Real-world evaluation of utilisation patterns of lipid-lowering therapies (LLTs) and quality of lipid control in Kuwait: a national multi-study project

by
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Declaration

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

Signed:

Date: 25-11-25

Dedication

“In the name of Allah, the Most Merciful, the Most Compassionate.”

This thesis is dedicated to:

My kind and supportive parents,

My beloved brothers,

And

My cherished homeland, **Kuwait**.

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List of publications and presentations

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Glossary

List of abbreviations	
95% CI	95% Confidence interval
ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
Apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CHD	Coronary heart disease
CKD	Chronic kidney disease
CMS	Central Medical Store
CVDs	Cardiovascular diseases
DDD	Defined daily dose
DM	Diabetes mellitus
DUR	Drug utilisation research
DYSIS	Dyslipidemia International Study
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	Familial hypercholesterolaemia
GPs	General practitioners
HDL-C	High-density lipoprotein cholesterol
HIC	High income country
HIST	High-intensity statin therapy
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
IQR	Interquartile range
LDL-C	Low-density lipoprotein cholesterol
LLTs	Lipid-lowering therapies
LP (a)	Lipoprotein (a)
MIST	Moderate-intensity statin therapy
MOH	Ministry of Health
NCD	Non-communicable disease
Non- HDL-C	Non-high-density lipoprotein cholesterol
PCIS	Primary Care Information System
PCSK9is	Proprotein convertase subtilisin-kexin type 9 inhibitors
PHCCs	Primary healthcare centres
RCTs	Randomised controlled trials
SD	Standard deviation
TC	Total cholesterol
TG	Triglycerides
WHO	World Health Organisation

Abstract

Introduction: Lipid-lowering therapies (LLTs), including statins and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is), are used to manage elevated low-density lipoprotein cholesterol (LDL-C). Over time, LLT prescribing patterns have been shaped by evolving guidelines. However, national data on LLT utilisation patterns and the quality of lipid control in Kuwait remain unknown.

Methods: This thesis comprised three nationwide quantitative studies conducted across healthcare settings governed by the Ministry of Health in Kuwait. First, a retrospective, repeated cross-sectional study utilising data from the Central Medical Store (CMS) was conducted to quantify utilisation trends of LLTs over an 11-year period (2012–2022). Second, a nationwide, cross-sectional design among patients attending primary healthcare centres (PHCCs) was employed to evaluate LLT prescribing patterns and assess the extent of lipid control. Third, a retrospective cohort study utilising routinely collected dispensing data from a tertiary cardiac care centre was performed to evaluate the real-world effectiveness of PCSK9is between 2016 and 2022. All data were analysed using descriptive statistics and regression methods, as appropriate.

Results: At the national level, findings from the CMS data demonstrated a significant overall increase in both utilisation and expenditure trends of LLTs. Utilisation, measured by number of supplied units per thousand inhabitants per year, rose by 52% (n= 71,839), from 138,549 in 2012 to 210,388 in 2022, while defined daily doses per thousand inhabitants per day increased by 119% (n= 62.2), from 52.4 in 2012 to 114.6 in 2022. Statins accounted for the increase in utilisation. At the PHCC level, findings from the cross-sectional study showed that most patients were prescribed statins (98.8%, n= 429/434). Lipid control was suboptimal, with only 20.4% (n= 65/318) achieving LDL-C targets across all cardiovascular (CV) risk categories. At the tertiary care level, the real-world effectiveness study showed that PCSK9is

significantly reduced LDL-C levels (n=104) by 41.9% (95% CI: -50.9% to -24.1%, p<0.001).

Conclusion:

The utilisation and expenditure of LLTs in Kuwait have increased substantially. Statins remain the cornerstone of treatment, reflecting their continued role as first-line therapy. Despite the widespread use of statins in PHCCs, lipid control remains suboptimal, particularly among patients at extreme CV risk. PCSK9is reduced LDL-C significantly (~42%) but less than in clinical trials (~60%). These findings highlight the urgent need for targeted interventions to optimise lipid management.

Summary

Introduction: Cardiovascular diseases (CVDs) are the leading cause of mortality in Kuwait, with a rate of 67.75 per 100,000 inhabitants in 2023. Uncontrolled lipid levels, particularly elevated low-density lipoprotein cholesterol (LDL-C), remain a key modifiable risk factor for CVDs. Lipid-lowering therapies (LLTs) are crucial for effective management. Statins serve as the cornerstone of treatment, with ezetimibe recommended as an adjunct in cases of inadequate lipid control. The third-line option for uncontrolled LDL-C levels is proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is), which was introduced in Kuwait in 2016. Over time, LLT prescribing patterns have evolved in response to updated clinical guidelines that advocate for stricter lipid thresholds and treatment targets aligned with CV risk categories. However, national data on LLT utilisation patterns and the quality of lipid control in real-world practice remain unknown.

Aim and objectives: This thesis aimed to examine prescribing patterns of LLTs and evaluate the quality of lipid control in clinical practice in Kuwait. The objectives were to: 1) assess national utilisation and expenditure trends of LLTs; 2) investigate LLT prescribing patterns and evaluate lipid target achievement, along with factors potentially associated with target attainment; and 3) evaluate the real-world effectiveness of PCSK9is, including both evolocumab and alirocumab, along with factors potentially associated with lipid reduction.

Methods: This thesis comprised three nationwide quantitative studies conducted across three different governmental healthcare settings governed by the Ministry of Health.

Firstly, a population-based, retrospective, repeated cross-sectional study was conducted using aggregated utilisation and expenditure data from the Central Medical Store (CMS) for statins, ezetimibe, and PCSK9is from 2012 to 2022 (objective 1). Utilisation was quantified as the number of supplied units per 1,000 inhabitants per year (NSU/TIY) and defined daily doses per 1,000 inhabitants per day (DDDs/TID). Expenditure was measured as the cost of supplied units (CSU) per TIY. The analysis was performed at the national level, followed by comparisons between primary healthcare centres (PHCCs) and hospital settings, as well as an investigation of regional disparities across the six governorates of Kuwait. LLTs were categorised by therapeutic class, with further stratification by individual agents within each class. Descriptive statistics (absolute and relative changes) and linear regression analysis was employed to estimate the average annual change in utilisation and expenditure over time.

Secondly, a nationwide, cross-sectional study was conducted in PHCCs in 2023 (objective 2). The questionnaire was developed based on the WHO STEPwise approach to surveillance (STEPS). Six PHCCs were selected across the six governorates, with one PHCC included from each governorate. The sample size was determined using population estimates from the Public Authority for Civil Information (PACI). Patients attending non-communicable disease clinics who were prescribed at least one LLT were included. CV risk categories and lipid treatment goals for LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) were defined according to the 2021 Middle East consensus. Prescribing patterns were categorised by therapeutic regimen (monotherapy vs. combination therapy), therapeutic class, and individual agents within each class. The quality of lipid control was assessed by calculating the proportion of patients achieving therapeutic lipid goals and stratified across CV risk categories. Multivariate binomial logistic regression analysis was performed to identify factors of lipid target attainment, focusing on LDL-C and non-HDL-C.

Thirdly, a retrospective cohort study was conducted at the tertiary cardiac care centre utilising routinely collected pharmacy dispensing data from 2016 to 2022 (objective 3). The study included patients who were newly dispensed a PCSK9i (evolocumab or alirocumab), defined as those with no PCSK9i prescriptions in the previous 12 months. The real-world effectiveness of PCSK9i was assessed by evaluating relative reductions in LDL-C and non-HDL-C within three months of initiation, along with the proportion meeting lipid targets based on the 2021 Middle East consensus. The analysis was performed for overall PCSK9is, followed by subgroup analysis of each PCSK9i agent. The linear mixed-effects model (LMM) was applied to identify factors associated with lipid reduction in both LDL-C and non-HDL-C levels.

Results:

Utilisation and expenditure trends of lipid-lowering therapies supplied by the CMS (2012–2022)

At the national level, the study demonstrated a significant overall increase in the utilisation and expenditure trends of all studied LLTs. Utilisation, measured by NSU/TIY, rose from 138,549 in 2012 to 210,388 in 2022 (52%, n = 71,839), while DDD/TID increased from 52.4 in 2012 to 114.6 in 2022 (119%, n = 62.2). Similarly, expenditure, measured by CSU/TIY, grew from 22,534 in 2012 to 53,161 in 2022 (136%, n = 30,627). Statins were the primary drivers of the observed increases in both utilisation and expenditure across all years. A comparison between PHCCs and hospitals revealed contrasting trends in the NSU/TIY for overall LLT utilisation, which increased in PHCCs but decreased in hospitals. In contrast, the DDD/TID showed an upward trend in both settings. In terms of regional variation, the six governorates exhibited generally similar upward trends in LLT utilisation and expenditure, with the one governorate showing the highest levels among all metrics.

Utilisation patterns and quality of lipid control among patients prescribed LLTs in PHCCs

The study included 434 patients, with a mean age of 54.3±9.7 years and a comparable distribution between males and females. Most participants attending PHCCs were prescribed monotherapy lipid-lowering regimens (88.7%, n= 385/434). Statins were the most frequently utilised LLT (98.8%, n= 429/434). Among statin users, simvastatin was the most frequently prescribed agent. Moreover, CV risk stratification demonstrated that the largest proportion of patients were classified as having extreme CV risk category, accounting for 36.3% (n= 122/336). Lipid target attainment was suboptimal across all CV risk categories, with only 20.4% (n= 65/318) and 26.6% (n= 84/316) of patients achieving LDL-C and non-HDL-C targets, respectively. Multivariate analysis revealed that individuals in lower CV risk categories significantly exhibited higher odds of achieving their respective lipid targets ($p<0.001$).

Real-world effectiveness **of PCSK9is at a tertiary cardiac care centre**

Of the 458 incident PCSK9is users, lipid data were available for effectiveness analyses in 115 patients (25.1%) for non-HDL-C and in 104 patients (22.7%) for LDL-C. The median baseline LDL-C among eligible patients (n=104) was 2.95 mmol/L (IQR: 1.96 to 3.83 mmol/L), which decreased to a median of 1.73 mmol/L (IQR: 0.76 to 2.6 mmol/L) among those with follow-up measurements (n= 84), reflecting a 41.9% reduction (95% CI: -50.9% to -24.1%, $p <0.001$) within three months of PCSK9is initiation. For non-HDL-C, the median baseline level (n=115) was 3.94 mmol/L (IQR: 2.85 to 5.16 mmol/L), which decreased to 2.38 mmol/L (IQR: 1.52 to 3.27 mmol/L) among patients with follow-up data (n= 93), corresponding to a relative reduction of 38.1% (95% CI: -46.53% to -23.88%, $p <0.001$). Lipid target attainment within three months was achieved by 43% of patients for LDL-C <1.4 mmol/L and by 45% for non-HDL-C <2.2 mmol/L.

Subgroup analyses indicated that evolocumab was associated with greater percentage reductions than alirocumab for both LDL-C (45.7% vs. 37.1%) and non-HDL-C (40.7% vs. 30.1%). However, the differences between these two agents were not statistically significant. The adjusted LMM confirmed significant reductions in both LDL-C and non-HDL-C following PCSK9i initiation, independent of PCSK9i agent type.

Conclusion:

Over the past decade, the utilisation and expenditure of LLTs in Kuwait have increased substantially. Statin remain the cornerstone of treatment, reflecting their continued role as first-line therapy. Expenditure trends closely mirrored utilisation patterns, with a notable rise following PCSK9i introduction. Despite the widespread use of statins in PHCCs, lipid control remains suboptimal, particularly among patients at extreme CV risk. While PCSK9is achieved significant lipid reductions, the extent of these reductions did not fully replicate those reported in clinical trials (~60%).

These findings highlight the urgent need for targeted interventions to optimise lipid management through the implementation of evidence-based LLT regimens. Such interventions are essential to narrow the gap between routine clinical practice and guideline recommendations. This thesis provides important insights for policy makers on strengthening the integration of comprehensive patient-level data within electronic health records, and for clinical practitioners on the importance of optimising LLT use and adhering to clinical guidelines to promote rational prescribing and improve dyslipidaemia management.

Chapter 1. Background

This chapter reviews the literature on the utilisation patterns of lipid-lowering therapies (LLTs) and the quality of lipid control, with the aim of identifying research gaps relevant to the Kuwait context. The chapter begins with a brief overview of non-communicable diseases (NCDs), which encompass cardiovascular diseases (CVDs) as a major subgroup. The chapter then examines the key factors that contribute to increased cardiovascular (CV) risk, with a particular emphasis on dyslipidaemia. Dyslipidaemia is then explored in detail, covering its definition, classification, and the pharmacological management options through LLTs. Subsequently, the chapter outlines LLT utilisation patterns using a funnel approach, starting from global trends, narrowing to the Middle East, and finally focusing on Kuwait. Additionally, the extent to which lipid targets are achieved in relation to the corresponding CV risk categories is examined. Moreover, the chapter provides an overview of the governmental healthcare system in Kuwait and the distribution of relevant healthcare facilities, given the national scope of this study. Finally, this chapter introduces the research questions and outlines the aim and objectives of this PhD thesis.

1.1. Non-communicable diseases overview

NCDs, also referred to as chronic diseases, are long-term conditions that are not caused by infectious agents (6). In 2021, NCDs accounted for 43 million deaths worldwide, representing 75% of all non-pandemic-related mortality (6). NCDs pose a major and increasingly urgent challenge to global health, threatening progress towards the 2030 Agenda for Sustainable Development Goals (SDGs). This agenda includes a specific target to reduce the probability of premature death from the four main NCDs among individuals aged 30 to 70 years by one third by 2030. These four conditions include CVDs, cancers, chronic respiratory diseases, and diabetes (6). Among NCDs, CVDs are the leading cause of NCD-related mortality, accounting for at least 19 million deaths globally in 2021 (6).

The burden of CVDs also remains the leading cause of mortality and morbidity in the Middle East and North Africa (MENA) region. However, a recent study using data from the 2021 Global Burden of Disease (GBD), covering a 31-year period (1991-2021), across 21 countries, including Kuwait, suggests that healthcare system in the region have shown resilience in responding to the CVD burden (7). The findings revealed that although the number of new CVD cases (incidence, referring to newly occurring cases within a defined period) has increased, the overall age-standardised incidence rate, which adjusts for differences in age distributions between populations) has slightly declined. Similarly, while the number of deaths due to CVD has risen, the age-standardised mortality rate has decreased, reflecting possible progress in healthcare system and improvements in population-level CVD management. The study primarily attributed the increase in total cases to population growth and ageing (7).

That study (7) also reported that Kuwait, as a high-income country (HIC), demonstrated a lower measured burden of CVD, in terms of fewer death and lower overall disability, relative to several other countries in the region (7). This was interpreted as a reflection of better disease control or lower CVD incidence. However, the progress in Kuwait in reducing the age-standardised burden of CVD over the past three decades was modest, which could be due to the high prevalence of key modifiable risk factors, particularly high systolic blood pressure (BP), unhealthy diet, and elevated low-density lipoprotein cholesterol (LDL-C). These findings could highlight the urgent need for targeted lifestyle interventions, improved access to healthcare, or optimisation of pharmacological therapies.

Recent data from the Kuwaiti Central Statistics Bureau, in collaboration with the National Centre for Health Information in the Ministry of Health (MOH), revealed a declining trend in the overall mortality rate from 87.27 per 100,000 inhabitants in 2020 to 67.75 per 100,000 inhabitants in 2023, across all nationalities (8, 9).

Nevertheless, the mortality rate attributed to CVDs in Kuwait remains alarmingly high compared to other diseases (9). Further details on NCDs in the MENA region, including the Gulf countries, are presented in **Appendix S1.1.**

Building on the review of NCDs and CVD risk factors in the MENA region, the following section focuses on one of the key cardiometabolic risk factors that contribute to CVDs: dyslipidaemia. This condition is significantly influenced by behavioural risk factors, including tobacco use, unhealthy dietary patterns, and sedentary lifestyle, and is also highly associated with diabetes, all of which are prevalent in the region and further exacerbate the CVD burden (10).

1.2. Dyslipidaemia overview

1.2.1. Definition and classifications

Dyslipidaemia is a chronic metabolic disorder characterised by abnormal levels of plasma lipids, including elevated total cholesterol (TC), LDL-C, and triglycerides (TGs), as well as reduced levels of high-density lipoprotein cholesterol (HDL-C), or a combination of these abnormalities (10). To support understanding of the classification and aetiology of dyslipidaemia, a brief overview of lipids and lipoproteins is presented first.

Lipids represent one of the four main classes of biological molecules in the human body, alongside carbohydrates, proteins, and nucleic acids. Lipids comprise several subclasses, including sterols, TGs, and fatty acids. Among these, cholesterol, a type of sterol, is essential for the synthesis of steroid hormones, the formation of cellular membranes, the production of bile acids, and the transport of fat-soluble vitamins such as vitamin D (11). TGs, on the other hand, serve as a major form of energy storage and can also be metabolised to generate energy (11). Additionally, large quantities of dietary fatty acids must be transported in the form of TGs to prevent toxicity associated with circulating free fatty acids (12).

Because lipids are hydrophobic, they cannot circulate freely in the aqueous environment of the bloodstream. To exert their physiological function, they require transport via protein-lipid complexes known as lipoproteins (12). Understanding the structure and function of lipoproteins is essential, as they act as important biomarkers for CV risk and are involved in the pathogenesis, diagnosis, and management of CVDs (11). The lipoprotein structure is presented in **Appendix S1.2.**

Plasma lipoproteins are divided into seven classes: chylomicrons, chylomicrons remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, HDL, and lipoprotein (a) [Lp (a)]. These classes differ in particle size, lipid content, and apolipoprotein type. A detailed comparison of their characteristics is provided in **Appendix S1.3**; however, only lipoproteins (LDL and HDL) relevant to this research are presented here in the main text.

LDL particles are the primary cholesterol carriers in the bloodstream and are generated from VLDL and IDL metabolism (12). They comprise a spectrum of particles that differ in size and density. Notably, small dense LDL (sdLDL) particles, often seen in individuals with hypertriglyceridaemia, low HDL levels, obesity, and type 2 diabetes mellitus (T2DM), are considered highly atherogenic. This is due to their reduced affinity for LDL receptors (LDLRs), increased arterial wall penetration, and heightened susceptibility to oxidation (12).The fundamental role of LDLRs in lipid uptake was discovered by Brown and Goldstein in 1985, a discovery that was later recognised with the Nobel Prize (13).

Further evidence from the Cholesterol Treatment Trialists' (CTT) Collaboration demonstrated a direct relationship between the extent of LDL-C reduction and reduction in CV event risk (14). In a large meta-analysis of individual participant data from over 170,000 participants across 26 randomised controlled trials (RCTs), the CTT demonstrated that greater absolute reductions in LDL-C were consistently associated with greater reduction in CV morbidity and mortality (14). The CTT found that each 1

mmol/L reduction in LDL-C achieved through statin therapy corresponded to an approximate 20% (one-fifth) decrease in the risk of major vascular events. Mendelian randomisation studies further support the long-term benefits of LDL-C reduction, showing that sustained exposure to lower LDL-C levels offers greater protection against CV events than short-term reductions (15, 16). Elevated LDL-C is therefore recognised as an independent predictor of atherosclerotic cardiovascular disease (ASCVD) (17, 18).

In contrast, HDL are enriched in cholesterol and phospholipids and play a vital role in reverse cholesterol transport, returning excess cholesterol from peripheral tissues to the liver. HDL particles also possess anti-oxidant, anti-inflammatory, and anti-thrombotic properties, all of which may contribute to their protective, anti-atherogenic effects (12). Indeed, HDL-C levels have been shown to be an independent, inverse predictor of ASCVD risk (19). However, despite this association, clinical trials have not provided conclusive evidence that raising HDL-C levels alone reduces ASCVD risk (20).

Building on the understanding of LDL and HDL particles, another well recognised marker of atherogenic risk, in addition to LDL-C, is non-HDL-C. Non-HDL-C encompasses all atherogenic apolipoprotein B-containing lipoproteins, including VLDL, IDL, LDL, and Lp (a), while excluding HDL. Non-HDL-C is calculated by subtracting HDL-C from TC, thereby providing a more comprehensive indicator of overall atherogenic burden than LDL-C alone (21). This marker is particularly relevant in individuals with elevated TGs or insulin resistance, in whom LDL-C levels may appear normal and thus underestimate CV risk (21).

A meta-analysis conducted by Robinson et al. (2009) demonstrated that reductions in non-HDL-C levels were significantly associated with lower coronary heart disease (CHD) risk, reflecting an approximately 1:1 relationship between non-HDL-C and risk reduction (22). International guidelines, including ESC/EAS and AHA/ACC (23, 24) endorse non-HDL-C as a secondary target alongside LDL-C. However, in the Middle East consensus, non-HDL-C is recommended as a co-primary lipid target due to the high prevalence of hypertriglyceridemia, T2DM, and metabolic syndrome (MetS) in the region (20). In such populations, non-HDL-C is more accurate estimate for ASCVD risk than LDL-C alone (20). Its importance is valuable in detecting residual CV risk in patients who have already reached LDL-C goals.

Building on the structural and functional characteristics of lipoproteins, dyslipidaemia can be classified as either primary or secondary according to the underlying cause. Primary dyslipidaemia is typically inherited and results from single or multiple gene mutations, often manifesting at any early age. It arises from abnormalities in lipid metabolism, including overproduction or impaired clearance of TGs and LDL-C, or the underproduction or excessive clearance of HDL-C (25, 26). A well-recognised form of primary dyslipidaemia is familial hypercholesterolaemia (FH), which is a genetic disorder characterised by lifelong elevated LDL-C levels. individuals with FH are at high risk of premature ASCVD and early mortality (27-29). Most cases are due to mutations in the LDLR gene, while others result from defects in the ApoB gene or the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene. FH exists in two forms: heterozygous FH (HeFH) and homozygous FH (HoFH). HeFH is the more common form, affecting approximately 1 in 250 to 1 in 500 individuals, whereas HoFH is much rarer, with an estimated prevalence of 1 in 160,000 to 1 in 300,000 individuals (27-29). In the Middle East, the prevalence of both forms is believed to be higher than global averages, likely due to the high rates of consanguineous marriages (30, 31). Alhabib et al. (2021) used data from the Gulf FH registry, which included 34,366 participants, estimating an FH prevalence of 0.9% (1 in 112), approximately three times higher than the global average (32).

Secondary dyslipidaemia (acquired), on the other hand, is the most common aetiology and is caused by predisposing factor not directly linked to genetics. It is often associated with conditions such as T2DM, obesity, sedentary lifestyle, and smoking (25). Additionally, certain medical conditions, including hypothyroidism, and nephrotic syndrome, as well as the use of certain medications, such as steroids, antiretroviral (anti-HIV) drugs, thiazide diuretics, and *β*-blockers can contribute to lipid abnormalities (25). Secondary dyslipidaemia is also highly prevalent in the Middle East region. In Kuwait, the substantial burden of T2DM and obesity further exacerbates dyslipidaemia and associated CV risk. According to the NCD-RisC, the age-standardised prevalence of T2DM among adults (≥18 years) in Kuwait was 23%-24% in females and 27%-28% for males between 2002 and 2022 (33). Additionally, data from the WHO show that the age-standardised prevalence of obesity (body mass index (BMI) ≥30) among adults in Kuwait was 41% between 2012 and 2022 (34). The CEPHEUS study, a multicentre survey in the Gulf region, including Kuwait, highlighted the interplay between obesity, diabetes, and dyslipidaemia (35). Among diabetic patients (n= 3,336), the average BMI was 32 kg/m², with 55% classified as obese. Furthermore, 76% had MetS, and 83% were categorised as having very-high ASCVD risk. Given these high rates, it is essential to understand the mechanisms by which T2DM and obesity contribute to dyslipidaemia, as outlined in **Appendix S1.4**.

Moreover, Hypertension (HTN) frequently coexists with lipid disorders, with an age-standardised prevalence of 41% among adults aged 30–79 years in Kuwait (2012-2019) (34). Smoking is another significant risk factor that exacerbates dyslipidaemia by increasing circulating LDL-C concentrations and promoting LDL oxidation, a key process in atherosclerosis and plaque formation. According to WHO data, the age-standardised prevalence of tobacco smoking among individuals aged ≥15 years in Kuwait was 20% (2015-2022) (34). Additionally, sedentary behaviour significantly contributes to these risks. The Global Obesity Observatory documented that 63% of adults in Kuwait (≥18 years) had insufficient physical activity in 2022 (36).

1.2.2. Epidemiology of dyslipidaemia and CV risk estimation

Dyslipidaemia is a major and growing public health concern in the Middle East region. A systematic review and meta-analysis of studies published between 2000 and 2021 reported a substantial and increasing burden of dyslipidaemia over the two decades (37). The analysis included three studies from Kuwait, conducted in 2006, 2011, and 2012, with a combined sample of 1880 patients (37). The overall prevalence of dyslipidaemia was 54.08% (95% CI: 43.83–66.71), based on criteria from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) or WHO. The prevalence of individual lipid abnormalities was also high. Elevated LDL-C was reported in 32.09% (95% CI: 22.17–42.01), hypertriglyceridaemia in 32.51% (95% CI: 28.59–36.43), hypercholesterolaemia in 29.44% (95% CI: 18.74–40.13), and low HDL-C levels in 44.71% (95% CI: 37.86–51.57) of participants (37). Notably, these earlier studies used relatively high LDL-C thresholds (>4.1 mmol/L or ≥3.35 mmol/L) compared with the current 2019 ESC/EAS guidelines (23). Recent recommendations advocate stratifying LDL-C targets according to CV risk category. Specifically, an LDL-C target of <1.4 mmol/L is recommended for patients with established ASCVD (secondary prevention) and for those at very-high CV risk in primary prevention (23).

Therefore, the use of validated CV risk calculators enables the tailored identification of individuals into appropriate CV risk categories. This, in turn, guides the selection of lipid targets required to achieve effective risk reduction. Risk prediction tools play a vital role in optimising primary prevention strategies (individuals without established CVD), allowing for appropriate initiation and intensification of LLTs (38). The 2019 ESC/EAS guidelines endorse the use of the Systematic Coronary Risk Estimation (SCORE) system to calculate the 10-year risk of fatal CVD events (23). In the Middle East region, a consensus on the management of dyslipidaemia has been developed by a panel of regional experts, drawing upon the latest international guidelines (ESC/EAS and AHA/ACC) and region-specific epidemiological evidence (20), adapted a risk classification system tailored to the Middle East population.

The Middle East consensus advocated the use of the QRISK2 scoring system (20); however, a more recent version, QRISK3, is available at the time of this research. Unlike SCORE, which estimates the 10-year risk of CV mortality, QRISK3 estimates the 10-year risk of both fatal and non-fatal CV events (38). QRISK3 also incorporates a broader range of risk factors, including ethnicity, chronic kidney disease (CKD), diabetes type, and socio-economic status, making it potentially more suitable for classifying CV risk among individuals in the Middle East region. **Table 1.1** presents a summary of the key features of these two CV risk prediction tools, adapted from Sofogianni et al (2022) (38).

Table 1.1 Key characteristics of SCORE and QRISK3 risk prediction equations (38)

Risk Equation	**Parameters Used to Estimate Risk**	**Predicted Outcome**
Systematic Coronary Risk Evaluation (SCORE)	Age, sex, SBP, TC and smoking status	10-year risk of cardiovascular mortality
QRISK3 score	Age, sex, SBP, TC/HDL-C ratio, T2DM, smoking status, ethnicity, social deprivation, body mass index, family history of CHD in a first-degree relative younger than 60 years, treated hypertension, rheumatoid arthritis, atrial fibrillation, stage 4 or 5 chronic kidney disease, migraine, corticosteroid use, systemic lupus erythematosus, treatment with atypical antipsychotic medications, severe mental illness, erectile dysfunction and variability of blood pressure	10-year risk of cardiovascular events

SBP: Systolic blood pressure; **TC**: Total cholesterol; **HDL-C**: High-density lipoprotein cholesterol; **T2DM**: Type 2 diabetes mellitus; **CHD**: Coronary heart disease

Given that Kuwait is part of the Middle East region, the studies of this thesis adopted the CV risk classification recommended in the Middle East consensus, utilising the QRISK3 scoring system. The Middle East consensus stratifies patients into five CV risk categories: extreme, very high, high, moderate, and low risk, compared to the four categories (very high, high, moderate, low) outlined in the 2019 ESC/EAS guidelines. Details for defining each CV risk category in both recommendations are provided in **Appendix S1.5**.

Each risk category is associated with specific LDL-C target thresholds. Both 2019 ESC/EAS and 2021 Middle East statement identify LDL-C as the primary lipid target. However, the Middle East consensus additionally recommends non-HDL-C as a co-primary target, given its strong predictive value for ASCVD (21). Notably, the LDL-C thresholds are largely consistent across the two guidelines, with the most intensive target set at <1.4 mmol/L, followed by 1.8, 2.6, and 3.4 mmol/L, according to the CV risk category. In the Middle East consensus, the very-high and high CV risk categories share the same targets, which accounts for the four threshold levels overall. The corresponding non-HDL-C targets are defined at 0.8 mmol/L higher than the respective LDL-C thresholds for each risk category. The primary lipid targets outlined in the 2021 Middle East consensus are presented in **Table 1.2**.

Table 1.2 Middle East primary lipid targets for LDL-C and non-HDL-C (20)

CV Risk category	LDL-C	non-HDL-C
Extreme	≥50% LDL-C reduction from baseline and LDL-C goal of <1.4 mmol/L (<55 mg/dL)	<85 mg/dL (<2.2 mmol/L)
Very high	≥50% LDL-C reduction from baseline and LDL-C goal of <1.8 mmol/L (<70 mg/dL)	<100 mg/dL (<2.6 mmol/L)
High	LDL-C goal of <1.8 mmol/L (<70 mg/dL)	<100 mg/dL (<2.6 mmol/L)
Moderate	LDL-C goal of <2.6 mmol/L (<100 mg/dL)	<130 mg/dL (<3.4 mmol/L)
Low	LDL-C goal of <3.4 mmol/L (<130 mg/dL)	<160 mg/dL (<4.2 mmol/L)

CV: Cardiovascular; **LDL-C**: Low-density lipoprotein cholesterol; **non-HDL-C**: Non-high-density lipoprotein cholesterol

Dyslipidaemia is a significant risk factor for the development of ASCVD, and medications that target lipoproteins are fundamental in lowering lipid levels and reducing CV risk. The following section outlines the LLTs primarily targeting LDL-C, based on those available in Kuwait during the period of this research.

1.2.3. Pharmacological management of dyslipidaemia

1.2.3.1 Statins

Over the years, the evolution of clinical guidelines has consistently reinforced the role of statins as the cornerstone of LLTs, demonstrating proven efficacy in improving CV outcomes in both primary and secondary prevention (23). Landmark secondary prevention trials include the 4S (Scandinavian, Simvastatin, Survival Study, 1994) (39) and PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection therapy, 2004) (40), while primary prevention trials such as WOSCOPS (West of Scotland Coronary Prevention Study, 1995) (41) and JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, 2008) (42) expanded statin eligibility to broader populations. The CTT Collaboration meta-analysis further shaped clinical guidelines for both primary and secondary prevention of CVDs (14, 18). Beyond their lipid-lowering capabilities, statins exhibit pleiotropic effects, including anti-inflammatory and antioxidant properties (23). Pharmacologically, statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis. This inhibition lowers intracellular cholesterol levels, which upregulates LDLR expression on hepatocytes and enhances the clearance of circulating LDL-C particles. In turn, plasma concentrations of LDL-C and other ApoB-containing lipoproteins, including triglyceride-rich lipoproteins, are reduced. The degree of LDL-C reduction is dose-dependent as high-intensity statin therapy (HIST) is defined as more than 50% reduction while moderate-intensity statin therapy (MIST) reduced LDL-C by 30%-49% (20, 24), acknowledging interindividual variation with the same dose. **Table 1.3** presents examples of statin agents and their respective intensity classification, adapted from the Middle East consensus (20), which incorporated recommendations from the 2018 ACC/AHA guidelines (24).

The four statins listed were selected because they were available in Kuwait during the periods covered by the studies included in this thesis.

Table 1.3 Classification of statin intensity by expected LDL-C reduction, based on the available strengths at the time of this study, adapted from the 2021 Middle East consensus (20)

Statins	High-Intensity Lowers LDL-C by ≥50%	Moderate-Intensity Lowers LDL-C by 30% to 49%
Atorvastatin	40mg	10mg – 20mg
Rosuvastatin	20mg	10mg
Simvastatin	-	20mg – 40mg
Pitavastatin	-	2mg – 4mg

LDL-C: Low-density lipoprotein cholesterol

Further details on statins, including their adverse effects and intolerance, are provided in **Appendix S1.6.** Additional or alternative treatments may be necessary in cases of statin intolerance or when LDL-C targets cannot be achieved with statin therapy alone. In such situations, non-statin LLTs play an important role. These include ezetimibe and PCSK9 inhibitors (PCSK9is). Fibrates are also discussed as the traditional LLT lowering TGs.

1.2.3.2. Cholesterol absorption inhibitor (Ezetimibe)

Ezetimibe, the only available cholesterol absorption inhibitor, is referred to by its agent name rather than by its class name throughout this research. Ezetimibe is recommended as the initial non-statin therapy, either in combination with statins when LDL-C targets are not achieved, or as an alternative in cases of statin intolerance (23). However, concerns have been raised regarding the use of ezetimibe due to its high cost and the initially limited evidence for improving CV outcomes. The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis Regression) trial, published in 2008, showed a greater LDL-C reduction with no significant difference in CV event (43). This uncertainty was addressed in 2015, when the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study demonstrated a 6.4% reduction in CV events with the addition of ezetimibe to simvastatin therapy in patients following an acute coronary syndrome

(ACS) (44). Subsequent guidelines, such as the 2016 and 2019 ESC/EAS and 2018 AHA/ACC, translated this into a recommendation for add-on to statins for patients needing aggressive LDL-C lowering (23, 24, 45). Ezetimibe lowers LDL-C levels by inhibiting the Niemann-Pick C1-like 1 (NPC1L1) protein in the upper small intestine, thereby reducing intestinal cholesterol absorption (10). This leads to decreased hepatic cholesterol stores and increased clearance of circulating cholesterol. As monotherapy, ezetimibe reduces LDL-C by approximately 15–22%. When added to statin therapy, it produces an additional LDL-C reduction of 21–27% compared to placebo in patients with hypercholesterolaemia, with or without established CHD. Notably, statin-ezetimibe combination therapy achieves greater reductions in LDL-C than simply doubling the statin dose (23).

1.2.3.3. PCSK9is

In 2003, Dr Nabil Seidah identified the role of PCSK9, a discovery that paved the way for the development of PCSK9is (46). PCSK9 is a plasma protein that binds to LDLRs on the surface of hepatocytes, stimulating endocytosis and lysosomal degradation of LDLR (10). This process reduces the availability of LDLRs, thereby limiting the clearance of LDL particles from the bloodstream and increasing circulating LDL-C levels. Additionally, PCSK9 has been implicated in the regulation of ApoB-containing lipoprotein metabolism, including effects on VLDL secretion, and has been shown to promote endothelial inflammation (10).

PCSK9is are the first LLT class to be introduced for subcutaneous (SC) administration. They are fully human monoclonal antibodies that bind circulating PCSK9 and prevent its interaction with hepatic LDLRs. By blocking this interaction, PCSK9is preserve LDLR integrity and increase receptor recycling, thereby enhancing the clearance of LDL-C from the blood (47, 48). The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved PCSK9is in 2015 (49), representing a significant advancement in LLTs.

PCSK9is achieve profound lipid reductions, including approximately 60% reduction in LDL-C, 50% in non-HDL-C, and 9–17% in TGs, as demonstrated in the OSLER trial for evolocumab (50) and the ODYSSEY LONG TERM trial for alirocumab (51). PCSK9is also reduce ApoB and Lp (a), both of which are associated with residual CV (52). The two currently approved PCSK9is, namely evolocumab (Repatha®) and alirocumab (Praluent®), were initially licensed as adjuncts to diet and maximally tolerated statin therapy, referring to the highest statin dose that can be maintained without unacceptable side effects, in adults with HeFH or clinical ASCVD requiring further LDL-C reduction (23). Evolocumab has also been indicated for use in patients with HoFH, although its LDL-C lowering efficacy is more limited (≈30%) due to minimal LDLR activity in these patients (53).

The CV benefits of PCSK9is were confirmed by two pivotal outcome trials: the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial for evolocumab (2017) and ODYSSEY OUTCOMES trial for alirocumab (2018). Both trials demonstrated a 15% reduction in major adverse cardiovascular events (MACE), reinforcing the principle that "the lower, the better" with respect to LDL-C levels (54, 55). **Appendix 1.7** shows a brief summary of these two trials.

These findings have informed recent clinical guidelines, such as the 2018 AHA/ACC and 2019 ESC/EAS recommendations, which advocate the use of PCSK9is in patients who fail to achieve LDL-C goals despite maximally tolerated statins therapy, with or without ezetimibe (23). Additionally, PCSK9is are recommended for patients with FH, as these individuals often require more stringent LDL-C targets that are difficult to achieve with the standard LLTs alone. LDL-C targets for FH are <1.8 mmol/L in the absence of established ASCVD and <1.4 mmol/L in those with ASCVD or additional high-risk factors (23). Notably, since statins are known to upregulate circulating PCSK9 levels, combination therapy with PCSK9is is often recommended to achieve optimal lipid reduction (23).

Although PCSK9is significantly reduced MACE, their impact on CV mortality remains inconclusive. In the FOURIER trial, evolocumab did not reduce the risk of CV death (Hazard Ratio: 1.05, 95% CI 0.88–1.25) or all-cause mortality (23). While the ODYSSEY OUTCOMES trial reported a reduction in all-cause mortality with alirocumab, this was an exploratory finding and not accompanied by a significant reduction in CV death (56). In terms of safety, PCSK9is have shown a favourable tolerability profile. The most commonly reported adverse events include nasopharyngitis and injection-site reactions. Concerns have been previously raised regarding the potential impact of achieving very low LDL-C levels on cognitive function. However, the EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) study, which evaluated cognitive outcomes among patients receiving evolocumab, reported no evidence of neurocognitive decline (56). Nevertheless, the long-term safety of PCSK9is remains limited.

1.2.3.4. Fibrates

Fibrates are among the older classes of LLTs and are primarily intended for the reduction of TG levels rather than LDL-C. They act as agonists of peroxisome proliferator-activated receptors (PPARs), with a particular affinity for PPARα. Activation of PPARα initiates a cascade of metabolic effects that contribute to a significant decrease in plasma TG levels and a modest increase in HDL-C. Fibrates may be particularly beneficial when added to statin therapy in patients with T2DM who have elevated TG and low HDL-C levels (57). This was supported by findings from the ACCORD-Lipid trial, in which a subgroup of participants with marked hypertriglyceridaemia and low HDL-C experienced a 31% reduction in CV event rates when treated with combination therapy of statin and fibrate, compared with statin monotherapy (58).

With the evolution of clinical guidelines and ongoing advancements in LLTs, it is essential to examine global and regional utilisation patterns and trends of LLTs over time. Such analysis provides insights into the extent to which real-world prescribing practices align with evidence-based recommendations. In parallel, evaluating the quality of lipid control in relation to CV risk is crucial, as effective lipid reduction plays a key role in preventing both the onset and recurrence of CV events. Before addressing these aspects, a brief overview of drug utilisation research (DUR) approaches is provided, followed by a review of real-world studies on LLT prescribing patterns and the quality of lipid control, with the aim of identifying research gaps within Kuwait context.

1.3. Drug Utilisation Research (DUR)

DUR is crucial in understanding and optimising the use of medicines in real-world settings. According to the EuroDURG community, DUR is defined as "quantitative and qualitative studies to describe, evaluate, understand, and improve the use of medicines" (59). DUR is a broad field of research that often overlaps with other scientific disciplines, particularly pharmacoepidemiology (59). Over time, the distinction between the two fields has diminished, and the terms are sometimes used interchangeably (59). However, some differences exist in that pharmacoepidemiology is defined as the study of the utilisation and effects of drugs in large populations, whereas DUR focuses more on evaluating the benefits and risks of medicines, typically using data sources such as prescribing databases. Furthermore, DUR often relies on various sources of information focusing on drugs, such as prescription registries, while pharmacoepidemiological studies are more population-based, linking health events to drug exposure (59). The main aim of DUR is to promote the safe and effective use of medicines across different populations (59).

To undertake such research on a large scale, the use of real-world data (RWD) is essential in generating real-world evidence. The FDA defines RWD as “data related to patient health status and/or the delivery of care, routinely collected from a variety of sources” (60). These include electronic health records (EHRs), medical claims data, disease registries, and data from digital health technologies (60), as well as insurance data and administrative records. Real-world evidence, in turn, is defined by the FDA as “clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD” (60). Real-world evidence offers valuable insights by characterising health conditions, interventions, and patient outcomes. Additionally, real-world evidence helps to evaluate medication safety and effectiveness, and is instrumental in identifying and addressing health disparities and access issues within populations (61).

While RCTs remain the gold standard for establishing the efficacy and safety of interventions due to their ability to minimise bias and confounding, they have some limitations. RCTs are conducted in controlled settings, involve selective patient populations, and often have strict eligibility criteria, which limits their generalisability to broader patient groups. Moreover, they may be impractical in certain cases, such as when randomisation would be unethical, funding is constrained, follow-up is limited, or when studying rare diseases (61)

This is where real-world studies become particularly valuable. RWD can fill evidence gaps by informing healthcare policies and enhancing the quality use of medicines. RWD is especially useful in post-marketing surveillance, effectiveness studies, treatment pattern evaluation, and the assessment of disease prevalence and incidence. However, RWD should not be used as a substitute for RCTs. Instead, it should be applied appropriately by ensuring the use of high-quality, reliable, and fit-for-purpose data, while maintaining methodological rigour and addressing potential sources of bias (61, 62).

DUR studies can be broadly categorised into descriptive and analytical types. Descriptive studies quantify patterns of medicine use within a population over time, evaluate prescribing trends, and compare these patterns across different countries or against existing clinical guidelines (59). Furthermore, these studies assess the real-world effectiveness of newly introduced drugs and evaluate their associated healthcare expenditures. On the other hand, analytical studies explore the underlying factors that influence prescribing behaviour or treatment outcomes, and may help predict future trends in medicine use (59). In addition to quantitative methods, qualitative study designs are also important in DUR. Qualitative studies explore the perceptions, attitudes, and behaviours of prescribers and patients to provide a deeper understanding of medication use (59).

Reviewing both descriptive and analytical studies helps identify research gaps that can be addressed to strengthen and expand the existing evidence base. Within the scope of LLTs, two main research gaps have been identified in Kuwaiti healthcare settings: utilisation patterns and trends of LLTs and quality of lipid control.

1.3.1. Utilisation patterns and trends of LLTs

With the evolution of dyslipidaemia management guidelines and the introduction of newer LLTs, numerous DUR studies have examined utilisation trends, prescribing patterns, and associated expenditure across countries. These studies have employed both aggregate-level data (63, 64) and patient-level data (65-67), allowing for comprehensive description of utilisation patterns and facilitating cross-national comparisons (CNCs) between HICs and low- and middle-income countries (LMICs).

Globally, the utilisation of LLTs has increased, with statins remaining the dominant class (63). For non-statin therapies, including ezetimibe and PCSK9is, RWD show rising but still modest utilisation (63). In particular, the use of PCSK9is remains limited, largely due to cost considerations and restrictions to high-risk populations (66-68). CNCs showed marked disparities in LLT utilisation. For instance, the Republic

of Srpska, a low-income country (LIC), reported a 167.7% increase in LLT utilisation, yet LLTs accounted for the smallest share of total CVD medications, compared with HICs, suggesting potential disparities in access and financial barrier (64).

While many countries have reported national level utilisation, evidence from Gulf countries is scarce. An important exception is the multi-country study by Blais et al. (2021), which included 83 countries between 2008 and 2018 and reported a significant global rise in LLT use (63). For Gulf countries such as Kuwait, Saudi Arabia, Oman, and UAE, the authors observed a 75% increase in LLT market share, with statins as the dominant therapy. In Kuwait, LLT utilisation increased by 129% (n= 1,219) across all included therapies (statins, ezetimibe, fibrates, omega-3 fatty acids, niacin, bile acid sequestrants, and PCSK9is). However, that study captured only about 35% of the total pharmaceutical market data, lacked data from the hospital sector, and did not provide specific LLT subgroups.

Given that Kuwait is a HIC with no cost constraints on medicines, a high prevalence of CV risk factors, and guideline updates that advocate intensive lipid management with strict lipid thresholds, a national-level study is warranted to strengthen the evidence base for the Gulf and, more broadly, the MENA region. The present research addresses the gap by quantifying LLT utilisation at national level (**chapter 3**), evaluating prescribing patterns of oral LLTs across primary healthcare centres (PHCCs) (**chapter 4**), and examining dispensing patterns of PCSK9is at a hospital setting (**chapter 5**). The findings are intended to inform policymakers and clinical practice in Kuwait and to offer insights for future research locally and regionally.

1.3.2. Quality of lipid control

The continuous updates to dyslipidaemia management guidelines, with progressively stricter lipid thresholds linked to CV risk categories, have been also reflected in DUR studies. Across countries, several studies report suboptimal lipid control, particularly for LDL-C, when assessed against CV risk categories. Although most patients receive LLT, with statins as the mainstay, a substantial proportion do not achieve recommended lipid levels (69, 70). When patients are reclassified using the more stringent targets introduced by the 2019 ESC/EAS guidelines, attainment rates appear even lower (69). An earlier study (2009-2010) across the six Gulf countries evaluated both LDL-C and non-HDL-C target achievement and likewise found inadequate control (35), although the thresholds applied at that time were wider.

Despite recent guideline advancements, there remains a lack of up-to-date evidence from the Gulf countries, including Kuwait, on the extent to which target lipid goals are achieved across CV risk categories. This gap is particularly important given the integration of PCSK9is into clinical practice and their ability to reduce LDL-C by up to 60% in clinical trials. Multiple real-world studies have replicated these reductions (71, 72), including research conducted in the Gulf region, notably form Saudi Arabia and Kuwait (73). However, these Gulf studies focused exclusively on evolocumab and evaluated changes in LDL-C levels only; none examined non-HDL-C despite its recognised prognostic value in ASCVD (21).

The present research addresses these gaps in two ways. First, it evaluates the quality of lipid control by assessing attainment of guideline-recommended lipid targets across CV risk categories in PHCCs (**chapter 4**). Second, it expands the regional real-world effectiveness by assessing the effectiveness of both available PCSK9is at another tertiary cardiac centre (**chapter 5**). The two studies included five lipid parameters: LDL C, non-HDL-C, TGs, HDL-C, and TC.

Having identified key gaps that justify the need for research in Kuwait, it is important to provide an overview of the national governmental healthcare system. This includes the structure and distribution of healthcare facilities responsible for procuring, prescribing, and dispensing medications.

1.4. Healthcare system in Kuwait

The governmental healthcare system is primarily overseen by the MOH, which is responsible for the regulation and provision of healthcare services at the national level (74). Healthcare services in Kuwait are delivered through an integrated network of PHCCs and secondary and tertiary hospitals.

Kuwait is divided into six governorates: Capital (CAP), Hawalli (HAW), Al-Farwaniyah (FAR), Al-Ahmadi (AHM), Al-Jahra (JAH), and Mubarak Al-Kabeer (MBK) (**Figure 1.1**) (75). Each governorate represents a health region bearing the same name; for example, the CAP governorate comprises the CAP Health Region. Within each health region, there are several residential areas, and at least one PHCC is available per area, depending on its size and population density. Each health region is also served by one secondary-level general hospital.

In addition, there is a distinct health region located within the CAP governorate known as the Specialised Sabah Health Region. This region does not include any PHCCs, as it is administratively affiliated with the CAP Health Region. Instead, Sabah health region houses one general secondary hospital alongside multiple tertiary-level specialist centres, such as the Chest Diseases Hospital and the Maternity Hospital. These specialised centres provide services that are not typically available in other health regions, and patients from across Kuwait are referred to Al-Sabah for such advanced care.

Kuwait offers universal healthcare through the MOH, which is entirely funded by the government. Healthcare services are provided free of charge to Kuwaiti citizens and to certain eligible groups (e.g., citizens of Gulf countries, and the wives or mothers of Kuwaiti nationals). Expatriates can access governmental healthcare services upon paying an annual health insurance fee, in addition to a nominal co-payment for visits to PHCCs (~1 Kuwaiti Dinars (KWD); £2.5) and hospitals (~2 KWD; £5), at the time of this study.

The MOH centrally regulates the medication supply through the Central Medical Stores (CMS). The CMS is responsible for procuring medications, negotiating prices with pharmaceutical suppliers, and overseeing storage and distribution (76). Every healthcare setting in Kuwait, including PHCCs and hospitals, has its own pharmacy. Pharmacists at each facility assess their medication requirements, and the CMS supplies the requested medicines accordingly.

Medications within the MOH system are categorised into two main groups: the Essential Medicines List (EML) and the Complementary Medicines List (CML) (77, 78). The EML includes medications that are universally available to all patients across MOH facilities. The CML, by contrast, contains medications restricted to specific patient groups, primarily Kuwaiti nationals, although certain non-Kuwaiti groups may also be eligible. When applied to LLTs, medications such as simvastatin and fibrates (fenofibrate, bezafibrate, and gemfibrozil) are listed under the EML and are therefore accessible to all patients. In contrast, atorvastatin, rosuvastatin, pitavastatin, ezetimibe, and the PCSK9is (evolocumab and alirocumab) are classified under the CML, restricting their use to certain patient categories (77, 78). Furthermore, certain medications are exclusively distributed by CMS to hospitals (secondary or tertiary level). In the case of LLTs, PCSK9is are only available at hospitals, and not dispensed through PHCCs.

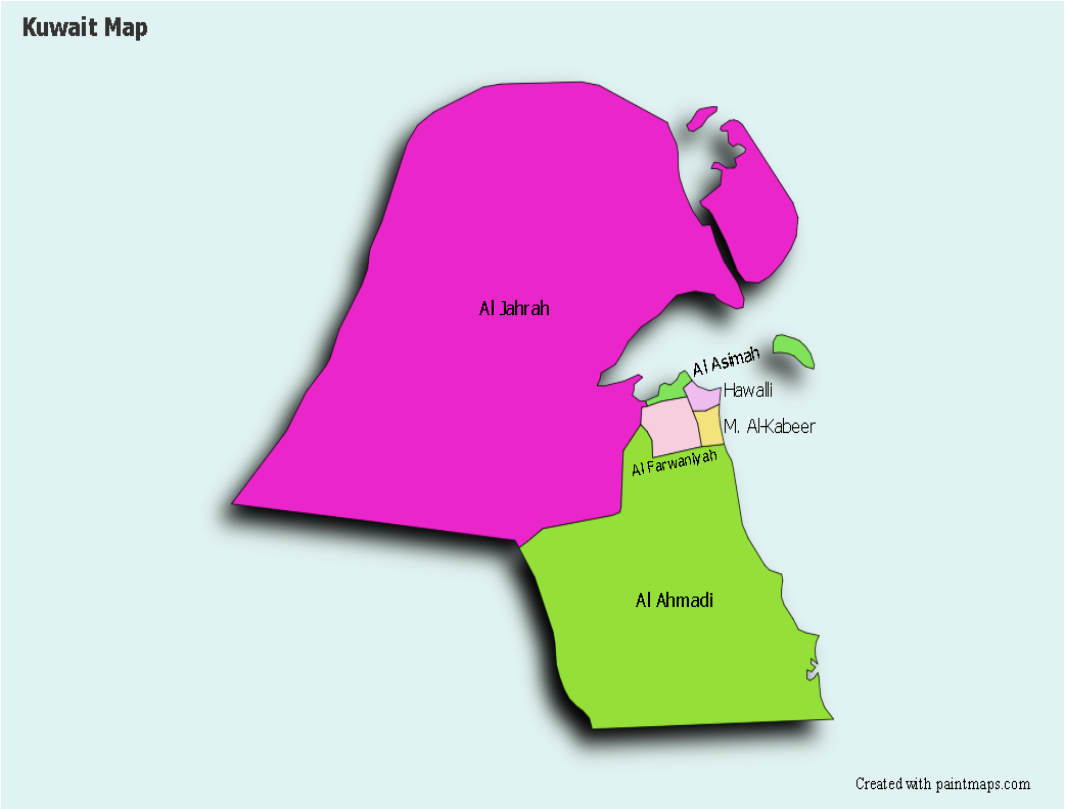

Figure 1.1 Kuwait map illustrating the six governorates. The area of Kuwait is 17,818 Km^2; Capital (Al-Asimah) is 175 Km^2; Hawalli is 85 Km^2; Al-Farwaniyah is 204 Km^2; Al-Ahmadi is 5,120 Km^2; Al-Jahra is 12,750 Km^2; and Mubarak Al-Kabeer is 104 Km^2; adapted from paintmaps.com.

1.5. Research questions (RQs)

The research focused on analysing RWD to assess utilisation and expenditure trends of LLTs, including statins, ezetimibe, fibrates, and PCSK9is, across all healthcare settings in the six governorates of Kuwait (chapter 3). In addition, the research evaluated the quality of lipid control among patients prescribing LLTs in PHCCs (chapter 4). As PCSK9is are exclusively supplied through hospitals, the thesis also included patients initiated on PCSK9is in a hospital setting to assess their real-world effectiveness in terms of extent of lipid reduction and target goal attainment (chapter 5). Thus, all three studies are employed quantitative methodologies, with different designs selected according to their respective RQs.

The RQs were categorised into three themes:

1. **Quantification of utilisation and expenditure trends (using aggregate-level CMS data):**
    a. What are the trends in the utilisation of LLT classes and their respective agents, measured by the number of supplied units and defined daily doses?
    b. What are the trends in the expenditure on LLT classes and their respective agents, measured by the cost of supplied units?
    c. Are there differences in the utilisation and expenditure trends of LLTs when stratified by PHCCs and hospitals?
    d. Are there regional variations in these trends, and how do they differ across the six governorates, if any?

2. **Utilisation patterns of LLTs (using patient-level data):**
    - What are the prescribing patterns of LLTs among patients managed at PHCCs?

