	1.21[0.46, 3.23]	1.12[0.51, 2.44]	0.51[0.20, 1.26]	0.66[0.32, 1.38]
>= 30 vs. <=24.9	**1.92[1.65, 2.23]**	**26.9[4.32, 167]**	**0.43[0.30, 0.63]**	**3.68[2.97, 4.56]**	1.37[0.92, 2.04]	1.46[0.57, 3.73]	1.22[0.58, 2.57]	0.9[0.40, 2.01]	0.53[0.26, 1.07]
HbA1c									
7- <9% vs. < 7%	**1.45[1.10, 1.92]**	**0.3[0.17, 0.54]**	**0.15[0.09, 0.25]**	0.91[0.66, 1.26]	1.69[0.73, 3.91]	2.04[0.23, 18.3]	**0.38[0.15, 0.97]**	0.99[0.15, 6.47]	0.34[0.10, 1.20]

>=9% vs. < 7%	0.81[0.62, 1.07]	**0.21[0.12, 0.38]**	**0.22[0.14, 0.35]**	**0.59[0.43, 0.82]**	1.22[0.53, 2.84]	1.44[0.16, 13.0]	0.42[0.17, 1.06]	1.04[0.16, 6.76]	0.6[0.18, 2.05]
eGFR									
< 60 vs. >= 60	**1.24[1.07, 1.44]**	1.39[0.78, 2.48]	**2.2[1.45, 3.35]**	**0.27[0.20, 0.37]**	1.1[0.71, 1.68]	0.74[0.26, 2.11]	**2.55[1.38, 4.72]**	0.41[0.10, 1.62]	1.6[0.69, 3.69]
HDL									
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.01[0.93, 1.09]	0.96[0.73, 1.27]	0.91[0.68, 1.23]	0.95[0.86, 1.04]	0.97[0.79, 1.19]	0.52[0.30, 0.91]	0.92[0.59, 1.43]	0.85[0.50, 1.46]	0.95[0.56, 1.62]
>= 60 vs. <40 (M) or <50 (F)	1.01[0.88, 1.17]	0.62[0.34, 1.15]	0.85[0.53, 1.37]	0.9[0.75, 1.08]	1[0.69, 1.44]	0.75[0.31, 1.84]	1.04[0.51, 2.14]	1.06[0.43, 2.62]	0.9[0.37, 2.21]
TG									
150-499 vs. < 150	0.99[0.91, 1.07]	0.95[0.71, 1.29]	0.85[0.63, 1.14]	1.01[0.91, 1.12]	0.98[0.79, 1.21]	0.94[0.56, 1.58]	0.93[0.59, 1.47]	1.35[0.74, 2.46]	0.8[0.47, 1.37]
>= 500 vs. < 150	**0.79[0.66, 0.94]**	0.91[0.53, 1.55]	1.39[0.82, 2.38]	0.9[0.73, 1.11]	1.02[0.65, 1.59]	0.75[0.26, 2.19]	1.2[0.54, 2.67]	2.19[0.88, 5.48]	0.58[0.18, 1.88]
Total cholesterol									
200-239 vs. < 200	0.97[0.88, 1.08]	**1.68[1.24, 2.27]**	1.07[0.77, 1.50]	1.02[0.91, 1.16]	0.94[0.72, 1.23]	1.01[0.52, 1.94]	1.23[0.73, 2.07]	1.42[0.81, 2.50]	1.2[0.63, 2.29]
>=240 vs. < 200	**0.79[0.69, 0.91]**	**1.73[1.19, 2.52]**	0.93[0.60, 1.43]	**0.81[0.69, 0.95]**	0.83[0.58, 1.19]	1.04[0.46, 2.39]	1.39[0.75, 2.57]	0.92[0.42, 2.00]	0.98[0.41, 2.34]

Appendix S.5.5: Univariable multinomial logistic regression analyses results at drug intensification of initial-sulfonylurea cohort

Univariable multinomial logistic regression of factors influencing prescribing of antidiabetic class for initial-sulfonylurea cohort (Cohort-2b: N=3952)

Studied factors	DPP4-I	insulin	SGLT2-I	TZD	biguanide+DPP4-I	biguanide+ insulin	P-value
1- Demographic factors							
Age at prescription	<0.001	0.046	0.002	0.002	0.5	0.11	<0.001
>= 65 vs. < 65 years	**2.29[1.85, 2.83]**	1.26[1.00, 1.57]	**0.55[0.37, 0.81]**	**2.28[1.34, 3.89]**	0.83[0.45, 1.52]	0.54[0.24, 1.19]	
SEX	<0.001	0.033	0.1	0.011	>0.9	0.5	<0.001
F vs. M	**1.6[1.31, 1.96]**	**1.28[1.02, 1.60]**	1.36[0.95, 1.94]	**1.94[1.17, 3.24]**	0.97[0.53, 1.79]	1.25[0.60, 2.62]	
2- Socioeconomic factors							
UR	0.2	0.8	0.2	0.7	0.068	0.5	0.3
2 vs. 1	1.33[1.05, 1.70]	1.03[0.78, 1.35]	1.37[0.89, 2.11]	1.39[0.73, 2.66]	1.91[0.85, 4.30]	1.46[0.62, 3.43]	
3 vs. 1	1.16[0.79, 1.70]	1.18[0.79, 1.77]	0.76[0.33, 1.71]	2[0.85, 4.71]	0.44[0.06, 3.52]	0.44[0.06, 3.52]	
4 vs. 1	0.62[0.26, 1.44]	0.96[0.45, 2.03]	1.49[0.52, 4.28]	2.58[0.74, 9.05]	1.53[0.19, 12.2]	0[0.00, 0.00]	
5 vs. 1	0.56[0.17, 1.82]	0.87[0.31, 2.46]	1.35[0.31, 5.77]	1.56[0.20, 12.0]	**5.53[1.16, 26.4]**	0[NA]	
6 vs. 1	1.06[0.73, 1.54]	1.14[0.78, 1.69]	1.22[0.64, 2.32]	1.95[0.85, 4.45]	**3.85[1.55, 9.56]**	0.77[0.17, 3.58]	
7 vs. 1	1.33[0.76, 2.33]	1.64[0.95, 2.85]	0.9[0.27, 2.98]	0.7[0.09, 5.30]	3.71[0.99, 13.9]	2.47[0.53, 11.6]	
8 vs. 1	1.42[0.75, 2.69]	1.24[0.60, 2.55]	**3.43[1.53, 7.65]**	0.99[0.13, 7.58]	1.76[0.22, 14.1]	3.52[0.75, 16.6]	
Unknown vs. 1	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, inf]	0[0.00, inf]	
SCOTTISH INDEX OF MULTIPLE DEPRIVATION-QUANTILE	0.7	0.5	0.2	0.14	0.3	0.7	0.4
2 vs. 1	1.09[0.81, 1.45]	1.19[0.87, 1.61]	1.51[0.94, 2.45]	**2.35[1.13, 4.88]**	0.78[0.35, 1.75]	0.59[0.18, 1.96]	
3 vs. 1	1.2[0.88, 1.63]	1.04[0.74, 1.47]	1.11[0.63, 1.93]	1.13[0.45, 2.84]	0.94[0.41, 2.15]	1.36[0.49, 3.78]	
4 vs. 1	1.17[0.86, 1.60]	0.97[0.68, 1.38]	0.78[0.41, 1.45]	1.31[0.54, 3.19]	0.85[0.36, 2.03]	1.2[0.41, 3.48]	