3. **Quality of lipid control:**
    a. To what extent are guideline-recommended lipid targets being achieved among patients attending primary care, based on their CV risk categories?
    b. Do patients newly initiated on PCSK9is achieve reductions in LDL-C levels comparable to those reported in clinical trials?
    c. What factors are associated with lipid target achievement in PHCCs?
    d. What factors influence the change in lipid levels following the initiation PCSK9is?

1.6. Aims and objectives

This PhD thesis aimed to provide a comprehensive understanding of LLT utilisation and expenditure trends in Kuwait, with a focus on prescribing patterns and the quality of lipid control among patients treated in PHCCs and a tertiary healthcare setting.

The objectives of this research were:

- To quantify the utilisation and associated expenditure trends of LLTs supplied by the CMS across Kuwait between 2012 and 2022, using aggregate level data (**RQ1**).
- To evaluate the prescribing patterns of LLTs and examine the quality of lipid control among patients receiving LLTs therapy at PHCCs in 2023 (**RQ2, RQ3a**).
- To investigate the real-world effectiveness of PCSK9is among patients treated at a single cardiac centre between 2016 and 2022 (**RQ3b**).
- To explore the factors influencing lipid target achievement (**RQ3c**) and those associated with the changes in lipid levels following a PCSK9i (**RQ3d**).

1.7. Ethical approval

Ethical approval for the study was granted by the Assistant Undersecretary for Planning and Quality at the MOH (**Appendix S1.8**).

Chapter 2. Introduction to thesis structure

The management of dyslipidaemia has undergone significant transformation in recent decades, driven by the emergence of new therapies, evolving clinical evidence, and updates to international guidelines. Statins remain the cornerstone of lipid-lowering therapy (LLT), consistently demonstrating efficacy in reducing cardiovascular (CV) morbidity and mortality across both primary and secondary prevention cases (23). Ezetimibe, a cholesterol absorption inhibitor, was introduced as the first non-statin agent for patients with inadequate low-density lipoprotein cholesterol (LDL-C) control or in case of statin intolerance (23). However, concerns were raised due to inconclusive evidence on CV outcomes and questions surrounding its cost-effectiveness. This debate was largely resolved with the 2015 IMPROVE-IT trial, which demonstrated a 6.4% reduction in CV events when ezetimibe was added to statin therapy in post-acute coronary syndrome (ACS) patients (44). This evidence led to its inclusion in international guidelines, such as the 2016 and 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) and 2018 American Heart Association/American College of Cardiology (AHA/ACC) recommendations for patients needing further LDL-C reduction (23, 24, 45).

The therapeutic landscape advanced further with the introduction of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is). These agents, approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2015, demonstrated profound LDL-C reduction (≈60%) in major clinical trials (54, 55), and have been recommended for patients with familial hypercholesterolaemia (FH) or those failing to reach targets on maximally tolerated statin and ezetimibe therapy (23, 24). However, their high cost poses a barrier to widespread adoption.

Global data suggest an upward trend in LLT use across 83 countries between 2008 and 2018 (63), but substantial variations exist in terms of prescribing patterns, agent selection, and intensification strategies (79). These differences are often attributed to healthcare system design, economic capacity, local policy guidelines, and the time of the study (64, 80-82). Yet, little is known about how these patterns have evolved in the Gulf region, and particularly in Kuwait, where no national-level study has systematically examined LLT utilisation or associated expenditure over time. This is especially relevant following the introduction of high-cost agents such as PCSK9is. This gap is examined in detail **chapter 3**.

Dyslipidaemia, as a key modifiable risk factor for cardiovascular diseases (CVDs), should be effectively addressed through evidence-based LLTs (23). However, real-world studies globally and regionally continue to show suboptimal lipid control, especially in high-risk and very high-risk populations. While Kuwait has participated in regional studies, such as the CEPHEUS (Centralised Pan-Middle East Survey on the Undertreatment of Hypercholesterolemia study) and DYSIS (DYSlipidaemia International Study) Middle East surveys (83, 84), these were conducted over a decade ago and no longer reflect current guideline targets or treatment practices. More recent guidelines, such as the 2019 ESC/EAS (23), advocate for stricter lipid thresholds, for example LDL-C <1.4 mmol/L for very high-risk patients, and <1.0 mmol/L for selected extreme-risk cases. The 2021 Middle East consensus (20), adapted from international guidelines, introduced tailored recommendations to better reflect the regional population and clinical context. Notably, the 2021 Middle East consensus emphasised the use of non-high-density lipoprotein cholesterol (non-HDL-C) as a primary treatment target alongside LDL-C, particularly in patients with diabetes or hypertriglyceridaemia, due to its stronger predictive value for atherosclerotic CV disease in these subgroups (20). Therefore, an updated study is needed to examine the prescribing patterns of LLTs and to evaluate the quality of lipid target achievement using recommendations tailored to the region. This gap is examined in detail **chapter 4**.

In line with this evolution, combination therapy has been recommended as a first-line strategy in very high-risk patients (85). This involves concurrent use of statins and ezetimibe, followed by the addition of PCSK9-targeted agents (monoclonal antibodies or siRNA therapies) if targets remain unmet. At the time of this research, PCSK9is were the only advanced agents available in Kuwait. Because PCSK9is are relatively new, several real-world effectiveness studies have been conducted to evaluate the extent of LDL-C reduction and to compare these findings with results from clinical trials (71, 72, 86). In Kuwait, the ZERBINI study (multiZonal obsERvational study conducted By clinIcal practitioners on Repatha® (Evolocumab) use iN subjects with hyperlipIdaemia study) was conducted at a single cardiac centre and evaluated only one PCSK9i agent (73). This created an opportunity to conduct a complementary real-world effectiveness study at another tertiary cardiac centre, involving both available PCSK9i agents and thereby expanding the patient cohort to strengthen the local evidence base. Moreover, the ZERBINI study focused exclusively on LDL-C as a surrogate marker, whereas the current study allows for the evaluation of additional lipid parameters to provide a more comprehensive assessment of treatment effectiveness. This gap is examined in detail **chapter 5**.

Therefore, this PhD research was designed to comprehensively assess LLT utilisation, prescribing patterns, and lipid target attainment to address the key gaps in the literature. This thesis aimed to generate insights that support lipid optimisation strategies and demonstrate the feasibility of using routinely collected health data to evaluate medicine use and treatment outcomes across multiple governmental healthcare settings managed by Ministry of Health (MOH), Kuwait. The thesis adopts a triangulation approach, drawing on datasets from Central Medical Store (CMS), primary healthcare centres (PHCCs), and a tertiary cardiac care centre for a deeper understanding of prescribing patterns of LLTs and examining the quality of lipid control. Ultimately, the findings of this thesis are intended to inform national health policy, support clinical decision-making, and lay the groundwork for future research, which discussed in details in **chapter 6**.

The PhD research is structured into six chapters, beginning with the **background chapter (chapter 1)**. The first chapter provides a comprehensive background to the research topic and establishes the foundation for defining the research questions. Chapter 1 explores the burden of CVDs, with particular emphasis on dyslipidaemia as a modifiable risk factor. Additionally, chapter 1 includes an overview of dyslipidaemia aetiology and the lipid parameters most pertinent to defining treatment targets. A concise summary of the clinical pharmacology of LLTs is also provided. The first chapter further reviews current knowledge and practice in drug utilisation research (DUR), with a specific focus on the lipid therapeutic domain. The review gradually narrows in scope, moving from global trends to those observed in the Middle East, and finally to the local context of Kuwait. The structure of the governmental healthcare system in Kuwait is subsequently outlined to support the formulation of the research questions and justify the study rationale, followed by presentation of the overall thesis aims and objectives. Chapter 1 is followed by the present chapter, which introduces the thesis structure.

Building on the structure of the healthcare system in Kuwait, this research utilised three distinct data sources across three studies, each representing a different level of care, to develop a comprehensive understanding of LLT practices. This multi-setting approach enabled a more holistic view of how LLTs are used in real-world clinical practice and allowed the findings to be translated into meaningful insights for evidence-based decision making.

The first study, presented in **chapter 3**, comprised a longitudinal, retrospective, repeated cross-sectional analysis based on national-level data obtained from the CMS. The CMS, operating under the MOH, is responsible for the central procurement and distribution of medications across all governmental healthcare facilities in Kuwait (76). This aggregate-level dataset captured 11 years of utilisation and expenditure trends (2012–2022) for key LLT classes, including statins, ezetimibe, fibrates, and

PCSK9is. The findings revealed a steady and substantial increase in both LLT utilisation and associated spending, reflecting a growing clinical focus to lipid management.
While CMS data offered rich insights into utilisation and expenditure trends and patterns, it lacked the level of detail required to examine prescribing patterns and patient-level outcomes. To address this, a second study was conducted in PHCCs, described in **chapter 4**. A cross-sectional design was employed to assess of the extent of lipid control against clinical guideline recommendations according to CV risk categories. The findings confirmed widespread use of statins as the mainstay therapy, which aligns with current guideline recommendations. Despite this, lipid control was suboptimal, with a significant proportion of patients failing to achieve LDL-C or non-HDL-C targets. chapter 4 further explored determinants of lipid goal attainment using multivariate binomial logistic regression modelling. The analysis demonstrated that patients classified in the extreme CV risk category had significantly lower odds of achieving lipid targets.

Recent clinical guidelines have identified PCSK9is as an effective add-on therapy for patients who remain uncontrolled despite standard LLTs (statin and ezetimibe) (23). Given that PCSK9is are available exclusively in hospital settings in Kuwait, it became necessary to conduct a hospital-based study to evaluate the real-world effectiveness of PCSK9is. Therefore, **chapter 5** presents a retrospective cohort study based on the hospital pharmacy and laboratory datasets, assessing the impact of PCSK9is on lipid levels. While significant reductions in LDL-C and non-HDL-C were observed within three months of PCSK9i initiation, the relative reduction was lower than reported in clinical trials (54, 55).

Finally, **chapter 6** brings together the findings from all three studies through triangulation, integrating evidence from national utilisation data, primary care prescribing patterns, and tertiary-level lipid outcomes. Chapter 6 also discusses the broader implications for clinical practice and health policy in Kuwait, alongside key recommendations for future research.

Overall, this thesis demonstrates a multi-study, real-world investigation of LLT utilisation patterns and lipid control in clinical practice in Kuwait. By integrating diverse data sources, including population-level datasets and targeted clinical samples, the thesis offers a comprehensive and relevant contribution to the field of pharmacoepidemiology.

Chapter 3. Utilisation and expenditure patterns and trends of lipid-lowering therapies (LLTs) supplied by the Central Medical Store (CMS): a retrospective, repeated cross-sectional, population-based study

3.1. Introduction

Dyslipidaemia is a key contributor to atherosclerotic cardiovascular disease (ASCVD) and is primarily characterised by abnormal lipid concentrations in the bloodstream (87). The most common form globally involves elevated low-density lipoprotein cholesterol (LDL-C) and remnant cholesterol carried by triglyceride-rich lipoproteins (TRLs) (88). LDL-C is a well-established causal factor in ASCVD development (14, 89). Similarly, non-high-density lipoprotein cholesterol (non-HDL-C), which includes LDL-C and remnant cholesterol, is also recognised as a causal contributor to ASCVD (21). Both LDL-C and non-HDL-C have been established as key targets in lipid lowering (20, 23). In addition to LDL-C and non-HDL-C, triglycerides (TGs) play a crucial role in lipid disorders. Elevated TG levels are associated with increased CV risk and are commonly seen in metabolic syndrome (MetS) and diabetes mellitus (DM), which are highly common in Gulf regions (20, 23, 35).

Effective lipid-lowering therapies (LLTs) targeting LDL-C and TG are essential for the management of dyslipidaemia. The evolution of LLT use over time has been shaped by advances in evidence, updates to existing clinical knowledge, and the development of new medications, all of which have contributed to evidence-based clinical decision-making. LLTs included statins and non-statin therapies. Statins remain the cornerstone of LLTs, demonstrating efficacy in improving CV outcomes in both primary and secondary prevention (23). Further details on statins are provided in **chapter 2, section 2.2.3.1**. Non-statin therapies include ezetimibe (**chapter 2, section 2.2.3.2**.), proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) (**chapter 2, section 2.2.3.3.**), and fibrates (**chapter 2, section 2.2.3.4.**).

Despite advancement in dyslipidaemia management, ASCVD remains the leading cause of mortality globally, accounting for nearly 17.9 million deaths annually (87). In the Middle East, including Kuwait, CVD occurs approximately a decade earlier than in Western populations, as reported by the INTERHEART study (90). In the Gulf countries, CVD accounts for up to 45% of all mortalities (91). In Kuwait, the Central Statistical Bureau (CSB) reported that CVD remains the top cause of death, with rates increasing from 64.3 per 100,000 inhabitants in 2016 to 67.75 per 100,000 inhabitants in 2023, peaking in 2020 at 87.27 per 100,000 inhabitants (9).

To address this challenge and as dyslipidaemia is one of the modifiable risk factors, understanding the utilisation trends of LLTs over time is critical due to their importance in lipid disorder management and CVD prevention. Such trends provide insights into how evidence from clinical trials and guideline recommendations translates into real-world practice. However, to date, no studies have examined the utilisation patterns and trends of statins and non-statin therapies in Gulf countries, including Kuwait. Instead, some studies have focused on the prevalence of dyslipidaemia in the Gulf region, acknowledging variations in study time, CV risk category, and sample size. The GULF RACE-1 (2007) and GULF RACE-2 (2008-2009) prospective studies reported a dyslipidaemia prevalence of 32% (92, 93), while the Gulf COAST registry showed a prevalence of 55% among young patients in the very-high-risk category (94). Importantly, Alhabib et al. (2021), using data from the Gulf registry of 34,366 participants, estimated the prevalence of familial hypercholesterolaemia (FH) at 0.9% (approximately 1 in 112), which is nearly three times higher than the global average (32). The CEPHEUS (2014) study highlighted suboptimal LDL-C control in high-risk (52.7%) and very-high-risk (32%) categories (83), while the Kuwait STEPS survey reported an increase in the prevalence of elevated total cholesterol (TC) from 38.6% in 2006 to 55.9% in 2014 (95, 96).

Given the lack of pharmacoepidemiology evidence on LLT use in Kuwait and the high prevalence of dyslipidaemia with persistently suboptimal control, though outdated, it is paramount to examine whether the rising burden of dyslipidaemia has been accompanied by corresponding changes in LLT utilisation. Although capturing data on LLT prescribing across all healthcare sectors is not feasible due to inconsistencies in electronic health record (EHR) systems between governmental and non-governmental settings, this study focused on public governmental healthcare facilities.

To achieve this, the study utilised data from the Central Medical Store (CMS), a department within the Ministry of Health (MOH) responsible for the procurement and distribution of medications to primary healthcare centres (PHCCs) and hospitals across all six governorates (76). As the CMS also manages contracts with pharmaceuticals suppliers, it can provide expenditure data, enabling an assessment of utilisation alongside cost trends.

Although CMS data are aggregated, they provide a valuable foundation for understanding national patterns and trends in LLT utilisation over time, upon which future patient-level studies can build. These trends offer a broad perspective on how LLT utilisation has evolved in response to emerging clinical evidence, updates in guideline recommendations, and the introduction of new LLTs.

3.2. Aim and objectives

This study aimed to evaluate the utilisation and expenditure patterns and trends of oral and injectable LLTs supplied by the CMS over an 11-year period, from January 2012 to December 2022. The objectives were:

- To quantify the utilisation patterns and trends of the four classes of LLTs (statins, cholesterol absorption inhibitor, PCSK9is, and fibrates) at the national level, stratified by drug class and individual agents within each class.
- To assess the expenditure patterns and trends of the four classes of LLTs (statins, cholesterol absorption inhibitor, PCSK9is, and fibrates) at the national level, stratified by drug class and individual agent within each class.
- To compare utilisation and expenditure trends between PHCCs and hospital settings.
- To investigate regional disparities in utilisation and expenditure trends across the six governorates.

3.3. Methods

3.3.1. Study design and data source

This study employed an observational, retrospective, repeated cross-sectional design, utilising an annually aggregated dataset extracted from the EHR of the CMS, covering the period from January 2012 to December 2022. The CMS serves as the central entity responsible for the procurement of medications, negotiating prices with pharmaceutical companies, and ensuring the purchase and storage of medications (76). The storage and logistical management of CMS operations are manged by Agility Logistics. The CMS functions as the main distributor of medications across healthcare settings. Pharmacists in each healthcare setting determine their medication needs, and based on these requirements, CMS supplies and distributes the requested medications accordingly. Every transaction is documented via a printed receipt provided with the delivery, which includes detailed information such as the name of the healthcare setting, the medication (brand and generic names), strength, unit type, total price, requested and issued quantities, and expiry date for each medicine.

The adoption of CMS data offers a comprehensive and reliable source for analysing both the utilisation and costs of medications. As the CMS supplies medications to all governmental healthcare settings and maintains a robust electronic record of all procurement and distribution transactions, the dataset is both complete and representative of medication usage and associated expenditures across the governmental healthcare system in Kuwait.

3.3.2. Study subjects

The study focused on LLTs supplied by the CMS to healthcare settings governed by the MOH. Medications supplied to facilities under other ministries, such as the Ministry of Defence, were excluded from this analysis. The LLTs of interest were selected based on their alignment with 2019 ESC/EAS guidelines for the management of lipid disorders (23) and their availability as part of the 'current stock' order at the CMS during the study period. The term 'current stock' refers to medications that pharmacists in healthcare facilities can request as part of their standard requests without the need for special forms or approvals (97). The inclusion and exclusion criteria for LLTs are detailed for classes and agents in the following sections.

3.3.2.1. LLT classes: inclusion and exclusion criteria

Four classes of LLTs were included in this study: statins, cholesterol absorption inhibitor, PCSK9is, and fibrates. The first three classes were chosen based on recommendations from the 2019 ESC/EAS guidelines for the pharmacological management of plasma lipid disorders (23). Statins are recommended as the first-line therapy for lowering LDL-C (23). Ezetimibe, the only agent from the cholesterol absorption inhibitor class, is suggested as an add-on therapy for patients who fail to achieve their LDL-C targets with the maximum tolerated dose of statins (23). For patients who still do not reach their LDL-C targets despite treatment with statins and ezetimibe, PCSK9is are recommended as a third-line option (23).

Although fibrates are not primarily indicated for LDL-C reduction, they were included as one of the LLTs in this study due to the high prevalence of metabolic dyslipidaemia in the Middle East, a condition characterised by elevated TG and reduced high-density lipoprotein cholesterol (HDL-C) (20). While statins are effective in metabolic dyslipidaemia, adding fibrates may be necessary to further lower TG levels and raise HDL-C levels (20, 23). Additionally, fibrates have historically been used in the management of LDL-C levels (98, 99). Their inclusion therefore enables assessment of changes in LLT utilisation over time.

In contrast, other classes of LLTs, such as bile acid sequestrants, nicotinic acid, and omega-3 fatty acids, were excluded for specific reasons. Although bile acid sequestrants provide modest reductions in LDL-C, they are primarily prescribed for other indications, such as managing diarrhoea caused by excess bile acids (100). Their inclusion could overestimate the utilisation of LLTs intended specifically for lipid management. Similarly, nicotinic acid and omega-3 fatty acids primarily target TG reduction than LDL-C, which was not the main focus of this study.

3.3.2.2. LLT agents: inclusion and exclusion criteria

The specific agents corresponding to each class were chosen based on their availability as 'current stock' items at the CMS. For statins, atorvastatin, simvastatin, rosuvastatin, and pitavastatin were included, while fluvastatin and pravastatin were excluded as these agents were reserved exclusively for patients receiving medical treatment abroad from health office departments, rendering them unavailable in the standard CMS stock. These agents were categorised as 'special order' items. For cholesterol absorption inhibitors, ezetimibe was the only available agent, at the time of the research, and was included in this study. For PCSK9is, two agents, evolocumab and alirocumab, were available, both of which were included in this study. For fibrates, gemfibrozil, bezafibrate, and fenofibrate were all available during the study period as 'current stock' items. Additionally, during the study period, no combination LLTs or generic versions of the included agents were available. **Figure 3.1** illustrates the LLT classes and agents, along with their corresponding strengths, included in this study.

3.3.2.3. LLT classification

The MOH classifies medications into two categories: the Essential Medicines List (EML) and the Complementary Medicines List (CML) (77, 78) (see details in **chapter 2**, **section 2.4, p28**). This classification was an important step in determining the appropriate study population for analysis, ensuring alignment between the medication eligibility and the selected population group. Accordingly, the total

population size was used when analysing simvastatin and fibrates (fenofibrate, bezafibrate, and gemfibrozil), whereas the Kuwaiti national population was used for atorvastatin, rosuvastatin, pitavastatin, ezetimibe, and PCSK9is (evolocumab and alirocumab) (77, 78).

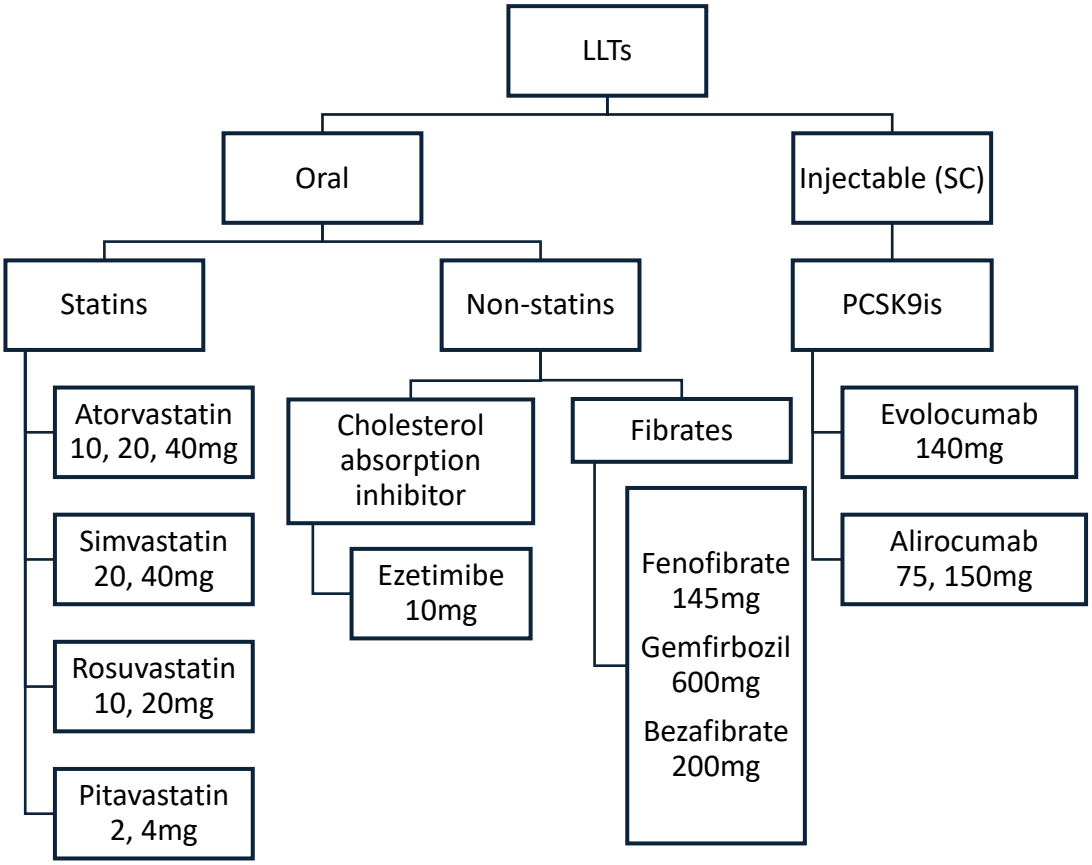

Figure 3.1 Lipid-lowering therapies, stratified by dosage form, class, individual agents within each class, and their corresponding strengths; **LLTs**: Lipid-lowering therapies; **SC**: Subcutaneous; **PCSK9is**: Proprotein convertase subtilisin/kexin type 9 inhibitors

3.3.3. Content of the dataset and data management

Two types of datasets were obtained for this study: one related to the annual utilisation of LLTs across healthcare settings and the other focused on associated costs data. Both datasets included the drug name (in both generic and brand forms) and a unique 13-digit item code specific to each drug. This code, assigned by the CMS, enables pharmacists to request the drugs. Additional information recorded included the strength of each LLT, the unit type (oral or injection), and the quantity supplied, which was expressed in units (per tablet for oral forms and per pre-filled pen for PCSK9is). The supply date was also documented in both datasets. It is worth mentioning that some items were not available at the beginning of the study period (January 2012), while others were discontinued before its end (December 2022). Additionally, certain items were temporarily suspended and later reintroduced. See **Appendix S.3.1**. for a detailed list of agents falling under these categories.

3.3.3.1. Utilisation dataset

Kuwait is divided into six governorates: Capital (CAP), Hawalli (HAW), Al-Ahmadi (AHM), Al-Jahra (JAH), and Al-Farwaniyah (FAR), and Mubarak Al-Kabeer (MBK) (**chapter 2**, **Figure 2.1**), as defined by the Public Authority for Civil Information (PACI) (75). PACI is the Kuwaiti governmental body responsible for issuing Civil ID cards to all citizens and residents (75). Each Civil ID card contains a unique 12-digit ID number used for official transactions. PACI also provides geographical and demographic statistics (75). However, the MOH divided the health regions into seven regions, with each of the six governorates matching the name of its respective health region. The seventh health region is called Specialised Sabah region, which contains secondary and multiple tertiary hospitals within CAP governorate (101) (see details in **chapter 2, section 2.4, p27).**

The utilisation dataset was categorised into six health regions: Specialised Sabah, CAP, HAW, AHM, JAH, and FAR. Within each region, the data were further stratified into PHCCs and hospitals, except for Specialised Sabah region, which only contained hospitals. However, this regional classification became outdated after the official establishment of the MBK health region in 2018, following the opening of a new hospital, Jaber Al-Ahmad, which is part of MBK health region (102). To ensure alignment with the administrative geographical structure defined by PACI, adjustments were made to reflect the corresponding governorates. The Specialised Sabah region was merged with the CAP governorate, as Al-Sabah is geographically located within the CAP governorate. Additionally, 14 PHCCs that were previously associated with the HAW and AHM health regions were reassigned to MBK health region following the ministerial decision, which recognised MBK as a distinct governorate (102). Based on this, amendments were performed to the dataset. These adjustments were applied retrospectively across all years of the study period to maintain consistency.

The utilisation dataset included the quantity of LLTs supplied to each individual PHCC and hospital across Kuwait. To prepare the data for utilisation calculations, the number of supplied units (NSU), with each unit corresponding to a single dosage form (for example, one tablet rather than one package), was first aggregated across all PHCCs within each governorate. The same process was then repeated for all hospitals within each governorate. **Figure 3.2** illustrates the stratification approach used in this study. For comparisons between PHCCs and hospitals at the national level, NSU values were aggregated across all PHCCs in Kuwait and, separately, across all hospitals. To examine regional disparities, NSU values from PHCCs and hospitals were combined to obtain a total NSU for each governorate. This approach enabled utilisation to be assessed at multiple levels, including national utilisation, which was calculated by summing NSU values from all PHCCs and all hospitals. All steps were repeated for each LLT agent and class for every calendar year. Data preparation and management were performed using Microsoft Excel.

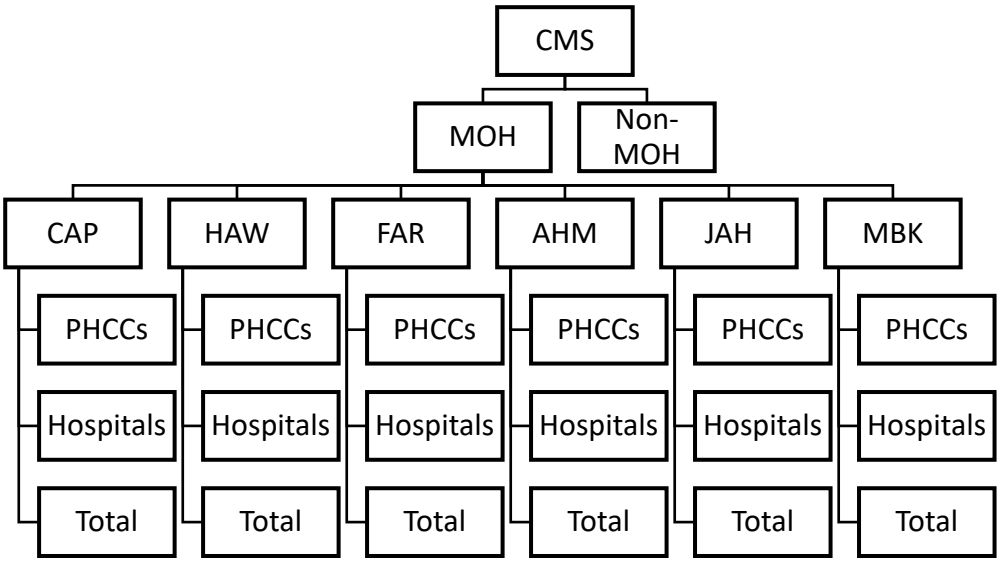

Figure 3.2 Stratification method of the medications supplied by the CMS across the six governorates and healthcare settings under the MOH, excluding non-MOH facilities. **CMS**: Central Medical Store; **MOH**, Ministry of Health; **CAP**: Capital; **HAW**: Hawalli; **FAR**: Al-Farwaniyah; **AHM**: Al-Ahmadi; **JAH**: Al-Jahra; **MBK**: Mubarak Al-Kabeer; **PHCCs**, Primary healthcare centres

3.3.3.2. Cost dataset

The second dataset provided monthly NSU data at the national level, along with the associated cost data. The total cost and total NSU were separately aggregated for each agent for each calendar year. Subsequently, all the data preparation steps mentioned under the utilisation section (**section 3.3.3.1, p41**) were repeated.

3.3.4. Study outcomes

The study outcomes were categorised into annual utilisation trends and expenditure trends of LLTs over the study period. Both outcomes were further stratified by LLT class and by individual items within each class. For statins, stratification was further divided into high-intensity statin therapy (HIST) and moderate-intensity statin therapy (MIST), as low-intensity statin therapy (LIST) was not available during the study period (20, 24) (**chapter 2, Table 2.3**). The primary analysis focused on national-level trends in utilisation and expenditure. Secondary analyses further explored these outcomes by healthcare setting (PHCCs vs. hospitals) and regionally across the six governorates.

3.3.4.1. Utilisation trends

Utilisation trends were measured using two metrics: the annual NSU per 1,000 inhabitants per year (TIY) and the annual defined daily dose (DDD) per 1,000 inhabitants per day (TID) (103). These metrics allowed for a standardised assessment of medication use over the study period.

The first metric, NSU/TIY, was selected as a utilisation metric because the CMS distributed medications by units, make this measure reflective of the supply system. NSU was determined based on the total number of units supplied within each calendar year of the study period. To ensure that the observed trends in medication supply reflected real changes rather than variations in population size over time, the NSU was adjusted annually using the appropriate population estimates (total or Kuwaiti population) for each corresponding year. This adjustment standardised the data and allowed for valid comparisons across years, ensuring that any observed variations in trends were not attributable to changes in population growth (103).

The population-size estimates data were obtained from the PACI (75). For this study, the population statistics for 2022 (December publication) were extracted from the PACI website. However, data for the years 2012–2021 were unavailable online because only the latest statistics was published. To access these earlier publications, the statistics administration at PACI was contacted directly. An official letter, detailing the specific data required and the reasons for using these demographic data, was sent to the head of PACI. The requested dataset was subsequently provided via email. The population data obtained from PACI were stratified by age groups, gender, nationality, and governorates. Since this study used aggregate-level data, age and gender-specific population statistics were not required.

As the MOH classifies LLTs into EML and CML (section 2.4, p28), population size adjustments were tailored to these classifications. For LLTs in the EML, the total population size estimates were used, as these medications are universally available. Whereas for LLTs in the CML, only the total Kuwaiti was applied. Although CML medications are not exclusively dispensed to Kuwaitis, they are predominantly used by this population. Using the Kuwaiti population size provides a more accurate reflection of clinical practice, as including the non-Kuwaiti population, which constitutes approximately 70% of the total population, would have led to an underestimation of utilisation rates. Therefore, the population size estimates based on nationality (Kuwaiti vs. non-Kuwaiti) was helpful. Additionally, the population size estimates for each governorate enabled the examination of regional disparities across the six governorates: CAP, HAW, AHM, JAH, FAR, and MBK.

The NSU/TIY metric was calculated by dividing the total NSU by the population size, then multiplying by 1,000 (as shown in **Equations 3.1-2**). This process was applied to each agent, and the agents within each class were aggregated to obtain the NSU/TIY rate for that class. Next, the NSU/TIY rates for each class were summed to yield the overall NSU/TIY rate for all LLTs. For statin intensities, the NSU/TIY for each agent at the relevant intensity level was added together to determine the NSU/TIY rate for either HIST or MIST (see agents in **chapter 2, Table 2.3**). Additionally, the proportion of agent utilisation relative to its corresponding class utilisation was determined by dividing the NSU/TIY of the agent by the NSU/TIY of its corresponding class and multiplied by 100 (Examples shown in **Equations 3.3-4**).

Equation 3.1: $\text{NSU/TIY of simvastatin 20mg in 2020} = \text{NSU of simvastatin 20mg in 2020} \times \frac{1000}{\text{population size (Total) in 2020}}$

Equation 3.2: $\text{NSU/TIY of atorvastatin 10mg in 2020} = \text{NSU of atorvastatin 10mg in 2020} \times \frac{1000}{\text{population size (Kuwaitis) in 2020}}$

Equation 3.3: Percentage of utilisation atorvastatin in 2020 =

$$\frac{\text{NSU/TIY for atorvastatin in 2020}}{\text{NSU/TIY for statins in 2020}} \times 100$$

Equation 3.4: percentage of utilisation HIST in 2020 =

$$\frac{\frac{\text{NSU}}{\text{TIY}}\text{for atorvastatin 40mg} + \frac{\text{NSU}}{\text{TIY}}\text{for rosuvastatin 20mg in 2020}}{\text{NSU/TIY for statins in 2020}} \times 100$$

The second utilisation metric, DDD/TID, was calculated using the Anatomical Therapeutic Chemical (ATC)/DDD methodology (104). The ATC system organises medicines hierarchically into five levels: anatomical main group, therapeutic subgroup, pharmacological subgroup, chemical subgroup, and chemical substance. DDDs are only assigned to medicines that have an ATC code, with one DDD assigned per ATC code and route of administration (104).

The DDD metric is an international standard for measuring drug utilisation. The WHO defines DDD as "the assumed average maintenance daily dose for a drug used for its main indication in adults" (104). This metric enables researchers to compare drug consumption internationally, monitor changes in utilisation patterns over time, and evaluate the impact of interventions on prescribing behaviours. Importantly, the DDD is a fixed unit of measurement and is independent of a strength, cost, or packaging (104). However, a key limitation of the DDD metric is that it does not necessarily reflect the prescribed daily dose due to therapeutic individualisation (e.g., adjustments based on patient-specific factors) (104). When applied the ATC codes to the LLTs in this study, **Table 3.1** demonstrates the hierarchal structure of ATC codes for LLTs, while **Table 3.2** provides the ATC codes and corresponding DDD values assigned to each LLT agent.

Table 3.1 The structure of the Anatomical Therapeutic Chemical (ATC) codes for lipid-lowering therapies (104)

C	Cardiovascular system
C10	Lipid Modifying Agents
C10A	Lipid Modifying Agents, Plain
C10AA	HMG CoA reductase inhibitors (statins)
C10AB	Fibrates
C10AX	Other Lipid Modifying Agents

Table 3.2 Lipid-lowering therapy classes and active substances, along with ATC classification system codes and DDD values (104)

Drug class	**Active substance**	**ATC Code**	**DDD value**
Statins	Atorvastatin	C10AA05	20mg
	Rosuvastatin	C10AA07	10mg
	Simvastatin	C10AA01	30mg
	Pitavastatin	C10AA08	2mg
Cholesterol absorption inhibitor	Ezetimibe		10mg
Fibrates	Fenofibrate	C10AB05	200mg
	Gemfibrozil	C10AB04	1200mg
	Bezafibrate	C10AB02	600mg
PCSK9is	Alirocumab	C10AX14	5.4mg
	Evolocumab	C10AX13	10mg

ATC: Anatomical Therapeutic Chemical; **DDD**: Defined daily dose; **PCSK9is**: Proprotein convertase subtilisin/kexin type 9 inhibitors

In this study, DDD/TID was calculated by first converting the annual total supplied units for each LLT into milligrams and dividing this value by the corresponding WHO-assigned DDD for that agent (104). The result value was then standardised by dividing using the appropriate population size and multiplying by 1,000. Finally, the value was divided by 365 (or 366 for leap years) (Example shown in **Equation 3.5**). Similar to NSU/TIY, the proportion of agent utilisation relative to its corresponding class was also calculated using DDD/TID, allowing for consistent comparison across both utilisation metrics (NSU/TIY and DDD/TID).

Equation 3. 5: DDD/TID of atorvastatin 10mg in 2020 =

$$\left(\frac{\text{NSU} \times \text{strength (10mg)}}{\text{DDD value (20mg)}}\right) \times \left(\frac{1000}{\text{Population size (Kuwaitis) in 2020}}\right)/366$$

3.3.4.2. Expenditure trends

The expenditure trend was measured using the annual costs of supplied units (CSU) per TIY. The CSU/TIY was calculated by dividing the annual total CSU for each agent by the proper population size, then multiplying the result by 1,000. This calculation accounted for the same population size adjustments used in the utilisation trends. Next, all the steps performed for NSU/TIY were repeated, substituting CSU in place of NSU. The proportion of each item was also calculated by dividing the CSU/TIY of the agent by the CSU/TIY of its corresponding class.

The cost per unit for each agent was also calculated by dividing the total costs for that agent by its corresponding NSU. This measure complemented the CSU/TIY analysis by providing additional insights into cost trends over time.

3.3.5. Statistical analyses

Changes in utilisation and expenditure trends during the study period were expressed as both absolute and relative changes. Absolute change was calculated by subtracting the utilisation metric or expenditure metric in the initial year from the corresponding metric in the final year of the study. Relative change was then determined by dividing the absolute change by the utilisation or expenditure metric in the initial year, with the result expressed as a percentage. Since the outcomes were continuous, trend analysis was performed using linear regression (105) to calculate the average annual change in utilisation and expenditure over time. All analyses were conducted using Microsoft Excel and figures were generated using RStudio software.

3.4. Results

The findings are structured in four parts: first, the national-level trends in the utilisation of LLTs; second, the national-level trends in the expenditure of LLTs; third, comparisons of between PHCCs and hospital settings; and fourth, regional variations across the six governorates. For utilisation outcomes, findings are presented using NSU/TIY and DDD/TID. For expenditure outcomes, results are presented using CSU/TIY and cost/unit. Each metric is described for overall LLTs, followed by LLT classes along with individual agents within each class. Ezetimibe is presented only once at the class level, as it is the sole agent representing its class. Findings related to fibrate utilisation and expenditure are then presented.

3.4.1. Utilisation trends at national level

3.4.1.1. NSU/TIY of LLTs at class level

The overall use of LLTs increased by 52% (n= 71,839) NSU/TIY, rising from 138,549 in 2012 to 210,388 NSU/TIY in 2022, with a significant average annual increase of 7,365 NSU/TIY ($p < 0.05$) (**Figure 3.3A**). The increase was largely driven by statins, which rose by 41% (n= 54,501) NSU/TIY, from 133,725 in 2012 to 188,226 NSU/TIY in 2022, representing a significant average annual increase of 5,800 NSU/TIY ($p < 0.0001$) (**Figure 3.3A**). Statins consistently accounted for more than 90% of total LLT use throughout the study period (**Figure 3.3B**).

Ezetimibe demonstrated a steady upward trend, increasing from 22 in 2013 to 10,640 NSU/TIY in 2022 (49,238%, n= 10,619 NSU/TIY) (**Figure 3.3A**), with a significant average annual increase of 1,221 NSU/TIY ($p < 0.0001$). By the end of the study period, ezetimibe accounted for approximately 5% of all LLTs (**Figure 3.3B**). PCSK9is also exhibited substantial growth, acknowledging the low baseline, with NSU/TIY rising from 3 in 2016 to 233 NSU/TIY in 2022 (8,787%, n= 231 NSU/TIY) (**Figure 3.3A**), showing a significant average annual increase of 37 NSU/TIY ($p < 0.0001$). PCSK9is remained the least utilised LLTs, accounting for 0.1% in 2022 (**Figure 3.3B**).

See **Appendix S.3.2A** for the absolute, relative, and average annual changes in NSU/TIY across all LLT classes.

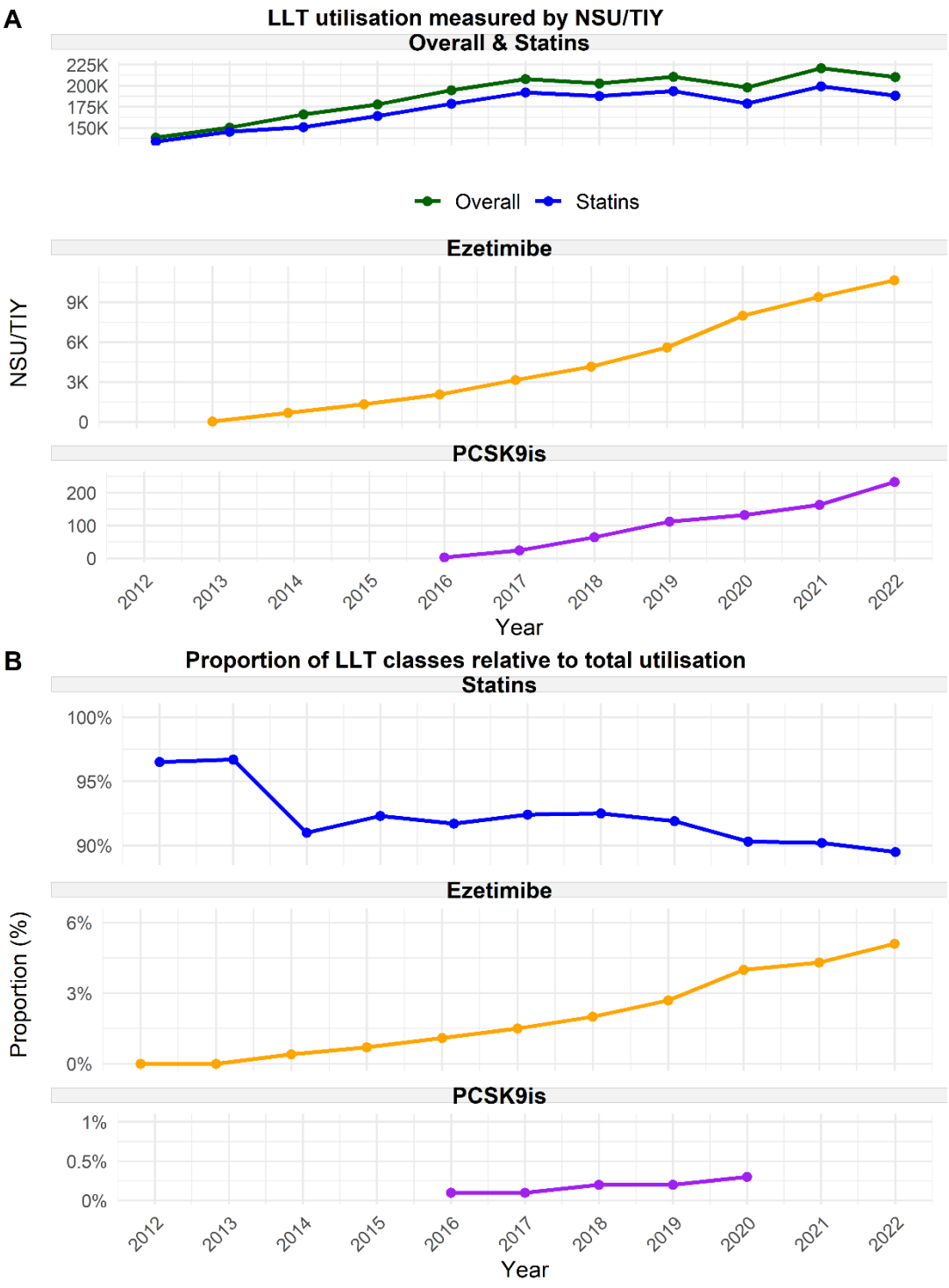

Figure 3.3 Annual utilisation trends of LLTs in Kuwait, measured as NSU/TIY, from 2012 to 2022. **Panel A (top):** NSU/TIY for overall LLTs and individual class; **Panel B (bottom):** Proportions of NSU/TIY of each LLT class relative to overall LLT utilisation. **LLT:** Lipid-lowering therapies; **NSU/TIY:** Number of supplied units per 1,000 inhabitants per year; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor.

3.4.1.2. NSU/TIY of LLTs at agent level

In terms of statins, atorvastatin accounted for the highest level of statin utilisation throughout the study period (Figure 3.4A). Despite this predominance, NSU/TIY for atorvastatin declined from 104,93 in 2012 to 80,671 in 2022 NSU/TIY (Figure 3.4A), representing a 23% decrease (n= 24,260) and a statistically significant average annual reduction of 3,394 NSU/TIY (p <0.0001). In parallel, the relative proportion of atorvastatin among total statin declined from 79% in 2012 to 42% in 2022 (Figure 3.4B).

Both simvastatin and rosuvastatin showed upward trend in the NSU/TIY over the study period. The NSU/TIY trend for simvastatin increased from 28,794 in 2012 to 38,203 in 2022, reflecting a 33% increase (n= 9,408) and a statistically significant average annual increase of 1,402 NSU/TIY (p <0.05) (Figure 3.4A). However, the relative share of simvastatin remained stable at approximate 20% of total statin use over the study period (Figure 3.4B). Rosuvastatin also showed a significant increase, from 4,182 in 2014 to 69,352 NSU/TIY in 2022, corresponding to a 1558% increase (n= 65,170), with a significant average annual increase of 7,890 NSU/TIY (p <0.0001) (Figure 3.4A). By 2022, rosuvastatin accounted for 36.8% of total statins use, approaching the proportion observed for atorvastatin (42.9%) (Figure 3.4B). Pitavastatin remained the least statin utilised, accounting for less than 1% of total statins use throughout the study period.

In terms of statin intensity, utilisation of HIST increased from 2,42 in 2014 to 49,599.5 NSU/TIY in 2022 (1946%, n= 47,176) (Figure 3.5A)**.** In contrast, the NSU/TIY trend of MIST increased only modestly, from 133,725 in 2012 to 138,627 NSU/TIY in 2022 (4%, n= 4,901) (Figure 3.5A). Despite this modest growth, MIST remained the predominant statin intensity throughout the study period. At the start of the study, all statins were utilised at MIST, with the proportion decreasing to 73.6% of total statin utilisation by 2022 (Figure 3.5B)**.**

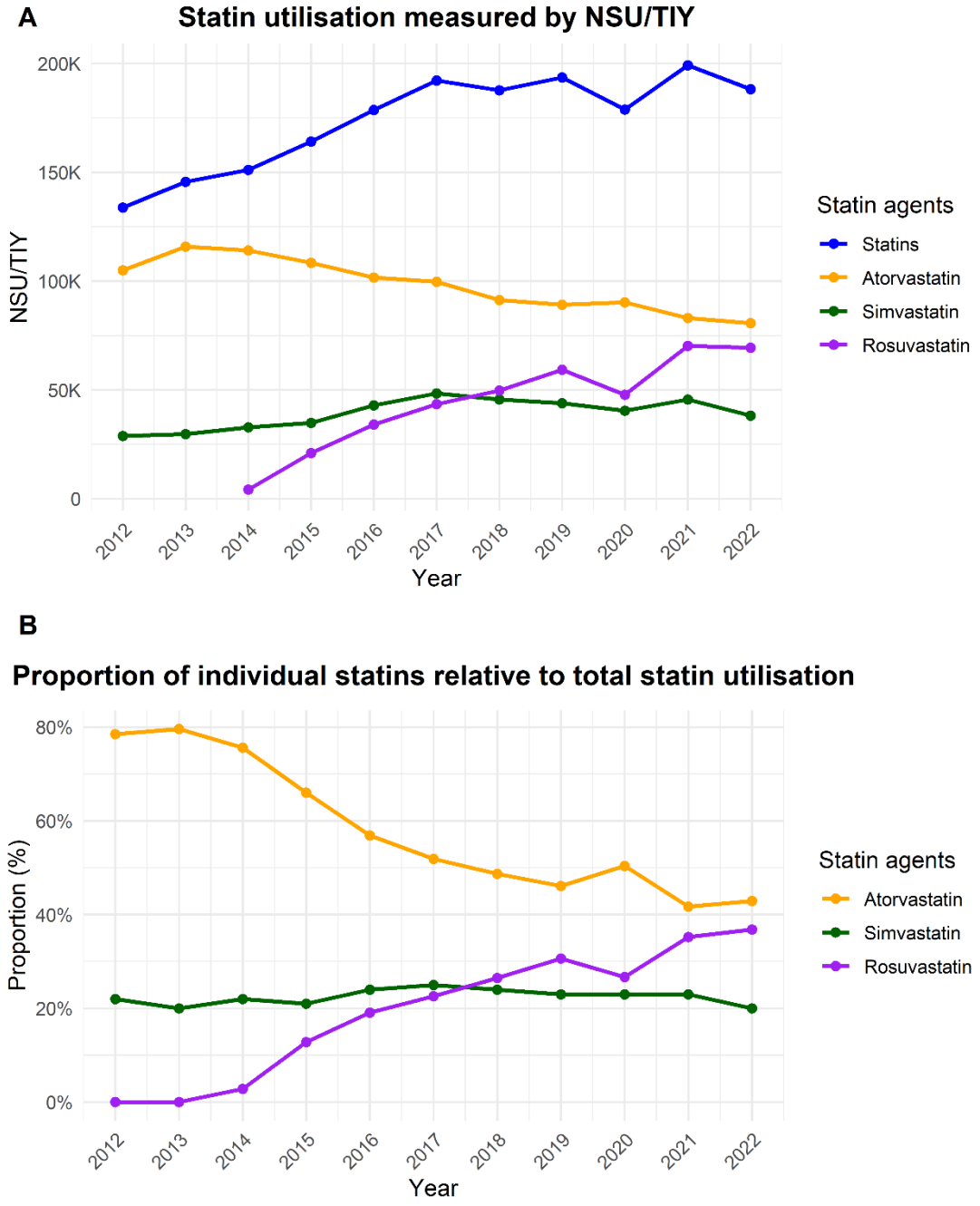

Figure 3.4 Annual utilisation trends of statin agents in Kuwait, measured as NSU/TIY, from 2012 to 2022. **Panel A (top):** NSU/TIY for overall statins and individual agents; **Panel B (bottom):** Proportions of NSU/TIY of each statin agent relative to overall statin utilisation. **NSU/TIY:** Number of supplied units per 1,000 inhabitants per year.

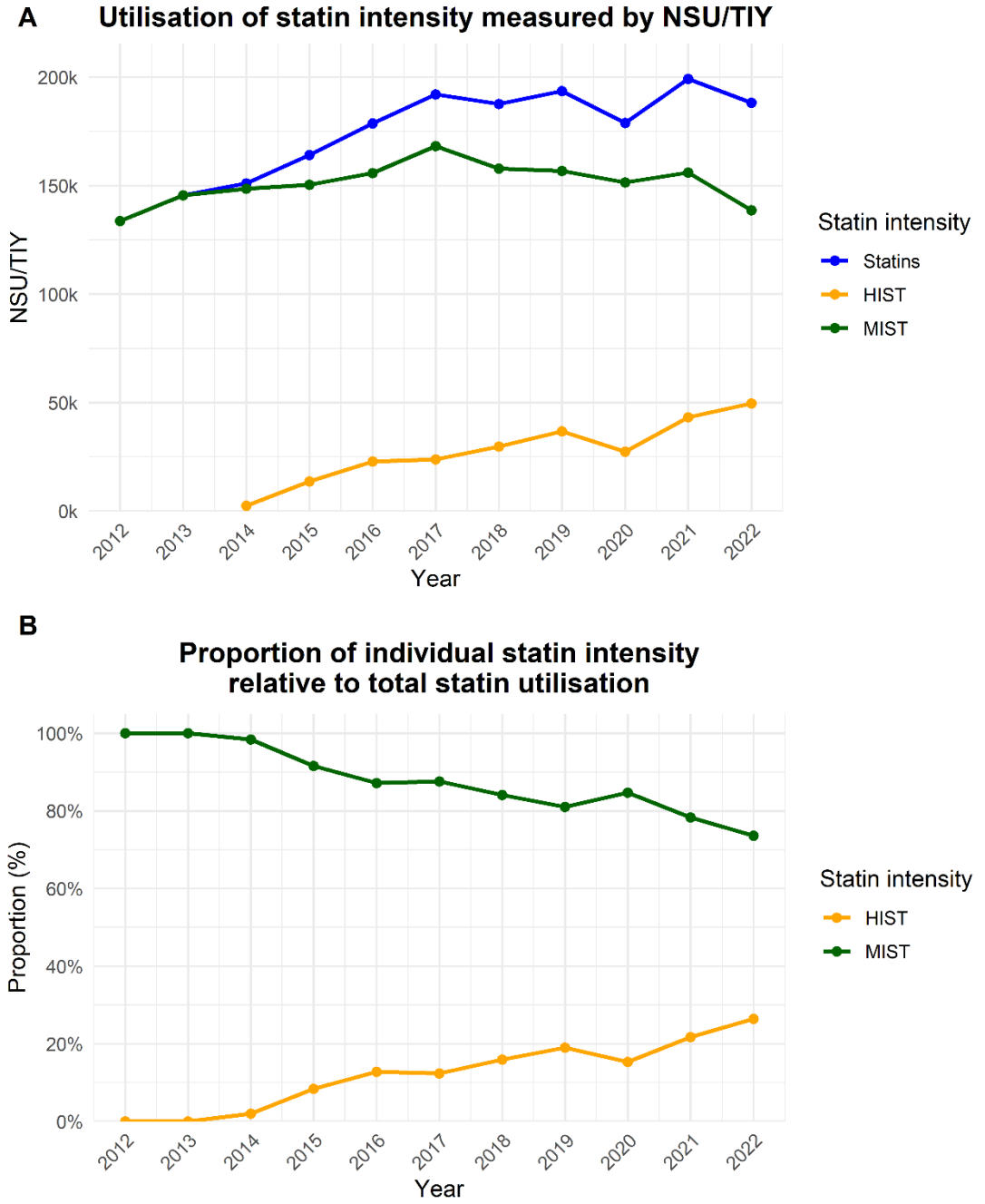

Figure 3.5 Annual utilisation trends of statin intensities in Kuwait, measured as NSU/TIY, from 2012 to 2022. **Panel A (top):** NSU/TIY for overall statins and individual intensity; **Panel B (bottom):** Proportions of NSU/TIY of each statin intensity relative to overall statin utilisation. **NSU/TIY:** Number of supplied units per 1,000 inhabitants per year.