5 vs. 1	0.98[0.70, 1.38]	0.86[0.59, 1.27]	0.94[0.51, 1.75]	1.83[0.79, 4.26]	0.24[0.06, 1.07]	0.91[0.27, 3.06]	
3- Prescriber-related factors							
Prescriber type	0.3	0.037	0.001	0.7	0.7	0.9	0.008
Non-GP vs. GP	1.24[0.84, 1.83]	0.56[0.31, 1.01]	**2.6[1.54, 4.39]**	0.79[0.25, 2.56]	0.73[0.17, 3.04]	1.13[0.27, 4.81]	
4- Clinical-related factors							
IHD	<0.001	<0.001	0.4	0.2	0.7	0.4	<0.001
Yes vs. No	**1.73[1.36, 2.21]**	**1.65[1.26, 2.16]**	0.8[0.47, 1.36]	1.46[0.79, 2.72]	0.85[0.36, 2.03]	0.62[0.19, 2.07]	
HTN	<0.001	<0.001	0.9	0.013	0.4	0.082	<0.001
Yes vs. No	**2.03[1.63, 2.53]**	**2.29[1.81, 2.91]**	1.03[0.66, 1.60]	**2.04[1.19, 3.48]**	0.73[0.33, 1.66]	2.04[0.94, 4.42]	
HF	<0.001	<0.001	0.4	0.1	0.2	0.7	<0.001
Yes vs. No	**2.33[1.63, 3.33]**	**3.81[2.72, 5.35]**	1.4[0.67, 2.93]	2.22[0.94, 5.24]	2.03[0.72, 5.77]	0.73[0.10, 5.38]	
Stroke	0.032	0.004	0.9	0.031	0.8	>0.9	0.01
Yes vs. No	**1.65[1.07, 2.57]**	**2.02[1.29, 3.16]**	1.08[0.43, 2.68]	0[0.00, inf]	1.22[0.29, 5.09]	0.91[0.12, 6.77]	
PVD	0.058	<0.001	0.3	0.4	0.2	0.11	<0.001
Yes vs. No	1.53[1.00, 2.33]	**2.49[1.68, 3.69]**	0.54[0.17, 1.73]	1.53[0.55, 4.29]	2.19[0.77, 6.20]	0[0.00, inf]	
Liver disease	0.8	<0.001	0.015	>0.9	0.3	0.003	<0.001
Yes vs. No	1.05[0.66, 1.66]	**3[2.11, 4.27]**	**2.26[1.24, 4.11]**	1[0.31, 3.23]	1.93[0.68, 5.47]	**5.03[2.02, 12.6]**	
CCI score	<0.001	<0.001	0.046	0.1	0.9	0.023	<0.001
1-2 vs. 0	**1.96[1.54, 2.50]**	**3.35[2.54, 4.41]**	1.18[0.75, 1.85]	**2.04[1.15, 3.61]**	0.74[0.31, 1.77]	1.31[0.48, 3.59]	
3-4 vs. 0	**2.44[1.71, 3.47]**	**7.58[5.47, 10.5]**	1.46[0.75, 2.87]	1.76[0.68, 4.54]	1.15[0.35, 3.78]	**4.89[1.89, 12.7]**	
>= 5 vs. 0	**2.37[1.44, 3.90]**	**7.53[4.86, 11.6]**	0[0.00, inf]	0.75[0.10, 5.54]	0.82[0.11, 6.04]	3.47[0.78, 15.3]	
Antihyperlipidemic drugs	0.05	<0.001	<0.001	0.021	0.6	0.01	<0.001