For PCSK9is, evolocumab was introduced in December 2016, followed by alirocumab in February 2017. Both agents showed upward trends in NSU/TIY, with a steeper rise observed for evolocumab. The NSU/TIY trend for evolocumab increased from 3 in 2016 to 181 NSU/TIY in 2022, showing a 5933% increase (n= 178) and a statistically significant annual average increase of 28 NSU/TIY, ($p < 0.0001$) (**Figure 3.6A**). Throughout the study period, evolocumab accounted for the higher NSU/TIY level, comprising 77.6% of total PCSK9i utilisation by 2022 (**Figure 3.6B**).

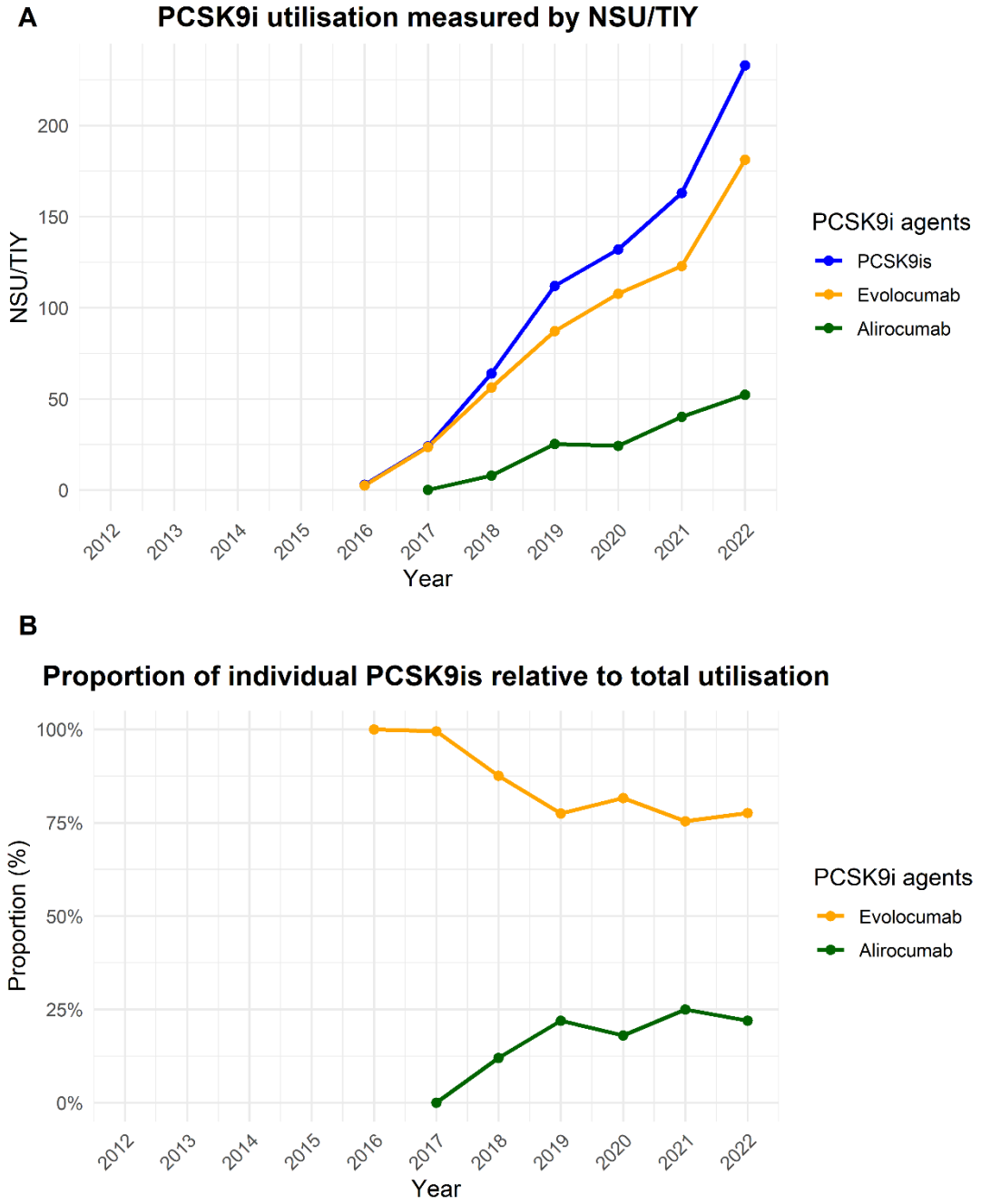

Figure 3.6 Annual utilisation trends of PCSK9i agents in Kuwait, measured as NSU/TIY, from 2012 to 2022. **Panel A (top):** NSU/TIY for overall PCSK9is and individual agents; **Panel B (bottom):** Proportions of NSU/TIY of each PCSK9i agent relative to overall PCSK9is utilisation. **NSU/TIY:** Number of supplied units per 1,000 inhabitants per year; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor.

3.4.1.3. DDD/TID at class level

For the second metric of utilisation, the DDD/TID trend for overall LTs increased by more than two-fold (119%, n= 62.2) compared with NSU/TIY. The DDD/TID increased from 52.4 in 2012 to 114.6 DDD/TID in 2022, with a statistically significant average annual increase of 6.2 DDD/TID (p <0.0001) (**Figure 3.7A**). This growth was largely driven by statins, which showed a 102% increase (n= 52.7), growing from 51.6 in 2012 to 104.3 DDD/TID in 2022, with a significant average annual increase of 9.6 DDD/TID (p <0.0001) (**Figure 3.7A**).

For other LLT classes, DDD/TID trends were comparable with NSU/TIY trends. Ezetimibe exhibited a steady upward trend (50126%, n= 5.3 DDD/TID), increasing from 0.01 in 2013 to 5.27 DDD/TID in 2022, with a statistically significant average annual increase of 0.6 DDD/TID (p <0.0001) (**Figure 3.7A**). The DDD/TID for PCSK9is also increased over the study period (**Figure 3.7A**). In alignment with the NSU/TIY findings, statins contributed to the higher DDD/TID levels among all LLT classes throughout the study period (**Figure 3.7B**).

See **Appendix S3.2B**. for the absolute, relative, and average annual changes in DDD/TID across all LLT and agents.

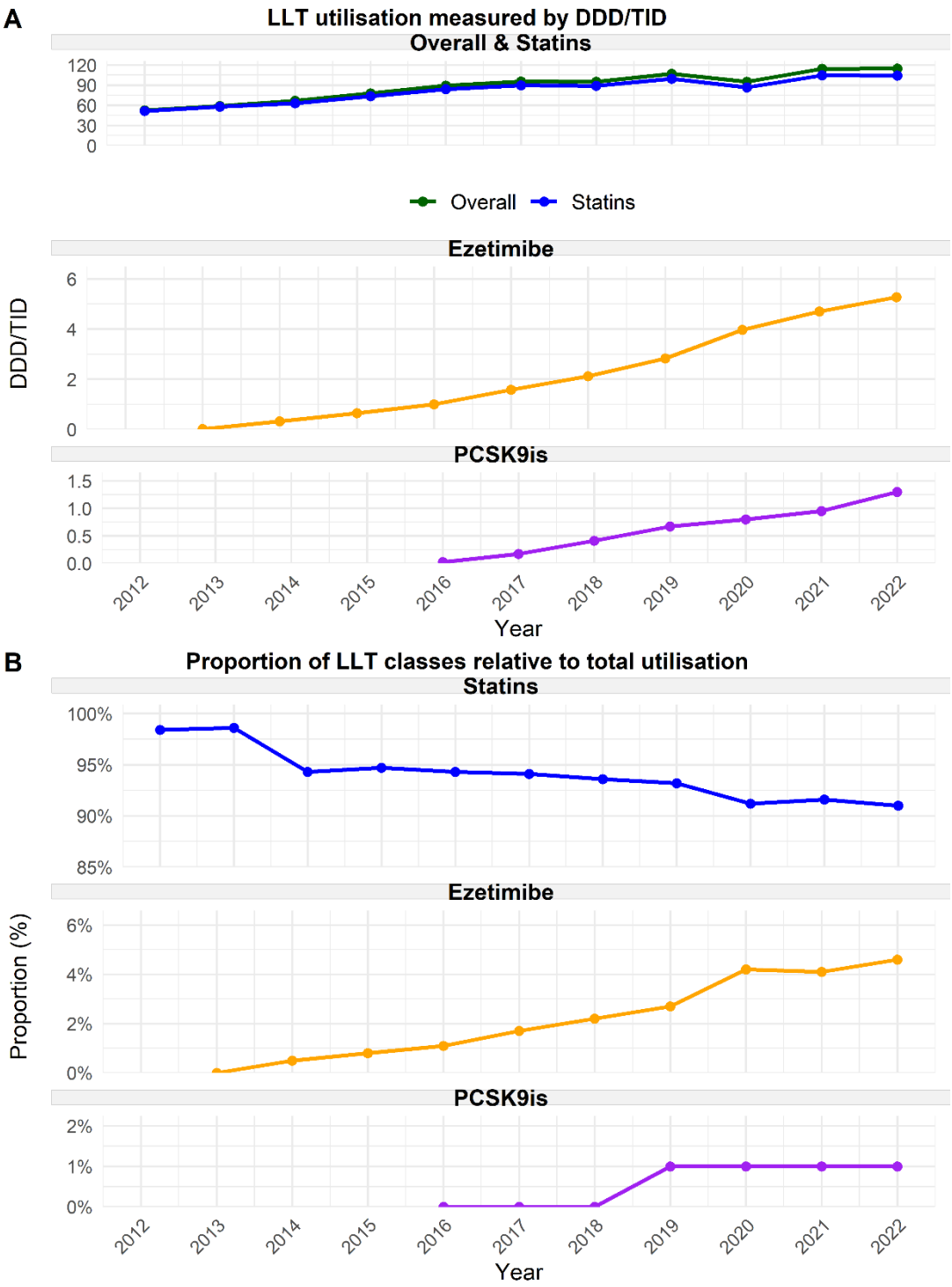

Figure 3.7 Annual utilisation trends of LLTs in Kuwait, measured as DDD/TID, from 2012 to 2022. **Panel A (top):** DDD/TID for overall LLTs and individual class; **Panel B (bottom):** Proportions of DDD/TID of each LLT class relative to overall LLT utilisation. **LLT:** Lipid-lowering therapies; **DDD/TID:** Defined daily doses per 1,000 inhabitants per day; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor.

3.4.1.4. DDD/TID at agent level

In terms of statins, the increase in DDD/TID was largely driven by atorvastatin, which maintained the highest proportion of statin use, decreasing from 80% in 2012 to 48% in 2020 (**Figure 3.8B**). Despite the decrease in relative share, the DDD/TID trend for atorvastatin remained relatively stable at around 40 DDD/TID over the study period (**Figure 3.8A**). This contrasts with the declining NSU/TIY trend for atorvastatin (-23%) (Figure 3.4A).

From 2021 onward, rosuvastatin became the most frequently utilised statin in terms of DDD/TID, accounting for approximately 45% of the total statin use in both 2021 and 2022 (**Figure 3.8B**). Rosuvastatin also demonstrated an upward trend in DDD/TID (1517% n= 44), increasing from 2.9 in 2014 to 46.8 DDD/TID in 2022 (**Figure 3.8A**). Simvastatin demonstrated an upward trend in DDD/TID, increasing from 10.3 in 2012 to 16.4 DDD/TID in 2022, reflecting a 59% increase (n= 6.1), with a statistically significant average annual increase of 0.5 DDD/TID ($p < 0.05$) (**Figure 3.8A**). This increase was nearly double the relative change observed using NSU/TIY (33%) (Figure 3.4A). Pitavastatin remained the least utilised, with its DDD/TID trend remaining stable over the study period.

In line with the NSU/TIY trends (Figure 3.5A), the DDD/TID for HIST increased from 2.4 in 2014 to 46.89 DDD/TID in 2022 (1830%, n= 44) (Figure 3.9A). MIST remained the predominant statin intensity throughout the study period, although only a modest increase was observed, from 51.6 in 2012 to 57.4 DDD/TID in 2022 (11%, n= 6) (Figure 3.9A). The relative proportion of HIST based on DDD/TID increased overtime, reaching 47% by 2022 and approaching that of MIST (57%) (Figure 3.9B). For PCSK9is, both evolocumab and alirocumab demonstrated increasing DDD/TID trends (Figure 3.10A) consistent with trends observed in NSU/TIY (Figure 3.6A). Evolocumab accounted for the majority of PCSK9i utilisation, comprising 97% of total DDD/TID by 2022 (Figure 3.10B).

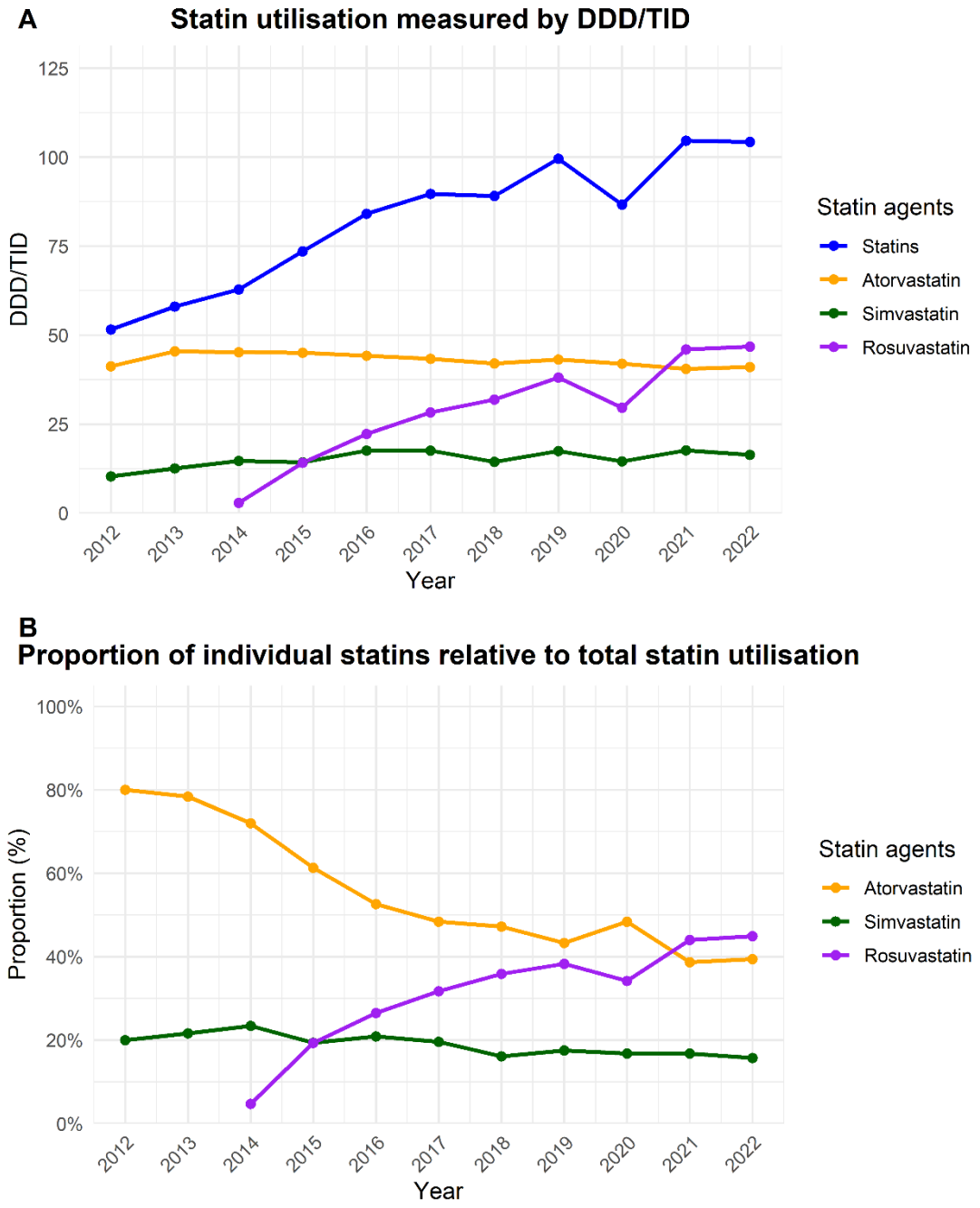

Figure 3.8 Annual utilisation trends of statin agents in Kuwait, measured as DDD/TID, from 2012 to 2022. **Panel A (top):** DDD/TID for overall statins and individual agents; **Panel B (bottom):** Proportions of DDD/TID of each statin agent relative to overall statin utilisation. **DDD/TID:** Defined daily dose per 1,000 inhabitants per day

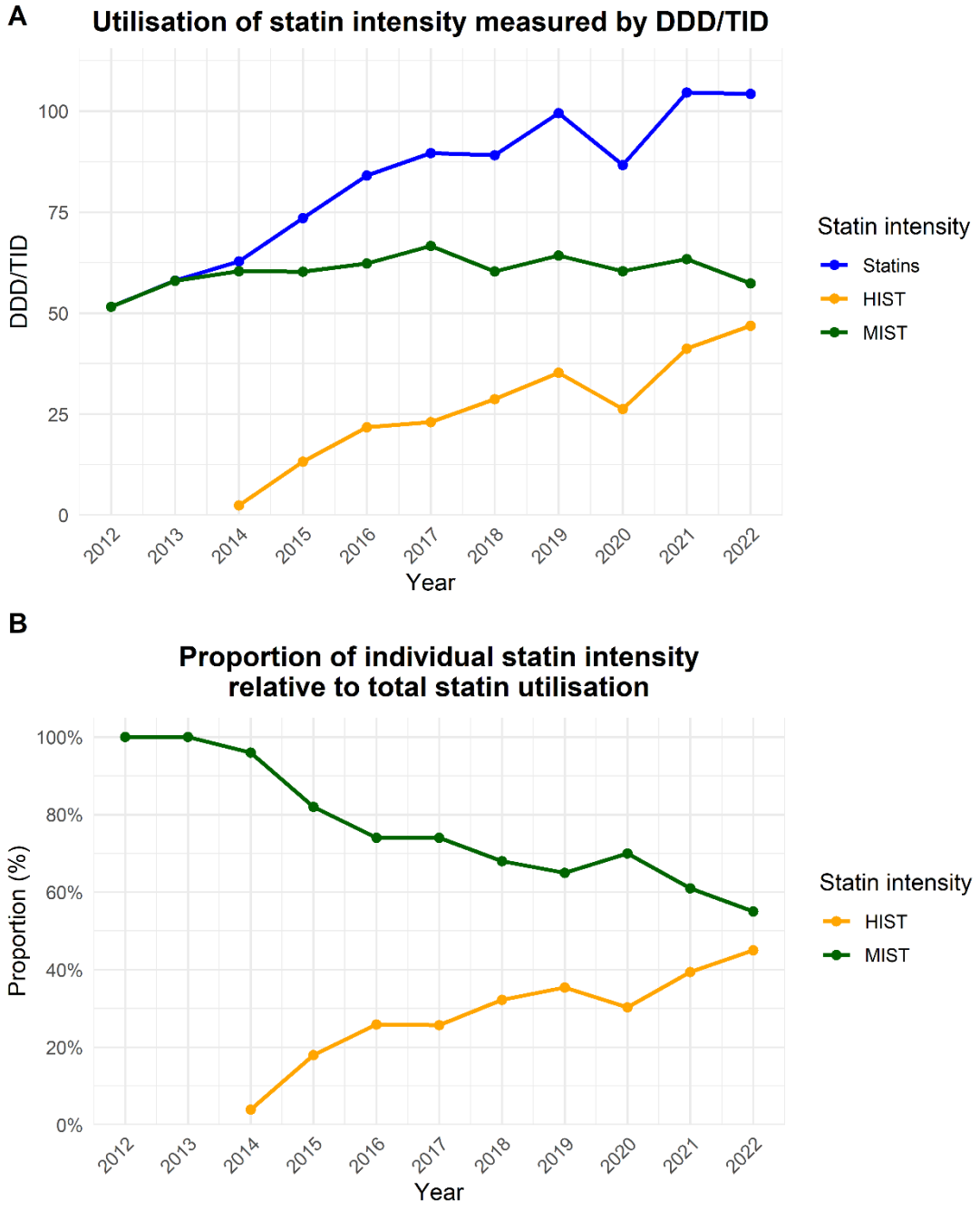

Figure 3.9 Annual utilisation trends of statin intensities in Kuwait, measured as DDD/TID, from 2012 to 2022. **Panel A (top):** DDD/TID for overall statins and individual intensity; **Panel B (bottom):** Proportions of DDD/TID of each statin intensity relative to overall statin utilisation. **DDD/TID:** Defined daily dose per 1,000 inhabitants per day

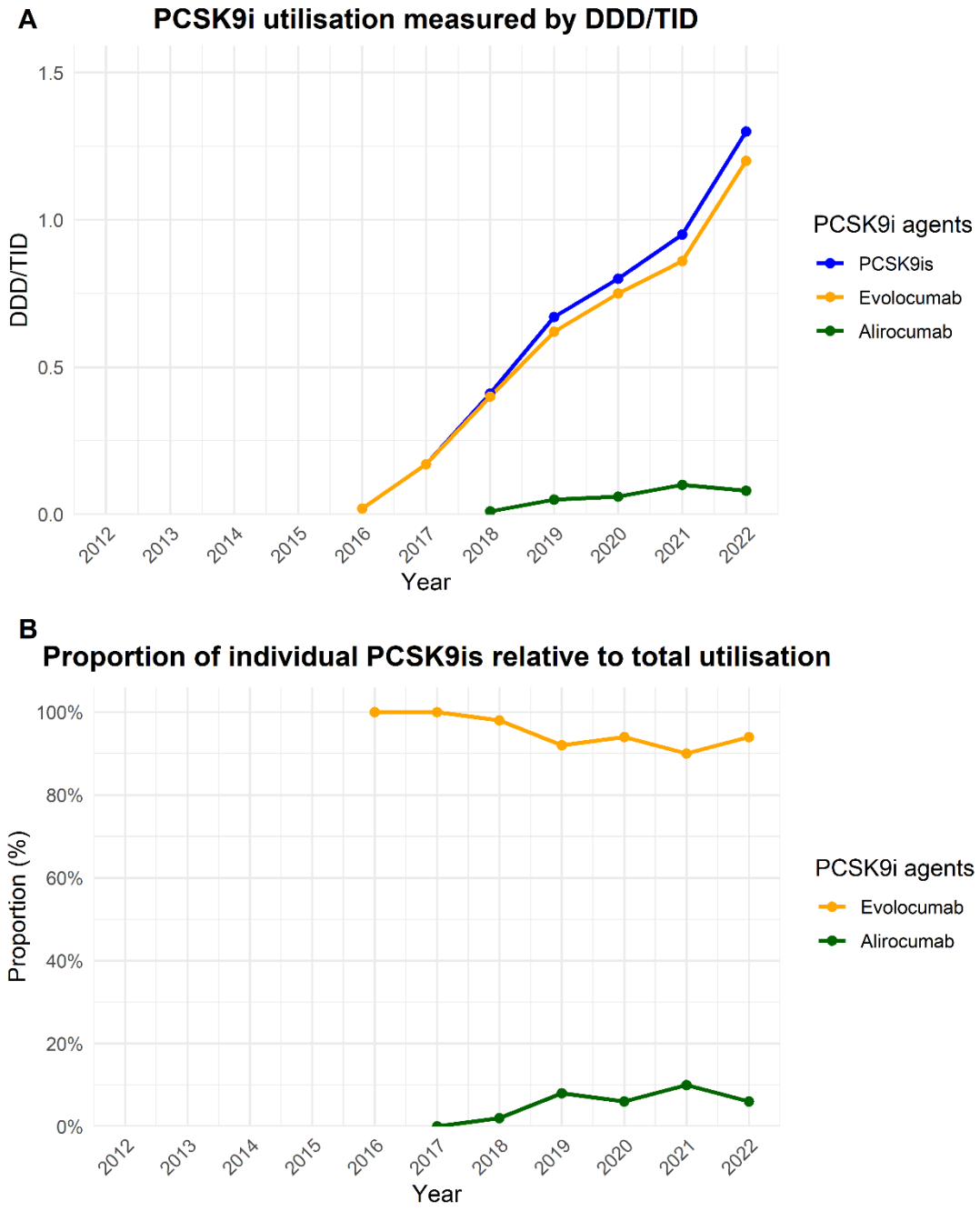

Figure 3.10 Annual utilisation trends of PCSK9i agents in Kuwait, measured as DDD/TID, from 2012 to 2022. **Panel A (top):** DDD/TID for overall PCSK9is and individual agents; **Panel B (bottom):** Proportions of DDD/TID of each PCSK9i agent relative to overall PCSK9is utilisation. **DDD/TID:** Defined daily dose per 1,000 inhabitants per day; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor.

3.4.2. Expenditure trends at national level

3.4.2.1. CSU/TIY at class level

Overall expenditure on LLTs, measured as CSU/TIY in Kuwaiti Dinar, demonstrated a steady increase over the study period, rising from 22,534 in 2012 to 53,161 CSU/TIY in 2022. This represents a 136% increase (n= 30,627), with a statistically significant average annual increase of 3,290 CSU/TIY (p <0.0001) (**Figure 3.11A**).

Statins remained the main contributor to LLT expenditure, increasing by 47% (n= 10,555 CSU/TIY) from 22,350 in 2012 to 32,905 CSU/TIY in 2022, with a significant average annual increase of 968 CSU/TIY (p <0.05) (**Figure 3.11A**). The relative proportion of statin expenditure decreased from 99.2% in 2012 to 61.9% in 2022 of total LLT expenditure during the observed period (**Figure 3.11B**).

The CSU/TIY for ezetimibe increased by 51500% (n= 4,120 CSU/TIY), from 8 in 2013 to 4,128 CSU/TIY in 2022, acknowledging the low baseline. This corresponded to a statistically significant average annual increase of 474 CSU/TIY (p <0.0001), (**Figure 3.11A**). Ezetimibe accounted for less than 10% of total LLT expenditure by 2022 (**Figure 3.11B**).

Following the introduction of PCSK9is in 2016, CSU/TIY increased rapidly from 355 in 2016 to 15,231 CSU/TIY in 2022 (**Figure 3.11A**), showing a 4195% increase (n= 14,877), acknowledging the low baseline. This growth corresponded to a statistically significant average annual increase of 2,468 CSU/TIY (p <0.05). By 2022, PCSK9is accounted for 29% of total LLT expenditure (**Figure 3.11B**).

See **Appendix S3.2C** for the absolute, relative, and average annual changes in CSU/TIY across all LLT agents.

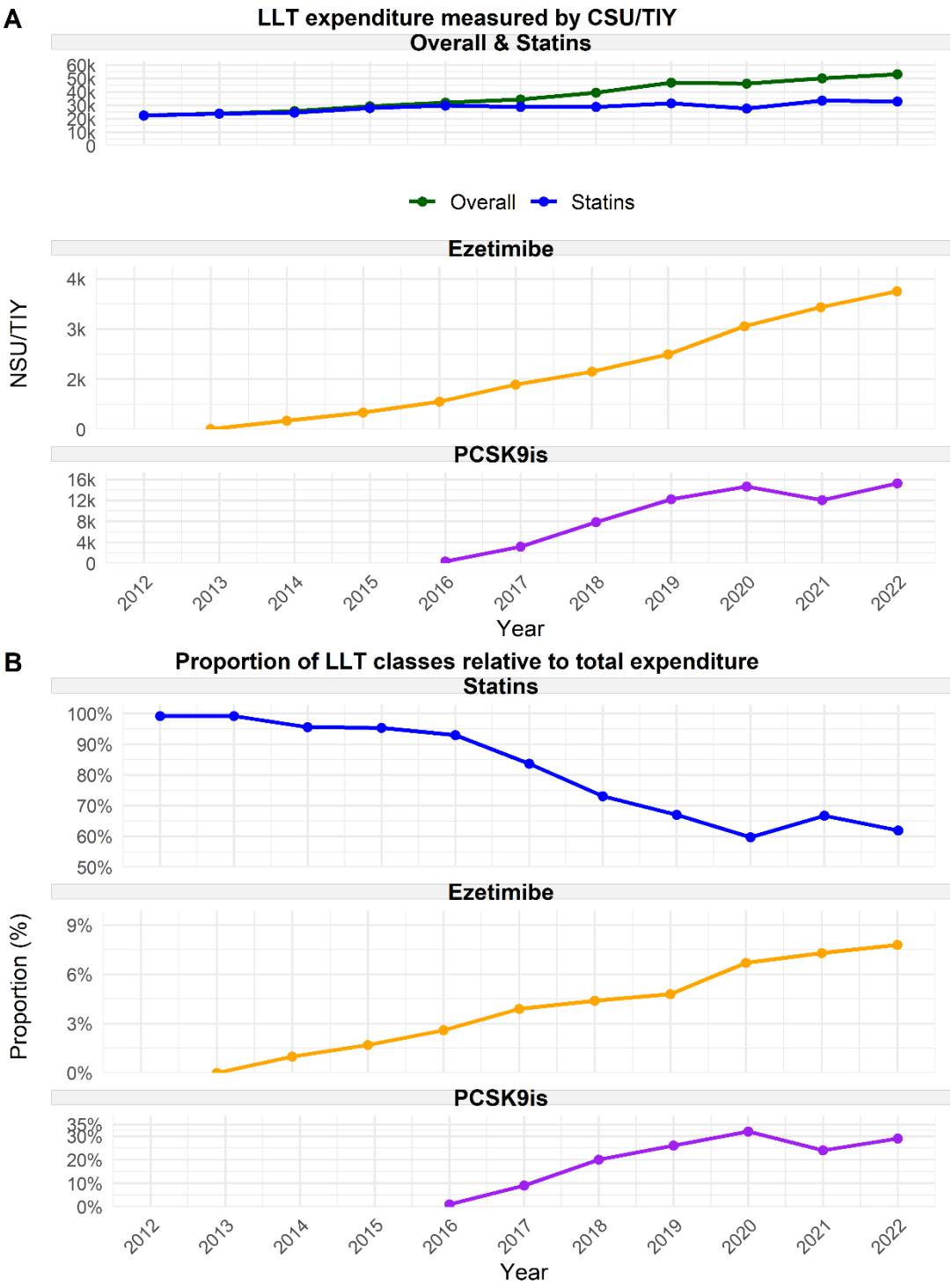

Figure 3.11 Annual expenditure trends of LLTs in Kuwait, measured as CSU/TIY, from 2012 to 2022. **Panel A (top):** CSU/TIY for overall LLTs and individual class; **Panel B (bottom):** Proportions of CSU/TIY of each LLT class relative to overall LLT expenditure. **LLT:** Lipid-lowering therapies; **CSU/TIY:** Cost of supplied units per 1,000 inhabitants per year; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor.

3.4.2.2. CSU/TIY at agent level

For statins, expenditure measured by CSU/TIY was highest for atorvastatin until 2020, after which rosuvastatin became the leading agent in the final two years (**Figure 3.12B**), In 2021 and 2022, atorvastatin accounted for approximately 40% of total statin expenditure, compared with around 50% for rosuvastatin (**Figure 3.12B**), consistent with patterns seen with DDD/TID metric (**Figure 3.8B**).

Atorvastatin demonstrated a downward expenditure trend, with CSU/TIY decreasing by 32% (n= 6,343 CSU/TIY) from 19,891 in 2012 to 13,548 CSU/TIY in 2022 (**Figure 3.12A**). This decline corresponded to a statistically significant average annual reduction of 898 CSU/TIY ($p < 0.0001$) and mirrored the downward trend observed for NSU/TIY metric (**Figure 3.4A**). Rosuvastatin showed an increase in CSU/TIY trend, rising from 968 in 2014 to 16,792 CSU/TIY in 2022. This reflected a 1634% increase (n= 15,823), with a statistically significant average annual increase of 1,901 CSU/TIY ($p < 0.0001$) (**Figure 3.12A**).

Simvastatin showed no statistically significant change in expenditure over the study period, remaining relatively stable at approximately 2,500 CSU/TIY (**Figure 3.12A**). Pitavastatin demonstrated a modest decline of 14% (n= 18) CSU/TIY, reducing from 127 in 2017 to 110 CSU/TIY in 2021, though its relative share to total LLT expenditure remained negligible (<1%).

In terms of statin intensity, the CSU/TIY trend for HIST increased by 2009% (n= 14,542 CSU/TIY), rising from 762 in 2014 to 15,304 CSU/TIY in 2022 (**Figure 3.13A**). However, MIST accounted for the majority of total statin cost throughout the study period (**Figure 3.13B**), consistent with the utilisation trends. Despite this predominance, the CSU/TIY for MIST declined by 21% (n= 4,750), decreasing from 22,350 in 2012 to 17,600 CSU/TIY in 2022 (**Figure 3.13A**).

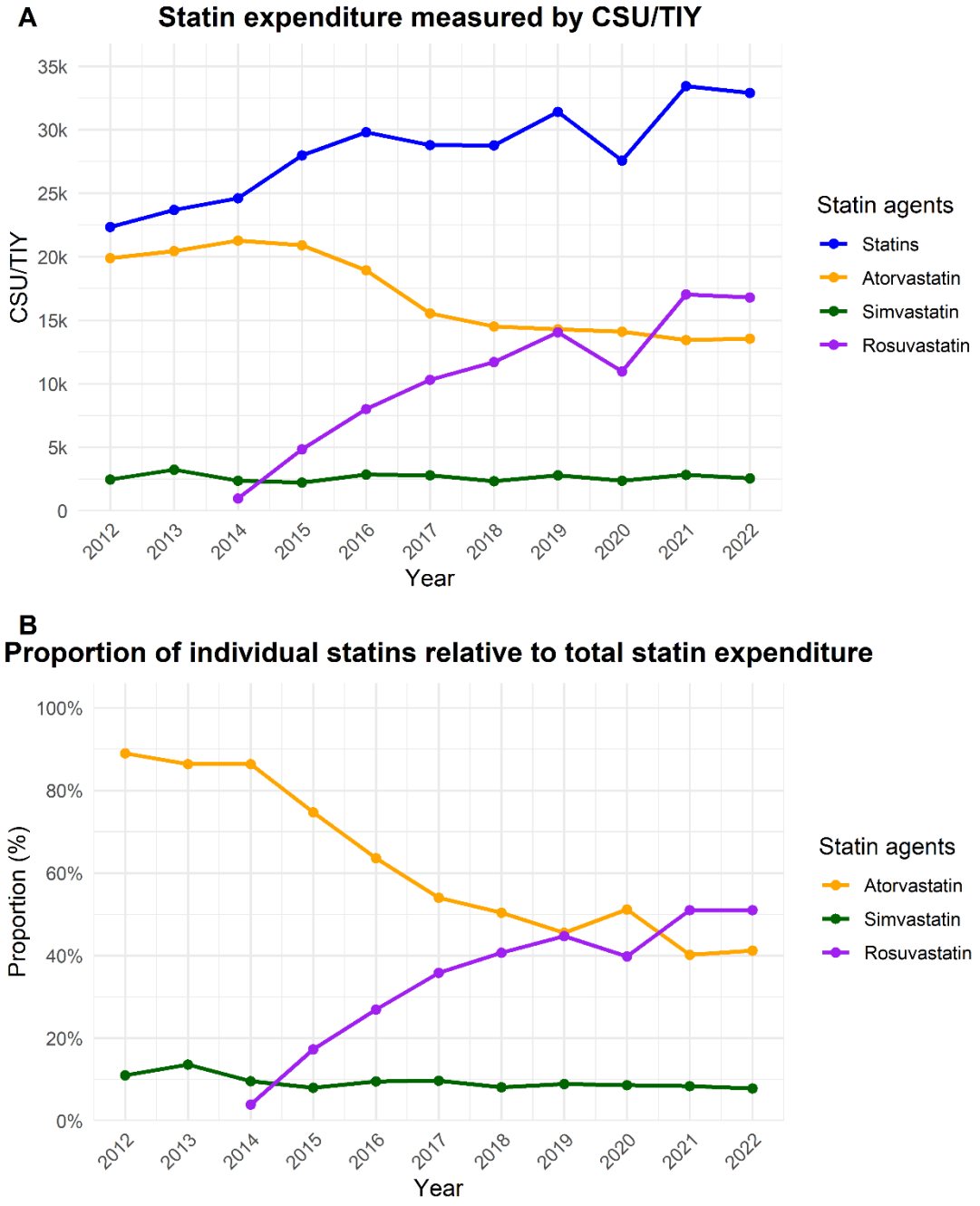

Figure 3.12 Annual expenditure trends of statin agents in Kuwait, measured as CSU/TIY, from 2012 to 2022. **Panel A (top):** CSU/TIY for overall statins and individual agents; **Panel B (bottom):** Proportions of CSU/TIY of each statin agent relative to overall statin expenditure. **CSU/TIY:** Number of supplied units per 1,000 inhabitants per year.

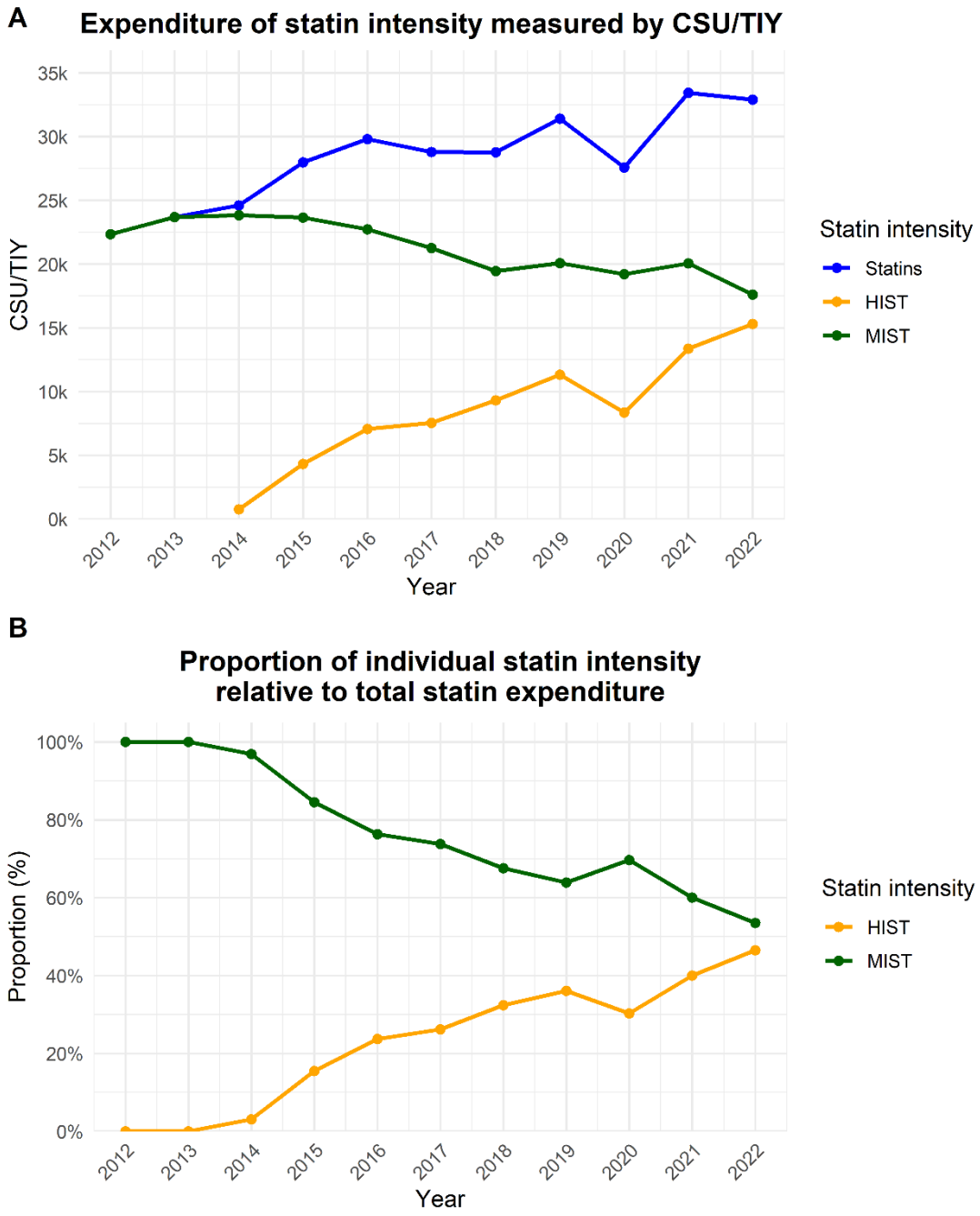

Figure 3.13 Annual expenditure trends of statin intensities in Kuwait, measured as CSU/TIY, from 2012 to 2022. **Panel A (top):** CSU/TIY for overall statins and individual intensity; **Panel B (bottom):** Proportions of CSU/TIY of each statin intensity relative to overall statin expenditure. **CSU/TIY:** Cost of supplied units per 1,000 inhabitants per year.

For PCSK9is, the CSU/TIY trends showed fluctuations (**Figure 3.14A**) compared with the more consistent growth observed in utilisation metrics. Expenditure on evolocumab increased by 3088% (n= 10,953 CSU/TIY), rising from 355 in 2016 to 11,308 CSU/TIY in 2022, peaking in 2020 (n= 13,103 CSU/TIY). Despite this growth, the average annual change (1,831 CSU/TIY) was not statistically significant Alirocumab also showed an increase in expenditure, with 31729% increase (n = 3,909 CSU/TIY), increasing from 12 in 2017 to 3,922 CSU/TIY in 2022 (**Figure 3.14A**), acknowledging the low baseline values

Consistent with utilisation patterns, evolocumab accounted for the majority of PCSK9i expenditure throughout the study period, contributing 74% of total PCSK9i CSU/TIY by 2022, compared with 26% for alirocumab (**Figure 3.14B**).

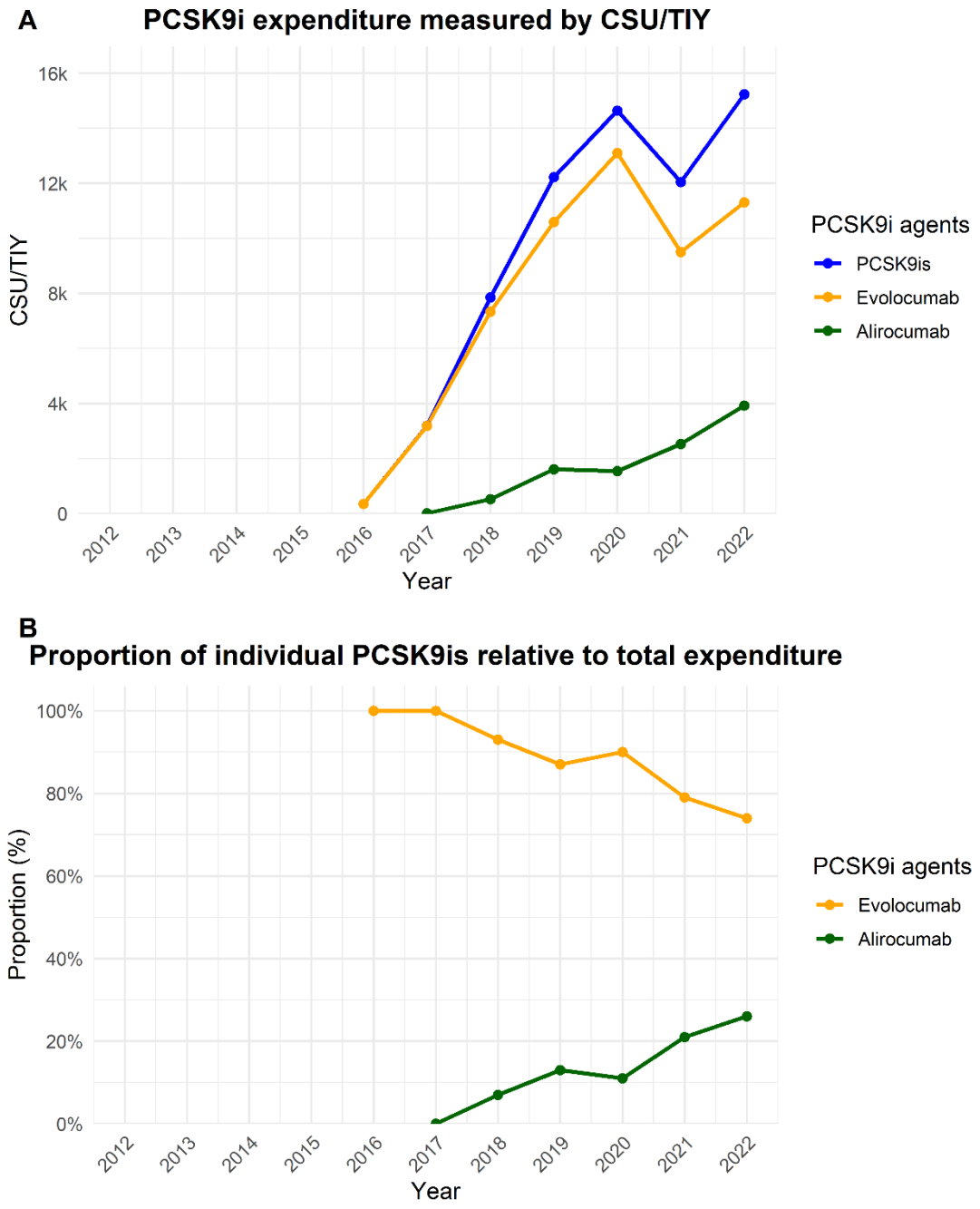

Figure 3.14 Annual expenditure trends of PCSK9i agents in Kuwait, measured as CSU/TIY, from 2012 to 2022. **Panel A (top):** CSU/TIY for overall PCSK9is and individual agents; **Panel B (bottom):** Proportions of CSU/TIY of each PCSK9i agent relative to overall PCSK9is expenditure. **CSU/TIY:** Cost of supplied units per 1,000 inhabitants per year; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor.

3.4.2.3. Cost per unit

Over the study period, both the trend and the level of cost/unit remained largely stable across LLTs. The most notable change was observed for PCSK9is, which had the highest cost/unit among all LLTs, although this cost declined over time.

The cost/unit of PCSK9is decreased by 52%, from 135 KWD (£330) in 2016 to 65.2 KWD (£160) in 2022. This reduction was primarily driven by a 54% decrease in the unit cost of evolocumab, which fell from 135 KWD (£330) in 2016 to 62.4 KWD (£152) in 2022. Similarly, the unit cost of alirocumab 75mg decreased from 106.7 KWD (£260) in 2017 to 62.3 KWD (£152) in 2022.

3.4.3. Fibrate utilisation and expenditure

Fibrates demonstrated notable increases in utilisation and expenditure trends at the national level over the study period. In terms of NSU/TIY, fibrates use increased by 134% (n= 6,465 NSU/TIY), from 4,824 in 2012 to a peak of 14,267 in 2014, before fluctuating and declining to 11,288 NSU/TIY by 2022, but with a non-statistically significant average annual increase of 420 NSU/TIY.

Utilisation measured using DDD/TID showed an upward trend, increasing by 342% (n= 2.84 DDD/TID), with a statistically significant average annual increase of 0.25 DDD/TID ($p < 0.05$). This relative increase was more than double that observed using NSU/TIY (134%). Regarding expenditure, CSU/TIY increased by 388% (n= 714 CSU/TIY), with a statistically significant average annual increase of 66 CSU/TIY ($p <0.05$).

Among all LLTs, fibrates accounted for a relatively small proportion of overall LLT use by 2022, comprising 5% of NSU/TIY, 3% of DDD/TID, and 1.7% of CSU/TIY.

At the agent level, fenofibrate emerged as the leading agent following its introduction in 2014. Fenofibrate utilisation increased by 52% (n= 3,860 NSU/TIY), with a statistically significant average annual increase of 483 NSU/TIY ($p <0.05$). From 2019 onwards, fenofibrate accounted for approximately 99% of all fibrate use. Similar trend was observed with DDD/TID metric. Bezafibrate discontinued after 2018 and gemfibrozil showing minimal use by 2022, recording 61 NSU/TIY in 2022 compared to 11,227 NSU/TIY for fenofibrate.

See **Appendix S3.2** for the absolute, relative, and average annual changes in all metrics.

3.4.4. Comparison between PHCCs and hospital settings

To avoid repetitions, the comparison between PHCCs and hospitals focuses on distinctive utilisation and expenditure patterns.

A key finding was the contrasting trends in overall LLT utilisation measured by NSU/TIY between PHCCs and hospitals (**Figure 3.15A-B**). In PHCCs, NSU/TIY for overall LLTs increased by 152% (n= 81,127), from 53,453 in 2012 to 134,580 in 2022, with a statistically significant average annual increase of 8,289 NSU/TIY ($p < 0.05$) (**Figure 3.15A**). In contrast, hospital NSU/TIY for overall LLTs declined by 11% (n= 9,288), from 85,096 in 2012 to 75,808 NSU/TIY in 2022, with a significant average annual decrease of 924 NSU/TIY ($p < 0.0001$) (**Figure 3.15B**). From 2015 onwards, the NSU/TIY level in PHCCs consistently surpassed that in hospitals (**Figure 3.15A-B**).

In contrast, when utilisation measured by DDD/TID, overall LLT increased in both settings (**Figures 3.16A-B**). In PHCCs, DDD/TID increased by 264% (n= 64.7 DDD/TID), from 17.7 in 2012 to 64.4 in 2022 (**Figure 3.16A**). Hospitals also showed an increase of 45% (n= 15.5 DDD/TID), from 34.7 in 2012 to 50.2 in 2022 (**Figure 3.16B**). Similar to NSU/TIY, DDD/TID levels in PHCCs surpassed those in hospitals from 2016 onwards (**Figures 3.16A-B**).

Expenditure trends, measured by CSU/TIY, increased in both settings. In PHCCs, CSU/TIY (**Figure 3.17A**) increased from 7,350 in 2012 to 20,841 CSU/TIY in 2022, showing a 184% increase (n= 13,490), mirroring the upward utilisation trend observed with NSU/TIY in PHCCs (**Figure 3.15A**). In hospitals, CSU/TIY increased by 113% (n= 17,137), from 15,184 in 2012 to 32,321 CSU/TIY in 2022 (**Figure 3.17B**), despite the decline in NSU/TIY observed in hospitals (**Figure 3.15B**). Unlike both utilisation metrics, hospital expenditure consistently exceeded that of PHCCs (**Figure 3.17A-B**). Notably, by 2022, hospital expenditure comprised of 13,393 CSU/TIY attributable to statins and 15,231 CSU/TIY to PCSK9is.

Across both healthcare settings, statins remained the principal contributors to overall LLT utilisation and expenditure. However, opposing utilisation trends were observed between PHCCs and hospitals when assessed using NSU/TIY (**Figure 3.15C-D**). In PHCCs, statin utilisation increased by 151% (n= 74,507 NSU/TIY), whereas a decline of 24% (n= 20,007 NSU/TIY) was observed in hospital settings. These trends mirrored the corresponding NSU/TIY trends for overall LLTs.

When measured using DDD/TID, statin utilisation increased in both settings, with a 256% increase (n= 43.6 DDD/TID) in PHCCs and 26% increase (n= 9.1 DDD/TID) in hospitals (**Figure 3.16C-D**). These trends were in line with the overall LLT DDD/TID trends.

Expenditure trends measured by CSU/TIY differed between PHCCs and hospitals (**Figure 3.17C-D**). In PHCCs, CSU/TIY increased by 171% (n= 12,317 CSU/TIY), whereas hospital CSU/TIY decreased by 12% (n= 1,762 CSU/TIY). These trends were different from the overall LLT CSU/TIY trends.

Stratification by statin intensity showed increasing utilisation of HIST across both NSU/TIY (**Figure 3.15C-D**) and DDD/TID (**Figure 3.16C-D**) metrics increased in both settings. Nevertheless, HIST utilisation consistently remained higher in hospital settings.