Yes vs. No	1.24[1.00, 1.55]	**0.55[0.44, 0.69]**	**0.49[0.34, 0.70]**	**1.98[1.07, 3.67]**	0.85[0.46, 1.57]	**0.38[0.18, 0.80]**	
Antipsychotic	>0.9	0.2	0.3	0.5	0.2	0.3	0.4
Yes vs. No	1[0.55, 1.80]	1.46[0.84, 2.56]	0.52[0.13, 2.15]	0.53[0.07, 3.87]	2.33[0.71, 7.67]	2.36[0.55, 10.1]	
Thiazide diuretics	0.2	<0.001	>0.9	0.8	0.7	0.066	0.006
Yes vs. No	1.3[0.87, 1.93]	**0.3[0.13, 0.68]**	0.99[0.46, 2.17]	0.86[0.27, 2.77]	0.79[0.19, 3.30]	0[0.00, inf]	
Beta blocker	<0.001	<0.001	0.9	0.8	0.3	0.15	<0.001
Yes vs. No	**1.96[1.55, 2.47]**	**1.8[1.39, 2.33]**	0.96[0.59, 1.56]	1.09[0.56, 2.11]	1.46[0.72, 2.98]	1.89[0.83, 4.30]	
Angiotensin inhibitors	0.3	0.007	0.4	0.2	0.7	0.5	0.093
Yes vs. No	0.88[0.67, 1.15]	**0.65[0.46, 0.90]**	1.19[0.77, 1.86]	1.47[0.81, 2.65]	0.85[0.38, 1.92]	0.72[0.25, 2.08]	
CCB	0.089	0.5	0.7	0.9	0.2	0.4	0.4
Yes vs. No	1.26[0.97, 1.64]	0.9[0.66, 1.24]	0.92[0.55, 1.53]	1.06[0.53, 2.10]	0.54[0.19, 1.52]	0.62[0.19, 2.07]	
Number of concomitant medications	<0.001	<0.001	0.7	0.055	0.3	0.2	<0.001
1-4 vs. 0	1.63[0.70, 3.83]	1.29[0.45, 3.65]	1.29[0.45, 3.65]	2299[0.00, inf]	0.4[0.11, 1.47]	0.3[0.06, 1.57]	
>= 5 vs. 0	**3.29[1.43, 7.53]**	**4.28[1.57, 11.7]**	1.12[0.40, 3.11]	3140[0.00, inf]	0.6[0.18, 1.99]	0.64[0.15, 2.78]	
BMI	0.033	<0.001	0.01	>0.9	0.9	0.4	<0.001
25-29.9 vs. <=24.9	0.72[0.50, 1.02]	**0.26[0.18, 0.37]**	1.88[0.81, 4.40]	0.88[0.38, 2.03]	0.75[0.28, 2.00]	2.11[0.45, 9.98]	
>= 30 vs. <=24.9	0.98[0.70, 1.36]	**0.26[0.19, 0.37]**	**3.1[1.39, 6.91]**	0.8[0.35, 1.83]	0.9[0.36, 2.26]	2.71[0.60, 12.2]	
Unknown vs. <= 24.9	1.08[0.78, 1.49]	0.56[0.42, 0.75]	2.49[1.11, 5.58]	0.92[0.42, 2.04]	0.74[0.29, 1.86]	1.39[0.29, 6.70]	
HbA1c	0.3	<0.001	0.12	0.039	0.3	<0.001	<0.001
7- <9% vs. < 7%	1.44[0.80, 2.60]	0.8[0.41, 1.54]	1.56[0.48, 5.10]	> 1000[inf, inf]	1.56[0.20, 11.9]	>1000 [inf, inf]	
>=9% vs. < 7%	1.62[0.90, 2.91]	1.79[0.95, 3.37]	2.29[0.71, 7.34]	> 1000[inf, inf]	2.56[0.35, 19.0]	>1000 [inf, inf]	