Ezetimibe utilisation increased in both settings; however, utilisation levels were higher in hospitals surpassed than in PHCCs (data not shown). Because PCSK9is were exclusively supplied through hospitals during the study period, the national utilisation trends for PCSK9is presented earlier reflect prescribing practices within hospital settings (**Figure 3.6A**, **Figure 3.10A**, **Figure 3.14A**)

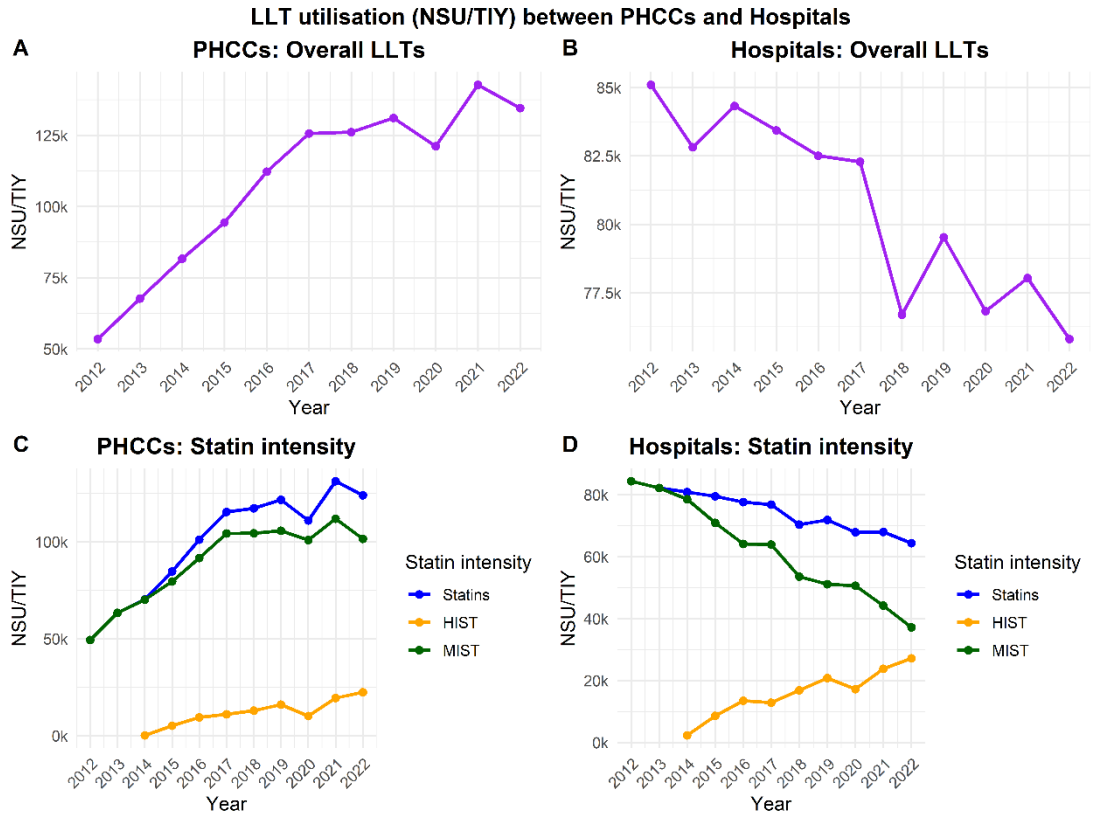

Figure 3.15 Annual utilisation trends in NSU/TIY for LLTs in PHCCs (left panels) and hospital settings (right panels) from 2012 to 2022. **Panels A&B**: Overall LLTs; **Panels C&D:** Statin intensity**. LLT:** Lipid-lowering therapies; **NSU/TIY:** Number of supplied units per 1,000 inhabitants per year; **PHCCs:** Primary healthcare centres; **HIST**: High-intensity statin therapy; **MIST**: Moderate-intensity statin therapy

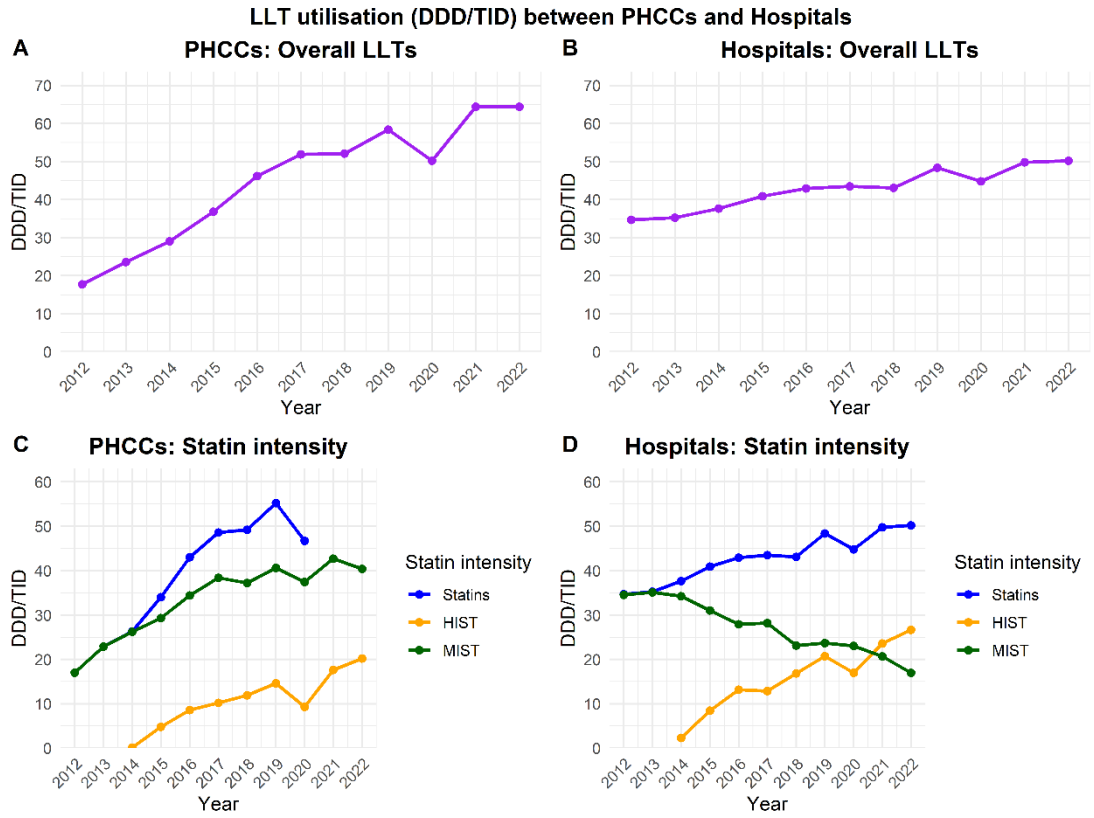

Figure 3.16 Annual utilisation trends in DDD/TID for LLTs in PHCCs (left panels) and hospital settings (right panels) from 2012 to 2022. **Panels A&B**: Overall LLTs; **Panels C&D:** Statin intensity**. LLT:** Lipid-lowering therapies; **DDD/TID:** Defined daily dose per 1,000 inhabitants per day; **PHCCs:** Primary healthcare centres; **HIST**: High-intensity statin therapy; **MIST**: Moderate-intensity statin therapy

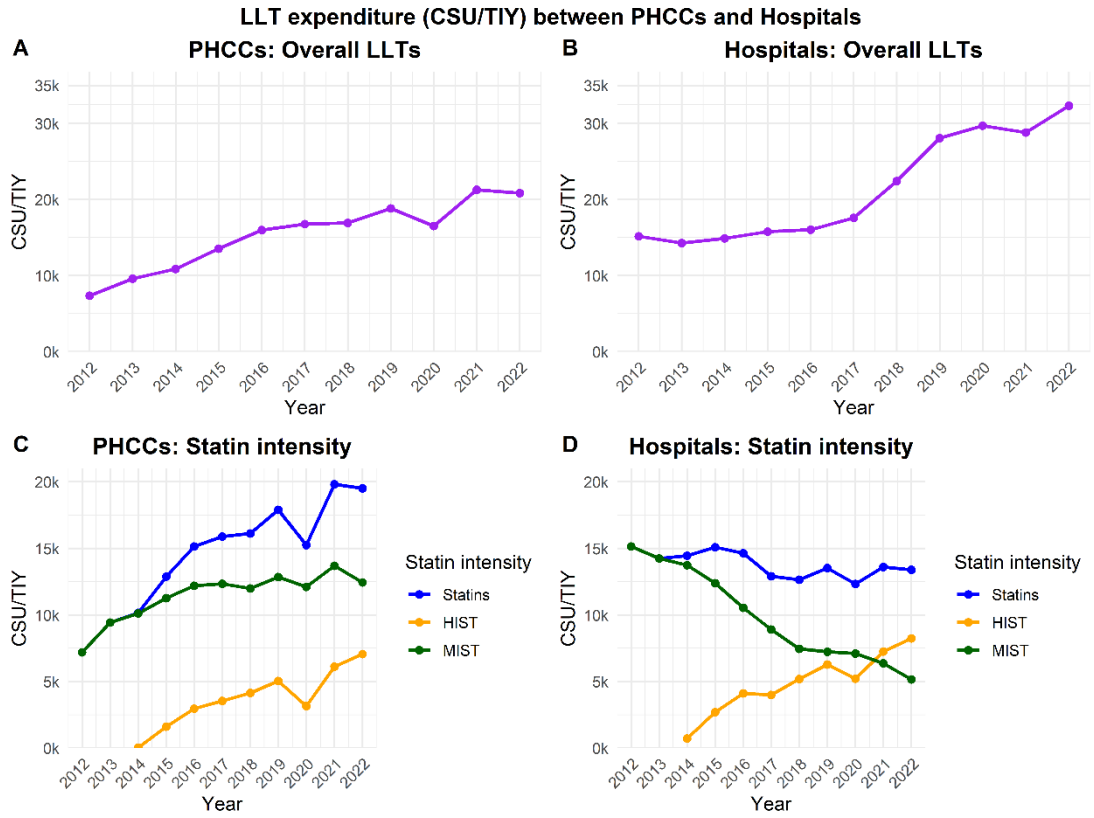

Figure 3.17 Annual expenditure trends in CSU/TIY for LLTs in PHCCs (left panels) and hospital settings (right panels) from 2012 to 2022. **Panels A&B**: Overall LLTs; **Panels C&D:** Statin intensity**. LLT:** Lipid-lowering therapies; **CSU/TIY:** Cost of supplied units per 1,000 inhabitants per year. **PHCCs:** Primary healthcare centres; **HIST**: High-intensity statin therapy; **MIST**: Moderate-intensity statin therapy.

3.4.5. Regional variations across six governorates

The main key findings are presented, as the overall trends were consistent with the national-level trends. Overall, the six governorates demonstrated broadly similar upward trends across all LLT utilisation (NSU/TIY & DDD/TID) and expenditure (CSU/TIY) metrics, with the CAP governorate consistently showing the highest levels (Figures 3.18-20).

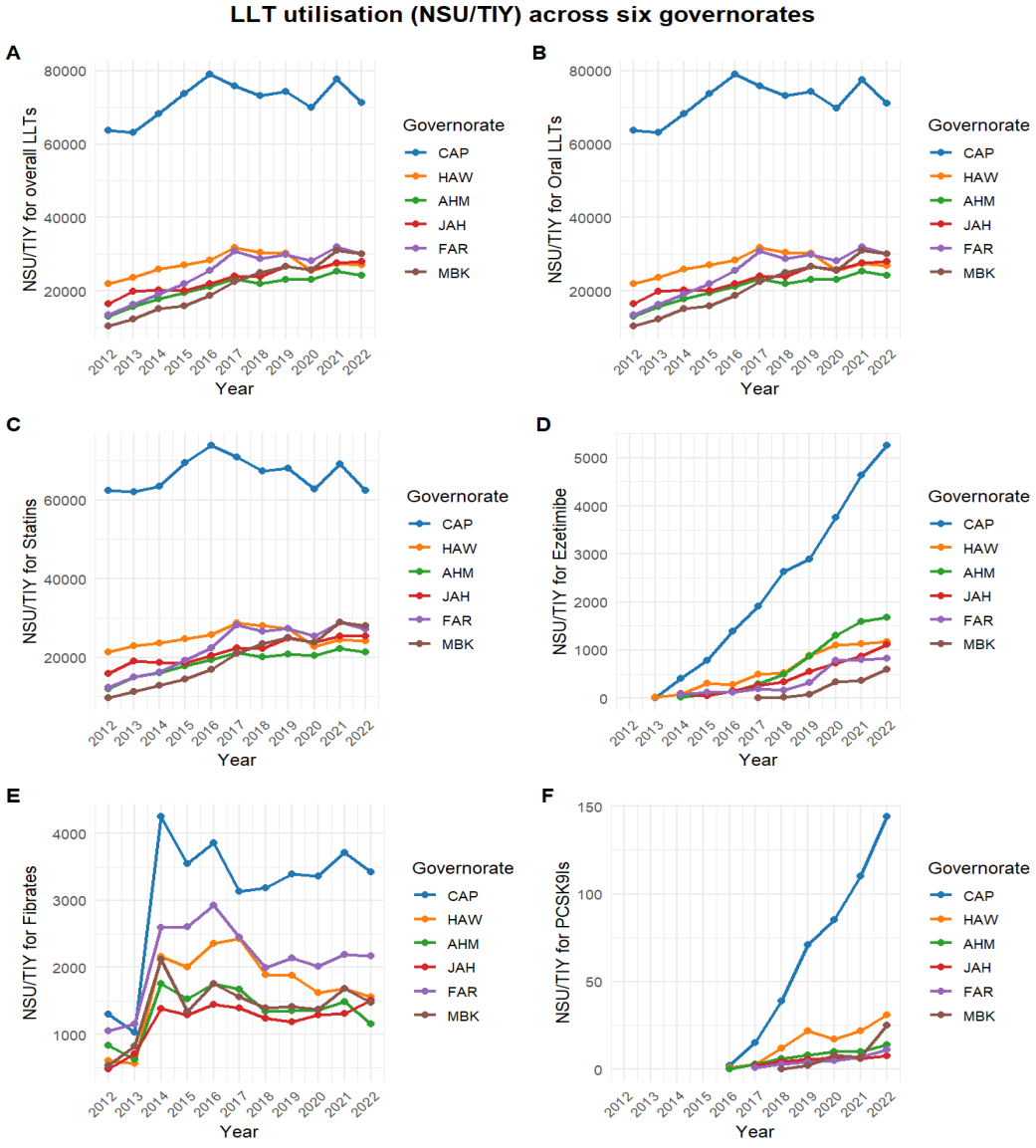

Figure 3.18 Annual utilisation trends in NSU/TIY for LLTs across the six governorates, from 2012 to 2022. **(A):** Overall LLTs; **(B):** Oral LLTs; **(C):** Statins; **(D):** Ezetimibe; **(E):** Fibrates; **(F):** PCSK9Is. **LLT:** Lipid-lowering therapies; **NSU/TIY:** Number of supplied units per 1,000 inhabitants per year; **PCSK9I:** Proprotein convertase subtilisin/kexin type 9 inhibitor; **CAP:** Capital; **HAW:** Hawalli; **AHM:** Al-Ahmadi; **JAH:** Al-Jahra; **FAR:** Al-Farwaniyah; **MBK:** Mubarak Al-Kabeer

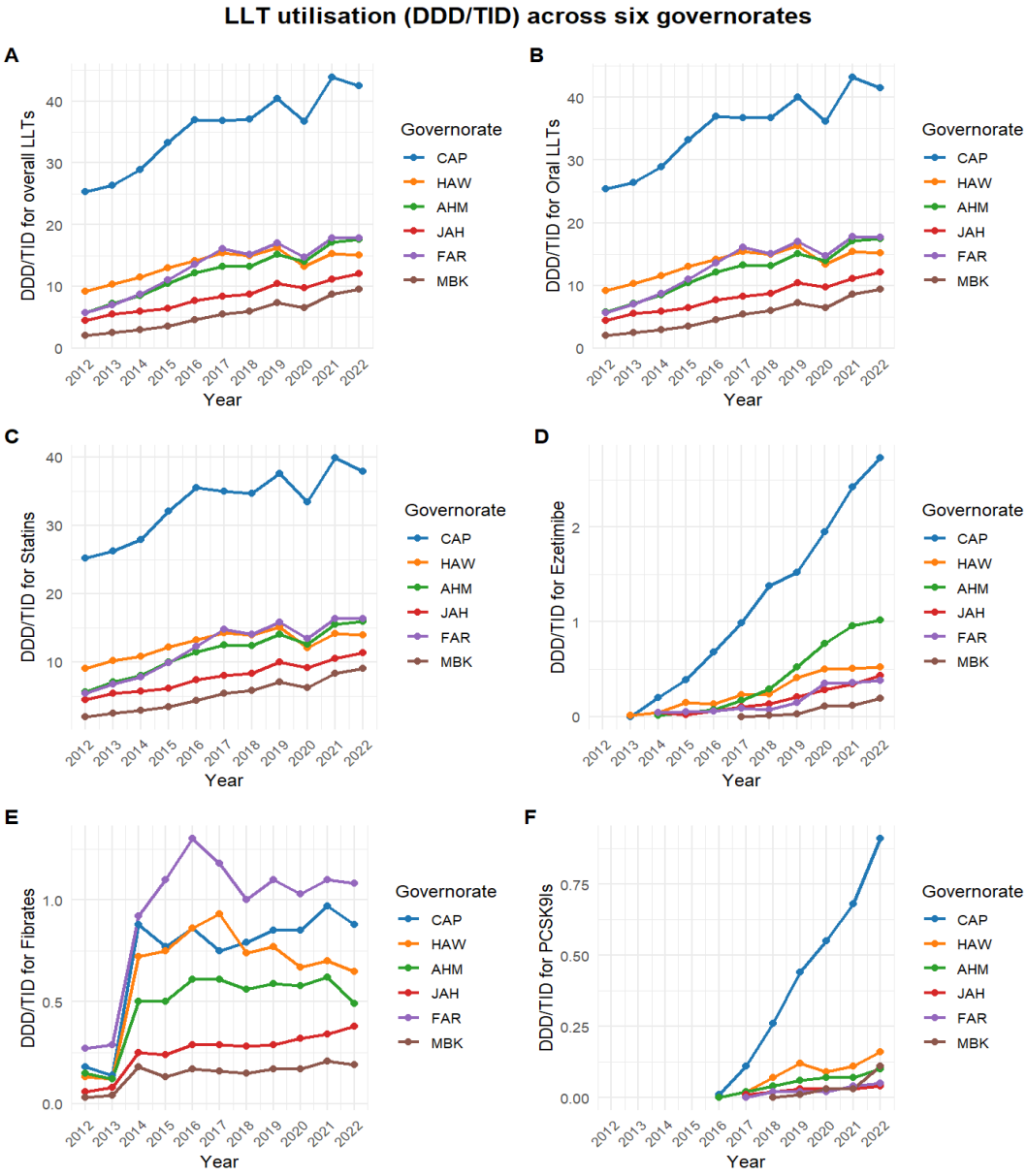

Figure 3.19 Annual utilisation trends in DDD/TID for LLTs across the six governorates, from 2012 to 2022. **(A):** Overall LLTs; **(B):** Oral LLTs; **(C):** Statins; **(D):** Ezetimibe; **(E):** Fibrates; **(F):** PCSK9Is. **LLT:** Lipid-lowering therapies; **DDD/TID:** Defined daily doses per 1,000 inhabitants per day; **PCSK9I:** Proprotein convertase subtilisin/kexin type 9 inhibitor; **CAP:** Capital; **HAW:** Hawalli; **AHM:** Al-Ahmadi; **JAH:** Al-Jahra; **FAR:** Al-Farwaniyah; **MBK:** Mubarak Al-Kabeer.

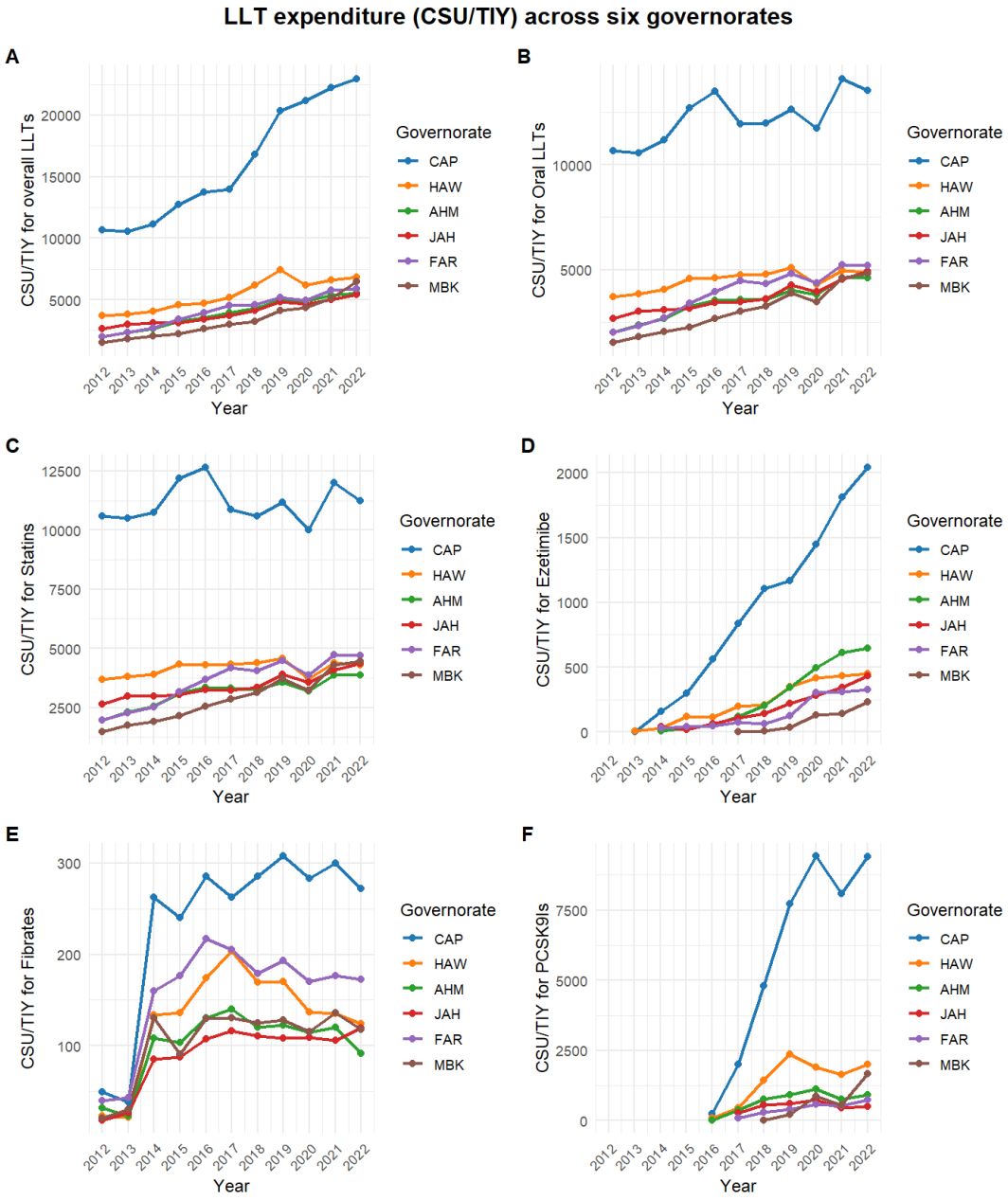

Figure 3.20 Annual expenditure trends in CSU/TIY for LLTs across the six governorates, from 2012 to 2022. **(A):** Overall LLTs; **(B):** Oral LLTs; **(C):** Statins; **(D):** Ezetimibe; **(E):** Fibrates; **(F):** PCSK9Is. **LLT:** Lipid-lowering therapies; **CSU/TIY:** Cost of supplied units per 1,000 inhabitants per year; **PCSK9I:** Proprotein convertase subtilisin/kexin type 9 inhibitor; **CAP:** Capital; **HAW:** Hawalli; **AHM:** Al-Ahmadi; **JAH:** Al-Jahra; **FAR:** Al-Farwaniyah; **MBK:** Mubarak Al-Kabeer.

3.5. Discussion

This study aimed to provide a comprehensive assessment of utilisation and expenditure trends for LLTs supplied by the CMS across all public governmental healthcare settings in Kuwait. Using aggregate-level data spanning an 11-year period (January 2012 to December 2022), the study examined national trends in LLT utilisation and expenditure, compared patterns between PHCCs and hospital settings, and explored regional disparities across the six governorates. Utilisation was quantified using the NSU/TIY and DDD/TID, while expenditure was assessed using CSU/TIY. LLTs were analysed by therapeutic class and further stratified by individual agents to enable a detailed evaluation of trends over time.

3.5.1. Key findings

At the national level, the study demonstrated a significant overall increase in both utilisation and expenditure trends across all LLTs examined. Utilisation, measured by NSU/TIY, rose from 138,549 in 2012 to 210,388 NSU/TIY in 2022 (52%, n = 71,839) (**Figure 3.3A**), while DDD/TID increased from 52.4 in 2012 to 114.6 DDD/TID in 2022 (119%, n = 62.2) (**Figure 3.7A**). Similarly, expenditure, measured by CSU/TIY, grew from 22,534 in 2012 to 53,161 CSU/TIY in 2022 (136%, n = 30,627) (**Figure 3.11A**).

Statins were the primary drivers of the overall increases in both utilisation (**Figure 3.3B** & **Figure 3.7B**) and expenditure (**Figure 3.11B**), accounting for the largest proportion of total LLT use throughout the study period. In terms of individual agents, atorvastatin was the most widely used statin when measured by NSU/TIY across the study period (Figure 3.4A) and remained the leading agent for both DDD/TID (**Figure 3.8B**) and CSU/TIY (Figure 3.12B) until 2020. Rosuvastatin became the predominant agent for these metrics (DDD/TID and CSU/TIY) in 2021 and 2022. When examining trends, atorvastatin showed a reduction trends in NSU/TIY and CSU/TIY trend, while its DDD/TID remained relatively stable. In contrast, rosuvastatin demonstrated upward trends across all utilisation and expenditure metrics. Stratification by statin intensity showed increasing utilisation of both HIST and MIST over time, with MIST

remaining the most utilised category (Figure 3.5A & Figure 3.9A). Expenditure trends showed an increase in HIST, while MIST demonstrated a declining expenditure trend (Figure 3.13A).

Ezetimibe demonstrated increases in trends across all utilisation and expenditure metrics, with rises of approximately ≈50000% in NSU/TIY (n= 10,618) (**Figure 3.3A**), DDD/TID (n= 5.3) (**Figure 3.7A**), and CSU/TIY (n= 4,120) (**Figure 3.11A**), considering the low baseline at the beginning of the study period.

PCSK9is also demonstrated upward trends following their introduction in 2016. Utilisation measured by NSU/TIY increased by 7667% (**Figure 3.3A**), and DDD/TID rose by 7200% (**Figure 3.7A**). In parallel, the CSU/TIY trend increased by 4190% (**Figure 3.11A**), taking into account the low baseline values. Throughout the study period, evolocumab consistently exceeded alirocumab in both utilisation (Figure 3.6A & Figure 3.10A) and expenditure (Figure 3.14A) metrics.

A comparison between PHCCs and hospitals revealed contrasting trends in the NSU/TIY for overall LLT utilisation, which increased in PHCCs but decreased in hospitals (Figure 3.15A-B). In contrast, the DDD/TID showed an upward trend in both healthcare settings (Figures 3.16A-B). Regarding regional variation, the six governorates exhibited generally similar upward trends in LLT utilisation and expenditure, with the CAP governorate recording the highest levels among all metrics (Figures 3.18-20).

3.5.2. Utilisation trends at the national level

This section first presents the utilisation trends for overall LLTs, followed by a detailed discussion of each class, organised by medications specifically used for LDL-C reduction: statins, ezetimibe, and PCSK9is.

3.5.2.1. Utilisation trends for overall LLTs

The utilisation of overall LLTs in Kuwait showed a sustained increase over time, as reflected by both NSU/TIY and DDD/TID, with growth observed across all LLT classes. This upward trend is largely consistent with the progressive evolution of clinical evidence and guideline recommendation that have increasingly emphasised more intensive lipid lowering. Notably, successive ESC/EAS guidelines have adopted more stringent lipid targets, with the LDL-C goal for individuals in very-high CV risk lowered from <1.8 mmol/L in 2016 to <1.4 mmol/L in 2019 (23). Guideline recommendations have also evolved in relation to treatment initiation and intensification. The 2016 ESC/EAS guidelines advised cautious initiation and gradual titration of LLTs in older adults, whereas the 2019 ESC/EAS guidelines recommend statin therapy at low dose in case of significant renal impairment, followed by intensification to achieve LDL-C targets (23). Similarly, dyslipidaemia management algorithms shifted from suggesting statin-ezetimibe combination therapy for suboptimal LDL-C in 2016 to clearly recommending this combination in 2019, with PCSK9is moving from a consideration in 2016 to a recommended option in 2019 when LDL-C goals remain unmet (23).

In parallel, regional guidance has further reinforced comprehensive lipid management. The 2021 Middle East consensus endorsed non-HDL-C as a co-primary lipid target alongside LDL-C, encouraging physicians to monitor and achieve multiple lipid goals concurrently, assuming adherence to this consensus recommendation (20). These developments provide a plausible explanation for the observed increases in LLT utilisation, with are discussed in more detail below for each LLT class.

The present study demonstrated that statins have consistently accounted for the highest utilisation level, followed by ezetimibe, and subsequently PCSK9is. This utilisation hierarchy aligns closely with the recommendations of current guidelines, including the 2019 ESC/EAS and 2018 ACC/AHA (23, 24), which advocate for a stepwise approach prioritising statins as the first-line therapy for reducing LDL-C, followed by ezetimibe and PCSK9is when lipid targets are not achieved.

Statins were the first LLT class to establish a causal relationship between LDL-C reduction and CV risk, supported by robust evidence for both primary and secondary prevention (23). The sustained dominance of statins across national healthcare settings in this study suggests a strong alignment with guideline recommendations and reinforces their role as the cornerstone of dyslipidaemia management. Following statins, the IMPROVE-IT trial in 2015 represented a key advance by demonstrating that adding ezetimibe to statin therapy further reduced LDL-C levels and improved CV outcomes (44). This evidence is highly reflected in the steady increase in ezetimibe utilisation observed in this study, increasing from 2,053 NSU/TIY in 2016 to 10,640 NSU/TIY in 2022, compared with a modest uptake following its initial introduction in late 2013, with 22 NSU/TIY increasing to 1,326 in 2015.

Over the past decade, the introduction of PCSK9is has further expanded dyslipidaemia management by providing substantial additional LDL-C reductions and significant CV benefits, particularly among patients at very high-risk CV risk or those with persistent suboptimal LDL-C control despite statin-ezetimibe combination therapy (54, 55). This evolving evidence base likely underpins the increasing utilisation trends of PCSK9i since their introduction. Although the aggregated nature of the dataset precludes assessment of prescribing appropriateness at the individual level, the upward utilisation trends for PCSK9is likely reflect the growing recognition of the need for intensive LLTs, given the high CV risk profile in Kuwait. Importantly, the absence of financial barriers within the public healthcare system may have facilitated access to these therapies when prescribed.

The overall increase in LLT utilisation suggests either an increase in the number of patients receiving LLTs or greater use of more intensive treatment regimens. Notably, DDD/TID for overall LLTs increased by 119%, from 52.4 in 2012 to 114.6 DDD/TID in 2022 (**Figure 3.7A**),which was more than double the relative increase observed for NSU/TIY (52%), from 138,549 in 2012 to 210,388 NSU/TIY in 2022 (**Figure 3.3A**). This difference indicates that treatment intensification, rather than growth in the number of treated patients, likely contributed to the upward utilisation trends. This pattern was particularly relevant with statins, where the increase in DDD/TID was approximately double that seen for NSU/TIY. This likely reflects greater use of higher statin doses, indicating intensification of statin therapy over time. Aa the DDD for statin agents corresponded to MIST (Table 3.2), increases in DDD/TID beyond NSU/TIY suggests a shift towards prescribing HIST regimens (further details in section 3.5.2.2).

The increased utilisation of ezetimibe and PCSK9is, suggests that these medications are typically used as add-on therapies to statins to achieve further LDL-C reduction (23). Thus, growing proportion of patients may fall into higher CV risk categories, necessitating more intensive lipid-lowering regimens. This interpretation is further supported by the 2019 ESC/EAS guidelines, which introduced more stringent LDL-C thresholds based on CV risk category and recommend intensification with ezetimibe and PCSK9is when LDL-C targets are not achieved (23) (further details in section 3.5.2.3 for ezetimibe and section 3.5.3.4 for PCSK9is).

Given the limited national-level evidence on LLT utilisation in Kuwait, the observed trends can be interpreted cautiously based on the clinical indications for LLTs. The growth in LLT utilisation could reflect prescribing for both primary and secondary prevention of CVDs, as well as for the management of primary and secondary dyslipidaemia, as discussed further below.

Individuals with CV risk factors, such as elevated LDL-C, have an increased predisposition to developing CVD (10). In these populations, primary prevention strategies using LLTs are fundamental to mitigate future CV risk. Evidence supporting this approach is provided by the JUPITER trial (42), which demonstrated the efficacy of statins in reducing CV events in primary prevention populations. In the present study, DDD/TID for all LLTs increased from 52.4 in 2012 to 114.6 DDD/TID in 2022 (**Figure 3.7A**). This corresponds to an increase in average daily exposure from 5.2% to 11.5% of the population in Kuwait receiving one DDD of an LLT per day. This growth in population-level exposure may partly explain the observed expansion of LLT use towards wider primary prevention populations.

Conversely, in patients with established CVD, secondary prevention aims to reduce the risk of recurrent CV events (14, 40). In Kuwait, the growing burden of CVD is likely to have contributed to greater use of intensified lipid-lowering regimens. CVDs remain the leading cause of mortality in Kuwait, with mortality rates increasing from 64 per 100,000 inhabitants in 2016 to 78 per 100,000 in 2022 across all nationalities (8, 106). Among Kuwaiti nationals, CVD-related mortality also increased, from 105 per 100,000 in 2012 to 111 per 100,000 in 2022 (8, 107, 108). Although national data directly linking elevated cholesterol levels to CVD mortality in Kuwait are unavailable, the increasing burden of cardiometabolic conditions that frequently coexist with dyslipidaemia may provide indirect support for more intensive lipid management. In particular, diabetes, which commonly coexists with dyslipidaemia (see **Appendix S2.4** for diabetic dyslipidaemia), has shown increase in associated mortality, increasing from 133 deaths in 2015 to 410 in 2022, with peaks of 566 in both 2019 and 2020 (8, 107, 109). Based on these data, the increase in the HIST utilisation, alongside ezetimibe and PCSK9is, may partly reflect a shift towards more aggressive lipid-lowering regimens in patients with established CVDs.

Stricter LDL-C thresholds recommended for secondary prevention provide a plausible explanation for the intensification of LLT utilisation (23). Current guidelines recommend an LDL-C target of <1.4 mmol/L for patients with established CVDs, with a more stringent target of LDL-C <1.0 mmol/L considered for those experiencing recurrent vascular events within two years (23). However, the interpretation of increased utilisation of intensified regimens should be made with caution, as it assumes appropriate adherence to guideline recommendation when lipid target remain unmet.

Moreover, the overall increase in LLT utilisation may also suggest the use of LLTs in the management of primary dyslipidaemia disorders, particularly FH, a genetic condition characterised by markedly elevated LDL-C levels from birth. If left untreated, FH is associated with a significantly increased risk of premature CVD (32), highlighting the importance of early identification and aggressive LLT. The 2019 ESC/EAS guidelines (23) recommend that individuals with FH classified as very-high risk in primary prevention should achieve an LDL-C target of <1.4 mmol/L. The prevalence of FH may be higher in the Middle East, partly due to the higher frequency of consanguineous marriages in the region (110, 111). Supporting this, the Gulf FH Registry (2021), a multicentre study conducted across five Gulf countries, including Kuwait, estimated the prevalence of FH to be approximately 1 in 112 individuals, which is nearly three times higher than the global estimates of 1 in 313 (32).

Furthermore, LLTs are also used in the management of secondary dyslipidaemia, which often coexists with other CV risk factors such as T2DM and obesity (25) (details in **section 2.2.1. p13**). In Kuwait, these cardiometabolic risk factors are highly prevalent, thereby compounding the burden of dyslipidaemia at the national level. According to the NCD Risk Factor Collaboration (NCD-RisC), the age-standardised prevalence of T2DM among adults (≥18 years) in Kuwait ranged from 23% to 24% in females and 27% to 28% for males between 2002 and 2022 (33). Similarly, WHO data indicate that the age-standardised prevalence of obesity (body mass index (BMI) ≥30)

among adults in Kuwait was approximately 41% between 2012 and 2022 (34). Although these conditions are often linked to primary prevention strategies, their coexistence with dyslipidaemia necessitates an integrated management approach that combine lifestyle modifications with pharmacological LLTs. This cardiometabolic interplay may partly explain the sustained increase in overall LLT utilisation over time.

The increase in LLT utilisation observed in this study is consistent with trends reported internationally. Comparisons are presented first with aggregate utilisation studies, followed by findings derived from patient-level data. Findings reported by Blais et al. (2021), who documented a significant global rise in LLTs use across 83 countries between 2008 and 2018 (63), using a comparable utilisation metric of units per 1,000 inhabitants per year. As a HIC, Kuwait demonstrated utilisation trends similar to those in Europe and North America, with significantly higher LLT uptake than that observed in LICs, particularly in Africa (63). Comparable findings have also been reported in LICs. A study conducted in the Republic of Srpska reported a 167.7% (n= 21.5) increase in LLT utilisation, using a similar utilisation metric (DDD/TID) over a similar timeframe (2010–2020). In alignment with the findings of the current study, statins accounted for more than 95% of total LLT use by 2020 (64). Despite difference in income settings, these findings reinforce the role of stains as the mainstay of LLT following the guideline recommendations.

Other findings, primarily at the patient level, still provide meaningful comparisons. In the US, two surveys showed similar trends in LLT utilisation. A survey conducted between 2002 and 2013, though a decade prior to this study, revealed a similar trend with a significant increase in both statin and non-statin use (65, 66). Statin usage rose by 79.8% (n= 17.4 million individuals), and prescriptions increased by 64.9% (n= 87 million). The use of non-statin therapies among adults doubled from 2.5% to 5.6%, with prescriptions rising by 128% (from 20.1 to 45.8 million) (66). Another retrospective cohort study of Medicare beneficiaries (2007–2011) reported an overall increase in statin use, alongside a decline in non-statin usage, specifically for

ezetimibe, niacin, fibrates, and bile acid sequestrants, but were grouped into a single category (112). The findings also mirrored utilisation trends in Western countries. A retrospective Swiss study conducted within a similar timeframe (2013-2019) reported a 14.3% increase in patients prescribed LLTs, with statins accounting for 90% of LLT prescriptions (67).

3.5.2.2. Utilisation trends for statins

A key finding of this study is that statin utilisation increased more than twofold when measured using DDD/TID (102%, n= 53) (**Figure 3.7A**) with NSU/TIY (41%, n= 54,501) (**Figure 3.3A**). This pattern mirrors the pattern observed for overall LLT utilisation and suggests that statin intensification, rather than an expansion in the number of statin users, was the major contributor to the upward trends, as previously described. This finding is largely attributable to the frequent prescribing of statin doses that exceed the WHO-defined DDDs for statins (simvastatin= 30mg, pitavastatin= 2mg, atorvastatin= 20mg, and rosuvastatin= 10mg) (Table 3.2) (104). This suggests that, in routine clinical practice, higher doses of simvastatin 40mg, pitavastatin 4mg, atorvastatin 40mg, and rosuvastatin 20mg are frequently prescribed, which likely contributed to the increase in DDD/TID trend for statin. Consequently, the upward DDD/TID trend is likely to reflect statin dose intensification, longer treatment duration, or both.

Notably, atorvastatin and rosuvastatin, which at higher doses fall within the HIST category (**chapter 2**, Table 2.3), contributed substantially to the increase in HIST utilisation across both utilisation metrics (a 1,946% increase in NSU/TIY (Figure 3.5A) and a 1,830% increase in DDD/TID (Figure 3.9A). These trends suggest a gradual shift towards more intensive lipid-lowering regimens over the study period. According to current guideline recommendation (23), HIST may be initiated either in statin-naïve patients at very-high CV risk, in both primary and secondary prevention, or in patients already receiving LLTs who require further LDL-C reduction to achieve recommend targets. The increasing adoption of HIST observed in this study may therefore reflect

the evolution of lipid management guidelines, particularly the narrowing LDL-C targets to <1.4 mmol/L and, in selected very high-risk patients, to <1.0 mmol/L (23).

However, as these data are aggregated, some degree of misclassification cannot be excluded. For example, patients receiving double doses of MIST may have been categorised as MIST rather than HIST. Despite this possibility, only modest increases in MIST utilisation were observed over the study period (4% for NSU/TIY (**Figure 3.5A**) and 11% for DDD/TID (**Figure 3.9A**). This suggests that widespread misclassification is unlikely, although it cannot be completely ruled out to.

Importantly, MIST remained the most utilised intensity category throughout the study period. However, this does not necessarily indicate less intensive LLT. Recent expert perspectives from ESC publications have emphasised a paradigm shift from an "intensive statin therapy first" or "wait and watch" approach towards earlier use of an "intensive LLT" approach in very high-risk CV patients (85). Therefore, patients may receive a MIST in combination with ezetimibe and/or a PCSK9i to achieve the LDL-C goal of LDL <1.4 mmol/L for patients with very-high CV risk. Combining a MIST with ezetimibe may achieve LDL-C targets more effectively than HIST monotherapy, as CV risk reduction is driven primarily by the extent of LDL-C lowering, rather than by the specific drug used to achieve it (85). Although these expert recommendations were published relatively late in the study period (2022), their application is plausible, particularly in hospital settings, where patients at very-high CV risk are more likely to be manged using combination-based therapies.

Evidence supporting this approach is provided by the RACING trial (113), a multicentre randomised study conducted in South Korea, enrolling 3,780 patients with established ASCVD between 2017 and 2018 to compare MIST plus ezetimibe with HIST monotherapy (113). After three years of follow-up, LDL-C levels <1.8 mmol/L were achieved in 72% of patients in the combination therapy group compared with 58% in the monotherapy group (113).

Variations in the utilisation levels and trends of individual statin agents may be partly explained by comparative efficacy evidence that has influenced prescribing patterns. Atorvastatin was the most widely used statin when measured by NSU/TIY (**Figure 3.4B**) throughout the study period and remained the leading agent for DDD/TID (**Figure 3.8B**) until 2020, after which rosuvastatin became predominant in 2021 and 2022. The consistent increase in NSU/TIY for atorvastatin may be related to its well-established efficacy in LDL-C reduction and CV risk reduction compared with simvastatin. Evidence from major trials supports this interpretation, including CURVES study, which showed that atorvastatin achieved a greater reduction in LDL-C level than equivalent doses of simvastatin (114). Additionally, a multicentre PROBE (prospective open-label blinded end point) trial (115) demonstrated that atorvastatin 10mg achieved a 37% reduction in LDL-C, which was greater than the reductions observed with simvastatin 10mg (28.9%) and 20mg (33.8%), with comparable safety profiles (115).

Additionally, atorvastatin was available earlier in the study period, initially at doses of 10mg and 20mg, whereas rosuvastatin became available later, towards the end of 2013. This earlier availability may have contributed to greater prescriber familiarity with atorvastatin and its sustained use before wider adoption of rosuvastatin, despite clinical guideline not expressing a preference between these two agents.

Evidence comparing the lipid-lowering efficacy of statins suggest that rosuvastatin may achieve greater LDL-C reduction. The subsequent introduction of atorvastatin 40mg in mid-2014 may have further supported atorvastatin uptake by providing greater flexibility for dose titration. In contrast, the shift towards rosuvastatin observed in DDD/TID during the final two years of the study may reflect increased use of high intensity rosuvastatin at 20mg dose.

When examining trends, atorvastatin showed a reduction in NSU/TIY trend over time (**Figure 3.4A**), while its DDD/TID remained relatively stable (**Figure 3.8A**). In contrast, rosuvastatin demonstrated consistent upward trends across all utilisation metrics. The reduction in atorvastatin NSU/TIY may plausibly be related to the introduction of the higher strength formulation of atorvastatin 40mg in mid-2014 (**Appendix S3.1**). The availability of this dose likely reduced the need for lower strength formulations, as both atorvastatin 10mg (n= -15,690) and 20mg (n= -27,333) declined by approximately 40% while the 40mg increased by 2555% (n= 18,056) (data not shown). Despite this shift in the NSU/TIY, the overall the DDD/TID for atorvastatin remained stable, as the decreases in atorvastatin 10mg (42%, n= -3.9) and atorvastatin 20mg (44%, n= -14.2) were offset by the substantial increase in atorvastatin 40mg (2372%, n= 17.2). By contrast, rosuvastatin demonstrated a sustained increase in utilisation, with both doses 10mg and 20mg strengths showing upward trend over the years (data not shown).

Meanwhile, the upward trend observed for rosuvastatin across both utilisation metrics (**Figure 3.4A** & **Figure 3.8A**) may be partly attributed to its superior potency in lipid lowering. Evidence from the STELLAR study demonstrated that rosuvastatin reduced LDL-C by 8.2% more than atorvastatin and 12-18% more than simvastatin (116). The study also reported that rosuvastatin was more effective in increasing HDL-C and in reducing TG and TC compared with other statins (116). Importantly, rosuvastatin achieved equivalent or superior lipid-lowering effects at lower doses compared to other statins (116). However, both rosuvastatin and its comparator statins were well tolerated, with no significant differences in adverse event profiles (116). Consistent with these findings, a systematic review and network meta-analysis of 50 RCTs involving 51,956 participants found that rosuvastatin ranked highest among seven statin in terms of LDL-C reduction (117). These findings may help explain prescribing preferences and could have contributed to the upward trend in rosuvastatin utilisation over time.

Simvastatin demonstrated modest increasing trends across both utilisation metrics were increased (**Figure 3.4A** & **Figure 3.8A**); however, it accounted for the low utilisation among statins, with a proportion of 20% in NSU/TIY and 15% in DDD/TID in 2022. Although the efficacy of simvastatin was established in the HPS trial (118), its use has declined potentially due to the available of more effective statin agents (e.g., atorvastatin and rosuvastatin) and the risk of myopathy risk at higher doses. Pitavastatin, which was available from 2017 to 2021, had minimal utilisation rates. Although favoured for its safety profile and minimal drug-drug interactions, it remains less widely studied and prescribed (20).

Globally, similar aggregate-level patterns of statin utilisation have been reported, with disparities across countries. A broader ecological cross-sectional analysis across 91 countries highlighted disparities in statin utilisation between HICs and LMICs (2015-2020) (80). Statin utilisation increased globally by 25% (n= 13.6) using DDD/TID, with HIC reporting seven times higher usage rates compared to LMICs by 2020 (80). These disparities could be due to differences in healthcare access and economic resources. In Western countries, a study by Vancheri et al. (79), which focused on statins in 12 countries, including Scotland, revealed a dramatic increase in statin utilisation from 2000 to 2012 using DDD/TID. The highest increase was observed in Denmark (+1,263%), while the lowest was in Belgium (+121%) (79).

A similar trend was observed in Lithuania (81), where statin use rose by 1,060%, from 8.28 to 96.1 DDD/TID between 2010 and 2020. Similarly, the study also observed growth in MIST alongside a shift towards HIST regimens. At the agent level, atorvastatin remained the most prescribed statin, while rosuvastatin showed a more pronounced increase over time, mirroring the patterns seen in the present study (81). However, unlike our findings, rosuvastatin utilisation in Lithuania surpassed atorvastatin as early as 2015, whereas similar shift was observed in the final years of the current study period. The authors attributed this earlier transition this to increased use of fixed-dose combination therapies, which predominantly included

rosuvastatin. Such combination products were not available in Kuwait during the study period, suggesting differences in formulary availability and prescribing practices between countries (81). In the Republic of Srpska (64), similar to our findings, atorvastatin and rosuvastatin showed the highest utilisation using DDD/TID, with significant shifts toward HIST. Consistent with our findings, atorvastatin increased by 107%, however, but, unlike our results, simvastatin use declined by 73% (64).

Furthermore, patient-level data could provide a more holistic picture of statin trends across different regions. In the US, data from Medicare showed a modest increase in statin utilisation among patients with coronary heart disease (CHD) (2007-2011), rising from 53.1% to 58.8% (112). Similarly, the use of HIST increased from 11.1% to 14.2%, although the adoption of more intensive lipid-lowering strategies remained limited. In alignment with our findings, a retrospective cohort study conducted in Switzerland (67) demonstrated a significant increase in the use of atorvastatin and rosuvastatin, has increased significantly, with minimal uptake of pitavastatin (67). Conversely, simvastatin utilisation decreased from 23.1% to 13.1% (67) due the preference of using potent statins. The overall adoption of HIST in the Swiss remained suboptimal due to intolerance to high doses (67). Similarly in Taiwan (82), a study conducted between 2002 to 2011, a decade before this study, revealed a steady increase in statin utilisation. The number of patients on statins grew from 10,299 to 50,687 (392%) (82). In line with this study, atorvastatin remained the most commonly prescribed statin, and rosuvastatin also experienced rapid growth (82). Likewise, MIST saw a marked increase in use, rising from 49% to 71% by 2011, whereas the use of HIST remained rare, accounting for only 2% of prescriptions (82). The low utilisation of HIST is likely influenced by formulary availability and the adoption of broader lipid targets at the time.

3.5.2.3. Utilisation trends for ezetimibe

The increasing utilisation trends of ezetimibe, across both NSU/TIY (49238%, n= 10,619) and DDD/TID (49531%, n= 4,119), are likely attributable to evolving clinical evidence and subsequent updates to international guideline recommendations. Following the introduction of ezetimibe in 2013, utilisation increased from 22 NSU/TIY and 0.01 DDD/TID in 2012 to 2,053 in NSU/TIY and 1.0 in DDD/TID by 2016. In the same year, the IMPROVE-IT trial (44), was published and demonstrated a 6.4% relative reduction in CV events when ezetimibe was added to simvastatin in patients ACS patients. This landmark trial resolved earlier uncertainty about the CV benefits of ezetimibe, leading to its inclusion in major guideline recommendations. The 2016 and 2019 ESC/EAS guidelines (23, 45) and 2018 AHA/ACC guidelines (24) recommended ezetimibe as an add-on to statins for patients requiring aggressive LDL-C lowering. Additionally, the 2016 and 2021 Middle East consensus endorsed ezetimibe as second-line therapy alongside maximally tolerated statins for additional LDL-C reduction (20, 119). By 2022, ezetimibe utilisation had reached 10,640 NSU/TIY and 5.3 DDD/TID, accounting for ≈5% of total LLT utilisation across both utilisation metrics, compared with around 90% for statins (**Figure 3.3** & **Figure 3.7**).

Interpretation of these findings should be made with caution due to the aggregate nature of the data. The disparity between statin and ezetimibe utilisation may suggest that many patients achieved lipid targets with statins monotherapy and therefore did not require further treatment intensification. Alternatively, it may reflect underuse of combination therapy for patients with suboptimal lipid control (23). Notably, although access to ezetimibe in Kuwait is largely limited to Kuwaiti nationals, this is unlikely to have affected utilisation, as all utilisation metrics for ezetimibe were adjusted to the Kuwaiti population size.

Aligning with the findings of this study, several earlier studies on statin utilisation also included ezetimibe. These findings collectively highlight how updates in clinical guidelines and the outcomes of clinical trials have shaped ezetimibe the global patterns of ezetimibe utilisation, albeit with significant regional disparities.

Similar to our findings, Blais et al. (2021) also observed a notable shift towards non-statin therapies, including ezetimibe between 2016 and 2018 (63). This trend reflects the impact of evolving clinical guidelines and updated recommendations. In contrast, the Republic of Srpska reported negligible utilisation of ezetimibe (64). Despite a similar timeframe to this study (2010–2020), the limited uptake highlights the challenges faced by LICs in accessing and adopting advanced therapies (64). In the US, ezetimibe usage initially surged, peaking in 2007–2008 (112). However, they claimed that this was followed by a sharp decline after the ENHANCE trial in 2008 and the SEAS trial, which raised safety concerns and questioned its CV benefits (112). Medicare data further highlighted this trend, with ezetimibe usage peaking at 12.1% in 2007 but dropping to 4.6% by 2011 (112). In accordance with our results, Western countries, such as Switzerland also exhibited an increasing trend in non-statin therapy utilisation, including ezetimibe, between 2013 and 2019, with an increase of 115.9% (67). This growth likely reflects the impact of the IMPROVE-IT trial, which reinforced the role of ezetimibe as an effective add-on therapy to statins (44). In agreement with our results, Australia followed a more consistent pattern, with ezetimibe usage steadily increasing over time, both as monotherapy and in combination (68). In Asia, Taiwan demonstrated notable uptake of ezetimibe in lipid management (82). By 2011, ezetimibe accounted for 66.2% of combination LLTs, likely reflecting early adoption of evolving guideline recommendations (82), even prior to the publication of the IMPROVE-IT trial.

3.5.2.4. Utilisation trends for PCSK9is

The utilisation of PCSK9is began at very low levels following their introduction in 2016 (NSU/TIY= 3 and DDD/TID= 0.02) and increased steadily through to 2022 (NSU/TIY= 233 and DDD/TID= 1.26) (**Figure 3.3** & **Figure 3.7**), ranking third in overall LTT utilisation after statins and ezetimibe. Despite this increase, PCSK9i utilisation remained relatively low, which likely reflects their position as a last-choice therapy, reserved for patients with inadequate LDL-C control despite maximally tolerated statin and ezetimibe therapy (23). Accordingly, patients initiated on a PCSK9i are typically already receiving oral LLTs. In Kuwait, PCSK9i prescribing is further restricted to specialist physicians, such as cardiologists, and is limited to hospital settings, usually for patients at very-high or high CV risk. Collectively, these factors are likely to have contributed to the limited uptake.

Importantly, affordability is unlikely to have been a barrier to PCSK9i use in Kuwait, as these medications are provided free of charge and supplied directly to public healthcare facilities from the CMS. Additionally, the absence of formal lipid threshold restrictions for prescribing PCSK9is (120) may further facilitate their use. This suggests that prescriber decision-making, rather than cost or access, plays a central role in determining PCSK9i utilisation. Notably, as PCSK9is are listed under the CML, where medications are primarily designated for the Kuwaiti population (**chapter2**, **section 2.4, p28**), demographic changes are unlikely to have influenced these findings. This is because that utilisation rates were standardised using the Kuwaiti population size rather than total population size.

Moreover, the low utilisation of PCSK9is compared to oral LLTs can also be attributed to dosing frequency, with PCSK9is typically administered biweekly, whereas oral therapies are taken daily. This difference is reflected in the NSU/TIY metric. For example, in 2022, oral LLTs accounted for 210,155 NSU/TIY compared to 233 NSU/TIY for PCSK9is, representing shares of 99.9% and 0.1%, respectively. However, when considering the DDD/TID metric, which reflects daily maintenance dosing, oral LLTs

accounted for 113.2 DDD/TID, while PCSK9is were at 1.4 DDD/TID, corresponding to shares of approximately 99% and 1 %, respectively. Therefore, dosing regimen could not be considered a strong contributor to the low uptake.