Unknown vs. < 7%	1.46[0.68, 3.13]	3.65[1.78, 7.50]	1.49[0.33, 6.79]	> 1000[inf, inf]	1.12[0.07, 18.0]	>1000 [inf, inf]	
eGFR	<0.001	<0.001	0.4	<0.001	0.13	0.13	<0.001
< 60 vs. >= 60	**5.64[4.48, 7.11]**	**5.22[4.06, 6.72]**	0.64[0.32, 1.28]	**4.74[2.77, 8.10]**	2.02[0.96, 4.26]	**2.6[1.09, 6.19]**	
Unknown vs. < 60	1.26[0.84, 1.89]	1.28[0.83, 1.98]	1.01[0.53, 1.90]	0.53[0.13, 2.21]	0.58[0.14, 2.42]	0.95[0.22, 4.09]	
HDL	0.11	<0.001	0.6	0.9	0.2	0.074	<0.001
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	**0.74[0.56, 0.97]**	0.9[0.65, 1.25]	1.11[0.71, 1.75]	0.84[0.43, 1.63]	1.49[0.68, 3.23]	0.58[0.16, 2.14]	
>= 60 vs. <40 (M) or <50 (F)	0.9[0.59, 1.38]	**1.66[1.08, 2.54]**	0.6[0.24, 1.52]	0.67[0.20, 2.21]	0.43[0.06, 3.27]	2[0.54, 7.44]	
Unknown vs. <40 (M) or <50 (F)	1.02[0.81, 1.30]	1.77[1.36, 2.31]	1.04[0.68, 1.61]	0.94[0.51, 1.72]	1.71[0.84, 3.49]	2.19[0.94, 5.09]	
TG	0.004	<0.001	0.2	0.9	0.2	0.2	<0.001
150-499 vs. < 150	**1.47[1.11, 1.95]**	**0.66[0.48, 0.91]**	1.29[0.79, 2.10]	1.02[0.51, 2.05]	1.12[0.49, 2.55]	0.88[0.28, 2.79]	
>= 500 vs. < 150	0.64[0.31, 1.31]	0.82[0.44, 1.56]	**2.23[1.04, 4.75]**	1.28[0.36, 4.57]	0[0.00, inf]	1.11[0.13, 9.60]	
Unknown vs. < 150	1.38[1.04, 1.85]	1.38[1.04, 1.83]	1.03[0.62, 1.73]	1.25[0.63, 2.48]	1.43[0.65, 3.19]	2.17[0.79, 5.96]	
Total cholesterol	0.7	<0.001	0.6	0.6	0.7	0.01	<0.001
200-239 vs. < 200	0.84[0.61, 1.15]	**0.51[0.32, 0.80]**	0.96[0.55, 1.67]	0.8[0.37, 1.71]	1.14[0.49, 2.66]	1.81[0.56, 5.91]	
>=240 vs. < 200	0.96[0.66, 1.40]	1.2[0.80, 1.81]	1.14[0.60, 2.19]	0.69[0.24, 1.94]	0.57[0.13, 2.40]	3.14[0.96, 10.3]	
Unknown vs. < 200	1.02[0.78, 1.33]	2.05[1.59, 2.64]	1.35[0.86, 2.10]	0.62[0.29, 1.32]	1.26[0.60, 2.65]	4.22[1.77, 10.1]	

DPP4-I; Dipeptidyl peptidase-4 inhibitors, GLP1-RA; Glucagon-like peptide receptors agonist, SU; sulfonylurea, TZD; thiazolidinedione, SGLT2-i; Sodium glucose co-transporter-2 inhibitors. UR; urban-rural, SIMD-Q; Scottish index of multiple deprivation-Quantile, GP; General practitioner, IHD; ischemic heart disease, HTN; hypertension, HF; heart failure, PVD; peripheral vascular disease, CCI; Charlson comorbidity index, CCB; calcium channel blocker, BMI; body mass index, eGFR; estimated glomerular filtration rate, HDL; high density lipoprotein, TG; triglyceride.

Appendix S.5.6: Complete case analysis regression results of the initial sulfonylurea cohort

Multivariable logistic regression of factors influencing prescribing of antidiabetic regimen type for complete-case initial-sulfonylurea users

Studied factor	OR[95%CI]	Overall p value
Age at prescription		0.03
>= 65 vs. < 65 years	0.35[0.12, 0.90]	
Sex		0.9
F vs. M	0.94[0.41, 2.09]	
UR		0.3
2 vs. 1	1.63[0.69, 4.01]	
3 vs. 1	1.26[0.24, 4.99]	
4 vs. 1	0[0.00, inf]	
5 vs. 1	5.04[0.20, 49.9]	
6 vs. 1	2.05[0.62, 6.35]	
7 vs. 1	0[0.00, inf]	
8 vs. 1	0[0.00, inf]	
SIMD-Q		0.15
2 vs. 1	0.29[0.08, 0.83]	
2 vs. 1	0.65[0.22, 1.79]	
2 vs. 1	0.35[0.09, 1.11]	
2 vs. 1	0.41[0.10, 1.33]	
Prescriber type	1.24[0.18, 4.82]	0.8
Non-GP vs. GP		
IHD		>0.9
Yes vs. No	1.03[0.28, 3.24]	
HTN		0.5
Yes vs. No	1.45[0.49, 3.98]	
HF		>0.9
Yes vs. No	1.02[0.14, 5.92]	
Stroke		0.12
Yes vs. No	0[0.00, inf]	
PVD		0.7
Yes vs. No	0.65[0.03, 4.14]	
Liver disease		0.7
Yes vs. No	1.4[0.26, 6.55]	
CCI-score		0.5
1-2 vs. 0	0.42[0.11, 1.32]	
3-4 vs. 0	0.9[0.12, 5.37]	
>= 5 vs. 0	0.84[0.06, 7.06]	
Lipid drugs		0.7
Yes vs. No	0.84[0.36, 1.96]	
Antipsychotic		0.9

Yes vs. No	1.18[0.16, 5.31]	
Thiazide diuretics		0.035
Yes vs. No	0[0.00, inf]	
Beta blocker		0.4
Yes vs. No	0.6[0.17, 1.90]	
Angiotensin inhibitors		0.3
Yes vs. No	0.54[0.16, 1.58]	
CCB		0.11
Yes vs. No	0.36[0.07, 1.25]	
Number of concomitant medications		0.8
1-4 vs. 0	0.59[0.14, 3.09]	
>= 5 vs. 0	0.64[0.14, 3.57]	
BMI (kg/m^2)		0.7
25-29.9	0.76[0.25, 2.37]	
>= 30	1.17[0.44, 3.35]	
HbA1c (%)		0.018
7-9 vs. < 7	>1000[0.00, inf]	
>= 9 vs. < 7	>1000[0.00, inf]	
eGFR:		
< 60 vs. >= 60 ml/min/1.73m^2	8.57[2.81, 27.3]	<0.001
HDL (mg/dl)		>0.9
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	1.01[0.41, 2.39]	
>= 60 vs. <40 (M) or <50 (F)	1.2[0.24, 4.52]	
TG (mg/dl)		0.7
150-499 vs. < 150	0.69[0.29, 1.64]	
>= 500 vs. < 150	0.72[0.13, 3.17]	
Total cholesterol (mg/dl)		0.3
200-239 vs. < 200	2.11[0.84, 5.12]	
>=240 vs. < 200	1.17[0.29, 3.91]	

Multivariable multinomial logistic regression of factors influencing prescribing of antidiabetic class for complete-case initial-sulfonylurea users

Studied factors	DPP4-I	Insulin	SGLT2-I	TZD	biguanide+DPP4-I	biguanide+ insulin
Age at prescription						
>= 65 vs. < 65 years	1.11[0.74, 1.68]	0.33[0.19, 0.58]	0.52[0.26, 1.06]	1.17[0.37, 3.70]	0.69[0.16, 3.00]	0.03[0.00, 0.51]
SEX						
F vs. M	0.97[0.66, 1.42]	1.14[0.70, 1.87]	1.69[0.90, 3.17]	1.69[0.52, 5.55]	0.8[0.22, 2.96]	0.9[0.16, 4.97]
UR						
2 vs. 1	1.23[0.81, 1.87]	1.15[0.66, 1.99]	1.21[0.62, 2.40]	0.31[0.07, 1.28]	1.65[0.41, 6.63]	2.47[0.44, 13.9]
3 vs. 1	1.76[0.93, 3.34]	1.5[0.59, 3.80]	0.38[0.08, 1.80]	2.17[0.37, 12.8]	0[0.00, inf]	1.44[0.09, 22.9]
4 vs. 1	1.01[0.27, 3.71]	0.88[0.20, 3.93]	2.23[0.48, 10.4]	2.02[0.12, 33.6]	0[0.00, inf]	0[0.00, inf]
5 vs. 1	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, 0.00]	0[0.00, 0.00]	10.5[0.36, 311]	0.02[0.00, inf]
6 vs. 1	1.56[0.85, 2.87]	2.19[1.05, 4.56]	0.84[0.28, 2.54]	1.79[0.37, 8.60]	4.24[0.76, 23.7]	2.32[0.15, 35.0]
7 vs. 1	1.25[0.44, 3.55]	1.84[0.48, 7.14]	0[0.00, 0.00]	0.94[0.05, 19.4]	0[0.00, inf]	0[0.00, 0.00]
8 vs. 1	0.42[0.05, 3.35]	3.35[0.87, 12.9]	8.85[2.23, 35.1]	6.44[0.51, 82.1]	0[0.00, inf]	0.04[0.00, inf]
SIMD_Q						
2 vs. 1	0.84[0.51, 1.38]	1.61[0.84, 3.11]	1.3[0.60, 2.82]	2.63[0.45, 15.4]	0.21[0.04, 1.20]	0.34[0.04, 2.98]
3 vs. 1	0.86[0.49, 1.52]	2.17[1.06, 4.40]	0.9[0.33, 2.48]	1.15[0.14, 9.59]	0.73[0.16, 3.34]	0.3[0.02, 3.89]
4 vs. 1	1.02[0.59, 1.77]	1.25[0.58, 2.70]	0.89[0.31, 2.52]	2.46[0.38, 15.9]	0.16[0.02, 1.63]	0.12[0.01, 2.57]
5 vs. 1	0.74[0.40, 1.34]	0.86[0.36, 2.04]	1.01[0.34, 2.95]	4.19[0.66, 26.6]	0.18[0.02, 1.77]	1.09[0.13, 9.34]
Prescriber type						
Non-GP vs. GP	1.39[0.69, 2.82]	1.71[0.70, 4.17]	2.47[1.08, 5.62]	3.33[0.52, 21.3]	3.79[0.60, 23.8]	0.01[0.00, inf]