Importantly, the sharp increase in PCSK9i utilisation observed can be largely attributed to the established CV outcome benefits demonstrated in landmark clinical trials, namely FOURIER for evolocumab (54) and ODYSSEY OUTCOMES for alirocumab (55). These trials reinforced the principle of that greater LDL-C reduction is associated with incremental CV risk reduction, often summarise as "the lower, the better" concept. The incorporation of this evidence into major guidelines, including the 2018 AHA/ACC and 2019 ESC/EAS recommendations, is likely to have facilitated wider adoption of PCSK9is in clinical practice (23, 24). These guidelines recommend PCSK9is for patients with persistently elevated LDL-C despite maximally tolerated statins and ezetimibe therapy, as well as for selected patients with statin intolerance or FH.

In terms of PCSK9i agents, the utilisation of evolocumab consistently surpassed that of alirocumab across all years, indicating its dominant share among PCSK9is. For instance, in 2022, evolocumab accounted for 78% of NSU/TIY and 89% of DDD/TID. Although clinical trials show no superiority between the two agents, one distinction is that the single-dose prefilled autoinjector of evolocumab contains dry natural rubber (a derivative of latex) (121). The high evolocumab utilisation may be attributed to its earlier introduction (December 2016), allowing patients to remain on the therapy if adherence was achieved. While alirocumab was introduced shortly after February 2017, irregular supply between June 2016 and December 2017, along with intermittent disruptions in 2022, likely influenced prescriber preferences and limited its uptake (**Appendix S.3.1**).

Furthermore, the availability of a single strength for evolocumab (140mg) may have made it more convenient for prescribing compared to the variable dosing options of alirocumab (75mg and 150mg), with the 150mg dose only becoming consistently available in March 2022 (47, 48). Another plausible explanation that may have contributed to the preference for evolocumab is the dosing schedules. A standard dose of evolocumab is 140mg every two weeks, or if needed 420mg monthly, corresponding to three subcutaneous pens (47). Whereas the standard dose of alirocumab is either 75mg or 150mg every two weeks, with a maximum of 300mg monthly (48), necessitating four pens of 75mg, if 150mg not available consistently. This variability, combined with supply issues, likely shifted prescriber focus towards evolocumab.

Aligning with the current findings, Blais et al. observed a shift towards non-statin therapies, including PCSK9is (63). In contrast, utilisation in LICs, such as the Republic of Srpska, remains negligible due to access barriers and cost concerns (64). Reinau et al. reported a substantial increase in PCSK9i prescriptions (439.2%) since their introduction in 2016 in Switzerland, though utilisation remains limited due to cost and restrictions to high-risk populations (67). Similarly, Australia noted emerging PCSK9i use since 2017, but it remains a small proportion of overall LLTs (68). These findings are consistent with the present study, in which PCSK9is accounted for the lowest utilisation among all LLTs.

3.5.3. Expenditure trends at national level

The expenditure trend for overall LLTs, as expressed by the CSU/TIY, increased by 136% (n= 30,627), from 22,534 in 2012 to 53,161 CSU/TIY in 2022 (**Figure 3.11A**). This surge was primarily driven by statin expenditure, which increased by 47% (n= 10,555), from 22,350 in 2012 to 32,905 CSU/TIY in 2022 (**Figure 3.11A**). The upward expenditure trend mirrors the trends observed in statin utilisation across both metrics (NSU/TIY and DDD/TID), likely reflecting the increased costs associated with higher utilisation levels. However, the discussion mainly focuses on utilisation measured by the NSU/TIY metric, since both NSU/TIY and CSU/TIY metrics are derived from similar calculations, with costs directly linked to the NSU.

It is reasonable to postulate that the increase in the overall LLT utilisation over time contributed significantly to the rise in total LLT expenditure. Similar factors discussed earlier regarding the increase in utilisation likely align with this expenditure trend. A plausible explanation is that the increase in LLT expenditure was largely driven by greater utilisation of statins, given their role as first-line therapy (**Figure 3.11A**). The introduction of new statin agents, including atorvastatin 40mg and two strengths of rosuvastatin (10mg and 20mg), likely contributed to the subsequent rise in expenditure, following the observed increase in utilisation (data not shown).

Furthermore, the adoption of PCSK9is in 2016 contributed to the growth in total LLT expenditure. The increase in PCSK9i trend was 4,195% (n= 14,877), rising from 355 in 2016 to 15,231 CSU/TIY in 2022. By 2022, statins accounted for 62% of total LLT expenditure (CSU/TIY= 32,905), while PCSK9is accounted for 29% (CSU/TIY= 15,231) (**Figure 3.11B**).

Although the NSU/TIY of PCSK9i in 2022 was considerably low (NSU/TIY= 233) compared to oral LLTs (NSU/TIY= 210,155), the cost/unit for PCSK9is likely amplified their impact on total expenditure. The cost/unit for PCSK9is decreased from 136 KWD (£332) to 65 KWD (£159) in 2022. This reduction was influenced both agents, in which the cost/unit for evolocumab dropped from 135 KWD (£329) to 62 KWD (£151), and for alirocumab, it decreased from 106 KWD (£258) to 75 KWD (£183). Despite the continuous increase in NUS/TIY for PCSK9is, the CSU/TIY trend increased steadily until 2020, reaching 14,637 CSU/TIY, before decreasing to 12,043 CSU/TIY in 2021. PCSK9is then peaked in 2022 at 15,231 CSU/TIY. This fluctuation was largely due to the reduction in the cost/unit of evolocumab, which fell from 122 KWD (£298) in 2020 to 77 KWD (£188) in 2021. While this cost further decreased to 62 KWD (£151) in 2022. The introduction of alirocumab 150mg in 2022, with a cost/unit of 107 KWD (£261), contributed also to the upward CSU/TIY trend.

Although the data were at the aggregate level, one potential reason for the overall LLT costs could be the increased use of combination therapies in recent years, incorporating agents such as ezetimibe and PCSK9is, which enhanced treatment effectiveness. For instance, triplet therapy with statins, ezetimibe, and PCSK9is has been shown to reduce LDL-C levels by approximately 85% (23). This approach likely contributed to the cumulative cost burden over time.

Moreover, it is reasonable to propose that the unavailability of generic medications in this study likely constrained the role of price reductions in shaping expenditure trends. Since all medications remained branded throughout the study period, cost changes were not influenced by the introduction or substitution of generics. Furthermore, the study did not adjust for inflation; therefore, the reported expenditure trends represent real prices, unadjusted for currency value over time.

Another plausible explanation of the upward trend could be related to the centralised pharmaceutical procurement policy in Kuwait, managed by the CMS (76). This policy likely facilitated cost containment by streamlining the procurement process. As a result, patients can access their prescribed medications without delays, as they are readily available at onsite pharmacies within the same facilities where prescriptions are issued. This efficient process enhances accessibility and eliminates additional barriers to obtaining treatment. Consequently, the ease of utilisation (prescribing/dispensing) likely contributed to the increase in overall costs. This means that patients in Kuwait do not face concerns about reimbursement or out-of-pocket expenses, as healthcare services, including medications, are provided free of charge, with nominal fee (ranging from 1 to 2 KWD, equivalent to ≈ £2.5 to £5) paid by non-Kuwaiti individuals at the time of this study.

There are limited studies that focus specifically on the expenditure trends of LLTs. However, several studies mentioned earlier in the utilisation section have incorporated discussions on expenditure trends. For example, in the Republic of Srpska, despite the use of different expenditure metrics, including absolute prices and price/DDD, a comparable upward trend in overall LLT expenditure was reported, with a 73% increase (64). In agreement with our results, this rise was primarily driven by statins, as measured by price per DDD (64). Similarly in Lithuania (81), mirroring our findings, a 260% rise in total LLT expenditure was observed (81). However, the widespread adoption of generics reduced the cost per DDD by 66.7%. The present study did not use the price per DDD metric, likely due to the unavailability of generics, which could influence cost trends. These findings highlight disparities in expenditure trends across countries, likely reflecting differences in healthcare policies, reimbursement systems, and out-of-pocket costs. However, all studies highlighted the critical role of generic adoption in reducing overall expenditure, particularly for statins, which is not applied in our study.

3.5.4. Fibrates utilisation and expenditure

The current study did not focus on fibrates as the primary therapy for LDL-C reduction, as recent guideline updates have shifted the emphasis towards other agents. However, historically, fibrates were used as adjuncts to statins before the rise of the "LDL-C hypothesis," which posited that lower LDL-C leads to better CV outcomes. This hypothesis gained stronger evidence through statin trials such as the 4S in 1994 and HPS in 2002 (39, 118), which demonstrated the superiority of statins in reducing LDL-C and improving CV outcomes across broader patient populations. The introduction of ezetimibe (early 2000s) and PCSK9is (approved in 2015) further provided highly effective options for LDL-C reduction, shifting the focus away from triglyceride-lowering therapies like fibrates. Therefore, examining fibrate utilisation remains crucial to understand how the evolution of LLTs has changed over time and whether these patterns align with real-world studies.

The utilisation of fibrates increased more than two-fold for NSU/TIY (134%, n= 6,465) and more than four-fold for DDD/TID (343%, n= 3) during the study period. This growth was largely driven by the increasing adoption of fenofibrate, introduced in 2014, which showed a notable upward trend compared to other fibrates, such as gemfibrozil and bezafibrate, both of which declined significantly over time. Bezafibrate usage dropped by approximately 83% in both metrics and was discontinued entirely in 2018. While bezafibrate has been shown to effectively reduce TG levels, it has been less extensively studied in CV outcome trials, with the Bezafibrate Infarction Prevention (BIP) study showing no significant reduction in overall CV events (122), despite some benefits in patients with elevated TGs. Similarly, gemfibrozil experienced a 93% reduction in both metrics reduction but remained available until the end of the study. The VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial, 1999) demonstrated a 22% reduction in non-fatal MIs and coronary deaths among men with low HDL-C, yet the limited impact of gemfibrozil on LDL-C, combined with its higher risk of myopathy when paired with statins, likely contributed to its decline (123).

Furthermore, the introduction of fenofibrate in 2014 offered a safer alternative to gemfibrozil, characterised by a lower risk of myopathy when used in combination with statins. Although fenofibrate has the potential for drug interactions, particularly with simvastatin through hepatic enzyme effects (23), its overall safer profile compared with gemfibrozil has likely led to reduced use of gemfibrozil in clinical practice.

This study showed a 52% increase in NSU/TIY and a 58% in the DDD/TID for fenofibrate over the study period. This increase is likely attributable to its use among patients with metabolic or atherogenic dyslipidaemia characterised by elevated TG levels (20). Fenofibrate was the only fibrate consistently available during the study period (**Appendix S.3.1**) and is generally well tolerated.

Clinical trial evidence supports this prescribing patterns. The FIELD Trial (2005) reported no significant reduction in overall CV events with fenofibrate; however, potential benefits were noted in subgroups with elevated TGs and low HDL-C levels (124). Similarly, the ACCORD Lipid trial (2010) found that the addition of fenofibrate to simvastatin did not improve overall CV outcomes but demonstrated modest benefits in patients with atherogenic dyslipidaemia (TG >2.3 mmol/L and low HDL-C) (125). Moreover, fenofibrate has been shown to confer additional renal and microvascular benefits, particularly among individuals with type 2 diabetes mellitus (T2DM) (23). These benefits, along with a safer profile when combined with statins, likely contributed to its preferential use over older fibrates such as gemfibrozil, which is associated with a higher risk of statin-related myopathy.

The 2019 ESC/EAS guidelines recommend use of fenofibrate or bezafibrate in high-risk patients with TGs >2.3 mmol/L when statins therapy alone is insufficient (23). This recommendation recognises the effectiveness of lowering TG of both agents while accounting for regional differences in drug availability. However, fenofibrate remains the preferred choice due to its broader evidence base from large trial (FIELD,

ACCORD), its additional benefits in slowing the progression of diabetic retinopathy, and its lower risk of myopathy when used in combination with stains (23).

The utilisation trends of fibrates reported in this study do not fully align with global trends reported in other regions. Blais et al. (2021) documented an overall global decline in fibrates use (63). Data from the Republic of Srpska indicated low fibrate utilisation, accounting for approximately 1–3% of all LLT use, which is comparable to the 3-5% observed in the present study. Additionally, fenofibrate was the predominant agent, while gemfibrozil discontinued during the study period and bezafibrate was not recorded (64). Patients-level evidence shows partially consistent findings. In the US, Medicare data reported a modest increase in fibrate use from 4.2% to 5% between 2002 and 2013, reflecting their continued role as adjunct therapy in selected patients (66). In contrast, data from Switzerland demonstrated an 11.5% reduction in fibrate utilisation over time (67).

Despite the historical role of fibrates in treating hypertriglyceridaemia, the introduction of newer therapies, such as omega-3 fatty acid derivatives (e.g., icosapent ethyl) has overshadowed fibrates. The REDUCE-IT trial highlighted the significant benefits of lowering TGs with newer agents, prompting a shift away from fibrates in clinical practice (126). For high-risk patients or those with TG levels between 1.5 and 5.6 mmol/L despite statin therapy, the guidelines advised considering n-3 polyunsaturated fatty acids (n-3 PUFAs), such as icosapent ethyl, in combination with statins (23). A 2022 systematic review and meta-analysis reported that triglyceride-lowering therapies, including fibrates, provided only modest CV benefits, with an 8% relative reduction in CV risk per 1 mmol/L reduction in non-HDL-C (127). However, these benefits were less pronounced compared to LDL-C lowering therapies. Further diminishing their relevance, the Pemafibrate to Reduce Cardiovascular Outcomes (2022) study was discontinued after failing to demonstrate significant CV risk reduction (128), leaving no new fibrate-related CV outcome trials in the pipeline.

In terms of expenditure, the introduction of fenofibrate in 2014 was accompanied by a sharp rise in fibrate expenditure, as reflected by increased CSU/TIY. This is because that fenofibrate had the highest cost/unit (0.09 KWD) compared to bezafibrate (0.04 KWD) and gemfibrozil (0.04 KWD). However, despite the constant cost/unit across fibrate agents, the CSU/TIY trend displayed fluctuations, mainly due to the changes in the NSU/TIY of fibrates themselves such as the discontinuation of bezafibrate and the sharp decline in gemfibrozil use.

3.5.5. Comparison of LLT utilisation and expenditure trends across healthcare settings

The contrasting trends in the NSU/TIY for overall LLTs between PHCCs and hospitals were primarily driven by statin utilisation (**Figure 3.15A-B**). The increased NSU/TIY trend of overall LLTs in PHCCs was largely attributed to the rising utilisation of statins, whereas, in hospitals, the decrease of NSU/TIY trend in the overall LLTs was mainly due to the decreased use of statins. These contrasting trends between PHCCs and hospitals are likely linked to the nature of care provided in these settings. PHCCs, primarily manage patients at earlier stages of disease and therefore tend to initiate LLT with statins, which are recommended as the first-line treatment for dyslipidaemia. This is reflected in the NSU/TIY levels of statin utilisation in PHCCs surpassing those observed in hospitals from 2015 onward (**Figure 3.15C-D**). This pattern is consistent with the role of PHCC in Kuwait as the first point of contact within the healthcare system, providing comprehensive services for the management of NCDs, including T2DM, HTN, and dyslipidaemia (129).

In contrast, hospitals primarily manage more complex and advanced cases, where more aggressive and intensified lipid-lowering regimens are often required. This interpretation is supported by the observed increase in the DDD/TID trend of overall LLTs in hospital settings (**Figures 3.16A-B**). Such increases are likely to reflect the use of statin doses exceeding the WHO-defined DDDs, indicating greater treatment intensity and longer duration of therapy. This is further supported by the upward

trends observed in both NSU/TIY (**Figure 3.15C-D**) and DDD/TID (**Figures 3.16C-D**) metrics for HIST in hospital settings. Although HIST utilisation also increased within PHCCs, overall utilisation levels, measured by NSU/TIY and DDD/TID, remained consistently higher in hospital settings. This pattern is in line with recent guidelines, as early initiation of HIST is recommended for statin-naïve ACS patients, given the rapid and sustained CV benefits, regardless of baseline LDL-C levels. Current evidence supports initiating HIST within the first 1 to 4 days of hospitalisation (23), reinforcing the role of hospital settings in implementing intensive lipid-lowering strategies.
Moreover, the upward trend observed in ezetimibe utilisation metrics (NSU/TIY and DDD/TID) within hospitals may reflect a shift toward more intensive lipid-lowering regimens (data not shown). Although ezetimibe utilisation also increased in PHCCs, their levels remained substantially higher in hospitals, with NSU/TIY values of 9,103 in hospitals compared with 1,537 in 2022.

The CSU/TIY trend is more closely aligned with NSU/TIY than with DDD/TID, as previously described. The observed increase in overall LLT expenditure (CSU/TIY) in hospitals, despite a declining trend in NSU/TIY, can be largely explained by the rising CSU/TIY of PCSK9is. These agents are not available in PHCCs and accounted for 47% of the total LLT CSU/TIY in hospitals by 2022. This increase is primarily driven by the higher cost/unit of PCSK9is compared to other LLTs.

3.5.6. Regional disparities in LLT utilisation and expenditure

Overall, no major disparities were observed in utilisation and expenditure trends for LLT across the six governorates (**Figures 3.18-20**), as all governorates demonstrated broadly similar upward trends over the study period. This consistency is likely attributable to the unified governance of public healthcare services under the MOH, whereby medication procurement and distribution are centrally managed through the CMS. Therefore, medication availability and accessibility appear to be relatively uniform across all governorates.

Despite this similarity in trends, differences in utilisation and expenditure levels existed. The CAP governorate consistently exhibited the highest utilisation and expenditure levels compared with other governorates. This finding can be largely attributed to the inclusion of the Specialised Sabah Region within the CAP governorate based on geographic classification. The CAP health region encompasses a secondary hospital and multiple PHCCs, all geographically located within the CAP governorate (101). The Specialised Sabah region comprises major secondary hospital and several tertiary centres that provide specialised services, including cardiology, oncology, and transplantation, and serve patients from across Kuwait rather than CAP residents alone (101). Nevertheless, the inclusion of these referral centres is therefore likely to have contributed to higher observed LLT utilisation and expenditure in CAP governorate (**Figures 3.18-20**).

In addition to methodological reasons, the clinical profile of patients managed within these specialised centres may further explain the higher utilisation levels. Patients attending tertiary cardiac centres and specialised services are more likely to be at high or very-high CV risk, which often requires more intensive and prolonged LLT. Ultimately, higher LLT utilisation and expenditure in CAP would be expected.

Moreover, demographic factors, particularly population aging, may have contributed to the observed growth in LLT utilisation (67). Although the aggregated nature of the data did not allow for age standardisation, age distribution can still be considered when interpreting the increasing utilisation of LLTs. Population statistics from the PACI (June 2022 publication) indicate that CAP has the highest proportion of older adults. In 2022, individuals aged ≥55 years accounted for 12.3% of the CAP population, compared with 10.0% in MBK and 6.8% in AHM (75). Moreover, the annual health report from the National Centre for Health Information indicated that CAP governorate recorded the highest proportion of deaths among individuals aged ≥55 years in 2020 (12.5%) (130). This pattern suggests a higher burden of CV risk factors and chronic diseases in this governorate, which could partly explain the higher levels of LLT utilisation observed in CAP. Other CV risk factors may also contribute to the higher utilisation levels observed in CAP; however, the absence of governmental data on CV risk factors among the six governorates limits further interpretation.

Although no clear local or regional disparities were identified to compare with the findings of the present study, evidence from a Swiss patient-level study provides useful context for understanding potential regional variation in the prevalence of LLTs (67). The Swiss study reported substantial regional differences in LLT prevalence, which were attributed to variations in dyslipidaemia screening practices, cultural and behavioural habits, and local healthcare policies. Notably, these regional differences were not explained by age, gender, or educational level, as these characteristics were accounted for at the patient-level (67).

3.5.7. Strengths and limitations

The study represents the first population-based retrospective, repeated cross-sectional analysis in Kuwait to quantify utilisation and expenditure trends for four major classes of LLTs, including statins, ezetimibe, PCSK9is, and fibrates, over an 11-year period. The quality of the data is robust, as the dataset was extracted from the CMS, the centralised department within the MOH responsible for medication procurement across all governmental health care settings in Kuwait (76).

Moreover, this study employed two key metrics to quantify utilisation trends. The first, NSU/TIY, is a standardised measure of drug supply that reflects the number of units supplied in alignment with CMS distribution policy. The second metric, DDD/TID, is an internationally recognised standard in drug utilisation studies, allowing for comparisons across settings and countries (104). For expenditure trends, cost/unit was examined alongside CSU/TIY to provide a more comprehensive understanding of overall expenditure patterns. Additionally, to ensure that utilisation and expenditure trends were not confounded by annual fluctuations in population size, all metrics (except cost/unit) were adjusted using the total population size Population statistics were obtained from the PACI, the nationally recognised authority for demographic data in Kuwait (75).

Furthermore, multiple levels of LLT stratification were applied across both utilisation and expenditure outcomes, including therapeutic class, individual agents, and intensity level (HIST and MIST) for statins. In addition to examining trends at the national level, comparisons were conducted between health care settings (PHCCs vs. hospitals) and across the six governorates to assess potential disparities in utilisation and expenditure trends.

Finally, the medication dispensing policy in Kuwait, which provides medications at no cost to patients, offered a unique opportunity to evaluate utilisation and expenditure trends independent of financial barriers.

Nevertheless, this study has several limitations that should be acknowledged. First, although utilisation and expenditure metrics were adjusted for total population size, further demographic standardisation by age, sex, or clinical characteristics was not feasible due to the aggregated nature of the CMS data. Such characteristics may act as potential confounders influencing LLT utilisation or expenditure, and their absence limits the ability to interpret utilisation patterns across different patient subgroups, particularly when exploring regional variations. However, this limitation is unlikely to alter the key findings, as the primary main aim was to describe overall utilisation and expenditure trends rather than identify patients-level risk factors. To mitigate this limitation, two complementary patient-level studies (**chapters 4** and **5**) were conducted to identify factors associated with lipid control outcomes.

Second, CMS records represent supply data rather than actual prescribing or dispensing data, as no record linkage exists between CMS and healthcare settings. This limitation introduces two possible explanations when interpreting utilisation trends. One possibility is that increasing CMS supply may not fully reflect real-world prescribing or dispensing practices, although this discrepancy would be more relevant for short-term fluctuations than for annual or long-term trends. Alternatively, increases in utilisation could reflect either a growing number of patients receiving LLTs or a smaller number of patients treated with intensified regimens, including combination therapy or higher-intensity statin dosing. To account for these uncertainties, this study combined the NSU/TIY metric, which directly reflects CMS supply, with DDD/TID to estimate the exposure at the population-level. Although DDD/TID has recognised advantages (described in strengths), it may underestimate or overestimate actual statin use due to discrepancies between the WHO-defined DDD and the PDD. Sinnott et al. (2016) reported that assuming one DDD per day underestimated statin exposure when compared with recorded days of supply (131). To minimise the impact of this limitation, all findings were interpreted with caution, and patient-level studies in **chapters 4** and **5** were used to support and inform the utilisation patterns observed.

Additionally, the COVID-19 pandemic and the national lockdown in 2020 may have influenced utilisation patterns, including the slight reduction observed in statin NSU/TIY and DDD/TID trends observed in that year. While this disruption may have contributed to short-term fluctuations, it is unlikely to have altered the overall direction of the trends. Nonetheless, this remains a plausible area for further investigation, as outlined in the implications section (**chapter 6, section 6.2.3**).

In examining regional disparities, the inclusion of the Specialised Sabah health region within the CAP governorate may have led to an overestimation of utilisation and expenditure in CAP. This is because the Specialised Sabah health region contains major secondary and tertiary hospitals, including cardiac centres, which attract patients from other governorates (101). This limitation reflects the constraints of the available PACI population data, which are reported only at the level of the six governorates rather than the seven health regions (75). To address this and maintain consistency, all calculations were based on the six-governorate structure to ensure accurate denominator estimates. Although this approach may elevate utilisation levels in CAP, the overall trend closely mirrored those observed in the other five governorates suggesting that the impact on the overall interpretation of regional patters is likely to be limited. Additionally, the establishment of the MBK governorate in 2018 required retrospective reclassification of PHCCs originally under HAW and AHM for the years 2012 onward. This may have slightly influenced utilisation levels attributed to individual governorates in the earlier years. However, this reclassification was necessary to maintain consistency across all six governorates throughout the study period.

Finally, this study aimed to assess LLT utilisation and expenditure trends within governmental public healthcare settings governed by the MOH. For this reason, CMS records relating to supplies for other governmental ministries (e.g. the Ministry of Defence), were excluded. Likewise, data from private hospital pharmacies and community pharmacies were not included, as these sectors operate through procurement systems that differ from CMS. The exclusion of these sources may have resulted in an underestimation of overall national LLT utilisation and expenditure. However, the extent of this impact is uncertain and is unlikely to have influenced the main trends, given that the majority of the population in Kuwait could obtain medications through governmental healthcare settings due to free access or nominal fees for residents. Nonetheless, this remains a valuable area for future investigation. Focusing specifically on governmental healthcare settings also ensured methodological consistency with the subsequent chapters of this thesis, which examined utilisations patterns using PHCC data (**chapter 4**) and hospital data (**chapter 5**) under the responsibility of the MOH.

3.5.8. Conclusion

Over time, the utilisation of LLT has been influenced by findings from clinical trials, evolving guideline recommendations, the introduction of new medicines, and the implementation of national policies tailored to specific regions. In Kuwait, this study demonstrates a significant increase in LLT utilisation over the past decade. This trend aligns with the global shifts toward evidence-based practices and mirrors patterns observed in other real-world studies.

The rise in statin use highlights their established role as first-line therapy for lipid-lowering and CVD prevention. Ezetimibe, the first non-statin therapy introduced into clinical practice, following the IMPROVE-IT trial, which demonstrated CV benefits when added to statin therapy. Similarly, PCSK9is, a relatively recent addition to clinical practice, have experienced increased utilisation following key CV landmark trials (FOURIER for evolocumab and ODYSSEY OUTCOMES for alirocumab), reflecting the growing need for aggressive lipid management in high-risk patients. Expenditure trends closely mirrored utilisation trend, with statins accounting for the majority of costs. The introduction of PCSK9is in recent years contributed significantly to expenditure due to their high cost per unit.

These findings emphasise the critical role of evidence-based guidelines in driving rational prescribing and optimising dyslipidaemia management.

Chapter 4. Patient-level evaluation of utilisation patterns and quality of lipid control among individuals prescribed lipid-lowering therapies (LLTs): a nationwide multicentre cross-sectional study in primary healthcare

4.1. Introduction

Non-communicable diseases (NCDs), also known as chronic diseases, encompass a broad range of conditions, including cardiovascular diseases (CVDs) (6) (For further details on NCDs, see **chapter 2**, **section 2.1**). The World Health Organization (WHO) plays a critical role in providing leadership, evidence-based recommendations, and policy frameworks to support international efforts in NCD surveillance, prevention, and control (132). Globally, NCDs represent the highest risk of mortality in low- and middle-income countries (LMICs). Nevertheless, they are also a significant public health concern in high-income countries (HICs) (133). In Kuwait, a HIC, the proportionate mortality rate from NCDs was 72.4% in 2016 (134).

Kuwait has fully achieved one of the ten progress indicators used to monitor commitments on NCDs (134). This indicator relates to the development of evidence-based national guidelines, protocols, and standards for the management of major NCDs through a primary care approach, which have been formally recognised and approved by the government (134). Kuwait has established the NCDs Prevention and Control Directorate, supported by a high-level committee involving various governmental and non-governmental sectors. Furthermore, specialised NCD clinics have been integrated within primary healthcare centres (PHCCs) to facilitate the early detection, prevention, and comprehensive management of chronic diseases (134). In Kuwait, primary healthcare services are organised through a centralised structure led by the Central Directorate of Primary Health Care (CDPHC) (129). The CDPHC defines primary healthcare as “the fundamental pillars and the entry point to the health system, through which all segments of society access the first level of healthcare, which ensures the provision of continuous healthcare for individuals at all life stages”.

The primary healthcare (PHC) system in Kuwait is well-established, comprising 116 operational PHCCs by mid-2024, distributed across the six governorates: the Capital (CAP), Hawalli (HAW), Al-Ahmadi (AHM), Al-Jahra (JAH), Al-Farwaniyah (FAR), and Mubarak Al-Kabeer (MBK) (129). These centres offer essential healthcare services tailored to community needs, with a number of selected centres operating on a 24/7 basis to enhance accessibility and continuity of care (129).

PHCCs, in Kuwait, provide a comprehensive range of promotive, preventive, diagnostic, and therapeutic services. These include general practitioner (GP) clinics, early detection clinics for CV risk factors and cancers, nutritional and smoking cessation clinics, well-baby and adolescent clinics, geriatric and women's health clinics, mental health services, and specialised clinics for NCDs (129). NCD clinics are typically managed by family medicine practitioners, and among the chronic conditions primarily manged in these clinics is dyslipidaemia. Additional services supporting dyslipidaemia management within PHCCs include the availability of on-site biochemical laboratories (135), which enable timely lipid profile testing. Moreover, each PHCC has an on-site pharmacy (135) stocked with lipid-lowering therapies (LLTs), facilitating the prompt initiation and continuation of treatment. As highlighted in **chapter 3**, **section 3.3.1**, the LLTs available within PHCC are procured though the Central Medical Store (CMS), ensuring a unified approach to treatment (76). The medicines distributed to PHCCs consist of oral LLTs, including statins, ezetimibe, and fibrates, thereby supporting comprehensive lipid management at the primary care level.

Importantly, statins remain the cornerstone of LLT for patient at risk of cardiovascular disease (CVD), as evidenced from a meta-analysis conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration showing that each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C) is associated with a 22% relative reduction in major CV events (14). Despite this well-established efficacy, several real-world studies reported suboptimal lipid control in routine clinical practice.

Findings from the ESC-EORP EUROASPIRE V (European Society of Cardiology–Eurobservational Research Programme, European Action on Secondary and Primary Prevention by Intervention to Reduce Events V) survey (2019) evaluated the implementation of European guidelines on dyslipidaemia management in patients with documented coronary heart disease (CHD) across 27 countries, including Egypt and the United Kingdom (69). The survey showed that while 84.3% (n= 6,514/7,732) of patients were receiving LLTs, primarily statins, only 30% of those at very-high risk achieved the LDL-C target of <1.8 mmol/L, demonstrating suboptimal lipid control. Notably, the survey applied the 2016 ESC/EAS guideline thresholds, which assign a more lenient LDL-C target for individuals at very-high risk compared with the more stringent <1.4 mmol/L target recommended in the 2019 ESC/EAS guidelines (23). Therefore, it is reasonable to expect that the proportion of patients attaining LDL-C targets would have been further reduced under the thresholds specified in recent guidelines.

Moreover, findings from the DYSIS (DYslipidaemia International Study), a large, multicentre, cross-sectional study conducted across 30 countries (2006–2013), including Kuwait, further demonstrating the widespread challenge of achieving recommended lipid targets globally (70). Among 57,885 statin-treated patients, only 26.8% achieved their risk-based LDL-C targets, despite the study applying the less stringent 2011 ESC/EAS guideline thresholds (very-high risk: <1.8 mmol/L) compared with the current 2019 recommendations (<1.4 mmol/L). Notably, combined data from the DYSIS of United Arab Emirates (UAE) and Kuwait demonstrated the highest rate of LDL-C target attainment (49.5%; n= 135/273); however, this still reflected suboptimal control and was based on a relatively small sample size. In contrast, Germany in the DYSIS reported the lowest LDL-C attainment (14.3%; n= 555/3,879), demonstrating the significant variations across countries.

Additionally, as part of this international DYSIS, the DYSIS-Middle East sub-study evaluated lipid control in four countries, including two from the Gulf countries (Saudi Arabia and the UAE) (84). Among 2,165 statin-treated patients, only 38.5% achieved LDL-C targets, with the lowest attainment observed among those classified at very-high CV risk (84). The findings revealed also a continued gap in lipid management across the region

Additionally, the CEPHEUS (Centralized Pan-Middle East Survey on the Undertreatment of Hypercholesterolemia) conducted between 2009 and 2010 across the six Gulf countries, evaluated LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) target achievement among 4,383 patients receiving LLTs (35). Although somewhat outdated, the findings similarly showed suboptimal lipid control, with only 31% of patients achieving their LDL-C target and 41% attaining their non-HDL-C target, based on the 2014 National Lipid Association (NLA) guideline. Under this guideline, the very-high risk targets were <1.8 mmol/L for LDL-C and <2.6 mmol/L for non-HDL-C (35).

In Kuwait, the most recent national-level WHO STEPwise Approach to NCD Risk Factor Surveillance (STEPS) was carried out in 2014 to assess the prevalence of NCD risk factors in the population (96). The findings revealed that 67% of individuals aged 18–69 years had LDL-C levels below 3.4 mmol/L, yet only 9.9% were receiving statin therapy. This suggests that the limited utilisation of LLTs may have contributed to suboptimal lipid control, particularly given considering the relatively high LDL-C threshold applied at the study time.

Following the findings from the CMS study (**chapter 3**, Figure 3.15A), which demonstrated a steady increase in the utilisation of LLTs across PHCCs over an 11-year period (2002-2022), several critical questions remain unaddressed. Although the aggregated-level data illustrate an overall upward trend in LLT utilisation, they do not provide insight into prescribing patterns at the patient-level. Therefore, patient-level data are required to evaluate the quality of lipid control against updated guideline-recommended thresholds stratified by CV risk categories. This need is particularly pertinent given that most existing studies from Kuwait are outdated, and no recent work has examined LLT prescribing patterns across all six governorates, including details on therapeutic regimens (monotherapy vs. combination therapy) and statin intensity. Furthermore, understanding the sociodemographic and clinical factors associated with lipid target achievement is essential for strengthening lipid management and supporting optimised treatment and improved CV outcomes. Addressing these knowledge gaps, encompassing prescribing patterns, quality of lipid control, and factors of lipid target achievement, is therefore crucial for informing healthcare policy, guiding clinical practice, and shaping evidence-based strategies.

4.2. Aims and objectives

This study aimed to analyse the prescribing patterns of LLTs at a patient level and evaluate the quality of lipid control among patients visiting PHCCs in 2023. The objectives were:

- To identify the sociodemographic and clinical characteristics of current LLT users
- To understand and describe the utilisation patterns of patients prescribed LLTs, stratified by LLTs classes and individual agents within each LLT class
- To evaluate the extent of lipid target attainment among patients on LLTs across different CV risk categories
- To identify factors associated with lipid control achievement, particularly with LDL-C and non-HDL-C parameters

4.3. Methods

4.3.1. Study design and data source

This nationwide, cross-sectional study was conducted in Kuwait between January and October 2023 at six PHCCs, one from each governorate. The study targeted patients who had been prescribed at least one LLT from the statin class, ezetimibe, fibrates, or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) class (see **section 4.3.2.3** for sampling details). The questionnaire used to assess LLT prescribing patterns and the quality of lipid control was primarily developed based on the WHO STEPwise approach (STEPS) (96). This approach offers a simple and standardised method for collecting, analysing, and disseminating data on key NCD risk factors globally. Additionally, STEPS also incorporates behavioural risk factors, allowing a broader evaluation of determinants relevant to CV risk. Its standardised methodology enables comparison of findings across countries over time. In the context of Kuwait, where STEPS-based surveys were previously implemented approximately a decade ago, adopting this approach also offers an opportunity to enrich existing national data and provide updated insights into current lipid management practices (96).

4.3.2. Study participants

The target participants included patients attending PHCCs who had been prescribed on the day of recruitment at least one LLT agent from one of the following four classes: statins, cholesterol absorption inhibitor (ezetimibe), fibrates, and PCSK9is (as outlined in **chapter 3**, **Figure 3.1**). Inclusion and exclusion criteria are provided below.

4.3.2.1. Inclusion criteria

Patients were recruited from NCD clinics within the selected PHCCs. NCD clinics were specifically chosen over GP clinics, as the latter mainly received patients presented with acute conditions, reducing the likelihood of encountering individuals with chronic diseases. In contrast, NCD clinics are exclusively dedicated to managing NCDs such as diabetes mellitus (DM), hypertension (HTN), and dyslipidaemia. These clinics operate on a scheduled-appointment system, which facilitate better anticipation of the number of patients likely to be prescribed LLTs, including those with DM, a

condition that frequently coexists with dyslipidaemia (25) (details on diabetic dyslipidaemia are provided in **Appendix S1.4**). Additionally, patients of both genders were eligible for inclusion, with no specific age restrictions applied, as NCD clinics exclusively receive adults. Only individuals who provided consent to participate were enrolled. To enhance representativeness and generalisability, the sample included both Kuwaitis and non-Kuwaitis from diverse racial backgrounds.

4.3.2.2. Exclusion criteria

Patients were excluded if they were not prescribed an LLT at the day of recruitment, even if they had previously been on an LLT. Importantly, patients with a newly prescribed LLT (on recruitment day) were included only for assessing the prescribing pattern but were excluded from the quality of lipid control analysis. This exclusion was necessary because clinical guidelines, such as the 2019 ESC/EAS (23), recommend evaluating lipid profiles at least 4 to 12 weeks after initiating statin therapy to accurately assess LDL-C reduction.

4.3.2.3. Sample size calculation and sampling technique

The sample size for this study was calculated using the following equation provided by the sample size calculator (https://www.calculator.net/sample-size-calculator.html) (136).

$$Sample\ size = \frac{z^2 \times \hat{p}\,(1-\hat{p})}{e^2}$$

Where:

- **z=** z-score
- **e=** margin of error
- **$\hat{p}$=** estimated proportion of the population achieving lipid control

The minimum sample size was determined using a 95% confidence interval (CI), corresponding to a z-score (z) of 1.96, and a margin of error (e) of 5%. Because the true prevalence of lipid control achievement among those who were on LLTs in PHCCs was unknown, an estimated population proportion ($\hat{p}$) of 50% was used (136). This value is incorporated into the variability term $\hat{p}$ (1- $\hat{p}$), which is maximised when $\hat{p}$=

0.5 and therefore represents the highest possible variability (137). Using this conservative estimate ensured the calculation of the largest required sample size, thereby providing sufficient precision across a wide range of possible prevalence estimates (precision-based approach). Based on this calculation, the minimum sample size required for this study was 385 participants, distributed across the six governorates (136).

Sampling techniques are broadly classified into probability and non-probability methods (138). Probability sampling ensures that every unit in the population has an equal chance of selection, whereas non-probability sampling does not provide equal selection chances for all elements (138). Both techniques were employed in this study: probability sampling was applied to recruit patients across Kuwait, while non-probability sampling was used to select the participating PHCCs. Details of each sampling approach are provided below.

Probability sampling can be further categorised into various types, including systematic sampling, cluster sampling, and stratified sampling (138). In this study, a stratified proportional sampling technique was used to determine the total sample size required for each of the six governorates, stratified by nationality. This approach aligns with the sampling strategy used by Oguoma et al. (2021) in their cross-sectional study, which applied the WHO STEPwise approach to examine the association between obesity and sociodemographic factors in Kuwait (139). Adopting this approach in the current study helped ensure that the sample reflected the population distribution within each governorate as closely as possible, thereby enhancing representativeness and generalisability while minimising sampling error.

To calculate the total sample size for each governorate, population estimate data were obtained from the Public Authority for Civil Information (PACI) (75). PACI is the official governmental body in Kuwait responsible for issuing Civil IDs to all residents, both Kuwaitis and non-Kuwaitis (75). Among its services, PACI provides detailed

geographical statistics, stratified by governorates, areas within governorates, alongside the nationality distributions (Kuwaitis vs. non-Kuwaitis) (75). Population statistics from the December 2022 publication by PACI was extracted from their official website during the time of sample size calculation. However, PACI arranges areas within each governorate according to administrative divisions, which differs slightly from the geographical distributions used in the six health regions defined by the CDPHC (129). To address these discrepancies, mathematical adjustments were made to accurately align the population size of certain areas with the governorate definitions used in the health regions. Details on the sample size calculation and the minimum required sample size required for each governorate are provided in **Appendix S4.1**.

On the other hand, non-probability sampling, specifically convenience and purposive sampling, was used to select one PHCC from each governorate (137, 140). This approach ensured the feasibility of recruiting the required number of participants from a single PHCC within the available timeframe. While selecting only one centre per governorate limits the ability to obtain a fully representative sample, the selection was guided by the need to maximise variation in key characteristics, including medical services, medication availability, and demographic diversity, particularly in terms of accessibility for both Kuwaiti and non-Kuwaiti populations. Selecting appropriate PHCCs was also essential to minimise potential administrative barriers, ensure effective coordination with staff, and ultimately facilitate efficient data collection. Additionally, involving these centres contributed to their ongoing research experience, building on their participation in previous studies.

The structure of the PHC system supported the selection process. All PHCCs in Kuwait operate under standardised protocols, policies, guidelines, and circulars (141). Each governorate (or health region) is led by a head of the PHC unit, and all units fall under the leadership of the CDPHC Director. Accordingly, expert input was sought from the CDPHC Director, who nominated two potential PHCCs from each governorate for

participation in the study. One PHCC from each governorate was then selected using convenience and purposive methods, with some exceptions, as detailed in **Appendix S.4.2**.

Following the calculation of the required sample size and the selection of the participating PHCCs, data collection and recruitment strategies were initiated.

4.3.3. Content of the questionnaire and data collection

The questionnaire was structured into three sections, in accordance with the WHO STEPS framework, with each section referred to as a "Step" (96). Step 1 captured demographic, behavioural, and clinical history data; Step 2 involved physical measurements; and Step 3 focused on biochemical assessments. The main section added to the questionnaire, beyond what is included in the WHO STEPS framework, focused on the prescribing patterns of LLTs. The structure and content of the questionnaire used in this study are outlined in **Appendix S4.3A**.

Key demographic characteristics, such as age, gender, and nationality are consistently available within the Primary Care Information System (PCIS), which acts as the official electronic medical record platform across all PHCCs in Kuwait (129). This integrated, computer-assisted system is designed to store and retrieve administrative and clinical information related to the provision of medical services at PHCCs. However, certain behavioural and physical data, such as smoking status, physical activity, dietary habits, and body mass index (BMI), were not routinely recorded or regularly updated. Moreover, the PCIS is not linked to hospital systems, resulting in incomplete medical records, particularly for conditions diagnosed or medications prescribed outside PHCCs.

Recognising these limitations, this study adopted a dual data collection approach to improve data completeness, combining routinely collected data from the PCIS with face-to-face patient interviews using a structured, researcher-administered questionnaire. The interviews were crucial for capturing demographics and behavioural data that were either absent or outdated in the PCIS. Additionally, interviews allowed the collection of information regarding medical conditions and medications obtained from other healthcare settings, which are not recorded in the PCIS. For instance, the use of PCSK9is, which are not available at PHCCs, might not be documented in the PCIS but could be reported during the interviews. The PCIS, on the other hand, provided accurate and up-to-date information on current prescriptions and laboratory results. Furthermore, the PCIS often facilitated the confirmation of patient-reported medical histories and concomitant medications, helping to address potential gaps arising from limited patient knowledge of medical terminology or difficulty recalling the names of prescribed drugs, thereby reducing recall bias.

4.3.4. Recruitment strategy

Participants were screened for eligibility prior to enrolment (see inclusion criteria in **section 4.3.2.1**), by trained members of the research team. The study procedures were explained thoroughly, including each participant's right to refuse participation or withdraw at any stage without consequence. Eligible individuals were then invited to provide both verbal and written informed consent. The consent form was prepared in Arabic using the standard Ministry of Health (MOH) template (**Appendix S4.3B**) and translated into English for non-Arabic-speaking participants (**Appendix S4.3C**). A copy of the consent form was provided to participants upon request.

As part of the patient recruitment strategy, consent forms and questionnaires were distributed to nurses, physicians, and external data collectors who were pharmacists. Nurses were responsible for completing the sections of the questionnaire related to the face-to-face patient interviews. Following the interview, the questionnaire was

forwarded to the physician's office to extract data from the PCIS, as authorised access to the system was restricted to physicians only. To facilitate linkage between interview and retrieving clinical data, nurses recorded the patient's Civil ID on a separate sheet of paper, which was temporarily attached to the questionnaire. To maintain confidentiality, this external sheet was securely disposed of after data entry. Physicians who participated as data collectors completed the questionnaires directly in their offices, either during or after the patient consultations. This process included both conducting the patient interview and extracting relevant information from the PCIS. External data collectors were assigned to nursing rooms or, where available, to private consultation areas within PHCCs to conduct patient interviews. Eligible patients were referred to external data collectors by physicians or nurses. Once completing the face-to-face interview, the questionnaires were forwarded to physicians for completion of the PCIS-related sections, following the same procedure used with nurses. All questionnaires were paper based and were securely stored in designated locations, either in the physician's office or nursing rooms, until they were collected by the researcher.

4.3.5. Data management

Data from the paper-based questionnaires were entered into Microsoft 365 Excel and double checked for unintentional error, particularly in lipid profile values.

4.3.6. Questionnaire reviewing and piloting

The questionnaire underwent expert review by a lipidologist and two board-certified family medicine physicians to enhance clarity and optimise data collection. Key modifications from them included the removal of detailed classifications of current smokers (e.g., cigarettes, vapes, or shisha) and the cessation date for ex-smokers, as these details were unnecessary for the current aims and could prolong patient interviews. However, alcohol consumption was retained in the questionnaire due to its relevance as a behavioural factor. Given that alcohol consumption is illegal in Kuwait, the question was simplified to a binary (yes/no) format without requesting

additional details (e.g., quantity consumed). Further refinements were made to improve the structure of the questionnaire to enhance clarity and improve data accuracy. Notably, individual table cells were introduced for each LLT prescription to record the medication name, strength, and dosing regimen separately, thereby minimising the risk of incomplete entries or data omissions.

A pilot study was then conducted in five PHCCs, involving a total of 10 patients. Although the sample size was limited, feedback from the pilot study indicated that the questionnaire was clear and that the average completion time of approximately 10 minutes was appropriate, particularly given that the questionnaire was adapted from the validated WHO STEPS tool. Nonetheless, minor modifications were made to improve response accuracy. These included clarifying dietary intake definitions, providing clearer options for physical activity levels, and omitting creatine kinase (CK) from the biochemical measurement section. CK is an enzyme found in the muscles, and elevated levels may indicate statin-associated adverse effects (142). CK was not routinely assessed in PHCCs and, importantly, was not essential to the objectives of this study.

4.3.7. Study outcomes

The primary outcome measures of this study were the prescribing patterns of LLTs and quality of lipid control, along with factors associated with lipid target achievement.

4.3.7.1. Prescribing patterns of LLTs

The prescribing patterns of LLTs were categorised into two groups: monotherapy and combination therapy. Monotherapy was defined as the use of a single LLT on the recruitment day, whereas combination therapy referred to the concurrent prescription of at least two LLTs on the same day. These definitions were adapted from a retrospective Taiwanese study examining 10-year trends in statin utilisation (82). Within each group, LLTs were stratified by drug class, which included statins,

cholesterol absorption inhibitor (ezetimibe), fibrates, and PCSK9is. Statins were further classified into two levels of intensity: high-intensity statin therapy (HIST) and moderate-intensity statin therapy (MIST), based on the 2018 AHA/ACC guidelines and the 2021 Middle East consensus (20, 24) (**chapter 2**, **Table 2.3**). Statins were further categorised by specific agents: atorvastatin, rosuvastatin, and simvastatin. Notably, only one agent was prescribed from each non-statin class: fenofibrate among the fibrates and ezetimibe from the cholesterol absorption inhibitor class. Evolocumab was the only PCSK9i captured.

4.3.7.2. Quality of lipid control

Once participants were enrolled, individuals who had been newly prescribed an LLT on the day of recruitment were excluded (see exclusion criteria in **section 4.3.2.2**). Subsequently, additional exclusion criteria related to lipid profile availability were applied to enable accurate assessment of lipid target achievement. Patients were excluded if no lipid measurement was available within the 12 months preceding recruitment. Where multiple lipid measurements were recorded, the value closest to the recruitment date was used. Although a 12-month look-back period may appear relatively wide, particularly given the cross-sectional design and the limited ability to ascertain previous prescriptions, this timeframe reflects routine practice in PHCCs, where lipid profiles are typically reviewed annually when results remain within target ranges. This approach meant that not all patients included in the lipid target attainment analysis were necessarily receiving an LLT at the time of lipid measurement. However, excluding newly initiated LLT users could minimise the risk of misclassification. Additionally, eligibility required the availability of at least one lipid parameter, including LDL-C, non-HDL-C, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), or total cholesterol (TC).

Following identification of eligible patients, the extend of lipid control was assessed. For patients without established CVD (primary prevention), a CV risk calculator was employed to estimate individual risk in order to define the appropriate lipid targets. This study followed the Middle East consensus recommendations for CV risk assessment (20) and applied the QRISK3 score as recommended (https://qrisk.org) (143) (**Appendix S2.5.1**).

Lipid targets were stratified according to CVD risk categories, with LDL-C defined as the primary lipid target and non-HDL-C as a co-primary target, in line with the Middle East consensus recommendations (**chapter 2**, **Table 2.2**) (20). For patients requiring secondary prevention (i.e., those with established CVD), the LDL-C target was <1.4 mmol/L, with the corresponding non-HDL-C target set at 0.8 mmol/L above the LDL-C goal, consistent with the extreme CV risk category (20).

Unmeasured LDL-C values were estimated using the Friedewald formula (FF) (23, 144), provided that TC, HDL, and TG levels were available and TG levels were below 4.5 mmol/L (**Formula 4.1**). In the FF, TG values are divided by 2.2 when expressed in mmol/L and by 5 when in mg/dL (23). For non-HDL-C, unmeasured values were calculated by subtracting HDL-C from TC levels (23). See **Table 4.1** for the number of missing values for LDL-C and non-HDL-C parameters before and after applying the relevant equations.

Formula 4.1: Friedewald Formula

$$\mathrm{LDL-C}\,\frac{\mathrm{mmol}}{\mathrm{L}} = \mathrm{TC} - (\mathrm{HDL-C}) - \frac{\mathrm{TG}}{2.2} \quad (\text{only if fasting TG} < 4.5\,\frac{\mathrm{mmol}}{\mathrm{L}})$$

Table 4.1 Number and proportion of missing values before and after applying the relevant equations, among 336 eligible patients

lipid parameters	Missing values (Before)	Missing values (After)	Proportion of Missingness (%)
LDL-C	35	18	18/336 (5.36%)
Non-HDL-C	309	20	20/336 (5.95%)

LDL-C: Low-density lipoprotein cholesterol; N**on-HDL-C**: Non-high-density lipoprotein cholesterol

Secondary lipid targets included TG and HDL-C, defined according to the 2021 Middle East consensus and applied regardless of CV risk category (**Table 4.2**). Although TC targets are not included in the 2019 ESC/EAS guidelines or the Middle East consensus, a threshold of <5 mmol/L was adopted based on the recommendation issued by NHS Inform, Scotland's national health information service, in September 2024 (145).

Table 4.2 Secondary lipid targets, defined by the 2021 Middle East consensus (20)

Lipid target	TGs	HDL-C	
Desired target	<1.7 mmol/L (150 mg/dL)	**Males**	>1.0 mmol/L (40 mg/dL)
		Females	>1.3 mmol/L (50 mg/dL)

TGs: Triglycerides**; HDL-C**: High-density lipoprotein cholesterol

4.3.7.3. Factors associated with lipid target achievement

Sociodemographic and clinical characteristics were described as study covariates, while lipid target achievement was defined as the categorical binary outcome. Study covariates were identified based on the WHO STEPS framework, encompassing demographic, behavioural, physical and biochemical variables (96). Additional relevant covariates were incorporated, including CV risk category, metabolic syndrome (MetS), and governorate. A summary of all covariates and their corresponding definitions is provided in **Table 4.3.**

Table 4.3 Summary of **s**ociodemographic and clinical characteristics of the study

Covariate	Data source	Definition
Step 1: Demographic data and behavioural measurements		
Age at recruitment	Interview or PCIS	Age was assessed as a continuous variable and as a categorical variable (four categories): <55, ≥55 - <65, ≥65 - <75, and ≥75 years
Gender	Interview or PCIS	Binary variable; male or female
Nationality	Interview or PCIS	Binary variable; Kuwaiti or non-Kuwaiti
Education level	Interview	Four categories: none, primary, intermediate-high school, and college/university
Marital status	Interview	Four categories: single, married, divorced, and widowed
Occupation	Interview	Five categories: unemployed, government employee, non-government employee, domestic workers, and retired
Family history of CVD	Interview	Binary variable; yes and no
Smoking status	Interview	Three categories: current, ex-smoker, and non-smoker
Alcohol consumption	Interview	Binary variable; yes and no
Diet (fruits/vegetables)	Interview	Number of days/week & number of servings/day (discrete variables)
Physical activity	Interview	Three categories: moderate-intensity, vigorous-intensity, and none

Table 4.3 Summary of **s**ociodemographic and clinical characteristics of the study

Covariate	Data source	Definition
History of HTN	Interview or PCIS	Binary variable; yes and no
History of DM	Interview or PCIS	Binary variable; yes and no
History of CVD	Interview	Binary variable; yes and no
Step 2: Physical measurements		
SBP and DBP (mmHg)	Interview	Assessed as a continuous variable and three categories; SBP <130, DBP <80, and both <130/80
Body Mass Index (Kg/m^2)	Interview	Assessed as a continuous variable and four categories: underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), and obese (≥30)
Step 3: Biochemical measurements		
Lipid profile (mmol/L)	PCIS	LDL-C, non-HDL-C, TG, HDL-C, and TC were presented as a continuous variable
HbA1c (%)	PCIS	Assessed as a continuous variable and three categories; <7, 7 - <9, and ≥ 9
Liver Function Test (U/L)	PCIS	Liver enzymes: AST & ALT were assessed as continuous variables
Renal Function Test (ml/min/1.73m^2)	PCIS	The calculated eGFR was presented as a continuous variable and two categories: ≥60 and <60 ml/min/1.73m^2
Additional clinical characteristics		
CV risk category	Calculated based on data from the interview and the PCIS	Four categories according to the QRISK3 score (143): extreme, very-high, high, and moderate (**Appendix S1.5**)
Metabolic Syndrome	Calculated based on data from the interview and the PCIS	Binary variable; yes and no. It was defined if at least three of the following criteria were met: 1) SBP ≥130 or DBP ≥85 or on antihypertensive medication; 2) waist circumference ≥102 cm for males or ≥88 cm for females, or a BMI ≥30 Kg/m^2; 3) FBG ≥5.6 mmol/L or on antidiabetic medication; 4) TG ≥1.7 mmol/L

Table 4.3 Summary of **s**ociodemographic and clinical characteristics of the study

Covariate	Data source	Definition
		or if on TG-lowering treatment; 5) HDL-C <1.0 mmol/L for males or <1.3 mmol/L for females
Governorate	Based on the selected PHCC	Six categories: Capital, Hawalli, Al-Ahmadi, Al-Jahra, Al-Farwaniyah, and Mubarak Al-Kabeer

PCIS: Primary Care Information System; **CVDs**: Cardiovascular diseases; **HTN**: Hypertensions; **DM**: Diabetes mellitus; **SBP**: Systolic blood pressure; **DBP**: Diastolic blood pressure; **LDL-C**: Low-density lipoprotein cholesterol; **non-HDL-C:** non-high-density lipoprotein cholesterol; **TG**: Triglycerides; **HDL-C:** High-density lipoprotein cholesterol; **TC**: Total cholesterol; **HbA1c**: Glycated haemoglobin; **AST**: Aspartate transaminase; **ALT**: Alanine transaminase; **eGFR**: estimated glomerular filtration rate; **FBG**: fasting blood glucose

4.3.8. Data analysis

4.3.8.1. Sociodemographic and clinical characteristics and LLT prescribing patterns

Descriptive statistics were used to summarise the sociodemographic and clinical characteristics of patients prescribed LLTs. Categorical variables were presented as frequency (percentage), while continuous variables were summarised as mean ± standard deviation (SD) or median ± interquartile range (IQR), depending on the data distribution (146). The normality of continuous variables was assessed visually using histograms. Characteristics were described for the overall sample and then stratified by therapeutic regimen (monotherapy vs. combination therapy). Prescribing patterns were analysed using the same stratification and summarised as frequency (percentage).