IHD						
Yes vs. No	0.77[0.46, 1.30]	0.63[0.31, 1.27]	0.85[0.30, 2.42]	2.07[0.51, 8.50]	0.42[0.03, 5.07]	1.22[0.11, 13.3]
HTN						
Yes vs. No	1.4[0.90, 2.19]	1.6[0.88, 2.90]	1.1[0.49, 2.46]	1.73[0.50, 6.01]	1.86[0.28, 12.5]	1.79[0.19, 16.8]
HF						
Yes vs. No	1.52[0.69, 3.32]	1.96[0.80, 4.78]	0.79[0.08, 7.45]	0[0.00, 0.00]	54.4[0.82, 3,603]	0[0.00, 0.00]
Stroke						
Yes vs. No	0.91[0.37, 2.19]	0.99[0.36, 2.74]	0.64[0.08, 5.37]	0[0.00, inf]	0[0.00, inf]	0[0.00, inf]
PVD						
Yes vs. No	1.36[0.61, 3.06]	1.53[0.56, 4.15]	1.69[0.31, 9.13]	1.35[0.09, 21.0]	0[0.00, 0.00]	0[0.00, 0.00]
Liver disease						
Yes vs. No	0.42[0.15, 1.18]	0.66[0.28, 1.58]	3.12[0.94, 10.3]	0.67[0.05, 9.55]	1.17[0.03, 48.3]	1.79[0.06, 51.6]
CCI score						
1-2 vs. 0	1.31[0.81, 2.12]	3.27[1.81, 5.90]	0.9[0.38, 2.13]	6.69[1.68, 26.7]	0.08[0.00, 2.93]	0.97[0.08, 11.5]
3-4 vs. 0	1.42[0.58, 3.44]	3.8[1.52, 9.51]	0.85[0.16, 4.68]	5.96[0.40, 89.1]	0[0.00, 0.00]	3.71[0.06, 226]
>= 5 vs. 0	3.07[1.19, 7.97]	9.85[3.61, 26.9]	0[0.00, inf]	0[0.00, 0.00]	0.32[0.00, 65.2]	9.88[0.18, 535]
Lipid drugs						
Yes vs. No	0.92[0.59, 1.42]	0.43[0.25, 0.73]	0.59[0.30, 1.16]	8.69[1.37, 55.0]	1.35[0.35, 5.18]	0.88[0.16, 4.93]
Antipsychotic						
Yes vs. No	1.64[0.62, 4.38]	0.68[0.15, 3.13]	0.63[0.07, 5.50]	0[0.00, 0.00]	1.31[0.11, 16.2]	16.2[0.85, 312]
Thiazide diuretics						
Yes vs. No	2.39[1.15, 4.96]	0.35[0.07, 1.70]	2.9[0.88, 9.61]	2.8[0.37, 21.0]	0[0.00, inf]	0.04[0.00, inf]