4.3.8.2. Lipid control quality in relation to CV risk category

Participants were assessed for lipid target goal achievement, including both primary lipid targets (LDL-C and non-HDL-C) and secondary lipid targets (TG, HDL-C, and TC). Lipid parameters were categorised into seven groups: LDL-C only, non-HDL-C only, LDL-C and non-HDL-C combined (primary targets), TG only, HDL-C only, TC only, and all parameters combined. This classification was designed to facilitate a better understanding of how participants were distributed across primary and secondary lipid targets, and to evaluate whether individuals achieved control across all relevant lipid measure. Additionally, this categorisation enabled to explore factors associated with the attainment of specific lipid target, particularly for LDL-C and non-HDL-C.

Descriptive analysis measured the frequency and percentage of patients overall and within each CV risk category who had available lipid parameters, followed by calculations of those achieving target goals. Further stratification was performed for monotherapy and combination therapy groups. The total number of patients across all CV risk categories was first determined. For each of the seven lipid groups, the number of patients with available lipid values for that specific group was then identified. Subsequently, the proportion of patients who achieved the target for each

group was calculated by dividing the number of patients meeting the target by the number of patients with available values for the corresponding group and multiplying the result by 100. This process was repeated for all seven lipid groups. These steps were then repeated for each CV risk category, with further stratification of patients into those on monotherapy and combination therapy. For example, the proportion of patients who met the LDL-C target was calculated as **Equation 4.1**:

Equation 4.1:

$$\text{Proportion of patients met LDL} - \text{C target} = \frac{\text{Number of patients who achieved LDL–C target}}{\text{Number of patients with available LDL–C values}} \times 100$$

4.3.8.3. Investigating the association between study covariates and lipid goal attainment as a binary categorical variable

To identify factors associated with lipid target attainment, two binary outcomes (LDL-C and non-HDL-C goal achievement) were analysed independently using multivariate binomial logistic regression (147). These two lipid parameters were selected based on the 2021 Middle East consensus, which identified them as the primary lipid targets (20).

Initially, univariate analyses were conducted for each lipid parameter, comparing patients who achieved the target (outcome group) with those who did not (reference group), as the majority belonged to the latter category. Multivariate logistic regression was then performed to calculate adjusted odds ratios (ORs) for all variables included in the univariate analysis, accounting for potential confounders. The ORs represented the association between the covariates (independent variables) and lipid target achievement (dependent variable).

Since logistic regression estimates are expressed in log odds, exponentiation was applied to compute ORs along with their 95% CIs. The p-values remained unchanged during this transformation. A p-value of <0.05 was considered statistically significant, indicating an association between a covariate and lipid target achievement.

For nominal or ordinal categorical variables (e.g., marital status or education level), global p-values were calculated using the likelihood ratio test (LRT) (148). In univariate analyses, this was performed by comparing a model including the studied factor with a model excluding that factor. In multivariate analyses, the full model was compared to a model omitting the studied factor.

Continuous variables were initially treated as continuous in the regression model. Then, model fit was assessed to determine whether the variable should be included as a continuous or categorical variable. The Akaike Information Criterion (AIC) was

used to assess model fit, where a lower AIC indicated a better-fitting model. LRTs were also performed to compare models and determine the significance of continuous variables. If categorising a continuous variable did not improve model fit, it remained as a continuous variable. The result was that all continuous variables remained continuous after the test.

Logistic regression models required complete data. In this study, the percentage of missing data was 5.4% for LDL-C and 6% for non-HDL-C (**Table 4.1**). Missing data mechanisms are generally classified into three categories: Missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (149). MCAR occurs when the probability of missing data is unrelated to both observed and unobserved variables, meaning that the missingness is entirely random (149). MAR implies that the probability of missing data is dependent on observed variables but not on the missing values themselves. MNAR occurs when the missingness is systematically related to unobserved data, meaning that the missing values depend on the missing data (149).

To assess whether the missing data could introduce bias, Little test was conducted to evaluate the plausibility of the MCAR assumption (150, 151). This test examines whether the pattern of missingness is completely random by comparing the means across different missing data patterns. A p-value <0.05 indicates a rejection of the null hypothesis (i.e., that there is no systematic difference between missing and observed data), suggesting that the missing data mechanism is not MCAR. The test for this study yielded a p-value > 0.05, suggesting that the missing values were MCAR, i.e., randomly distributed and not dependent on any observed patient characteristics or study variables. Given that the data were MCAR, listwise deletion (complete case analysis) was employed. This method is considered appropriate under MCAR conditions, as it ensures that the result remain systematically unbiased (149). Since the proportion of missing data was relatively low and the MCAR assumption was met, listwise deletion was sufficient for maintaining the robustness of the model without

introducing additional complexity. This is because, under MCAR, the probability of missing data is independent of both observed and unobserved values (149).

Finally, the model was assessed for goodness-of-fit (GOF) to evaluate how well the fitted model reflects the real data (152). The Hosmer-Lemeshow GOF test, one of the most widely used measures for logistic regression models, indicated an adequate fit with a non-significant p-value (>0.05) (152, 153). Specifically, the Hosmer-Lemeshow test results were 0.68 for LDL-C and 0.86 for non-HDL-C, suggesting a good model fit for both parameters.

4.3.9. Ethical approval

Ethical approval for the study was granted by the Assistant Undersecretary for Planning and Quality at the MOH (**Appendix S2.8**). This approval necessitated subsequent endorsements from the head of the health region in each governorate, followed by approval from the PHC Unit in each governorate. Once these approvals were secured, the head of each PHCC was provided with an invitation letter outlining the objectives and procedures of the study (**Appendix S4.3D**). This letter asked their agreement to participate and encouraged them to inform the medical staff about the research implementation. It also emphasised the importance of collaboration between the medical staff and the researcher to facilitate the smooth conduction of the research.

4.4. Results

4.4.1. Sociodemographic and clinical characteristics of the study participants

Before presenting the characteristics of the participants, the distribution of individuals enrolled in this study across the six governorates, stratified by nationality, is summarised in **Table 4.4**. A total of 434 eligible patients were recruited from six PHCCs, one in each governorate. Recruitment was proportional to population density, with the highest proportion of participants enrolled from FAR (24.4%, n= 106/434) and the lowest from MBK (8.8%, n= 38/434). The majority of patients were non-Kuwaiti, accounting for 69.6% (n= 302/434), with the largest proportion recruited from FAR (27.8%, n= 84/302) and the smallest from MBK (5.3%, n= 16/302). Kuwaitis constituted 30.4% of the sample (n= 132/434), with the highest proportion enrolled from AHM (20.5%, n= 27/132) and the lowest from HAW (9.9%, n= 13/132).

Table 4.4 Distribution of the total sample across governorates, stratified by nationality

Governorate, n (%)	**Total sample (n= 434)**	**Kuwaiti sample (n=132, 30.4%)**	**Non-Kuwaiti sample (n= 302, 69.9%)**
CAP	58 (13.39%)	26 (19.7%)	32 (10.6%)
HAW	88 (20.28%)	13 (9.85%)	75 (24.83%)
AHM	89 (20.51%)	27 (20.45%)	62 (20.5%)
JAH	55 (12.67%)	22 (16.67%)	33 (10.93%)
FAR	106 (24.42%)	22 (16.67%)	84 (27.81%)
MBK	38 (8.76%)	22 (16.67%)	16 (5.3%)

CAP: Capital; **HAW**: Hawalli; **AHM**: Al-Ahmadi; **JAH**: Al-Jahra; **FAR**: Al-Farwaniyah; **MBK**: Mubarak Al-Kabeer

Patient characteristics are summarised in **Table 4.5**, structured in accordance with the WHO STEPwise approach (Step 1: demographic data; Step 2: physical measurements; Step 3; biochemical assessments) and stratified by monotherapy and combination therapy groups.

Step 1, which included demographic characteristics, showed that the mean age for the study participants at recruitment was 54.3 $\pm$ 9.7 years. Half of the participants (50.5%, n= 219/434) were under 55 years old. The proportion of both genders was similar, with females accounting for a slightly higher proportion (51.4%, n= 223/434). Regarding education level, nearly half of the participants (47.2%, n= 205/434) had attained intermediate to high school education. Additionally, the majority of the individuals was married (85.7%, n= 372/434). In terms of occupation, 87.8% of participants (n= 381/434) were employed across various sectors, including governmental, non-governmental, and domestic workers. Notably, nearly half of the participants (50.5%, n= 219/434) were employed as domestic workers (driver, housemaid, servant, or cooker).

Analysis of smoking status revealed that approximately one-fifth of participants (21.4%, n= 93/434) were identified as smokers, whereas the vast majority (98.8%, n= 429/434) reported no alcohol consumption. Regarding dietary habits, the median frequency of fruit consumption was three days per week (IQR: 2, 7), while vegetable were consumed more frequently, with a median of seven days per week (IQR: 4, 7). In terms of quantity, the overall median intake was two fruit servings per day (IQR: 1, 3) and two vegetable servings per day (IQR: 1,3). For physical activity levels, more than half of the participants (57.4%, n= 249/434) had a sedentary lifestyle. The remaining participants were engaged in either moderate-intensity activity (35.3%, n= 153/434) or vigorous-intensity activity (7.4%, n=32/434).

For clinical features, only one quarter of the sample (25.6%, n= 111/434) had a first-degree relative with a family history of CVD. Majority of patients were diagnosed with HTN (71.4%, n= 310/434) and type 2 diabetes mellitus (T2DM) (94.2%, n= 409/434), while only 10% (n= 44/434) had a history of CVD. In terms of concomitant medications, 94.9% (n= 412/434) and 64.5% (n= 280/434) were on antidiabetics and antihypertensives, respectively, while 12% (n= 52/434) were prescribed either antiplatelet or anticoagulant therapy.

Step 2, which involved physical measurements, showed that the overall median BMI was 28 kg/m^2 (IQR: 24.9, 32). One quarter of the participants (24.9%, n= 108/434) had a normal weight, while the remaining participants were classified as overweight (38.7%, n= 168/434) or obese (35.7%, n= 155/434). Another anthropometric measure was blood pressure (BP) which was available for 97% (n= 421/434) of the participants, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) was 132.4 $\pm$ 17.8 and 79.4 $\pm$ 10.7 mmHg, respectively. For 331 patients with available glycated haemoglobin (HbA1c) measurements, the median HbA1c was 7.8% (IQR: 6.8, 9.2). Among them, only 27.2% (n= 90/331) patients had HbA1c levels below 7%.

Step 3, which focused on biochemical measurements, included renal function assessment for 85.7% (n= 372/434) of patients. The mean eGFR was 93.6 $\pm$ 19.5 ml/min/1.73m^2 , with 94.4% (n= 351/372) having an estimated glomerular filtration rate (eGFR) of 60 or higher. For liver function, only 45.6% (n= 198/434) and 68.7% (n= 298/434) of patients had a record of aspartate transaminase (AST) and alanine transaminase (ALT), respectively. The median AST was 19 (IQR: 15, 24.9) U/L, while the median ALT was 21 (IQR: 15.5, 30.1) U/L.

Table 4.5 Sociodemographic and clinical characteristics of patients on LLTs, stratified by therapeutic regimen (monotherapy vs. combination therapy)

Variables		Total patients (n= 434)	Monotherapy (n= 385, 88.7%)	Combination therapy (n= 49, 11.3%)
Step 1: Demographic data and behavioural measurements				
Age (years)	Mean ± SD	54.3 ± 9.7	54.2 ± 9.8	55 ± 8.5
	<55, n (%)	219 (50.5%)	195 (50.6%)	24 (49%)
	≥55 - <65, n (%)	155 (35.7%)	137 (35.6%)	18 (36.7%)
	≥65 - <75, n (%)	48 (11.1%)	42 (10.9%)	6 (12.2%)
	≥75, n (%)	12 (2.76%)	11 (2.86%)	1 (2.04%)
Gender, n (%)	Male	211 (48.6%)	181 (47%)	30 (61.2%)
	Female	223 (51.4%)	204 (53%)	19 (38.8%)
Nationality, n (%)	Kuwaiti	132 (30.4%)	112 (29.1%)	20 (40.8%)
	Non-Kuwaiti	302 (69.6%)	273 (70.9%)	29 (59.2%)
Education level, n (%)	No formal schooling	72 (16.6%)	69 (17.9%)	3 (6.12%)
	Primary school	57 (13.1%)	53 (13.8%)	4 (8.16%)
	Intermediate-high school	205 (47.2%)	179 (46.5%)	26 (53.1%)
	College/University	100 (23.1%)	84 (21.8%)	16 (32.7%)
Marital status, n (%)	Single	15 (3.5%)	13 (3.4%)	2 (4.1%)
	Married	372 (85.7%)	32 (86.2%)	40 (81.6%)
	Divorced	10 (2.3%)	8 (2.1%)	2 (4.1%)
	Widowed	37 (8.5%)	32 (8.3%)	5 (10.2%)
Occupation, n (%)	Unemployed	53 (12.2%)	49 (12.7%)	4 (8.2%)
	Government	31 (7.1%)	28 (7.3%)	3 (6.1%)
	Non-government	71 (16.4%)	63 (16.4%)	8 (16.3%)

Table 4.5 Sociodemographic and clinical characteristics of patients on LLTs, stratified by therapeutic regimen (monotherapy vs. combination therapy)

Variables		Total patients (n= 434)	Monotherapy (n= 385, 88.7%)	Combination therapy (n= 49, 11.3%)
	Domestic workers	219 (50.5%)	201 (52.2%)	18 (36.7%)
	Retired	60 (13.8%)	44 (11.4%)	16 (32.7%)
Smoking status, n (%)	Lifelong non-smoker	308 (71%)	280 (72.7%)	28 (57.1%)
	Ex-smoker	33 (7.6%)	26 (6.75%)	7 (14.3%)
	Current	93 (21.4%)	79 (20.5%)	14 (28.6%)
Alcohol consumption, n (%)	No	429 (98.8%)	381 (99%)	48 (98%)
	Yes	5 (1.2%)	4 (1.0%)	1 (2.0%)
Diet (Fruits), median (IQR)	Number of days/week	3 (2, 7)	3 (2, 7)	4 (1, 7)
	Number of servings/day	2 (1, 3)	2 (1, 3)	2 (1, 3)
Diet (Vegetables), median (IQR)	Number of days/week	7 (4, 7)	7 (4, 7)	7 (3, 7)
	Number of servings/day	2 (1, 3)	2 (1, 3)	2 (1, 3)
Physical activity, n (%)	None	249 (57.4%)	223 (57.9%)	26 (53.1%)
	Moderate-intensity	153 (35.3%)	138 (35.8%)	15 (30.6%)
	Vigorous-intensity	32 (7.4%)	24 (6.23%)	8 (16.3%)
Family history of CVD, n (%)	No	323 (74.4%)	291 (75.6%)	32 (65.3%)
	Yes	111 (25.6%)	94 (24.4%)	17 (34.7%)
History of HTN, n (%)	No	124 (28.6%)	110 (28.6%)	14 (28.6%)
	Yes	310 (71.4%)	275 (71.4%)	35 (71.4%)
History of DM, n (%)	No	25 (5.8%)	23 (6.0%)	2 (4.08%)
	Yes	409 (94.2%)	362 (94%)	47 (95.9%)

Table 4.5 Sociodemographic and clinical characteristics of patients on LLTs, stratified by therapeutic regimen (monotherapy vs. combination therapy)

Variables		**Total patients (n= 434)**	**Monotherapy (n= 385, 88.7%)**	**Combination therapy (n= 49, 11.3%)**
History of CVD, n (%)	No	390 (89.9%)	350 (90.9%)	40 (81.6%)
	Yes	44 (10.1%)	35 (9.1%)	9 (18.4%)
Concomitant medications, n (%)	Antidiabetics	412 (94.9%)	365 (94.8%)	47 (95.9%)
	Antihypertensives	280 (64.5%)	244 (63.4%)	36 (73.5%)
	Antiplatelets or anticoagulants	52 (12%)	41 (10.6%)	11 (22.4%)
	None	3 (0.7%)	-	-
Step 2: Physical measurements				
BMI (Kg/m^2)	Median (IQR)	28 (24.9, 32)	27.8 (24.8, 31.6)	29.2 (25.4, 32.4)
	Under weight (<18.5), n (%)	3 (0.7%)	3 (0.8%)	-
	Normal weight (≥18.5-<25), n (%)	108 (24.9%)	99 (25.7%)	9 (18.4%)
	Overweight (≥25-<30), n (%)	168 (38.7%)	151 (39.2%)	17 (34.7%)
	Obese (≥30), n (%)	155 (35.7%)	132 (34.3%)	23 (46.9%)
BP (mmHg)		**Total patients (n= 421)**	**Monotherapy (n= 376, 89.3%)**	**Combination therapy (n= 45, 10.7%)**
	SBP, mean ± SD	132.4 ±17.8	132.7 ± 18.1	129.5 ± 15.8
	DBP, mean ± SD	79.4 ± 10.7	79.7 ± 10.9	77 ± 9.2
	SPB <130, n (%)	181 (43%)	160 (42.6%)	21 (46.7%)
	DBP <80, n (%)	191 (45.4%)	166 (44.1%)	25 (55.6%)
	SBP <130 + DBP <80, n (%)	117 (27.8%)	101 (26.9%)	16 (35.6%)
Step 3: Biochemical measurements				

Table 4.5 Sociodemographic and clinical characteristics of patients on LLTs, stratified by therapeutic regimen (monotherapy vs. combination therapy)

Variables		**Total patients (n= 434)**	**Monotherapy (n= 385, 88.7%)**	**Combination therapy (n= 49, 11.3%)**
HbA1c (%)		**Total patients (n= 331)**	**Monotherapy (n= 297, 89.7%)**	**Combination therapy (n= 34, 10.3%)**
	Median (IQR)	7.8 (6.8, 9.2)	7.8 (6.8, 9.2)	7.6 (7, 9.1)
	< 7, n (%)	90 (27.2%)	82 (27.6%)	8 (23.5%)
	7- <9, n (%)	149 (45%)	132 (44.4%)	17 (50%)
	>=9, n (%)	92 (27.8%)	83 (27.9%)	9 (26.5%)
RFT (ml/min/1.73m^2)		**Total patients (n= 372)**	**Monotherapy (n= 327, 87.9%)**	**Combination therapy (n= 45, 12.1%)**
	eGFR, mean ± SD	93.6 ± 19.5	95.1 ± 19.4	83 ± 16.7
	eGFR ≥ 60, n (%)	351 (94.4%)	310 (94.8%)	41 (91.1%)
	eGFR < 60, n (%)	21 (5.6%)	17 (5.2%)	4 (8.8%)
LFT (U/L), median (IQR)		**Total patients (n= 198)**	**Monotherapy (n= 179)**	**Combination therapy (n= 19)**
	AST	19 (15, 24.9)	19 (15, 24.3)	20.7 (17, 26.3)
		Total patients (n= 298)	**Monotherapy (n= 264)**	**Combination therapy (n= 34)**
	ALT	21 (15.5, 30.1)	21 (15.5, 30.3)	26.4 (17, 30.0)

LLT: Lipid-lowering therapy**; SD**: Standard deviation; **IQR**: Interquartile range; **CVD**: Cardiovascular disease; **HTN**: Hypertension; **DM**: Diabetes mellitus; **BMI**: Body mass index; **BP**: Blood pressure; **SBP**: Systolic blood pressure; **DBP**: Diastolic blood pressure; **HbA1c**: Glycated haemoglobin; **RFT**: Renal function test; **eGFR**: Estimated glomerular filtration rate; **LFT**: Liver function test; **AST**: Aspartate transaminase; **ALT**: Alanine transaminase

Key findings from **Table 4.5** indicate that among the 434 participants prescribed an LLT, the majority were receiving monotherapy (88.7%, n= 385). Approximately half of the patients were younger than 55 years, with a comparable distribution between genders. Around one-fifth of participants were smokers, and 57.4% of patients were categorised as sedentary. Most patients (94.2%) had T2DM, and 71.4% had HTN. Three-quarters of the patients were overweight or obese. The majority of patients had normal renal and liver function test results.

4.4.2. Prescribing patterns of LLTs among the study participants

Among the 434 patients prescribed LLTs, the vast majority (88.7%, n= 385/434) were prescribed monotherapy, while 11.3% (n= 49/434) received combination therapy. Among those on monotherapy, 98.7% (n= 380/385) patients were prescribed a statin, with the majority were on MIST (93.2%, n= 354/380). The remaining five patients (1.3%, n= 5/385) were on fibrate monotherapy, and no patients received ezetimibe as monotherapy (**Figure 4.1**).

Among those on combination therapy, the most frequent regimen was statin and fibrate (71.4%, n= 35/49), of which 88.6% (n= 31/35) involved a MIST. This was followed by statin and ezetimibe (22.4%, n= 11/49), with 18.2% (n= 2/11) involved a MIST. Additionally, two patients (4.1%, n= 2/49) were prescribed triplet therapy (a statin, ezetimibe and a PCSK9I), with one on MIST. There was only one patient (2%, n= 1/49) received a combination of HIST, ezetimibe, and a fibrate combination (**Figure 4.1**).

The study findings indicate that, aside from statins, only one agent from each of the fibrate and cholesterol absorption inhibitor classes was available, namely fenofibrate and ezetimibe, respectively. In contrast, statins were represented by three different agents: simvastatin, atorvastatin, rosuvastatin.

Among the 434 patients prescribed LLTs, the vast majority (98.8%, n= 429/434) received statins. Of these, 88.6% (n= 380/429) were prescribed statin monotherapy, while 11.4% (n= 49/429) were on combination therapy (**Figure 4.2**).

In the statin monotherapy group, simvastatin was the most frequently prescribed agent (75.8%, n= 288/380), with all prescriptions classified as MIST. This was followed by rosuvastatin (12.9%, n= 49/380), of which 57.1% (n= 28/49) were on MIST. Atorvastatin was the least utilised agent (11.3%, n= 43/380), and the majority of these prescriptions were categorised as MIST (88.4%, n= 38/43) (**Figure 4.2**).

Among patients on statin combination therapy, simvastatin also emerged as the most commonly prescribed statin (59.2%, n= 29/49), with all prescriptions considered as MIST. Rosuvastatin was the second most frequently used (26.5%, n= 13/49), with 15.4% (n= 2/13) of these prescriptions were at MIST. Atorvastatin accounted for the remaining 14.3% (n= 7/49), with 42.9% (n= 3/7) on MIST (**Figure 4.2**).

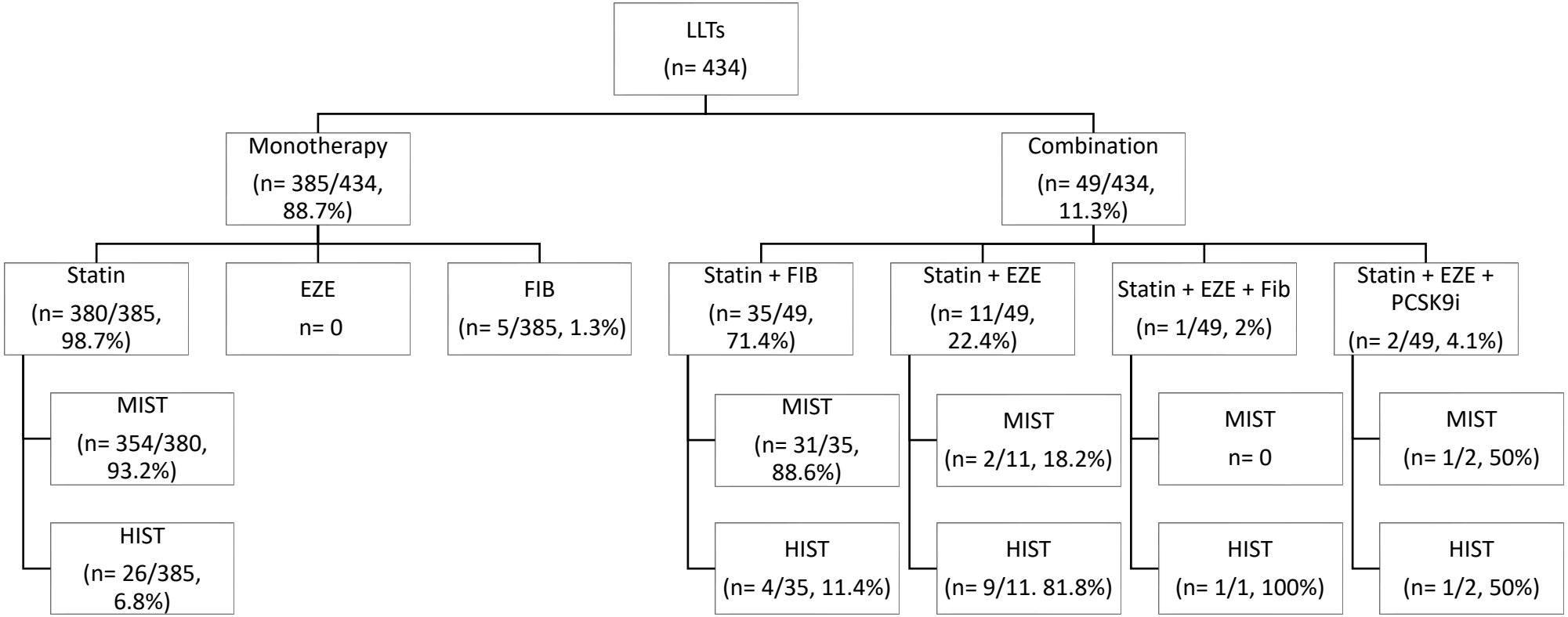

Figure 4.1 Flowchart illustrating the utilisation of lipid-lowering therapies by the class, stratified by monotherapy and combination therapy.
LLTs: Lipid-lowering therapies; **EZE**: Ezetimibe; **FIB**: Fibrate; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor; **MIST**: Moderate-intensity statin therapy; **HIST**: High-intensity statin therapy

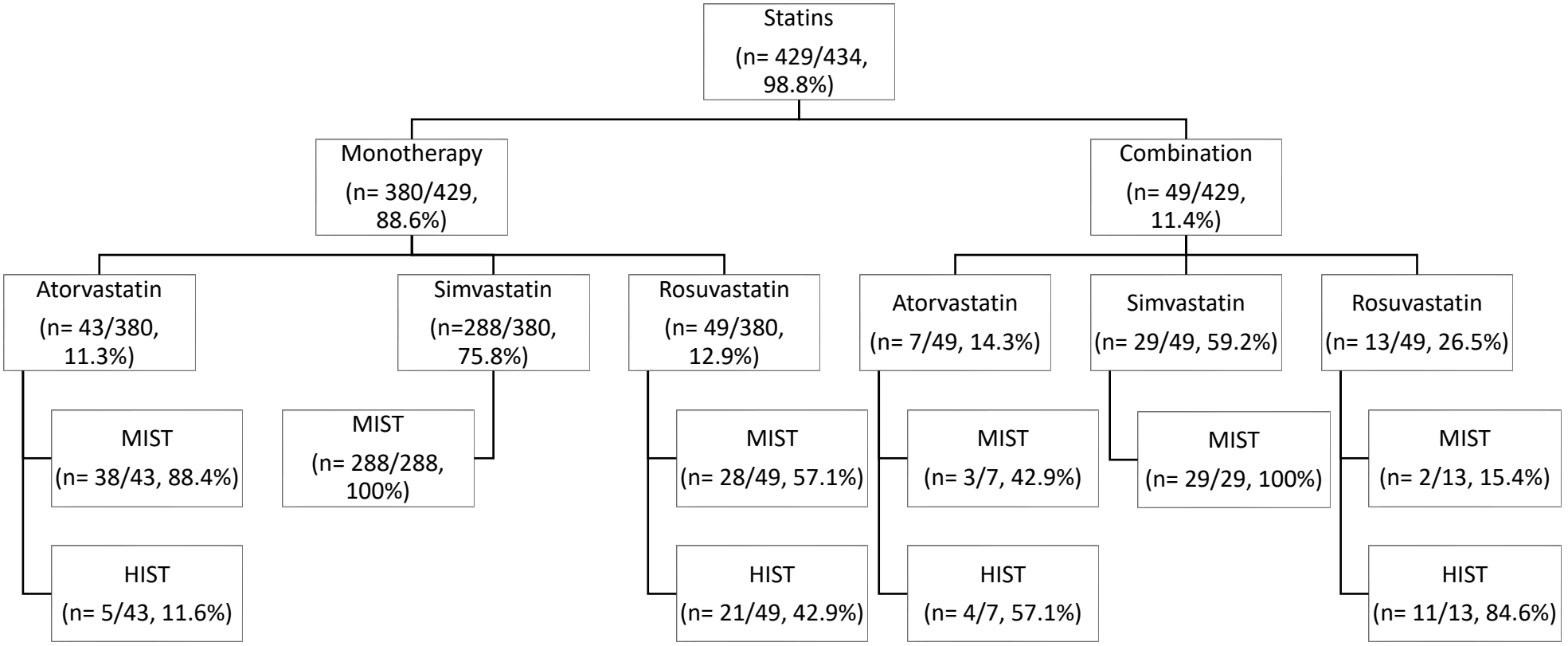

Figure 4.2 Flowchart illustrating the utilisation of statins by agent and intensity, stratified by monotherapy and combination therapy. **MIST**: Moderate-intensity statin therapy; **HIST**: High-intensity statin therapy

4.4.3. Achievement of guideline-recommended lipid targets

4.4.3.1. Study participants for the lipid target assessment

Of the 434 participants, 336 individuals (77.4%) met the inclusion criteria for the assessment of lipid goal attainment (**Figure 4.3**). Among the 336 participants, 42% (n= 141/336) were identified as having MetS. The remaining 58% were identified as not having MetS, but some of these individuals had missing data for one or more MetS criteria (**Table 4.6**). The distribution of patients across the three highest CV risk categories was relatively comparable, with 36.3% (n= 122/336) classified as extreme risk, 33% (n= 111/336) as very-high risk, and 30.1% (n= 101/336) as high risk. Only two participants (0.6%) were classified as moderate CV risk (**Table 4.6**).

Regarding lipid profile assessments, 94.6% (n= 318/336) of participants had available LDL-C measurements, with a median LDL-C level of 2.3 mmol/L (IQR: 1.8, 3.1). Non-HDL-C data were available for 94% (n= 316/336), with a median level of 3.1 mmol/L (IQR: 2.4, 4.0). TG levels were recorded in 95.5% of patients (n = 321/336), showing a median of 1.5 mmol/L (IQR: 1.2–2.0). Similarly, HDL-C data were available for 95.8% (n = 322/336), with a mean HDL-C level of 1.2 $\pm$ 0.3 mmol/L. TC was measured in 96.7% of participants (n = 325/336), with a median value of 4.3 mmol/L (IQR: 3.7–5.2) (**Table 4.6**).

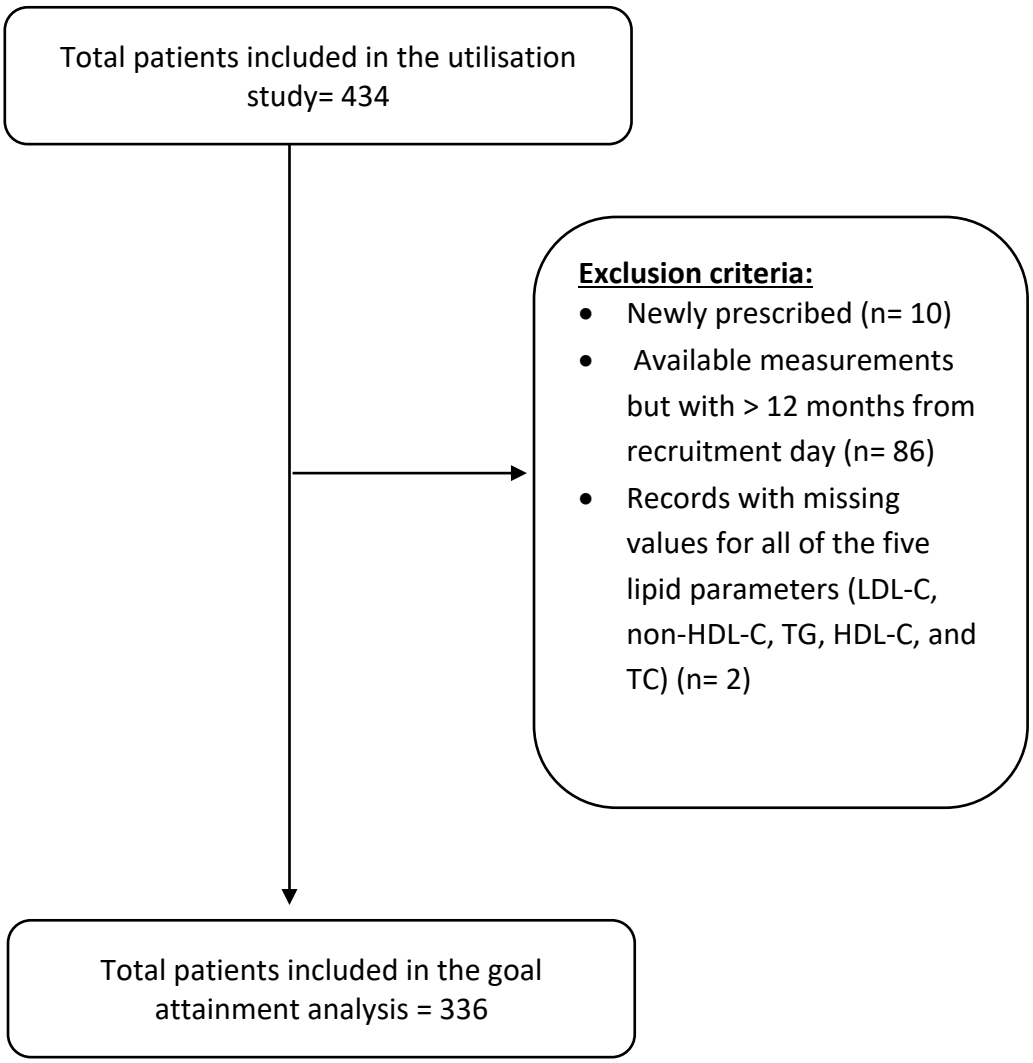

Figure 4.3 Study flowchart reporting the number of patients included in the lipid target attainment analysis. **LDL-C**: Low-density lipoprotein cholesterol; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **TG**: Triglycerides; **HDL-C**: High-density lipoprotein cholesterol; **TC**: Total cholesterol

Table 4.6 Assessment of metabolic syndrome, CV risk categories, and lipid profile among 336 patients, stratified by therapeutic regimen (monotherapy and combination therapy)

Variables		**Total patients (n= 336)**	**Monotherapy (n= 295, 87.8%)**	**Combination therapy (n= 41, 12.2%)**
Metabolic syndrome, n (%)	No	195 (58%)	172 (58.3%)	23 (56.1%)
	Yes	141 (42%)	123 (41.7%)	18 (43.9%)
CV risk category, n (%)	Extreme	122 (36.3%)	100 (33.9%)	22 (53.7%)
	Very-high	111(33%)	98 (33.2%)	13 (31.7%)
	High	101 (30.1%)	95 (32.2%)	6 (14.6%)
	Moderate	2 (0.6%)	2 (0.7%)	-
Lipid profile (mmol/L)	LDL-C, median (IQR)	**Total patients (n= 318)**	**Monotherapy (n= 282, 88.7%)**	**Combination therapy (n= 36, 11.3%)**
		2.3 (1.8, 3.1)	2.4 (1.8, 3.1)	2.0 (1.8, 3.0)
	Non-HDL-C, median (IQR)	**Total patients (n= 316)**	**Monotherapy (n= 278, 88%)**	**Combination therapy (n= 38, 12%)**
		3.1 (2.4, 4)	3.1 (2.3, 3.9)	3.3 (2.8, 4.5)
	TG, median (IQR)	**Total patients (n= 321)**	**Monotherapy (n= 283, 88.2%)**	**Combination therapy (n= 38, 11.8%)**
		1.5 (1.2, 2)	1.5 (1.1, 1.9)	2.2 (1.5, 3.2)
	HDL-C, mean (SD)	**Total patients (n= 322)**	**Monotherapy (n= 284, 88.2%)**	**Combination therapy (n= 38, 11.8%)**
		1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
	TC, median (IQR)	**Total patients (n= 325)**	**Monotherapy (n= 285, 87.7%)**	**Combination therapy (n= 40, 12.3%)**
		4.3 (3.7, 5.2)	4.3 (3.6, 5.1)	4.3 (3.9, 5.4)

CV: Cardiovascular; **LDL-C**: Low-density lipoprotein cholesterol; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **TG**: Triglycerides; **HDL-C**: High-density lipoprotein cholesterol; **TC**: Total cholesterol; **IQR**: Interquartile range; **SD**: Standard deviation

4.4.3.2. Lipid target attainment

This section reveals the number and percentage of patients across all CV risk categories who attained lipid targets. The analysis is further stratified by CV risk categories, comparing study outcomes among all patients, those on monotherapy, and those on combination therapy.

4.4.3.2.1. Lipid target attainment across all CV risk categories

Among all CV risk categories (n= 336), and focusing first on the primary lipid targets, only one-fifth of patients attained the LDL-C target (20.4%, n= 65/318), while just over one-quarter achieved the non-HDL-C target (26.6%, n= 84/316). Patients who met both lipid parameters accounted for only 18.8% (n= 58/309) (**Table 4.7**).

For other lipid targets, 61.6% (n= 196/321) of patients achieved the TG target, while 53.4% (n= 172/322) reached the HDL-C target. Regarding TC, which is of lesser clinical significance compared to other lipid parameters, 69.8% (n = 227/325) attained the target level (**Table 4.7**).

When considering all five lipid parameters together, only 8.4% of patients (n= 26/309) achieved the corresponding target levels. Notably, patients on monotherapy demonstrated higher rates of goal attainment for each individual lipid parameter compared with those on combination therapy (**Table 4.7**). To determine whether these differences were statistically significant, logistic regression analyses were conducted, as described in detail in section 4.4.4. Briefly, the analyses showed no significant differences between monotherapy and combination therapy for LDL-C (**Table 4.8**) or non-HDL-C (Table 4.9).

Table 4.7 Number and proportion of patients across all CV risk categories with available measurements and target achievements, stratified by therapeutic regimen

Lipid parameter		Total patients (n= 336)	Monotherapy (n= 295, 87.8%)	Combination (n= 41, 12.2%)
LDL-C	Available measurements	318 (94.6%)	282 (95.6%)	36 (87.8%)
	Target met	65 (20.4%)	58 (20.6%)	7 (19.4%)
Non-HDL-C	Available measurements	316 (94%)	278 (94.2%)	38 (92.7%)
	Target met	84 (26.6%)	78 (28.1%)	6 (15.8%)
LDL-C + Non-HDL-C	Available measurements	309 (92%)	274 (92.9%)	35 (85.4%)
	Target Met	58 (18.8%)	54 (19.7%)	4 (11.4%)
TG	Available measurements	321 (95.5%)	283 (95.9%)	38 (92.7%)
	Target met	196 (61.1%)	184 (65%)	12 (31.6%)
HDL-C	Available measurements	322 (95.8%)	284 (96.3%)	38 (92.7%)
	Target met	172 (53.4%)	154 (54.2%)	18 (47.4%)
TC	Available measurements	325 (96.7%)	285 (96.6%)	40 (97.6%)
	Target met	227 (69.8%)	204 (71.6%)	23 (57.5%)
All	Available measurements	309 (92%)	274 (92.9%)	35 (85.4%)
	Target Met	26 (8.4%)	24 (8.8%)	2 (5.7%)

LDL-C: Low-density lipoprotein cholesterol; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **TG**: Triglycerides; **HDL-C**: High-density lipoprotein cholesterol; **TC**: Total cholesterol

Key findings from **Table 4.7** demonstrate suboptimal lipid control across all lipid parameters and CV risk categories. For the LDL-C, 94.6% of measurements were available (n= 318/336). In this calculation, the numerator reflects the number of available measurements for the respective lipid parameters, while the denominator represents the total number of patients eligible for lipid target assessment. Among those with available measurements, only 20.4% of patients (n= 65/318) achieved the LDL-C target. In this calculation, the numerator reflects the number of patients who attained the LDL-C target, while the denominator represents the number of patients

with available measurements for LDL-C. The same principle was applied to all other lipid parameter categories.

Following the overall lipid target assessment, patients were further stratified by individual CV risk category (**Figure 4.4**). Additional details for each CV risk category, further stratified by monotherapy and combination therapy users, are provided in **Appendix S4.5**.

4.4.3.2.2. Extreme CV risk category

Among the 36.3% (n= 122/336) patients classified as extreme CV risk category, lipid target attainment was generally low. For primary lipid targets, only 8% (n= 9/113) achieved the LDL-C target, while a slightly higher proportion (13.8%, n= 16/116) attained the non-HDL-C target. When considering both targets together, only 6.3% (n= 7/111) met the target (**Figure 4.4A; Appendix S4.5A**). For other lipid targets, 56.9% (n= 66/116) patients reached the TG target, and 55.2% (n= 64/116) achieved the HDL-C target. TC was achieved by 64.2% (n= 77/120) of patients. However, when considering all five lipid parameters together, only 1.8% (n= 2/111) met the recommended targets (**Figure 4.4A; Appendix S4.5A**). When comparing monotherapy with combination therapy, goal attainment was generally higher among monotherapy users, except for non-HDL-C, where combination therapy users (15.8%, n= 3/19) had a slightly higher attainment rate than monotherapy users (13.4%, n= 13/97) (**Figure 4.4A; Appendix S4.5A**).

4.4.3.2.3. Very-high CV risk category

Among the 33% (n= 111/336) patients classified as very-high CV risk category, lipid target attainment varied across parameters. For primary lipid targets, 25.5% (n= 27/106) attained the LDL-C target, while a higher proportion (34.3%, n= 35/102) attained the non-HDL-C target. When considering both targets together, 25.7% (n= 26/101) met the recommended levels (**Figure 4.4B; Appendix S4.5B**). For secondary lipid targets, 65.1% (n = 69/106) reached the TG target, and 47.2% (n = 50/106)

achieved the HDL-C target. TC attainment was achieved by 76.2% (n= 80/105) of patients. However, when considering all five lipid parameters together, only 9.9% (n= 10/101) achieved full target attainment (**Figure 4.4B; Appendix S4.5B**). When comparing monotherapy with combination therapy, target goal attainment was generally higher among monotherapy users, except for HDL-C, where combination therapy users (53.8%, n= 7/13) had a slightly higher attainment rate than monotherapy users (46.2%, n= 43/93) **Figure 4.4B; Appendix S4.5B**).

4.4.3.2.4. High CV risk category

Among the 23.3% (n= 101/434) patients classified as high CV risk, lipid target attainment showed some variability across parameters. For primary lipid targets, 29.9% (n = 29/97) achieved the LDL-C target, while a slightly higher proportion (34.4%, n = 33/96) attained the non-HDL-C target. When considering both targets together, 26.3% (n = 25/95) met the recommended levels (**Figure 4.4C; Appendix S4.5C**). For secondary lipid targets, 60.8% (n = 59/97) reached the TG target, and 58.2% (n = 57/98) achieved the HDL-C target. TC attainment was achieved by 71.4% (n = 70/98) of patients. However, when considering all five lipid parameters together, only 14.7% (n = 14/95) achieved full target attainment (**Figure 4.4C; Appendix S4.5C**). When comparing monotherapy with combination therapy, target attainment was generally higher among monotherapy users for non-HDL-C (34.4%, n= 31/90 vs. 33.3%, n= 2/6), TG (63.7%, n= 58/91 vs. 16.7%, n= 1/6), and TC (71.7%, n= 66/92 vs. 66.7%, n= 4/6). However, for the remaining, combination therapy users had higher attainment rates than monotherapy users (**Figure 4.4C; Appendix S4.5C**).

4.4.3.2.5. Moderate CV risk category

Only two (0.6%, n=2/336) patients were classified as having moderate CV risk, both of whom had complete lipid parameter measurements. However, neither of them achieved target levels for the primary lipid markers (LDL-C and non-HDL-C) or TC. Both patients met the TG target, while only one achieved the HDL-C target. Notably, both patients were on monotherapy regimen.

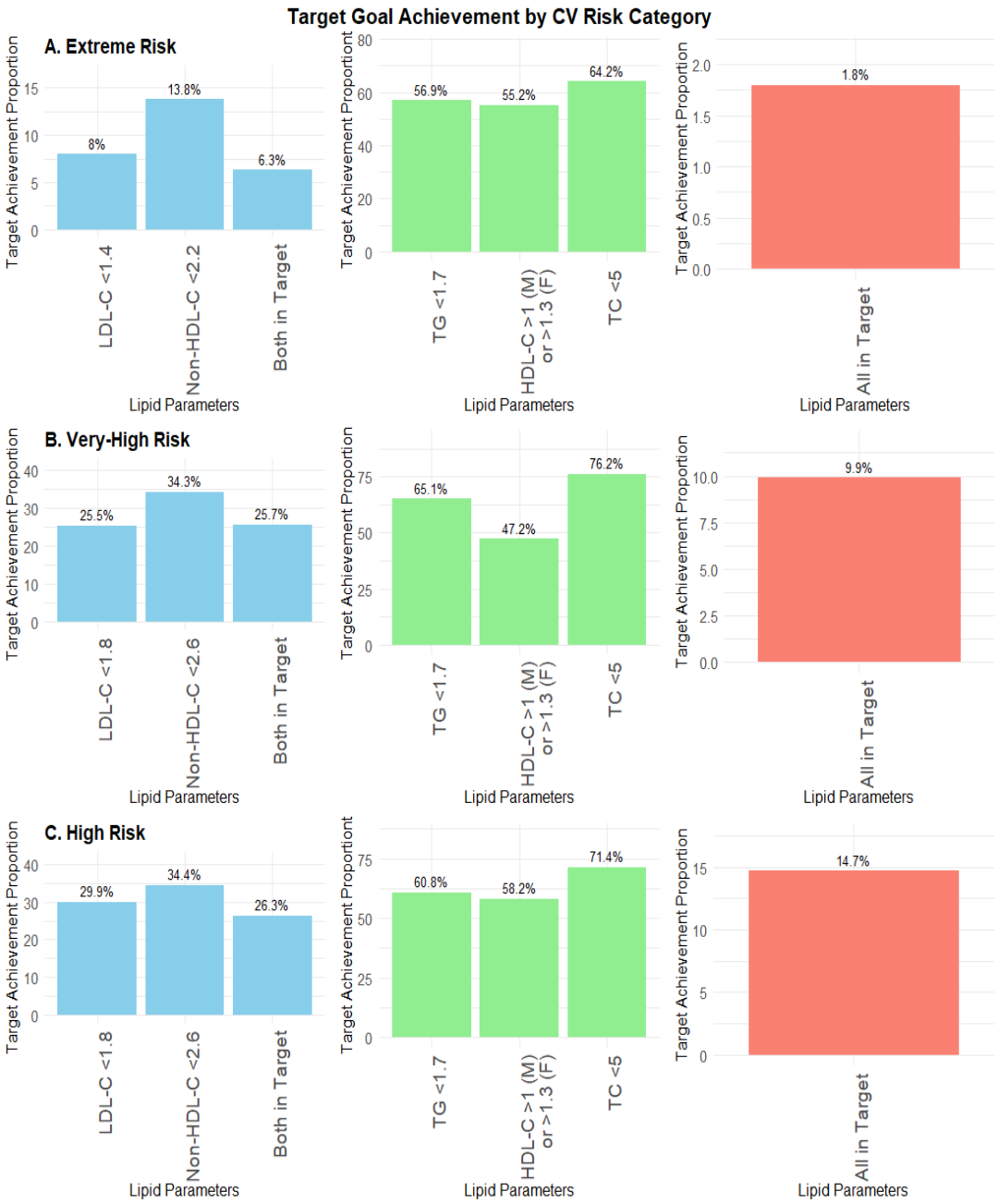

Figure 4.4 Target goal achievement by cardiovascular risk category for primary lipid targets (blue bars), secondary lipid targets (green bars), and all lipid targets (red bars)**:** **A**. Extreme risk**, B.** Very-high risk**, C.** High risk**.** Lipid parameter values are expressed in mmol/L. **CV**: cardiovascular; **LDL-C**: Low-density lipoprotein cholesterol; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **TG**: Triglycerides; **HDL-C**: High-density lipoprotein cholesterol; **TC**: Total cholesterol; **M**: Males; **F**: Females

To briefly summarise, **Figure 4.4** depicts suboptimal lipid control across the extreme, very-high, and high CV risk categories for all lipid parameters. Notably, for the primary lipid parameters (blue bars), the lowest attainment was observed in the extreme CV risk category, where only 8% achieved the LDL-C target and 13.8% achieved the non-HDL-C target.

4.4.4. Factors associated with lipid goal achievement

The binomial logistic regression was conducted primarily for LDL-C and non-HDL-C at targets, as the 2021 Middle East consensus considered them as primary lipid targets (20). Summary of sociodemographic and clinical characteristics among patients achieving lipid targets for LDL-C and non-HDL-C is provided in **Appendix S4.6**. **section 4.4.4.1** presents the univariate and multivariate analyses of factors associated with the LDL-C target attainment, and **section 4.4.4.2** displays the analysis of factors associated with the non-HDL-C target achievement.

4.4.4.1. Factors associated with the LDL-C target attainment

Table 4.8 presents the results of the univariate and multivariate binomial logistic regression analyses of factors associated with LDL-C target attainment. In the univariate analysis, education level was the only demographic characteristic significantly associated with LDL-C target attainment, with a global p-value= 0.006. Individuals with a higher level of education (college/university) had 75% lower odds of achieving LDL-C targets compared to those with an intermediate to high school education (OR= 0.25, 95% CI: 0.08–0.61, p= 0.005). Patients with no formal schooling also exhibited lower odds of LDL-C target attainment; however, this association was not statistically significant (OR= 0.90, 95% CI: 0.42–1.85, p= 0.779).

Marital status, as a whole, was not significantly associated with LDL-C target achievement (global p-value= 0.118). However, widowed individuals had a significant 2.5 times higher odds of achieving LDL-C targets compared to married individuals (OR= 2.50, 95% CI: 1.01–5.88, p= 0.0397). While single individuals also exhibited higher odds, the association was not statistically significant (OR= 2.47, 95% CI: 0.73–7.46, p = 0.119).

Among clinical variables, CV risk category was the only factor significantly associated with the LDL-C target achievement (global p-vale= 0.0001). Patients classified in the very-high CV risk category were nearly four times more likely to achieve LDL-C targets compared to those in the extreme risk category (OR= 3.95, 95% CI: 1.82–9.33, p= 0.0008). Similarly, individuals in the high-risk category had nearly five times higher odds of achieving LDL-C targets compared to those in the extreme risk group (OR= 4.93, 95% CI: 2.28–11.64, p < 0.001). For patients in the moderate-risk category, the OR was estimated as 0 with a p-value of 0.990, suggesting that no individuals in this category reached LDL-C targets and that the sample size was too small (only two patients) to generate a reliable estimate.

Lastly, significant variation in LDL-C target attainment was observed across governorates (global p-value= 0.037), indicating potential regional disparities. Among the six governorates, patients treated in AHM had a 77% lower likelihood of reaching LDL-C targets compared to those in FAR (OR= 0.23, 95% CI: 0.07–0.61, p = 0.005), representing a statistically significant poor outcome. While patients from HAW and JAH exhibited higher odds of achieving LDL-C targets, these associations were not statistically significant. Similarly, patients in CAP and MBK had nearly identical odds of LDL-C target attainment compared to FAR, suggesting no meaningful difference.

Other sociodemographic and clinical variables exhibited varying odds (higher (>1), lower (<1), or unchanged (=1)) compared to the reference category in the case of categorical variables, or across the range of continuous variables. However, none of these associations were statistically significant.

After adjusting for confounders in the multivariate analysis, the final model showed only one change compared to the univariate analysis in that the global p-value for governorate variable (p= 0.143) was not statistically significant. However, consistent with the univariate analysis, patients in AHM had 78% lower odds of achieving LDL-C targets compared to those in FAR (adjusted OR= 0.22, 95% CI: 0.06–0.75, p = 0.020). This statistically significant finding suggests that patients in AHM had a substantial poor control of reaching LDL-C targets.

Education level was significantly associated with LDL-C target attainment (global p-value= 0.0216). Individuals with a college/university education were significantly 83% less likely to achieve LDL-C targets compared to those with an intermediate to high school education (adjusted OR= 0.17, 95% CI: 0.04–0.61, p= 0.011). Marital status was not significantly associated with LDL-C target attainment overall (global p= 0.196), indicating no strong evidence of an effect across marital categories. However, widowed individuals had significantly higher odds of attaining LDL-C targets compared to married individuals (adjusted OR= 4.18, 95% CI: 1.12–16.09, p = 0.034). This suggests that being widowed is a strong factor of better LDL-C target attainment.

Similar to the univariate analysis, the CV risk category was significantly associated with LDL-C target attainment (global p-value= 0.002). Individuals in the very-high risk category had 8.18 times higher odds of attaining LDL-C targets compared to those in the extreme risk category (adjusted OR= 8.18, 95% CI: 2.42–31.88, p= 0.001). This association was statistically significant, suggesting a strong relationship between lower CV risk classification and greater likelihood of LDL-C target achievement. Individuals in the high-risk category were even more likely to achieve LDL-C targets, with 18.45 times higher odds compared to those in the extreme risk category (adjusted OR= 18.45, 95% CI: 3.54–111.6, p = 0.001). For the moderate risk category, an OR of 0 with a p-value of 0.992 suggests that no individuals in this category reached LDL-C targets, likely due to insufficient data to generate a reliable estimate (two patients only).

Table 4.8 Univariate and multivariate binomial logistic regression of factors associated with **LDL-C** target achievement

Factors	**Univariate**		**Multivariate**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age Continuous	0.97 (0.94, 1.0)	0.061	1.03 (0.97, 1.1)	0.345
Gender M vs. F (ref)	0.74 (0.42, 1.28)	0.281	2.25 (0.81, 6.55)	0.126
Nationality K vs. NK (ref)	0.58 (0.30, 1.09)	0.102	0.27 (0.04, 1.66)	0.161
Education level		**0.006*‡**		**0.0216*‡**
Intermediate-high school	1		1	
No formal schooling	0.90 (0.42, 1.85)	0.779	0.77 (0.26, 2.16)	0.631
Primary school	1.33 (0.60, 2.83)	0.464	1.41 (0.52, 3.77)	0.491
College/University	0.25 (0.08, 0.61)	**0.005***	0.17 (0.04, 0.61)	**0.011***
Marital Status		0.118‡		0.196‡
Married	1		1	
Single	2.47 (0.73, 7.46)	0.1191	1.48 (0.29, 7.29)	0.627
Divorced	0.74 (0.04, 4.46)	0.7826	0.86 (0.03, 9.65)	0.912
Widowed	2.50 (1.01, 5.88)	**0.0397***	4.18 (1.12, 16.09)	**0.034***
Occupation		0.3003‡		0.876‡
Domestic workers	1		1	
Government employee	0.47 (0.11, 1.47)	0.243	2.04 (0.18, 18.83)	0.541
Non-government employee	0.52 (0.20, 1.19)	0.145	0.71 (0.19, 2.42)	0.585
Unemployed	0.65 (0.25, 1.51)	0.345	1.74 (0.3, 8.74)	0.512
Retired	0.52 (0.20, 1.19)	0.145	1.44 (0.16, 11.66)	0.735
Family history of CVD Yes vs. No (ref)	0.98 (0.51, 1.8)	0.962	1.17 (0.5, 2.69)	0.710
Smoking status		0.2492‡		0.8208‡
Non-smoker	1		1	
Ex-smoker	1.64 (0.60, 4.08)	0.302	1.3 (0.34, 4.67)	0.696
Current	0.64 (0.28, 1.33)	0.254	1.4 (0.42, 4.47)	0.573
Alcohol consumption Yes vs. No (ref)	1.3 (0.064, 10.36)	0.82	0.95 (0.04, 11.56)	0.972

Table 4.8 Univariate and multivariate binomial logistic regression of factors associated with **LDL-C** target achievement

Factors	**Univariate**		**Multivariate**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Fruits: days per week Continuous	0.96 (0.86, 1.08)	0.505	0.97 (0.81, 1.16)	0.761
Fruits: servings per day Continuous	0.85 (0.67, 1.07)	0.186	1.02 (0.68, 1.53)	0.924
Vegetables: days per week Continuous	0.98 (0.87, 1.12)	0.777	1.05 (0.88, 1.27)	0.598
Vegetables: servings per day Continuous	0.93 (0.71, 1.19)	0.565	1.22 (0.82, 1.83)	0.325
Physical activity		0.867‡		0.326‡
None	1		1	
Moderate-intensity	1.13 (0.63, 2.02)	0.681	0.53 (0.23, 1.22)	0.142
Vigorous-intensity	1.24 (0.43, 3.17)	0.665	0.8 (0.2, 3.01)	0.747
HTN No vs. Y (ref)	1.02 (0.55, 1.83)	0.952	0.78 (0.34 – 1.70)	0.534
DM No vs. Y (ref)	1.16 (0.33, 2.71)	0.783	0.71 (0.13, 3.36)	0.670
CVD Yes vs. No (ref)	0.60 (0.17, 1.61)	0.356	1.81 (0.3, 10.22)	0.505
MetS Yes vs. No (ref)	0.81 (0.46, 1.41)	0.466	1.03 (0.45, 2.35)	0.945
BMI Continuous	1.0 (0.95, 1.05)	0.997	1.01 (0.95, 1.08)	0.691
BP Yes vs. No (ref)	0.92 (0.50, 1.66)	0.796	0.86 (0.38, 1.92)	0.719
eGFR Continuous	1.01 (0.99, 1.02)	0.246	1 (0.98, 1.02)	0.822
CV risk category		**0.0001*‡**		**0.002*‡**
Extreme	1		1	
Very-high	3.95 (1.82, 9.33)	**0.0008***	8.18 (2.42, 31.88)	**0.001***
High	4.93 (2.28, 11.64)	**<0.001***	18.45 (3.54, 111.6)	**0.001***
Moderate	0	0.990	0	0.992
Therapeutic regimen Comb vs. Mono (ref)	0.93 (0.36, 2.13)	0.875	1.1 (0.34, 3.31)	0.863

Table 4.8 Univariate and multivariate binomial logistic regression of factors associated with **LDL-C** target achievement

Factors	**Univariate**		**Multivariate**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Statin intensity, if used				
HIST vs. MIST (ref)	0.88 (0.32, 2.1)	0.783	3.33 (0.73, 15.82)	0.121
Governorate		**0.037*‡**		0.143‡
FAR	1		1	
HAW	0.66 (0.28, 1.45)	0.308	0.93 (0.31 – 2.75)	0.899
CAP	1.02 (0.45, 2.23)	0.966	1.25 (0.42, 3.66)	0.685
AHM	0.23 (0.07, 0.61)	**0.005***	0.22 (0.06, 0.75)	**0.020***
MBK	1.03 (0.34, 2.84)	0.960	0.94 (0.18, 4.13)	0.935
JAH	0.56 (0.21, 1.39)	0.234	0.63 (0.17, 2.20)	0.475

***p value <0.05; ‡global p-value. M:** Male**; F:** Female**; K:** Kuwaiti**; NK:** Non-Kuwaiti**; CVD**: Cardiovascular disease; **HTN**: Hypertension; **DM**: Diabetes mellitus; **MetS**: Metabolic syndrome; **BMI**: Body mass index; **BP**: Blood pressure; **RFT**: Renal function test; **eGFR**: Estimated glomerular filtration rate; **LFT**: Liver function test; **Comb**: Combination; **Mono**: Monotherapy; **HIST**: High-intensity statin therapy; **MIST**: Moderate-statin therapy; **CAP**: Capital; **HAW**: Hawalli; **AHM**: Al-Ahmadi; **JAH**: Al-Jahra; **FAR**: Al-Farwaniyah; **MBK**: Mubarak Al-Kabeer

4.4.4.2. Factors associated with the non-HDL-C target attainment

Table 4.9 presents the results of the univariate and multivariate binomial logistic regression analyses, assessing association between various demographic and socioeconomic factors and non-HDL-C target attainment. In the univariate analysis, education level was marginally associated with non-HDL-C target attainment (global p-value= 0.053). Individuals with a higher level of education (college/university) were significantly less likely to achieve non-HDL-C targets compared to those with an intermediate to high school education (OR= 0.39, 95% CI: 0.18–0.81, p= 0.015). Similar to the LDL-C outcome, patients with no formal schooling (OR= 1.05, 95% CI: 0.52–2.05, p= 0.896) and those with a primary school education (OR= 1.02, 95% CI: 0.48–2.1, p= 0.957) showed no significant difference in non-HDL-C target attainment.

Marital status was significantly associated with non-HDL-C target attainment (global p-value= 0.007), differing from the LDL-C findings. Widowed individuals had a significant 3.25 times higher odds of achieving non-HDL-C targets compared to married individuals (OR= 3.25, 95% CI: 1.38–7.66, p= 0.006). Single individuals also had significantly higher odds of attaining non-HDL-C targets (OR= 3.79, 95% CI: 1.22–12.17, p= 0.02). Divorced participants had lower odds of reaching non-HDL-C targets (OR= 0.54, 95% CI: 0.03–3.25, p= 0.574), but this association was not statistically significant. In addition to these demographic characteristics, gender was significantly associated with non-HDL -C target achievement. Males were 45% less likely to achieve the targets compared to females (OR= 0.55, 95% CI: 0.33–0.92, p= 0.023).

Among clinical variables, CV risk category was the only factor significantly associated with the non-HDL-C target achievement (global p-value= 0.0004). Patients classified in the very-high CV risk category were 3.26 times more likely to achieve non-HDL-C targets compared to those in the extreme risk category (OR= 3.26, 95% CI: 1.7–6.5, p= 0.001). Similarly, individuals in the high-risk category had 3.26 times higher odds of achieving non-HDL-C targets compared to those in the extreme risk group (OR= 3.26, 95% CI: 1.69–6.5, p= 0.001). As in the LDL-C analysis, the moderate-risk category

had an odds ratio of 0 with a p-value of 0.984, suggesting that no individuals in this category achieved non-HDL-C targets. Unlike LDL-C target attainment, there was no evidence of regional disparities among the six governorates. Other variables exhibited varying odds (higher (>1), lower (<1), or unchanged (=1)) compared to the reference category in the case of categorical variables, or across the range of continuous variables. However, none of these associations were statistically significant.

After adjusting for confounders in the multivariate analysis, the final model showed some differences from the univariate analysis in that the education level was no longer significantly associated with non-HDL-C target attainment (global p-value= 0.292). Also, no individual education category comparisons remained statistically significant. Moreover, gender was also no longer significantly associated with non-HDL-C target achievement (adjusted OR= 1.36, 95% CI: 0.56–3.39, p = 0.501).

Consistent with the univariate analysis, marital status remained significantly associated with non-HDL-C target attainment (global p-value= 0.024). Widowed individuals had 4.72 times higher odds of achieving non-HDL-C targets compared to married individuals (adjusted OR= 4.72, 95% CI: 1.43–16.37, p= 0.012). Unlike in the univariate analysis, single individuals were no longer significantly associated with non-HDL-C target attainment (adjusted OR= 3.45, 95% CI: 0.8–15.73, p= 0.098).

CV risk category remained a strong predictor of non-HDL-C target attainment (global p-value= 0.007). Individuals in the very-high risk category had 4.28 times higher odds of attaining non-HDL-C targets compared to those in the extreme risk category (adjusted OR= 4.28, 95% CI: 1.55–12.58, p= 0.006). Individuals in the high-risk category were even more likely to achieve non-HDL-C targets, with 6.7 times higher odds compared to those in the extreme risk category (adjusted OR= 6.7, 95% CI: 1.68–28.43, p = 0.008). Both associations were statistically significant. As in the univariate analysis, the moderate risk category had an odds ratio of 0.

Table 4.9 Univariate and multivariate binomial logistic regression of factors associated with **non-HDL-C** target achievement

Factors	Univariate		Multivariate	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age Continuous	0.99 (0.96, 1.01)	0.370	1 (0.94, 1.06)	0.970
Gender M vs. F (ref)	0.55 (0.33, 0.92)	**0.023***	1.36 (0.56, 3.39)	0.501
Nationality K vs. NK (ref)	0.91 (0.52, 1.56)	0.728	0.55 (0.12, 2.53)	0.444
Education level		0.053‡		0.2923‡
Intermediate-high school	1		1	
No formal schooling	1.02 (0.48, 2.1)	0.957	1.21 (0.48, 2.97)	0.685
Primary school	1.05 (0.52, 2.05)	0.896	0.87 (0.33 – 2.17)	0.764
College/University	0.39 (0.18, 0.81)	**0.015***	0.43 (0.16, 1.10)	0.088
Marital Status		**0.007*‡**		**0.024*‡**
Married	1		1	
Single	3.79 (1.22, 12.17)	**0.020***	3.45 (0.8, 15.73)	0.098
Divorced	0.54 (0.03, 3.25)	0.574	0.45 (0.02, 4.33)	0.535
Widowed	3.25 (1.38, 7.66)	**0.006***	4.72 (1.43, 16.37)	**0.012***
Occupation		0.343‡		0.686‡
Domestic workers	1		1	
Government employee	0.58 (0.16, 1.65)	0.343	2.14 (0.28, 14.24)	0.443
Non-government employee	0.52 (0.21, 1.14)	0.119	0.71 (0.22, 2.18)	0.561
Unemployed	1.27 (0.59, 2.66)	0.530	2.04 (0.48, 8.31)	0.322
Retired	0.79 (0.37, 1.62)	0.537	2.63 (0.43, 15.93)	0.292
Family history of CVD Yes vs. No (ref)	1.02 (0.57, 1.8)	0.937	0.98 (0.46, 2.04)	0.951
Smoking status		0.257‡		0.539‡
Non-smoker	1		1	
Ex-smoker	1.29 (0.5, 3.08)	0.579	1.91 (0.57, 6.18)	0.283
Current	0.61 (0.29, 0.47)	0.157	1.35 (0.47, 3.8)	0.571
Alcohol consumption Yes vs. No (ref)	0	0.984	0	0.99
Fruits: days per week	0.97 (0.87, 1.07)	0.531	0.96 (0.82, 1.13)	0.648

Table 4.9 Univariate and multivariate binomial logistic regression of factors associated with **non-HDL-C** target achievement

Factors	**Univariate**		**Multivariate**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Continuous				
Fruits: servings per day Continuous	0.88 (0.71, 1.09)	0.2603	1.01 (0.72, 1.42)	0.942
Vegetables: days per week Continuous	1.04 (0.93, 1.18)	0.5	1.16 (0.99, 1.38)	0.075
Vegetables: servings per day Continuous	0.94 (0.74, 1.18)	0.609	0.96 (0.68, 1.36)	0.823
Physical activity		0.482‡		0.175‡
None	1		1	
Moderate-intensity	0.84 (0.49, 1.43)	0.525	0.53 (0.25, 1.11)	0.095
Vigorous-intensity	0.57 (0.18, 1.47)	0.276	0.44 (0.11, 1.54)	0.216
HTN No vs. Y (ref)	0.84 (0.47, 1.45)	0.5383	0.79 (0.39, 1.57)	0.504
DM No vs. Y (ref)	1.42 (0.52, 3.54)	0.4704	1.34 (0.32, 5.48)	0.681
CVD Yes vs. No (ref)	0.64 (0.23, 1.52)	0.341	1.57 (0.36, 6.42)	0.536
MetS Yes vs. No (ref)	1.03 (0.62, 1.7)	0.922	1.14 (0.55, 2.34)	0.721
BMI Continuous	1.02 (0.98, 1.06)	0.349	1.01 (0.95, 1.07)	0.744
BP Yes vs. No (ref)	0.93 (0.53, 1.58)	0.780	0.79 (0.38, 1.6)	0.512
eGFR Continuous	1 (0.99, 1.01)	0.872	0.99 (0.97, 1.01)	0.269
CV risk category		**0.0004*‡**		**0.007*‡**
Extreme	1		1	
Very-high	3.26 (1.7, 6.5)	**0.001***	4.28 (1.55, 12.58)	**0.006***
High	3.26 (1.69, 6.50)	**0.001***	6.7 (1.68, 28.43)	**0.008***
Moderate	0	0.984	0	0.993
Therapeutic regimen Comb vs. Mono (ref)	0.48 (0.18, 1.12)	0.115	0.59 (0.18, 1.71	0.35
Statin intensity, if used HIST vs. MIST (ref)	0.88 (0.32, 2.1)	0.783	0.42 (0.1, 1.46)	0.186

Table 4.9 Univariate and multivariate binomial logistic regression of factors associated with **non-HDL-C** target achievement

Factors	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Governorate		0.463‡		0.915‡
FAR	1		1	
HAW	0.59 (0.26, 1.31)	0.208	0.95 (0.34, 2.62)	0.925
CAP	1.16(0.53, 2.49)	0.714	1.17 (0.43, 3.19)	0.756
AHM	0.69 (0.31, 1.47)	0.344	0.76 (0.28, 2.05)	0.587
MBK	1.19 (0.41, 3.19)	0.741	0.72 (0.16, 2.93)	0.662
JAH	1.27 (0.57, 2.49)	0.555	1.31 (0.44, 3.88)	0.625

***p** value <0.05**; ‡**global p-value**. M:** Male**; F:** Female**; K:** Kuwaiti**; NK:** Non-Kuwaiti**; CVD**: Cardiovascular disease; **HTN**: Hypertension; **DM**: Diabetes mellitus; **MetS**: Metabolic syndrome; **BMI**: Body mass index; **BP**: Blood pressure; **RFT**: Renal function test; **eGFR**: Estimated glomerular filtration rate; **LFT**: Liver function test; **Comb**: Combination; **Mono**: Monotherapy; **HIST**: High-intensity statin therapy; **MIST**: Moderate-statin therapy; **CAP**: Capital; **HAW**: Hawalli; **AHM**: Al-Ahmadi; **JAH**: Al-Jahra; **FAR**: Al-Farwaniyah; **MBK**: Mubarak Al-Kabeer

The multivariate logistic regression analyses presented in **Table 4.8** and Table 4.9 demonstrated that patients classified into higher CV risk categories had significantly lower odds of achieving both LDL-C and non-HDL-C targets. Education level was significantly associated with LDL-C target attainment overall but not with non-HDL-C. In particular, individuals with a higher level of education (college/university) had 75% lower odds of achieving LDL-C targets compared with those with intermediate to high school education. Marital status was significantly associated with non-HDL-C target attainment overall, with widowed individuals had 4.72 times higher odds of achieving non-HDL-C targets compared with married individuals. In contrast, marital status was not significantly associated with LDL-C target attainment overall. However, widowed individuals had significantly higher odds of attaining LDL-C targets compared to married individuals Regarding regional variations, no significant overall differences were noted for either LDL-C or non-HDL-C target attainment. Nevertheless, patients attending PHCCs in AHM had 78% lower odds of achieving LDL-C targets compared to those in Al-Farwaniyah.

4.5. Discussion

This, multicentre, patient-level cross-sectional study examined the prescribing patterns of LLTs across PHCCs in six governorates in 2023, with stratification by therapeutic regimen, LLT class, and individual agents. Additionally, the study evaluated the quality of lipid control, defined as the proportion of patients achieving guideline-recommended lipid targets according to CV risk categories (20). Furthermore, factors associated with primary lipid target achievement for LDL-C and non-HDL-C were explored.

4.5.1. Key findings

Overall, the findings revealed that the majority of participants attending PHCCs were prescribed monotherapy lipid-lowering regimens (88.7%, n= 385/434). Statins emerged as the most frequently utilised LLT (98.8%, n= 429/434) (**Figure 4.1**). Among statin users, simvastatin was the most frequently prescribed agent (73.9%, n= 317/429), with MIST being the predominant regimen (90.4%, n= 388/429) (**Figure 4.2**). Utilisation of the statin-ezetimibe combination regimen was low, accounting for only 28.6% (n= 14/49) of all patients receiving combination therapy.

Additionally, CV risk stratification demonstrated that the highest proportion of patients fell into the extreme CV risk category, accounting for 36.3% (n= 122/336) (**Table 4.6**). Lipid target attainment was suboptimal across all CV risk categories, with approximately one-fifth of patients achieving the LDL-C target and about one-quarter meeting the non-HDL-C target (**Table 4.7**). Multivariate analyses for LDL-C (**Table 4.8**) and non-HDL-C (**Table 4.9**) identified that individuals in lower CV risk categories exhibited higher odds of achieving their respective lipid targets.

4.5.2. Prescribing patterns of LLTs

The prescribing of LLTs among patients attending PHCCs was predominantly monotherapy (88.7%, n= 385/434), with statins comprising almost all prescriptions (98.7%, n= 380/385) (**Figure 4.1**). This widespread use aligns with the well-established role of statins as the cornerstone therapy of lipid management, supported by robust evidence demonstrating a 22% relative risk reduction in CV events for every 1 mmol/L decrease in LDL-C (14, 23, 24). Statins are strongly endorsed in international guidelines as the first line LLT for both primary and secondary CV prevention, which likely explains their high utilisation in primary care. Given that PHCCs serve as the initial point of contact for patients with NCDs, this prescribing pattern is expected and reflects adherence to guideline-direct therapy. However, whether this utilisation pattern translate into adequate lipid target achievement is explored in the following section (section 4.5.3)

Within the monotherapy group, fibrates were prescribed for only 1.3% of patients (n= 5/385), reflecting the global decline in fibrate utilisation observed over the past decade (63). Current lipid guidelines reserve fibrates primarily for managing severe hypertriglyceridaemia rather than LDL-C lowering (154). If these prescriptions were intended for hypertriglyceridaemia, statins would typically remain first-line in high-risk patients with TG levels above 2.3 mmol/L, with fenofibrate considered as an adjunct when additional TG reduction is needed (23). The small number of fibrate monotherapy cases may be explained by patient-level factor, such as statin intolerance, which can lead to non-adherence and eventual discontinuation (**Appendix S2.6**). A system-level factor may also explain this finding, as some patients required LDL-C reduction but had contraindications to statins, for whom ezetimibe would be the recommended second-line agent (23). However, prescribing may have been influenced by formulary restriction, as ezetimibe is listed under the Complementary Medicines List (CML) (77) (**chapter2**, **section 2.4, p28**), which limits its use to specific patient groups. Patients who did not meet criteria for CML may

therefore have received fibrate monotherapy as a practical, although suboptimal, alternative.

The predominance of LLT monotherapy observed in this study is consistent with findings from the CEPHEUS study (35), which reported that the most patients (94%) were treated with statin monotherapy. This pattern likely reflects the period in which CEPHEUS was conducted (2009-2010), before the publication of the IMPROVE-IT trial, which subsequently strengthened the evidence supporting ezetimibe as an effective add-on therapy to statins (44). Similarly, a multicentre cross-sectional study conducted in Malaysia (2016-2017) examined LLT prescribing patterns among 816 patients with T2DM attending PHCCs, 82 of whom were not receiving any LLT (155). Among those prescribed LLTs, 96.6% (n= 709/734) were on monotherapy, with statin monotherapy accounting for 97.3% of these cases (n= 690/709) (155).

The present study demonstrated a low utilisation of LLT combination regimens, accounting for 11.3% (n= 49/434) (**Figure 4.1**), indicating that combination therapy tends to be infrequently prescribed in primary care. Among these combinations, the majority (71.4%, n= 35/49) consisted of statin-fibrate therapies, most commonly simvastatin combined with fenofibrate (80%, n= 28/35). This prescribing pattern is likely influenced by local formulary restrictions (77) (**chapter2**, **section 2.4, p28**), as both simvastatin and fenofibrate are included in the Essential Medicines List (EML) and are therefore eligible for prescribing across all patient groups (77). In contrast, 28.6% (n= 14/49) of patients received a statin-ezetimibe combination (**Figure 4.1**). Since ezetimibe is listed under the CML and therefore restricted to specific patient groups, it is more likely that these 14 patients were predominantly among the 20 Kuwaiti patients receiving combination therapy (**Table 4.5**), who have access to all medications.

The findings also showed that 4.1% (n= 2/49) of patients in the combination therapy group were prescribed a triplet regimen comprising a statin, ezetimibe, and a PCSK9i (**Figure 4.1**). The use of a PCSK9i in conjunction with statin and ezetimibe is consistent with current lipid management guidelines (23), which recommend this regimen for patients with inadequate LDL-C control with oral LLTs alone (23). Although PCSK9is were exclusively utilised in hospital settings (as demonstrated in **chapter 3**), the dual-source data collection in this study highlights the importance of capturing LLT use across different healthcare settings. The low utilisation of PCSK9is among patients attending PHCCs likely reflects the fact that patients requiring such intensive regimens are typically managed in general or specialised hospital clinics. Nevertheless, such patients may continue to visit their affiliated PHCCs for routine follow-up or other services, such as retinal screening, due to the proximity and accessibility of PHCCs (129).

Among statin users, simvastatin was the most frequently prescribed agent (73.9%, n= 317/429) (**Figure 4.2**), which strongly reflects formulary restrictions that designate simvastatin as the only option available under the EML (77). This pattern is consistent with the demographic profile of the participants, in which approximately 70% of patients were non-Kuwaitis (**Table 4.5**), who are mainly subject to EML prescribing policies. With regard to intensity, most statin prescriptions fell under the MIST category (90.4%, n= 388/429). This high utilisation is largely explained by the fact that all simvastatin prescriptions were for doses between 20 and 40mg, which are categorised as MIST (24) (**chapter 2**, **Table 2.3**). Even among users of atorvastatin (11.6%, n= 50/429) and rosuvastatin (14.5%, n= 62/429), both of which allow flexibility in dosing intensity, MIST remained the predominant regimen (63.4%, n= 71/112).

Importantly, in the absence of statin formulary restrictions, it would have been expected that prescribers would tend to use atorvastatin or rosuvastatin more widely. This expectation is supported by the proportion of patients prescribed these two agents (~30%) (**Figure 4.2**), which closely mirrors the proportion of Kuwaiti patients in the sample (~30%) (**Table 4.5**). Given that Kuwaiti patients have access to all LLTs, this pattern suggests that, when prescribers are not restricted by formulary policy, atorvastatin and rosuvastatin are more likely to be selected. However, the proportional sampling strategy used to obtain a nationally representative sample may also have contributed to the observed distribution of Kuwaitis (30%) and non-Kuwaitis (70%).

International evidence supports the expectation that atorvastatin and rosuvastatin would be more widely utilised than simvastatin due to their greater potency, flexibility for intensification, well-established efficacy, and favourable tolerability profiles (115-117, 156). For example, a multicentre, randomised PROBE trial published in 2000 demonstrated that atorvastatin 10mg resulted in a greater mean percentage reduction in LDL-C (-37.0%) compared with simvastatin 20mg (-33.8%) in patients with primary hypercholesterolaemia (115).

Similarly, the STELLAR trial (2003), a 6-week, multicentre trial, reported that rosuvastatin (10 to 80mg) achieved LDL-C reductions 8.2% greater than atorvastatin (10 to 80mg) and 12% to 18% greater than simvastatin (10 to 80mg) (116). Moreover, 79% to 92% of rosuvastatin users reached the LDL-C <3 mmol/L target, compared with 52% to 81% of atorvastatin users (116). More recent evidence reinforces these findings. A systematic review and network meta-analysis (2020) of 50 RCTs involving 51,956 participants ranked rosuvastatin as the most effective statin in lipid-lowering efficacy, followed by atorvastatin (117).

Evidence of statin intensity also supports the preference toward rosuvastatin and atorvastatin. A recent systematic review and network meta-analysis (2022) of 42 RCTs including 20,193 adults with diabetes demonstrated that rosuvastatin at moderate- and high-intensity doses, as well as high intensity simvastatin and atorvastatin, were the most efficacious at reducing non-HDL-C levels. In that study, atorvastatin (40–80mg) and rosuvastatin (20–40mg) were grouped as HIST, and simvastatin 80mg was also classified as HIST (156). However, the current study did not classify simvastatin 80mg as HIST, following the 2018 AHA/ACC guidelines (24), which discourage the use of this dose due to safety concerns (**chapter 2**, **Table 2.3**).

However, despite the availability of potent statins in PHCCs, including atorvastatin and rosuvastatin, and the opportunity to prescribe them at HIST levels, the uptake of HIST remained relatively low in the present study (36.7%, n= 41/112). The clinical relevance of this finding becomes clearer when considered alongside the suboptimal lipid control observed in this study, which is discussed in detail in **section 4.5.3**. Accordingly, and briefly, limited use of HIST is a plausible contributor to the suboptimal lipid control.

Several multifactorial barriers may contribute to the low utilisation of HIST, including patient-related, therapy-related, and clinician-related factors (157). From the patient perspective, limited awareness of dyslipidaemia as a modifiable ASCVD risk factor may reduce willingness to accept statin intensification (157). Therapy-related factors include fear of actual or perceived side effects (158), which remains as a barrier to statin titration. This concern may be become more apparent by the influence of social media on perceptions of statin safety (159), even though most participants in this study had an acceptable educational level (**Table 4.5**). From the clinician perspective, therapeutic inertia, defined as the failure to initiate or intensify therapy when therapeutic goals are not achieved (157), may arise from uncertainty about appropriate therapeutic targets, insufficient review of LLT adherence, or irregular lipid monitoring (157, 158).

Repetitive prescribing is a well-recognised contributor to therapeutic inertia (159), as long refill intervals may allow continuation of the therapy without clinical review. In primary care settings in Kuwait, patients can refill prescriptions for up to 6 months without necessarily consulting a physician, which may further reinforce this practice. Given that ~90% of participants in this study were categorised as primary prevention (**Table 4.5**), it is plausible that clinicians preferred continuation of existing statin therapy rather than intensification.

Despite the overall low use of HIST, rosuvastatin accounted for most HIST prescriptions (78%, n= 32/41), followed by atorvastatin (22%, n= 9/41) (**Figure 4.2**). This prescribing pattern aligns with recent evidence demonstrating superior LDL-C lowering efficacy of high-dose rosuvastatin. A recent systematic review and meta-analysis of 44 RCTs and cohort studies (2023) found that rosuvastatin 40mg achieved significantly greater LDL-C reductions than atorvastatin 80mg (160). Nonetheless, current guidelines do not express a preference for one HIST agent over another, recommending both as acceptable options for achieving lipid targets (20, 23).

In Kuwait, limited research has examined statin utilisation within PHCCs. A clinical audit published in 2018 from the JAH governorate (161), conducted at the same centre included in the present study, assessed statin utilisation among patients with T2DM. The audit reported low utilisation of statins both before and after an intervention aimed at achieving optimal LDL-C level, with only 55.5% (n= 111/200) of patients prescribed a statin. Among statin users, 85.6% (n= 95/111) of patients were prescribed simvastatin and 14.4% (n= 16/111) of patients were receiving atorvastatin, with no data reported on intensity (161). The predominance of simvastatin in that study aligns with the findings of the present study and likely reflects the high proportion of non-Kuwaiti patients (~80%) included. Moreover, the absence use of rosuvastatin seems that the study was conducted before rosuvastatin inclusion in the MOH formulary (**Appendix S3.1**).

Globally, Elnaem et al. (155) found that simvastatin was the most commonly prescribed statin monotherapy (96.1%, n= 663/690), followed by atorvastatin (3.5%, n= 24/690) in Malaysia. The high utilisation of simvastatin in that study was attributed to limited adherence to the national formulary, which recommended atorvastatin as first-line therapy. Consistent with the findings of the present study, the majority of patients in the Malaysian participants were treated with MIST (80.7% n= 577/715), while HIST use remained notably low (1.5% n= 11/715) (155). Simia low uptake of HIST has been reported in Turkey, where only 10% of statin users received HIST (162). The authors attributed this to the timing of the study, which was conducted before the publication of updated guidelines recommending lower LDL-C targets for patients with T2DM, and by concerts about statin-associated adverse effects, which have been driven by negative messages in social media (162). Health misinformation disseminated through the media may influence public opinion, potentially affecting adherence to prescribed treatments. Nielsen et al. (163) have shown that negative media coverage of statins was linked to increased early discontinuation of statin therapy.

In contrast, prescribing trends in the US differ significantly, with atorvastatin (47.5%) being the most prescribed statin, followed by simvastatin (32.1%) (164). Among statin users in the US, 59.3% received MIST and 16.6% were prescribed HIST. This disparity likely reflects differences in healthcare system, including availability of generic atorvastatin, which resulted in greater uptake of HIST. Furthermore, prescribing intensities in the US included low-intensity statin therapies (LISTs), which are not available in Kuwait at the time of recruitment.

4.5.3. Quality of lipid control and factors associated with lipid target achievement

The study findings reveal suboptimal lipid target achievement, particularly for LDL-C and non-HDL-C, across all CV risk categories in both the monotherapy and combination therapy groups (**Table 4.7**). Unexpectedly, the combination therapy group exhibited lower proportions of target attainment across all seven classifications (**Table 4.7**). However, after adjusting for relevant factors, the therapeutic regimen type (monotherapy vs. combination) was not independently associated with achieving LDL-C or non-HDL-C (**Table 4.8**, **Table 4.9**). This raises the possibility that factors other than the use of combination therapy may have influenced the lipid target achievement, including the specific type of the combination regimen prescribed.

The lack of statistical significance observed in the regression model may be partly explained by the predominance of statin–fibrate combinations. As discussed earlier (**section 4.5.2**), this regimen is suboptimal for LDL-C reduction, as fibrates primarily target TGs rather than LDL-C (23). Furthermore, although statin-ezetimibe combinations are aligned with the 2019 ESC/EAS guideline recommendations (23), their effectiveness among the study participants may still have been suboptimal. This may be attributable to insufficient statin intensity, potentially influenced by concerns regarding real or perceived side effects, limited patient understanding of the importance of achieving guideline recommended targets, and suboptimal adherence to therapy (85). In addition, reliance on two separate tablets, which were the only formulations available at the time of the study, rather than fixed-dose combination formulations, may have contributed to reduce treatment effectiveness (85). Although this study did not account for polypharmacy, nearly all patients (99.3%) were receiving concomitant medications, including antidiabetics, antihypertensives, and antiplatelets or anticoagulant therapies (**Table 4.5**). The relatively small sample size within the combination therapy group may also have reduced the statistical power

of the mode to detect a statistically significant association between therapeutic regimen and lipid target achievement.

Another plausible contributor to suboptimal control is the low utilisation of HIST among atorvastatin and rosuvastatin users (36.7%, n= 41/112) (**Figure 4.2**). However, the multivariate analysis showed no statistically significant association between HIST use and lipid target achievement (**Table 4.8**, **Table 4.9**).

Nevertheless, the observed underutilisation of HIST may suggest a tendency to underestimate individual CV risk in clinical practice, particularly in patients without established CVDs (165). Such underestimation may contribute to reluctance among physicians to intensify LLT (165). Ultimately, this could result in patients being classified into lower CV risk categories than appropriate, thereby leading to the application of less stringent lipid targets and a lower threshold for the perceived lipid control. This potential misclassification may partly explain the observed gap in lipid target achievement, especially among those at extreme CV risk. This interpretation is supported by the multivariate analyses, which identified that patients with extreme CV risk category had lower odds of LDL-C and non-HDL-C target attainment (**Table 4.8**, **Table 4.9**). Patients in the high- and very-high-risk categories were significantly more likely to achieve lipid goals compared to those classified in the extreme CV risk category (**Table 4.8**, **Table 4.9**).

Moreover, this misclassification is believed to be potentially arising from poor documentation of relevant sociodemographic and clinical variables within the PCIS, including incomplete or missing data required for calculation CV risk categories. This limitation further supports the methodology adopted in this study, which incorporated dual-data collection to enhance the completeness and appropriateness of CV risk assessment.

Additionally, a possible explanation for suboptimal lipid management may relate to the limited awareness of prescribers in the availability of certain LLTs outside the primary care settings, particularly PCSK9is, which were available at the time of recruitment but restricted to hospital use (**chapter 3**). Since PCSK9is are only exclusively supplied to the hospitals, a lack of familiarity with their availability and clinical benefits, such as LDL-C reductions of up to 60% (54, 55), may contribute to delayed referrals and missed opportunities for timely treatment intensification. Ray et al. (2022) advocated the early initiation of combination therapy, incorporating a statin, ezetimibe, and a PCSK9-targeted agent as first-line treatment for patients at extremely high CV risk (85). Limited access to PCSK9is in primary care, coupled with delays in referral, may further compound CV risk. Consequently, policies governing the distribution and accessibility of advanced LLTs should be carefully reviewed and prioritised to ensure timely escalation of LLT and equitable patient access across healthcare levels.

Findings from the DA VINCI study, a large cross-sectional analysis of 5,888 patients across 18 European countries (2017-2018), demonstrated that 33% of patients achieved the 2019 ESC/EAS LDL-C goals (166). Most patients in DA VINCI were treated with MIST monotherapy, indicating a persistent gap between guideline recommendations and clinical practice. The authors attributed this gap largely to systematic-level and clinician-level barriers, including lack of familiarity with ESC/EAS recommendations, patient reluctance to accept HIST, and financial barriers, especially related to access to PCSK9is (166). Notably, the latter is less relevant in Kuwait, where finical barriers to medication access are minimal.

The findings of the current study are consistent with those of the DA VINCI study (166), which demonstrated lipid target attainment was lowest among patients at very-high CV risk. However, this observation in the DA VINCI was reported descriptively, without multivariate modelling. The DA VINCI authors noted that further statin dose escalation among patients receiving MIST monotherapy would be

expected to obtain only modest additional LDL-C reduction (166). According to the "rule of six" (167), doubling the statin dose typically results in an additional LDL-C reduction of 6%. Therefore, increasing the dose of MIST alone is unlikely to achieve the recommended LDL-C targets, particularly among patients at the highest CV risk. Accordingly, the DA VINCI study supports the need for earlier use of combination LLT rather than reliance on stain intensification alone (166).

The guidelines advocate the use of combination statin with non-statin agents, including ezetimibe and PCSK9is, which provide additional LDL-C reductions of approximately 20-25% and 50-60%, respectively (23, 166). This approach is particularly relevant for patients in primary prevention without established CVD, in whom physicians may be more hesitant to intensify LLT. However, individuals in primary prevention group may have a high burden of CV risk factors and may therefore require lipid targets similar to those recommended for secondary prevention. In the present study, about 30% categorised as primary prevention (extreme CV risk) were required to achieve the same LDL-C targets as those applied in secondary prevention.

Current guideline recommendations (20, 23) emphasise achieving a ≥50% reduction in LDL-C from the untreated baseline in addition to achieving absolute LDL-C targets, particularly among patients at high CV risk categories (**chapter 2, Table 2.2**). Although the cross-sectional design of this study limited assessment of baseline LDL-C values, the low proportions of patients achieving lipid targets suggest that achievement of guideline-recommended criteria is likely to remain suboptimal.

Additionally, a cross-sectional study conducted in Romania in 2022 involving 2,615 patients with T2DM reported very low LDL-C target attainment when applying the 2019 ESC/EAS guideline thresholds. Among patients classified as very-high CV risk, only 5.0% (n= 41/821) met the recommended LDL-C targets, however only 2.7% of patients (n= 22/821) were on a statin therapy (165).

Similarly, Bayram et al reported comparable findings in their 2017 nationwide cross-sectional study conducted in Turkey, which assessed LDL-C target attainment among 4,504 adults with T2DM (162). Fewer than 10% of patients achieved the LDL-C targets defined by the 2019 ESC/EAS guidelines. Findings from the DYSIS study (70) showed that the odds of achieving the LDL-C target were significantly lower among individuals with a SCORE ≥10% risk, reflecting a higher 10-year risk of CV events according to the SCORE risk model. This finding aligns with the findings of the present study, in which patients with a SCORE ≥10%, corresponding to the extreme CV risk category, demonstrated the lowest rates of lipid target attainment.

Collectively, the observed suboptimal lipid control may be attributable to a phenomenon called as therapeutic inertia, a well-recognised barrier to optimal management of chronic conditions, including dyslipidaemia (157). Without reiterating the potential underlying reasons, the exact drivers of therapeutic inertia in Kuwait remain uncertain and warrant further investigation. Future studies should specifically examine adherence to LLTs and guideline recommendations, as therapeutic inertia is multifactorial and may arise from physician-, patient-, and system-related factors (157).

Unexpectedly, the present study showed that diabetes was not statistically significantly associated with lipid target attainment (**Table 4.8**, **Table 4.9**). Although T2DM is well recognised to frequently coexist with dyslipidaemia (**Appendix S2.4**), the finding may be explained by the study design. Participants were recruited from NCD clinic (**section 4.3.2.1**), resulting in an overwhelming predominance of patients with T2DM (~95%). This limited variability within the sample likely reduce the statistical power to detect meaningful differences between diabetic and non-diabetic groups.

In addition to clinical-related factors that largely explain the quality of lipid control, sociodemographic characteristics also appear to play a role. The multivariate analysis identified that education level and marital status were significantly associated with LDL-C target achievement (**Table 4.8**) and non-HDL-C a target attainment (**Table 4.9**), respectively (global p-vale <0.05). Individuals with high education level tended to experience lower attainment for LDL-C targets (**Table 4.8**). A plausible explanation for higher education with low LDL-C target achievement could be related to adherence issue (unmeasured confounder), particularly due to apprehensions about the long-term side effects of statins or reluctance to initiate combination or intensified therapy (157, 168, 169). Given that higher education is often linked to greater health literacy, these individuals might misinterpret or overestimate the risks associated with statin use, such as the possible development of diabetes or muscle-related side effects (170). Moreover, it is likely that individuals with higher education perceive themselves as healthier if they are not taking any medication, reinforcing a reluctance to adhere to LLTs. This misconception about medication-free health status, coupled with potential clinical inertia, could contribute to suboptimal adherence and resistance to treatment intensification, ultimately impacting LDL-C target achievement (170).

Findings from a cross-sectional study conducted in Brazil enrolled 1,614 individuals to investigate the association between lipids and higher socioeconomic status (SES) and educational level (171), agreed partly with our results. The study revealed that, among males, higher SES and education level were associated with increased levels of LDL-C, TC, and TG, alongside lower HDL-C levels, without analysing non-HDL-C. However, an important distinction was observed when stratifying by gender, as women with higher education levels exhibited lower LDL-C levels. The study emphasised that education and SES should not be used interchangeably, as they exert distinct influences on lipid profiles. However, it is important to note that this study was conducted in a population of adults not taking LLTs, and the current multivariate did not identify gender as a significant factor. Additionally, differences in ethnicity,

lifestyle factors, and a larger sample size in their study may contribute to the observed discrepancies (171).

Conversely, marital status was significantly associated with non-HDL-C target achievement (global p-value <0.05), with widowed individuals demonstrating significantly higher odds in achieving non-HDL-C target (**Table 4.9**). A possible explanation of higher odds for widowed individuals in achieving lipid target could be related to the continuity of primary care (CoC), which is defined as the ongoing therapeutic relationship between a healthcare provider and a patient (172). If the couple previously maintained a structured lipid-lowering regimen, the surviving spouse might continue these health practices, particularly if they were already integrated into their daily routine before their partner's death. An Australian retrospective cohort study with a large cohort of 36,144 participants estimated the association of CoC on statin adherence (173). Authors observed that greater CoC has a positive association with higher statin adherence. Another retrospective cohort study was conducted in England among 173,993 patients to investigate whether CoC was associated with improved adherence. The findings showed that patients with perfect continuity had higher odds of being prescribed statins and CoC was strongly associated with adherence of statins used for secondary prevention (172).

While this study supports the lipid target achievement for widowed individuals, it could be argued that other widowed individuals might experience grief-related stress, social isolation, or depressive symptoms, which are often associated with worsened dietary habits, reduced physical activity, and lower adherence to medication (174). A systematic review and meta-analysis of 34 studies consisted of over 2 million participants (175) concluded that being unmarried (single, divorced, or widowed) was associated with higher odds of CVD (OR: 1.42), CHD (OR: 1.16), CHD-related mortality (OR: 1.43), and stroke-related mortality (OR: 1.55), compared to married individuals (175).

A geographical factor could also be related to the lipid target achievement, as regional disparities were observed to be significantly associated with LDL-C target attainment in the univariate analysis of this study. However, in the multivariate analysis, the association between governorate and LDL-C attainment was no longer statistically significant overall (global p-value >0.05), except for AHM, where patients remained at significantly lower odds of achieving LDL-C targets compared to those in FAR (**Table 4.8**). In terms of non-HDL-C, no statistically significant regional differences were observed in target achievement (**Table 4.9**). These findings further reinforce the role PHCCs operating under the CDPHC, which ensures standardised medication availability, established NDC clinics, and uniform lipid testing services across Kuwait (129).

Other potential factors that could be associated with lipid target achievement but were not addressed in this study include patient-related factors, such as medication adherence, genetic background, and other unmeasured factors, which are detailed in **Appendix S4.7**

The findings of the present study align with international evidence demonstrating persistent suboptimal lipid control in real-world practice. However, variations across studies are likely influenced by differences in patient characteristics, availability and accessibility of LLT, CV risk categories, and, importantly, the application of different lipid management guidelines at the time of each study. Evidence from Malaysia (155) illustrates suboptimal lipid control in primary care settings. The study reported higher proportion of patients achieved LDL-C targets (37%) than observed in the present study. However, this difference is likely attributable to the use of more lenient thresholds (<1.8 mmol/L and <2.6 mmol/L). While a similar proportion of patients met the TG targets (62%), a higher proportion attained HDL-C targets (77.5%). This potentially reflect ethnic variations and a lower burden of diabetes and MetS, conditions that are highly associated with elevated TG and reduced HDL-C.

Similarly, findings from a nationwide study from Thailand showed suboptimal lipid control (176), where LDL-C target attainment reached 43.5% and non-HDL-C target attainment reached 46.6%. The higher proportions may also be explained by the application of less stringent LDL-C thresholds (<2.6 mmol/L), without stratifying patients into CV risk categories

Data from Germany (177) revealed that 19.5% of statin users met LDL-C targets (<1.8 mmol/L), closely mirroring the 20.5% observed in this study, acknowledging the disparities in LDL-C thresholds. Similarly in the US (164), the suboptimal control of LDL-C was notably observed with using higher thresholds (LDL-C <1.8 mmol/L: 31.7%; LDL-C <2.6 mmol/L: 68.5%), further reinforcing the global challenge of achieving optimal LDL-C control, particularly when lower thresholds are employed..

4.5.4. Strengths and limitations

This study provides a comprehensive multicentre real-world evolution of lipid management across the six governorates. A notable strength is the exclusive focus on governmental PHCCs, which ensured uniformity in medication availability, as all PHCCs are supplied centrally from the CMS, resulting in consistent drug formulations across the study participants. Moreover, this study employed a proportional stratified sampling method across the six governorates, further refined by nationality, using population statistics from PACI, the national demographic authority in Kuwait (75). This sampling technique enabled the study to account for differences in medication accessibility across regions and population groups, thereby providing a more representative assessment of lipid management among both citizens and residents.

Furthermore, the dual-source data collection approach, which combined electronic health record extraction from the PCIS with researcher-reported data, enhanced data completeness, accuracy, and validity. This strengthened the evaluation of prescribing patterns for all LLTs and supported a more reliable assessment of lipid target attainment. An additional major strength is the detailed stratification of lipid target attainment according to CV risk categories, which aligns with the most recent regional lipid management recommendations, namely the 2021 Middle East consensus. Unlike many previous studies, this research also incorporates non-HDL-C as a co-primary lipid target, providing a more comprehensive evaluation of lipid control that extends beyond LDL-C alone.

Despite the strengths of this study, several limitations should be acknowledged. The main limitation relates to its cross-sectional design, which precludes the assessment of longitudinal changes in treatment response or dose adjustments overtime. In the absence of follow-up prescribing data, it is not possible to determine whether observed lipid levels reflect treatment intensification, changes in adherence, or other clinical interventions. Although, this limitation may affect interpretation, the suboptimal lipid control identified in this study is broadly consistent with findings reported in other populations, suggesting that a persistent gap remains between clinical practice and guideline recommendations.

A further limitation relates to the inclusion criterion requiring participants to be receiving at least one LLT. This may have introduced self-selection bias, potentially overestimating statin utilisation within the broader PHCC population. Nonetheless, this criterion was appropriate for the aim of this study, which focused specifically on evaluating lipid target attainment among individuals receiving LLT. Future research exploring lipid target attainment among untreated individuals is discussed in the implications section (**chapter 6, section 6.2.3**).

The accuracy of self-reported lifestyle factors represents another challenge. Alcohol consumption, in particular, is a sensitive topic in Kuwait due to religious and legal restrictions, making under-reporting highly likely and introducing reporting bias. The pattern observed in this study is consistent with findings from the previous WHO STEPS survey conducted in Kuwait (96), which also documented minimal reported alcohol intake. Although the true prevalence of alcohol use remains uncertain, it is not possible to determine whether the low reporting reflects the actual abstinence in accordance with regulations or under-reporting due to stigma or fear of disclosure.

Another important methodological limitation relates to the estimation of LDL-C using the FF. The FF is known to underestimate LDL-C when TG levels are elevated (23, 178), potentially resulting in some degree of misclassification. However, the use of the FF

was necessary to maintain consistency with the current standard laboratory practice in Kuwait, thereby ensuring uniformity of LDL-C estimation across all patients. The implications of adopting more contemporary LDL-C estimation methods are explored further in **chapter 6, section 6.2.3**.

Additionally, as the study was conducted exclusively within PHCCs, the findings may not be fully generalisable to lipid management practices in secondary and tertiary healthcare settings, particularly for patients with more complex conditions such as familial hypercholesterolaemia or those treated with PCSK9is. Hospital settings typically have access to a broader range of LLTs and may follow more intensive therapeutic strategies. Because the EHR system used in hospitals differs from those used in PHCCs, the current study appropriately focused on primary care. Nonetheless, a complementary study from a tertiary-care cohort is presented in **chapter 5**, providing additional insights on lipid control on patients using PCSK9is.

Finally, although the study incorporated a wide range of demographic, behavioural, physical, and biochemical variables to identify factors associated with lipid target achievement, it did not examine determinants of prescribing behaviour. This may be less critical in the context of dyslipidaemia management, as major lipid guidelines demonstrate a high level of agreement and advocate a largely standardised treatment algorithm, beginning with statins, followed by ezetimibe and subsequently PCSK9is. In contrast, therapeutic decision-making in conditions such as T2DM or HTN involves greater variability, with multiple acceptable second-line options influenced by patient-related factors (179). Given the relatively standardised nature of dyslipidaemia management, investigating prescribing determinants was unlikely to provide additional insights to clinical decision-making. However future research could focus on the timeliness of LLT initiation and intensification in relation to CV risk category, as delays in treatment escalation may contribute to the suboptimal lipid control.

4.5.5. Conclusion

This study demonstrates a persistent gap between guideline-recommended lipid targets and real-world practice, despite the widespread use of statins in primary care. Lipid target achievement was strongly influenced by CV risk category, with patients at higher risk, for whom more stringent targets are recommended, showing the lowest rates of target attainment. These findings emphasise the critical importance of accurate CV risk stratification and the consistent application of risk-based lipid targets. A personalised approach to optimising lipid management, in line with updated guidelines and lower recommended thresholds, is required to bridge the gap towards optimal lipid control.

Chapter 5. Real-world effectiveness of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) at a cardiac care centre in Kuwait: a retrospective cohort study

5.1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global morbidity and mortality, and in the Arabian Gulf region, they account for up to 45% of all mortalities (91). According to a 2023 report from the Kuwaiti Central Statistics Bureau-Ministry of Health (MOH), the mortality rate attributed to CVDs declined from 86.57 per 100,000 inhabitants in 2021 to 67.75 per 100,000 inhabitants in 2023. Despite this improvement, CVD-related mortality remains alarmingly high in Kuwait compared with other causes of death during the same period (2021-2023) (9).

Multiple modifiable risk factors contribute to the development of CVDs, including dyslipidaemia. Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established and independent causal factor in the pathogenesis of CVDs (20). In addition, non-high-density lipoprotein cholesterol (non-HDL-C) has been reported to be a more predictive of CVD risk than LDL-C alone (21).

Moreover, elevated triglyceride (TG) levels are also associated with an increased risk of CVDs (20). A post hoc analysis from the Treating to New Targets (TNT) trial demonstrated that triglyceride-rich lipoprotein cholesterol functions not only as a marker of CV risk but may also represent a potential target for therapeutic intervention (180). Elevated plasma TG should therefore be recognised as an indication to intensify LDL-C lowering therapy to mitigate associated risks. The addition of fibrate to statin therapy may be beneficial, particularly in patients with metabolic dyslipidaemia characterised by high TG and low high-density lipoprotein cholesterol (HDL-C) levels, such as those with type 2 diabetes mellitus (T2DM) (23).

Alongside lifestyle modifications, lipid-lowering therapies (LLTs) that primarily target reductions in LDL-C levels are crucial approaches for reducing CV events (23). The 2019 ESC/EAS guidelines recommend using the maximum tolerated dose of statins to achieve lipid targets (23). If target levels are not achieved, or if statin intolerance occurs, ezetimibe is recommended as an add-on therapy (23). However, despite their proven benefit, many individuals still fail to reach recommended lipid targets (166). Several factors may contribute to this, including markedly elevated baseline LDL-C levels, as manifested in familial hypercholesterolaemia (FH) (32), suboptimal adherence to oral therapies (181, 182), and limited effectiveness of ezetimibe monotherapy in cases of statin intolerance (23).

When further lipid lowering is required, the recommended third-line option is the use of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is), which not only help achievement of target lipid levels but also contribute to significant improvements in CV outcomes (23). The FOURIER trial for evolocumab (54) and the ODYSSEY OUTCOMES trial for alirocumab (55) demonstrated substantial LDL-C reductions of up to 60%, depending on the dose and baseline lipid levels. PCSK9is also achieve profound reductions in other lipid parameters, including approximately 50% in non-HDL-C and 9–17% in TGs (50, 51). Further details on PCSK9is are provided in c**hapter 2**, s**ection 2.2.3.3**. In Kuwait, two PCSK9is are currently available, evolocumab and alirocumab, both of which are administered in injectable form.

Several real-world studies have been conducted to evaluate the real-world effectiveness of PCSK9is in lowering lipid levels, particularly LDL-C. While many of these studies have replicated the lipid-lowering effects observed in RCTs, others have reported modest reductions compared to those observed in trials.