Beta blocker						
Yes vs. No	3.11[1.78, 5.42]	1.06[0.55, 2.05]	1.13[0.37, 3.45]	1.57[0.27, 9.15]	0.27[0.02, 3.25]	2.92[0.36, 23.8]
Angiotensin inhibitors						
Yes vs. No	1.93[1.13, 3.29]	0.74[0.37, 1.48]	1.34[0.55, 3.25]	2.45[0.52, 11.6]	0.48[0.08, 2.83]	1.24[0.12, 13.3]
CCB						
Yes vs. No	1.51[0.83, 2.74]	0.33[0.14, 0.78]	1.94[0.80, 4.70]	1.44[0.25, 8.19]	0.19[0.02, 2.29]	0.96[0.07, 13.8]
Number of concomitant medications						
1-4 vs. 0	0.83[0.27, 2.57]	3.9[0.43, 35.1]	1.63[0.32, 8.21]	>1000[6.29, >1000]	0.58[0.08, 4.29]	0.14[0.01, 2.76]
>= 5 vs. 0	0.68[0.21, 2.17]	8.48[0.94, 76.4]	1.4[0.27, 7.36]	683[0.78, >1000]	0.59[0.07, 5.12]	0.1[0.00, 2.57]
BMI						
25-29.9 vs. <=24.9	0.69[0.42, 1.13]	0.18[0.10, 0.33]	3.44[0.94, 12.6]	1.74[0.39, 7.66]	0.4[0.07, 2.26]	1.07[0.12, 9.90]
>= 30 vs. <=24.9	0.69[0.43, 1.12]	0.17[0.09, 0.30]	4.55[1.27, 16.3]	0.94[0.20, 4.37]	0.99[0.21, 4.57]	1.05[0.13, 8.68]
HbA1c						
7-9% vs. < 7%	3.08[0.90, 10.5]	3.16[0.56, 17.7]	1.14[0.23, 5.50]	>1000[137, >1000]	>1000[>1000, >1000]	>1000[519, >1000]
>=9% vs. < 7%	2.55[0.75, 8.66]	7.11[1.30, 38.8]	1.42[0.30, 6.74]	>1000 [334, inf]	>1000[>1000, >1000]	>1000[>1000, >1000]
eGFR						
< 60 vs. >= 60	3.67[2.35, 5.75]	6.63[3.60, 12.2]	1.22[0.40, 3.76]	6.24[1.74, 22.4]	4.58[0.63, 33.1]	30.5[2.62, 356]
HDL						
40-59 (M) or 50-59 (F) vs. <40 (M) or <50 (F)	0.93[0.62, 1.40]	1.06[0.61, 1.83]	1.65[0.85, 3.19]	0.91[0.29, 2.91]	1.28[0.35, 4.66]	0.44[0.06, 3.31]
>= 60 vs. <40 (M) or <50 (F)	1.01[0.52, 1.93]	1.97[0.97, 4.00]	0.77[0.20, 3.02]	0.27[0.03, 2.70]	0[0.00, inf]	1.76[0.19, 16.1]

TG						
150-499 vs. < 150	1.22[0.81, 1.83]	0.81[0.48, 1.35]	1.47[0.72, 3.01]	1.14[0.32, 4.05]	0.9[0.26, 3.20]	0.23[0.04, 1.55]
>= 500 vs. < 150	0.42[0.13, 1.36]	0.96[0.31, 2.97]	2.88[0.74, 11.2]	4.47[0.43, 46.0]	0[0.00, inf]	0.28[0.01, 7.90]
Total cholesterol						
200-239 vs. < 200	1.03[0.61, 1.74]	0.39[0.18, 0.86]	0.69[0.31, 1.52]	2.45[0.63, 9.46]	2.62[0.68, 10.1]	3.41[0.58, 20.0]
>=240 vs. < 200	1.3[0.69, 2.43]	0.75[0.35, 1.63]	0.42[0.14, 1.31]	0[0.00, inf]	0.74[0.06, 8.53]	1.33[0.06, 27.4]