The HEYMANS study (CHaractEristics of HYperlipidaeMic PAtieNts at Initiation of Evolocumab and Treatment PatternS), a multicountry prospective registry conducted between 2015 and 2020 across 12 European countries (excluding the UK), largely mirrored clinical trial findings (71). Among a cohort of 1,951 patients, a median LDL-C reduction of 58.1% was achieved within 3 months of evolocumab initiation. However, the HEYMANS study also reported suboptimal LDL-C target attainment, with only 58% of patients reaching guideline-recommended LDL-C targets, ranging from 35% in Sweden to 71% in Belgium (71).

Similarly, a study conducted at a tertiary hospital in Spain reported findings consistent with those from trials, demonstrating a significant LDL-C reduction of 59.9% (86). The Spanish study evaluated 115 patients who received PCSK9i (evolocumab or alirocumab) between 2017 and 2022 (86). Unlike many studies that focused exclusively on LDL-C, the analysis also examined changes in other lipid parameters. Following the use of PCSK9is, substantial reductions were observed in non-HDL-C (50.4%), TGs (13.3%), and total cholesterol (TC) (40.9%) levels. However, no significant increase in HDL-C was observed (86).

Moreover, a Scottish study conducted at NHS Tayside evaluated the real-world effectiveness of PCSK9is in a tertiary specialist clinic (2017-2021), involving a relatively small cohort of 62 patients (183). The findings revealed an LDL-C reduction of 63% with evolocumab, consistent with trial results. In contrast, alirocumab achieved a lower LDL-C reduction of 46% at 6 months post-initiation, possibly due to the administration of the 75mg rather than 150mg dose. This finding aligns with the ODYSSEY OUTCOMES trial, which reported a more modest reduction of 45% - 48% with the 75mg biweekly regimen (55).

Furthermore, the ZERBINI (multiZonal obsERvational study conducted By clinIcal practitioners on Repatha® (Evolocumab) use iN subjects with hyperlipIdaemia) study, conducted between 2017 and 2019, was the first intercontinental, observational, ambispective (retrospective/prospective) evaluation of patients receiving evolocumab in countries in Northa America (Canada, Mexico), South America (Colombia), and the Middle East (Saudia Arabia, Kuwait) (72). Overall, the study reported a median LDL-C reduction of 70.2%, exceeding reductions typically observed in clinical trials. Despite the significant reduction in LDL-C levels, only 63.6% (n= 283/445) of patients achieved the guideline-recommended LDL-C target of <1.4 mmol/L, indicating a gap in achieving optimal lipid targets (72).

Focusing on the Middle East sub-analysis of the ZERBINI study, patients from Saudi Arabia (n= 155) and Kuwait (n= 68) were included (73). In this Gulf cohort, LDL-C reductions were 61.7% in Kuwait and 57.5% in Saudi Arabia, aligning closely with reductions reported in clinical trials. Notably, a decline in LDL-C target attainment was observed when shifting from less stringent to more stringent LDL-C threshold, indicating the need for more aggressive lipid control, particularly among very-high CV risk groups. For instance, in Kuwait, 93.1% of patients achieved the LDL-C target of <1.8 mmol/L; however, this proportion declined to 75.9% when the more stringent target of <1.4 mmol/L was applied (73). Within the Gulf context, a retrospective study conducted in the United Arab Emirates (UAE) between 2017 and 2020 included 183 patients and evaluated similar outcomes (184). The study reported a lower LDL-C reduction of 48.3% (184). Similarly, target attainment was modest, with 57.8% of patients achieving LDL-C <1.8 mmol/L and only 40.9% reaching the more stringent target of <1.4 mmol/L (184).

These regional data offer valuable insights into the real-world use of PCSK9is in Gulf countries. These regional studies conducted in Saudi Arabia, Kuwait (73), and the UAE (184) focused on evolocumab and reported changes in LDL-C levels. However, neither assessed non-HDL-C level, despite its recognised role as a predictor of CVD (21). Although evidence on the effectiveness of PCSK9is in Kuwait has previously been published from a single tertiary cardiac centre (73), the present study was conducted at a different tertiary cardiac centre, thereby contributing to multicentre evidence in Kuwait. This research is particularly relevant to hospital-based settings (secondary and tertiary care), where PCSK9is are exclusively supplied, as confirmed by national Cantal Medical Store (CMS) data (chapter 3). By focusing on patients attending cardiac care centres, where individuals with established CV events are routinely managed, this study provides valuable real-world insights into the effectiveness of PCSK9is in routine clinical practice for patients at very-high CV risk. Moreover, the present study involved a larger cohort and expanded on existing research by including both available PCSK9i agents (evolocumab and alirocumab). The analysis also incorporated a broader range of lipid parameters, including non-HDL-C, TGs, HDL-C, and TC. Covering the period from the introduction of PCSK9is in 2016 to 2022, the study offers comprehensive and contemporary perspective that strengthens and enriches the evidence base in Kuwait. Notably, the study also demonstrates the value of using secondary data sources in generating real-world evidence.

5.2. Aims and objectives

This study aimed to evaluate the real-world effectiveness of PCSK9is at a single tertiary cardiac care centre between 2016 and 2022. The objectives were:

- To describe and examine the baseline characteristics of incident (new) PCSK9i users
- To evaluate the real-world effectiveness of PCSK9is by assessing the percentage change in lipid levels and the proportion of patients achieving guideline-recommended lipid targets
- To investigate the determinants of lipid level changes following the initiation of PCSK9i therapy

5.3. Methods

5.3.1. Study design and data source

This study was a retrospective cohort analysis of incident patients treated with a PCSK9i, either evolocumab or alirocumab, covering the study period from 1 January 2016 to 31 December 2023 (**Figure 5.1**). The study utilised routinely collected dispensing data from the pharmacy department at Al-Dabbous cardiac centre (DCC). The DCC is based at Al-Adan Hospital, one of the largest secondary public hospitals in Kuwait (185). DCC is located in Al-Ahmadi governorate, situated in the southern part of the country. Al-Ahmadi governorate is the second largest of Kuwait's six governorates, covering an area of 5,120 km^2, with a total population of 1,095,805 as reported by Public Authority for Civil Information (PACI) in June 2024 (186). Al-Ahmadi has the largest Kuwaiti population and ranks second in overall population size among all governorates (186).

DCC is a specialised facility for the treatment of all types of CVDs for both out-patients and in-patients, with a particular focus on advanced cases, including open heart surgery and heart transplantation (185). DCC was the first centre in Kuwait to introduce primary percutaneous coronary intervention (PCI) and to establish an advanced heart failure clinic (185). DCC also made history by performing Kuwait's first heart transplantation surgery in 2019, with a recent one in 2025. In May 2025, the centre marked a major milestone with a groundbreaking achievement in minimally invasive cardiac care, where the medical team successfully performed a complex aortic valve replacement using highly specialised techniques for Transcatheter Aortic Valve Replacement (TAVR), eliminating the need for open-heart surgery (187). This rare procedure highlights the centre's growing expertise in managing complex CV conditions and positions Kuwait as a regional leader in advanced cardiac interventions.

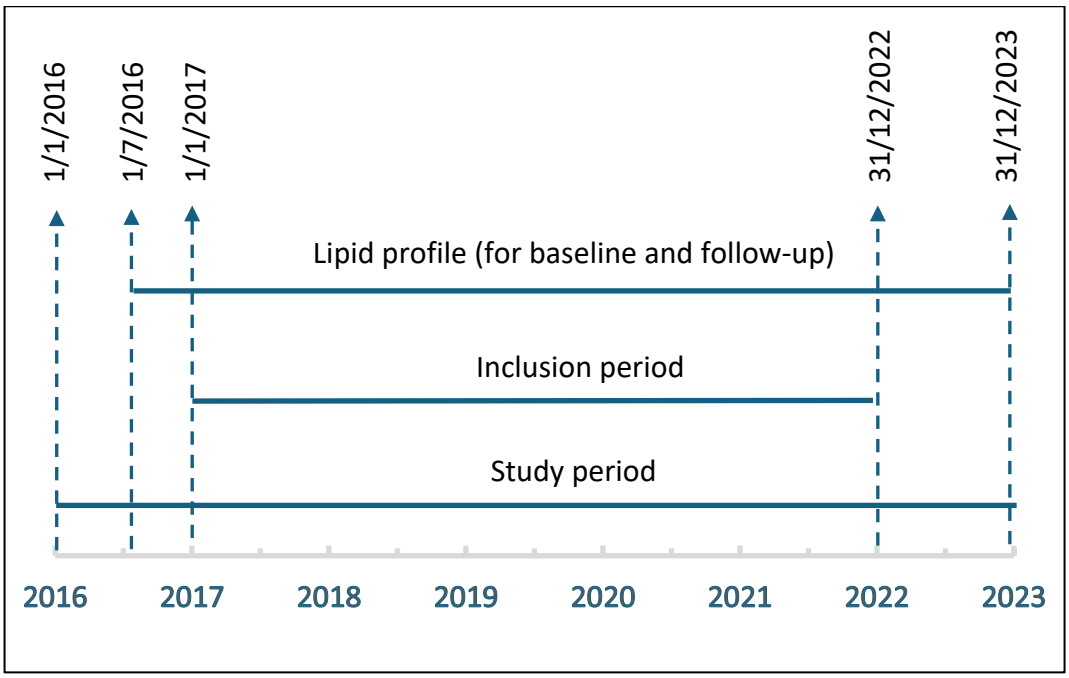

Figure 5.1 Timeframe of the retrospective cohort study for incident PCSK9i users

5.3.2. Study cohort identification and selection (Inclusion and exclusion criteria)

Data were obtained from the electronic pharmacy dispensing records at the DCC, based on a request to include all patients who were dispensed a PCSK9i (evolocumab or alirocumab) between 1 January 2016 and 31 December 2022 (**Figure 5.1**). Patients were included even if they had received only one dispensed prescription. The dataset provided also included information on oral LLT classes (statins, cholesterol absorption inhibitor, and fibrates) to determine whether patients were receiving background LLT prior to initiating PCSK9i. Details of the available LLT agents are presented in **Table 5.1**.

Table 5.1 Summary of the variables included in the dispensing dataset

Variables	Description	After management
Dispensing dates	DD-MM-YYYY	-
Agent names and strengths	Atorvastatin 10, 20, 40mg Rosuvastatin 10, 20mg Simvastatin 20, 40mg Pitavastatin 2, 4mg	Grouped under statin class and further categorised into HIST (atorvastatin 40mg and rosuvastatin 20mg) and MIST (other agents)
	Ezetimibe 10mg	Grouped under cholesterol absorption inhibitor class
	Fenofibrate 145mg	Grouped under fibrates class
	Evolocumab 140mg Alirocumab 75mg	Grouped under PCSK9i class
Quantity dispensed	Free text- per unit (tablet/pen)	-
Date of birth (DOB)	DD-MM-YYYY	Used to calculate the age on index date; dispensing date - DOB
Gender	Character	Male or female
Nationality	Country name	Two categories: Middle East and others

PCSK9is: Proprotein convertase subtilisin/kexin type 9 inhibitors; **HIST**: High-intensity statin therapy; **MIST**: Moderate-intensity statin therapy

The study aimed to identify incident (new) users of PCSK9is, defined as patients whose first recorded dispensation occurred between 1 January 2017 and 31 December 2022, regardless of the specific agent. Individuals whose first recorded use was evolocumab were classified as new PCSK9i users, and likewise, those whose initial recorded use was alirocumab were also classified as new users. The date of the first PCSK9i dispensing was defined as the index date for each patient. To ensure accurate identification of new users, a minimum one-year look-back period was applied to confirm no prior use of PCSK9is. Accordingly, data collection commenced on 1 January 2016 as a washout period to allow for this pre-index assessment (**Figure 5.1**). This definition of incident users was adapted from a Scottish study that examined newly initiated statin users (188).

Thus, each patient was required to have at least 12 months free of any PCSK9i use prior to their index date. For example, a patient with an index date of 4th April 2020 would have no record of PCSK9i use between 1st January 2016 and 3rd April 2020. It is important to mention that the definition of incident users was applied only within DCC. Due to the absence of linked health records across different healthcare settings, it is possible that some patients may have received LLT prescriptions elsewhere, such as in governmental or private hospitals, primary healthcare centres, or community pharmacies.

5.3.3. Contents of the dataset

The retrieved dataset included detailed information on all dispensed LLTs per patient, including dispensing dates for each agent. LLTs were recorded by drug name, provided in both generic and brand formats. For each chemical substance, a single brand was consistently used throughout the study period, as supplied from the CMS (e.g. Lipitor® for atorvastatin). Additional variables included the strength of each medication, quantity dispensed, the date of birth (DOB), as well as gender and nationality. It is important to note that the pharmacy dispensing records did not contain clinical information such as diagnoses, comorbidities, or medical procedures (**Table 5.1**).

5.3.4. Data management

Data were recorded either as free texts or as numerical values, depending on the variable. LLT agents were grouped according to their respective therapeutic classes. Among statins, atorvastatin 40mg and rosuvastatin 20mg were classified as high-intensity statin therapy (HIST), while all other statins were categorised as moderate-intensity statin therapy (MIST) (**chapter 2**, **Table 2.3**) (20). The DOB was used to calculate the patient's age on the index date by subtracting the DOB from the index date (initial dispensing date). Details of all variables included in the dataset, along with their descriptions and any applied adjustments, are summarised in **Table 5.1**.

5.3.5. Study outcomes

The primary outcomes of this study were the real-world effectiveness of PCSK9is and factors potentially associated with changes in lipid levels following PCSK9i therapy.

5.3.5.1. Baseline characteristics of incident PCSK9i-treated patients

The study covariates were determined based on previous literature (73, 86) examining the baseline characteristics of PCSK9i users, as well as the availability of relevant variables within the dataset. Baseline characteristics included demographic factors such as age, gender, and nationality, along with drug-related variables, including the specific PCSK9i agent used, the initial PCSK9i dose, and background LLTs (**Table 5.2**). For patients receiving statins as part of their background LLT, statin intensity was also documented. All variables were measured at the index date. These demographic and drug-related covariates are described in detail in the subsequent sections.

5.3.5.1.1. Demographic factors

Age was expressed both as a continuous variable and as a categorical variable. Categorical age groups were defined beginning with those younger than 55 years, informed by literature reporting an approximately 10-year earlier onset of CVD in Arab populations compared with counterparts in Europe and North America (90, 93). The remaining age categories are presented in **Table 5.2**. Gender distribution was included, as a categorical variable (male or female), to ensure the study cohort reflected the general population and as a factor could be associated with PCSK9i effectiveness, as found by Vicente-Valor et al. (86). Nationality was also included as a categorical variable (Middle East and other nationalities) (**Table 5.2**), based on evidence from Al-Ashwal et al. (2024), who reported a higher prevalence of FH in the Middle East region (189).

Table 5.2 Definition of baseline characteristics for new PCSK9i users in this study

Covariate	Definition
Demographic variables	
Age at index date (initial dispensing date)	Age was assessed as a continuous variable and as a categorical variable (four categories): <55, ≥55 - <65, ≥65 - <75, and ≥75 years.
Gender	Binary variable; male or female
Nationality	Binary variable; Middle East or others
Drug-related variables	
PCSK9i agent	Binary variable; evolocumab or alirocumab
PCSK9i dose at initiation	The dose was categorised into two licensed doses: Q2W and QM. Another category was added if one pen was dispensed
Background LLT at baseline	Whether oral LLTs (statin, ezetimibe, or a fibrate) prescribed six months within the index date. It was categorised into 7 categories (none, statins only, ezetimibe only, fibrates only, statin + ezetimibe, statin + fibrate, and statin + ezetimibe + fibrate)
Statin intensity (if applicable)	The statin intensity used was categorised into HIST for atorvastatin 40mg and rosuvastatin 20mg and MIST for other statin agents

LLT: Lipid-lowering therapy; **HIST**: High-intensity statin therapy; **MIST**: Moderate-intensity statin therapy; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitors; **Q2W**: Biweekly; **QM**: Monthly

5.3.5.1.2. Drug-related variables

The type of PCSK9i agent (evolocumab or alirocumab) and the initial PCSK9i dose were included (**Table 5.2**) to describe dispensing patterns and dosing variability among patients (73). However, information on the prescribed dose was not available in the dataset. Therefore, dosing regimens were inferred primarily from the licensed dosing recommendations (190), and in certain cases from the quantity dispensed.

During the study period, the available PCSK9i strengths were 140mg for evolocumab and 75mg for alirocumab. Evolocumab can be administered as 140mg every two weeks (Q2W) or 420mg once monthly (QM), with both regimens providing equivalent LDL-C reduction (191), corresponding to one or three 140mg pens, respectively. For alirocumab, the recommended initiation doses are 75mg Q2W, 150mg Q2W, or 300mg QM (192), corresponding to one, 2 pens, or 4 pens of 75mg, respectively.

To inform assumptions regarding dosing patterns of evolocumab, evidence from the ZERBINI study conducted in Kuwait reported that all participants received 140mg Q2W (73). Accordingly, this study adopted Q2W as the initial dosing regimen for all incident evolocumab users, equivalent to one pen of 140mg Q2W. For alirocumab, the assumption of 75mg Q2W as the initial regimen was supported by FDA labelling, which indicates that most patients achieve adequate LDL-C reduction with one pen of 75mg Q2W (48).

Although dosing can vary in real-world practice, the regimen was generally assumed to follow the standard one pen Q2W to ensure consistency. However, based on the researcher's clinical experience in a cardiac care centre, and considering the standard dispensing policy in Kuwait, which is typically a two-month supply, specific exceptions were applied for both evolocumab and alirocumab. For evolocumab, when the dispensed quantity was 3 or 6 pens of 140mg, the dosing assumption was adjusted to the alternative QM regimen rather than Q2W. This is because 3 pens provide a one-month supply of the 420mg QM dose, and 6 pens provide a two-month supply.

For alirocumab, a dispensed quantity of eight 75mg pens was observed. Under a simple one-pen Q2W assumption, this would imply a four-month supply, which is unlikely given local dispensing policy. The quantity of eight pens could represent either two 75mg pens Q2W (150mg Q2W) or four 75mg pens QM (300mg QM), both of which provide two months of treatment. Selecting between these up-tittered regimens required considering whether patients would adhere to multi-pen self-injection on a single day. Thus, the two-pen Q2W regimen (150mg Q2W) was favoured over the four-pen Q2W regimen. This decision was further reinforced through expert consultation with a lipidologist, who noted that the 150mg Q2W regimen is more commonly prescribed than the 300mg QM alternative. Accordingly, the two 75mg pens Q2W regimen was adopted for this analysis.

There were also cases in which the dispensed quantity of evolocumab and alirocumab exceeded a two-month supply if interpreted under the Q2W assumption. However, no adjustments were made due to insufficient justifications for altering the assumed regimen. Additionally, the dataset included cases in which only one pen was dispensed at a time. The inferred dosing regimen for PCSK9i users, for each dispensed quantity recorded in the dataset, are presented in **Table 5.3**.

Table 5.3 Inferred dosing regimen and estimated days of supply for PCSK9i users

Evolocumab 140mg			Alirocumab		
Dispensed quantity, pens (Given)	**Inferred dosing regimen***	**Days of supply‡** (Calculated)	**Dispensed quantity, pens** (Given)	**Inferred dosing regimen***	**Days of supply‡** (Calculated)
1	Once	15	1	Once	15
2	One pen Q2W	30	2	One pen Q2W	30
3	Three pens QM	30	-	-	-
4	One pen Q2W	60	4	One pen Q2W	60
6	Three pens QM	60	6	One pen Q2W	90
8	One pen Q2W	120	8	Two pens Q2W	60

*Inferred dosing regimen assumed one pen Q2W, with exceptions explained in the text. ‡Days of supply calculated by dividing the quantity dispensed by the number of pens per dose and multiplying by the dosing interval (Q2W or QM). **PCSK9i:** proprotein convertase subtilisin/kexin type 9 inhibitor; **Q2W**: Biweekly; **QM**: Monthly

It is important to note that inferring the dosing regimen was not only relevant for understanding initial dispensing patterns but was also essential for estimating the duration of each PCSK9i dispensation, referred to as the days of supply. This estimation was required for evaluating the real-world effectiveness of PCSK9is, which is presented in the following section (section 5.3.5.2). However, the process for calculating days of supply is described in this section, as it directly complements the interpretation of dosing regimen.

Days of supply for each PCSK9i dispensation were calculated by dividing the quantity dispensed by the number of pens per dose and then multiplied by the dosing interval (190) (**Equation 5.1**).

Equation 5. 1.

$$\text{Days of supply} = \frac{\text{Quantity dispensed}}{\text{Pens per dose}} \times \text{Dosing interval}$$

Where:

- **Quantity dispensed** was taken directly from the dataset.
- **Pens per dose** was inferred from the dosing regimen (e.g. one, two, or three pens) (Table 5.3).
- **Dosing interval** was also inferred from the dosing regimen (e.g. Q2W or QM); this study defined Q2W as 15 days and QM as 30 days (Table 5.3).

For example, if 4 pens of evolocumab 140mg were dispensed, Table 5.3 indicates that the dosing regimen corresponds to one pen Q2W. The calculation is shown in **Equation 5.2**.

Equation 5. 2.

$$\text{Days of supply} = \frac{\text{Quantity dispensed (n = 4)}}{\text{Pens per dose (n = 1)}} \times \text{Q2W (n = 15)} = 60 \text{ days}$$

Another example from the exception cases is when 3 pens of evolocumab 140mg were dispensed. As shown in Table 5.3, this quantity corresponds to a regimen of 3 pens QM. the calculation is shown in **Equation 5.3**.

Equation 5.3.

$$\text{Days of supply} = \frac{\text{Quantity dispensed (n = 3)}}{\text{Pens per dose (n = 3)}} \times \text{QM (n = 30)} = 30 \text{ days}$$

Thus, dispensing 3 pens corresponds to a one-month supply, which strongly supports interpreting this as the 420mg QM regimen. In contrast, assuming a as 140mg Q2W regimen would result in 45 days of supply, a duration that is rarely prescribed in practice.

Another baseline characteristics was background LLT, which was included as a covariate (**Table 5.2**) based on clinical guidelines recommending initiation of oral LLTs (statin, or ezetimibe, or their combination) prior to adding a PCSK9i in cases of inadequate lipid control (20, 23). The concurrent use of other LLTs alongside a PCSK9i is associated with greater reductions in LDL-C levels, reaching up to 85% (23).

Background LLTs were identified by reviewing dispensing records within a six-month (180-day) window prior to the PCSK9i index date for each patient, following the approach used in the ZERBINI study conducted in Kuwait (73). The days of supply for each oral LLT were calculated to determine whether at least 28 days of use occurred within this six-month period, acknowledging that some LLT packaging contains 28 or 30 tablets. Although the standard dispensing cycle in Kuwait is typically two months, a one-month threshold was applied as the minimum prescription duration in clinical practice.

Background LLTs included in the dataset comprised statins, a cholesterol absorption inhibitor, and a fibrate, with the corresponding agents listed in **Table 5.1**. Although fibrates are not used for direct LDL-C reduction, their inclusion provided additional insight into dispensing patterns of oral LLTs. Moreover, because fibrates are primarily indicated as adjuncts to statins for the management of hypertriglyceridaemia, capturing their use could help identify whether patients may have had coexisting metabolic dyslipidaemia.

Thus, to calculate the duration of each medication, a similar approach based on the licensed dosing recommendations was applied. For ezetimibe and fenofibrate, the only agents representing their respective classes (**Table 5.1**), dosing regimens are typically once daily (193, 194). Accordingly, the duration of ezetimibe and fibrate use was estimated by adding the quantity dispensed directly to the dispensing date to estimate the end date of supply.

In contrast, statin dosing may vary from one or more tablets per day depending on the available strengths and the total prescribed daily dose (195-197). Statin agents and their available strengths are listed in **Table 5.1**. For instance, atorvastatin was available in 10mg, 20mg, and 40mg strengths in the dataset, and patients may have been prescribed two 20mg tablets to achieve a 40mg daily dose during periods of 40mg tablet shortage, or two 40mg tablets to achieve an 80mg daily dose when the 80mg strength was unavailable. Given the standard two-month dispensing policy in Kuwait, a quantity of 120 tablets of either atorvastatin 20mg or 40mg would therefore represent a two-tablet daily regimen.

Accordingly, estimating days of supply for statins could not be done by simply adding the quantity dispensed to the dispensing date, as was appropriate for ezetimibe and fenofibrate with once-daily dosing. This distinction was particularly important for classifying statin intensity. For example, a 20mg of atorvastatin tablet could represent a MIST if taken once daily, but a HIST if taken twice daily (see statin intensity classification in **chapter 2**, **Table 2.3**.

As emphasised in the 2019 ESC/EAS guidelines, determining statin intensity is essential during PCSK9i use, as combining a PCSK9i with HIST and ezetimibe can achieve LDL-C reductions of up to 85% (23). Therefore, it was necessary to estimate the most plausible statin dosing regimen to minimise misclassification of statin intensity. To support this, the refill gap method was applied, although this method is typically used to evaluate medication persistence and adherence, as described by Rasmussen et al. (2022) (198).

The refill gap was defined as the number of days between the end of supply for one dispensing and the dispensing date for the subsequent refill (198). Hence, it is important to outline the possible dosing scenarios that may arise when applying the refill gap method, as this method also underpins the approach used to evaluate PCSK9i effectiveness in the following **section 5.3.5.2**.

Four refill gap scenarios obtained from the dataset are illustrated in **Figure 5.2**. The refill gap could be negative, indicating an early refill (**Figure 5.2A**); positive, indicating a delayed refill (**Figure 5.2B**); or zero, indicating that the refill occurred exactly on the day the previous supply ended (**Figure 5.2C**). In cases where only a single dispensing record was available or no subsequent dispensing was recorded; the refill gap could not be calculated (**Figure 5.2D**).

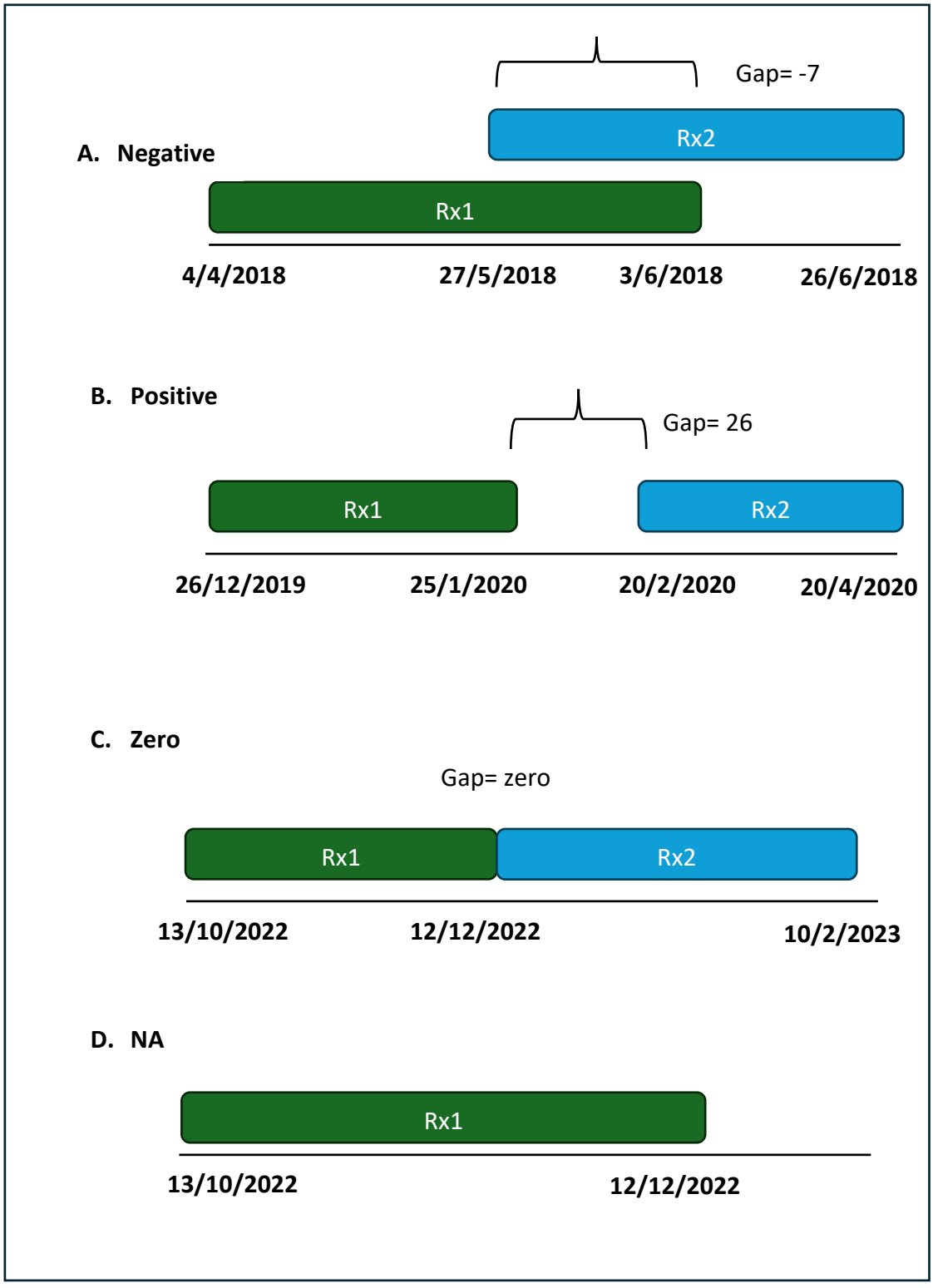

Figure 5.2 Schematic illustration of the refill gap method used to describe different scenarios. The gap is calculated by subtracting the end date of **Rx1** from the start date of **Rx2** for the same patient. **(A) Negative gap** indicates overlap, meaning the patient refilled earlier than expected; **(B) Positive gap** indicates the patients refilled later than expected; **(C) A gap of zero** suggests the patient refilled on the exact day the previous prescription (**Rx1**) ended; **(D) NA:** The gap cannot be calculated when no subsequent dispensing record was available or when only a single dispensing record existed. **Rx**: Prescription. **NA**: Not applicable

Thus, to estimate the end date of supply for statins, dispensing records for each patient were first reviewed chronologically. For each dispensation, the quantity dispensed was added directly to the dispensing date, assuming a once-daily regimen., and the refill gap was subsequently calculated. In interpreting this refill gap, normal working days in the governmental healthcare settings were considered as the threshold to estimate the most plausible statin dosing regimen. In Kuwait, public hospitals operate on approximately 20 to 23 working days per month, excluding weekends and public holidays that may fall on weekdays. This corresponds to roughly 40-46 working days over a standard two-month dispensing interval.

Accordingly, a 40-day threshold was selected to estimate the statin dosing regimen. If the calculated refill gap was < -40 days, this indicated that the patient refilled their prescription more than 40 days earlier than expected. Such a pattern suggested that the patient was likely taking a higher daily dose than initially assumed (i.e. more than one tablet daily). In these cases, the inferred regimen was adjusted by doubling the strength and halving the quantity dispensed to reflect a more intensive regimen. For example, if the refill gap was -60 days for atorvastatin 20mg and the quantity dispensed was 120 tablets, the inferred dosing regimen was interpreted as two 20mg tablets of atorvastatin daily over a 60-day period (**Figure 5.3**). Based on this adjusted calculation, the statin therapy was classified as HIST rather than MIST.

Conversely, If the refill gap was ≥ -40 days, the original dosing assumption (one table daily) was retained, and the intensity classification remained unchanged. In cases where no subsequent dispensing record was available (i.e. the final statin dispensing record or where only a single record existed), the refill gap could not be calculated; therefore, statin intensity was determined solely based on the strength of the dispensed agent (**chapter 2**, **Table 2.3**).

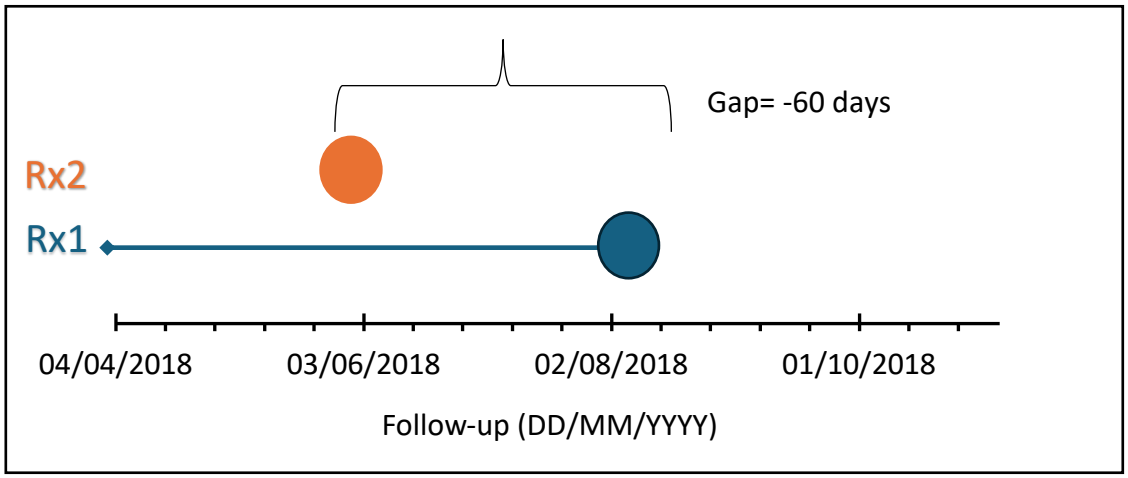

Figure 5.3 Schematic illustration of the refill gap method used to infer the statin dosing regimen of statins. First, the quantity dispensed is added to the start date of Rx1 to calculate the end date of supply (blue circle). Second, the start date of Rx2 (orange circle) is identified from the dataset. Third, the gap is calculated by subtracting the end date of supply for Rx1 (blue circle) from the start date of Rx2 (orange circle). A refill gap of less than -40 days indicates that the patient was likely taking a higher daily dose than initially assumed, suggesting the need to double the statin strength.

To ensure the appropriateness of the 40-day threshold, a sensitivity analysis was conducted comparing this threshold-based method with a simpler strength-based approach. The level of agreement between the two methods exceeded 95% for both MIST and HIST categories, supporting the robustness of the 40-day threshold in inferring intensified dosing. It was also observed that most cases of inferred intensification occurred when rosuvastatin 10mg or atorvastatin 20mg was dispensed in quantities of 112 or 120 tablets, respectively, reflecting two-tablet daily regimens over 56 or 60 days.

There was one case in which two dispensing records for the same patient appeared on the same date, one for atorvastatin 20mg and the other for atorvastatin 40mg. This case was classified as HIST, as doses between 40mg and 80mg fall within the HIST range (**chapter 2**, **Table 2.3**). However, clinical interpretation of this case was challenging. Based on standard dosing practices, which typically follow a doubling pattern (10mg, 20mg, 40mg, 80mg), and the commonly referenced 6% LDL-C reduction rule per doubling of dose (167), a combined dose of 60mg does not align with standard dosing regimens. Therefore, it is unclear whether this pattern resulted from patient preference, a data entry error, or a clinical decision to initiate treatment at 20mg and escalate to 40mg.

5.3.5.2. Real-world effectiveness of PCSK9is

The real-world effectiveness of PCSK9is was evaluated through changes in lipid levels following PCSK9i initiation and subsequent attainment of guideline-recommended lipid targets. Changes in lipid levels were assessed using both absolute changes (median differences) and relative changes (percentage changes). Lipid target attainment was evaluated by determining the number and proportion of patients who achieved the recommended thresholds. The lipid parameters assessed included the primary lipid targets LDL-C and non-HDL-C, and secondary lipid targets TGs, HDL-C (20), as well as TC.

Given the importance of tailoring lipid targets to individual patient risk in primary prevention, particularly for LDL-C and non-HDL-C targets (**chapter 2**, **Table 2.2**), a key limitation of this study was the absence of detailed data on comorbidities and clinical history. However, because the study was conducted in a tertiary cardiac centre and based on consultation with a lipidologist, it was assumed that all patients were being managed for established ASCVD. Consequently, all individuals were categorised under secondary prevention, and CV risk calculation was not required.

Under this assumption, the LDL-C target was set at <1.4 mmol/L, as recommended by the 2019 ESC/EAS guidelines and the 2021 Middle East consensus (20, 23). A sensitivity analysis using a more stringent LDL-C target of <1.0 mmol/L was also performed to account for the possibility that some patients may have experienced two vascular events within two years and would therefore require a more aggressive lipid-lowering goal (23). Additionally, a broader LDL-C target of <1.8 mmol/L was examined to enable comparison across three relevant thresholds. The corresponding non-HDL-C targets were determined by adding 0.8 mmol/L to each LDL-C threshold (20, 23). The remaining lipid parameters (TGs and HDL-C) were assessed independently of CV risk category, in line with definitions presented in **chapter 4**, **Table 4.1**. A TC threshold of <5 mmol/L was adopted based on guidance issued by NHS Inform, Scotland's national health information service (145).

After identifying incident PCSK9i users from pharmacy dispensing records and defining the relevant lipid targets, it was important to evaluate lipid changes in relation to the PCSK9i continuation status of each patient. Continuation, which represents a pattern of persistence with therapy, indicates that the patient remained on treatment throughout the observation window. Continuation of PCSK9i therapy was defined using the refill gap method, with the possible scenarios illustrated in **Figure 5.2**. This method was applied to determine the appropriate follow-up period for lipid profile measurements, using a 12-month follow-up from the index date (PCSK9i initiation), consistent with the Kuwait ZERBINI study (73).

As with earlier statin calculations, all PCSK9i dispensing records for each patient were ordered chronologically by dispensing start date. The estimated days of supply, which previously calculated (**Table 5.3**), were added to each dispensing start date to obtain the corresponding end date of supply. The refill gap was then calculated by subtracting the end date of supply for one dispensing from the start date of the subsequent dispensing (198).

Following the calculation of the refill gap, an appropriate grace period was applied to determine the continuation pattern. The grace period accounts for possible delays in prescription refills and potential medication stockpiling (198). Although grace periods vary across PCSK9i studies, a 60-day period was chosen to reflect the standard two-month dispensing policy in Kuwait and to align with the Kuwait ZERBINI study (73). Other studies have used similar or shorter periods, such as 56 days in Canada (199) and 30 days in studies conducted in the UAE and Germany (184, 200).

Moreover, continuation was assessed only for patients who remained on the same index PCSK9i throughout the follow-up period. Importantly, if a patient switched from evolocumab to alirocumab, or vice versa, and the refill gap between the end date of supply of the previous dispensation and the start date of the new agent was ≤60 days, the follow-up period ended on the day immediately preceding the initiation

of the switched PCSK9i agent. This approach ensured that follow-up period did not overlap with the exposure of the switched agent. Using only one agent during the follow-up allowed for a valid comparison of effectiveness between evolocumab and alirocumab, similar to the methodological approach used in a real-world study from Spain (86).

Thus, PCSK9i continuers were defined as patients who remained on their index PCSK9i agent throughout the 12-month period following initiation, with a refill gap of ≤60 days (190). Follow-up ended in cases of switching to another PCSK9i, or continuing PCSK9i therapy beyond 12 months. While these scenarios may reflect treatment discontinuation, the term "continuation" was used in this study to maintain clarity and avoid introducing additional terminologies related to the adherence behaviour.

Figure 5.4 illustrates three real scenarios for PCSK9s continuers and the corresponding observation windows for lipid profile measurements. **First** (**Figure 5.4A**), PCSK9i dispensations continued throughout the 12-month follow-up period, with all refill gaps ≤ 60 days. In this scenario, the end date of supply for the final dispensing within the 12-month window was extended by a 60-day grace period. This adjusted date represented the end of follow-up and defined the last date from which lipid profile retrieved. **Second** (**Figure 5.4B**), PCSK9is dispensations continued beyond the 12-month period; however, a refill gap >60 days occurred within 12-month period. Here, the end date of supply within 12-month period was extended by a 60-day grace period. This adjusted date again represented the end of follow-up for lipid profile assessment. **Third** (**Figure 5.4C**), when only a single dispensing record of the index PCSK9i therapy was available in 2022 and the calculated end date of supply extended into 2023, this calculated end date was considered the end of follow-up for lipid profile assessment. In this case, no 60-day grace period was applied because continuation could not be verified beyond 31 December 2022; therefore, the end of supply date corresponded the end of the follow-up date.

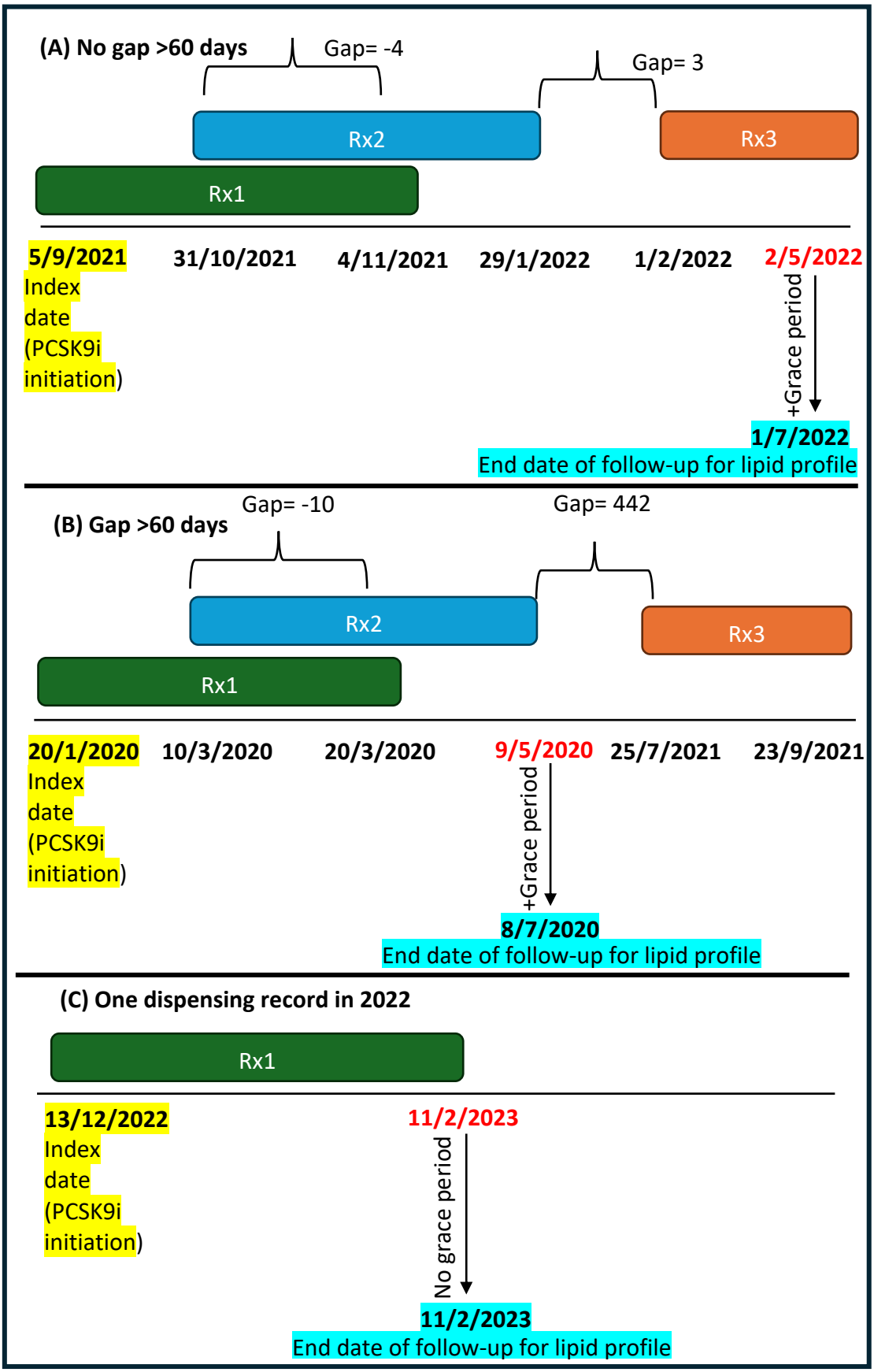
(A) No gap >60 days
Gap= -4
Gap= 3
Rx2
Rx3
Rx1
5/9/2021
Index date (PCSK9i initiation)
31/10/2021
4/11/2021
29/1/2022
1/2/2022
2/5/2022
+Grace period
1/7/2022
End date of follow-up for lipid profile
(B) Gap >60 days
Gap= -10
Gap= 442
Rx2
Rx3
Rx1
20/1/2020
Index date (PCSK9i initiation)
10/3/2020
20/3/2020
9/5/2020
25/7/2021
23/9/2021
+Grace period
8/7/2020
End date of follow-up for lipid profile
(C) One dispensing record in 2022
Rx1
13/12/2022
Index date (PCSK9i initiation)
11/2/2023
No grace period
11/2/2023
End date of follow-up for lipid profile

Figure 5.4 Schematic illustration of PCSK9i continuation cases and the corresponding follow-up lipid windows. PCSK9i continuers were defined as patients who remained on the same index PCSK9i agent throughout the 12-month period following the index date. **(A)** No refill gap >60 days within the 12-month period. **(B)** Refill gap > 60 days within the 12-month period. For both **(A)** and **(B)**, the end date of supply for the final dispensing within the 12-month window was extended by a 60-day grace period, which represented the end of follow-up for lipid profile retrieval. **(C)** Only one dispensing record in 2022, where the calculated end date of supply was also the end of follow-up, as a grace period could not be applied.

Once the end of follow-up for each PCSK9i user was identified, lipid measurements were extracted over a four-day period (20th– 23rd March 2024), requiring more than 30 hours of manual review at the biochemical laboratory at Al-Adan Hospital, which provides services for both Al-Adan Hospital and DCC. Extraction was performed using the unique patient identifier. To be eligible for inclusion in the real-world effectiveness analysis, each incident PCSK9i user was required to have at least one comparable lipid parameter (LDLC, non-HDL-C, TG, HDL-C, and TC) both before and after the index date.

As the cohort included incident PCSK9i users between 1st January 2017 and 31st December 2022, baseline lipid parameters were defined as those measured within the six months prior to the index date, using the value closest to the index date. This corresponded to a baseline window beginning on 1 July 2016. Follow-up lipid measurements were collected for up to 12 months after the index date, taking into account the end of the follow-up for each patient.

The post-index period was further divided into four quarters (0-90, 91-180, 181-270, and 271-360 days) to provide a better understanding of these drugs on the lipid levels over time. Although some patients continued PCSK9i for the full 12-month period, no lipid measurements were available in the last quarter; therefore, analyses were restricted to the first three quarters. For the first quarter (0-90 days), lipid measurements were included only if taken ≥ 30 days after PCSK9i initiation, consistent with the recommended 4-week interval for initial lipid assessment (47, 48). For each quarter, the mean lipid value was calculated, resulting in up to three post-index measurements per lipid parameter. This approach was adapted from the Colombian ZERBINI study (201), which estimated LDL-C values using the average within each time window. When more than one lipid result was available within a given month, the mean of those value was used.

When LDL-C was not directly measured, the Friedewald Formula (FF) (**Formula 5.1**) was applied, provided TG levels were <4.5 mmol/L and both and HDL-C and TC values were available (23). Similarly, non-HDL-C was calculated by subtracting HDL-C from TC when not directly measured (**Formula 5.2**) (23).

Formula 5.1:

$$\mathrm{LDL-C}\,\frac{\mathrm{mmol}}{\mathrm{L}} = \mathrm{TC} - (\mathrm{HDL-C}) - \frac{\mathrm{TG}}{2.2} \quad (\text{only if fasting TG} < 4.5\,\frac{\mathrm{mmol}}{\mathrm{L}})$$

Formula 5.2:

$$\mathrm{Non-HDL-C}\,\frac{\mathrm{mmol}}{\mathrm{L}} = \mathrm{TC} - (\mathrm{HDL-C})$$

5.3.5.3. Factors potentially associated with changes in lipid levels following PCSK9i therapy

This study investigated whether specific demographic or drug-related characteristics were associated with the effectiveness of PCSK9i therapy in reducing lipid levels. Potential influencing factors included demographic variables, such as age (measured at the index date) and gender. Drug-related variables included the type of PCSK9i agent used (evolocumab or alirocumab), which was examined to determine whether the choice of agent influenced the degree of lipid reduction. Background LLT use, previously discussed for its clinical relevance, was also examined to explore whether concurrent therapy contributed to lipid reductions following PCSK9i initiation. It is necessary to acknowledge that while inclusion clinical variables, such as comorbidities, CV risk categories, and lifestyle-related factors, could have provided a more comprehensive assessment of potential confounding, their incorporation was limited by data available.

A linear mixed-effects model (LMM) was employed to account for repeated lipid measurements within individuals BD to evaluate changes in lipid levels over time following PCSK9i initiation, while adjustment for relevant covariates. The LMM is particularly well-suited to longitudinal data with repeated measurements, as it accounts for both fixed effects, which represent variables that remain consistent across individuals, and random effects, which capture individual-level variability in lipid changes over time (202, 203).

This model was appropriate because the outcome variable (changes in lipid levels) is continuous and measured repeatedly within the same individuals. The LMM was applied to LDL-C and non-HDL-C, as these represent the primary lipid targets recommended by the 2021 Middle East consensus (20).

5.3.6. Statistical analyses

5.3.6.1. Baseline characteristics of new PCSK9i-treated patients

Baseline characteristics of new PCSK9i-treated patients were summarised as frequencies and percentages for categorical variables, including age. Age was also expressed as a continuous variable and summarised using means ± standard deviation (SD), as it followed a normal distribution, verified through histograms and Q-Q plots (146).

In addition to describing the baseline characteristics of PCSK9i users, comparisons were conducted between the evolocumab and alirocumab groups to identify any significant differences in these characteristics. The choice of statistical tests was based on the type of variable and the assessment of normality assumptions.

For continuous variables such as age, group means were compared using the independent samples t-test (Student's t-test), a parametric test appropriate when the normality assumption is met (204). For categorical variables with cell frequencies fewer than 5, such as age groups, baseline LLTs, and initial PCSK9I doses, Fisher's exact test was applied (205). In contrast, Pearson's Chi-square test was used for categorical variables with cell frequencies of at least 5, including gender and statin intensity (205).

Baseline lipid parameters (LDL-C, non-HDL-C, TG, HDL-C, and TC) were summarised as median ± interquartile range (IQR), given their skewed distribution, as verified by histograms (146). The Mann-Whitney U test (Wilcoxon rank-sum test), a non-parametric test that ranks data without assuming normality (206), was used to compare the differences in medians between the evolocumab and alirocumab groups.

5.3.6.2. Real-world effectiveness of PCSK9i: percentage change in lipid levels and target goal attainment

Following the application of eligibility criteria to the incident PCSK9i users, the cohort was reduced by 74.9%, from 458 to 115 patients (**Figure 5.5**). Given this substantial reduction in the cohort number, a post hoc power analysis was performed to assess whether the final cohort (n= 115) provided sufficient statistical power to detect changes in lipid parameters following PCSK9i initiation (power-based approach) (207). The statistical power was calculated using G*Power (version 3.1) (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). The post hoc analysis required three key inputs: the effect size (|ρ|), the significance level (α error probability), and total sample size.

LDL-C and non-HDL-C were selected for this assessment due to their established role as primary lipid targets (20). Starting with non-HDL-C, the total cohort of 115 patients and a significance level (α= 0.05) were known; therefore, effect size needed to be estimated. Cohen's d formula for paired samples was applied (208):
Cohen's d= Mean (or median) difference/SD

Because lipid parameters were reported as medians (IQR), the median difference and an estimated SD were applied. The median baseline non-HDL-C level was 3.94 mmol/L (IQR: 2.85-5.16), decreasing to 2.38 mmol/L (IQR: 1.52 to 3.27) following PCSK9i initiation. This reflected an absolute median reduction of 1.36 mmol/L (**Appendix S5.2**, Table S5.2.2A).

The IQR was calculated as:
Q_3-Q_1 = 5.16 – 2.85= 2.31

The SD was estimated from the IQR using the standard conversion (209):
SD= IQR/1.35
SD= 2.31/1.35= 1.71

Thus, the effect size was:

d= 1.36/1.71= 0.8

Using this effect size (d= 0.8), a sample size of 115, and α= 0.05, the post hoc analysis demonstrated a power (1-β error probability) of 1.0 (100%) (207), confirming that the study was sufficiently powered to detect the observed change in non-HDL-C levels. The same steps were applied for LDL-C, using the sample size of 104 patients. The post hoc analysis also yielded a power estimate of 1.0 (100%) (207).

The analysis of real-world effectiveness included all new users of PCSK9is and was further stratified by individual agents: evolocumab and alirocumab. The histogram used to assess normality revealed a skewed distribution of lipid values. Consequently, changes in lipid parameters over time were evaluated using absolute median differences, calculated by subtracting the baseline median lipid value from the corresponding lipid value at each follow-up period. These differences were then summarised with their respective median (IQR). The calculations were first performed at the individual level and then aggregated to report the overall cohort-level median (IQR) values.

In addition, relative median percentage changes were calculated by dividing the absolute median difference by the baseline lipid value and multiplying by 100%. For instance, the formula used to calculate the relative change in LDL-C was: ((follow-up LDL-C - baseline LDL-C)/baseline LDL-C) × 100. Since the lipid values did not meet normality assumptions, 95% confidence intervals (CIs) for the percentage changes were estimated using bootstrapping, a non-parametric method that repeatedly resamples the observed data without requiring any assumptions about the underlying distribution (210). Like the absolute differences, relative percentage changes were calculated at the individual level and then summarised at the group level using the median and corresponding 95% CIs.

Non-parametric tests were used to compare median changes in lipid parameters before and after PCSK9i initiation. The Wilcoxon signed-rank test was applied to assess within-group differences in lipid levels between the pre- and post-index periods (206). To compare median lipid levels between the evolocumab and alirocumab groups over the same period, the Mann-Whitney U test (also known as the Wilcoxon rank-sum test) was employed (206). The number of patients using a PCSK9i with recorded lipid values was documented at the index date and for each subsequent post-index period. Box plots were used to visualise the median and IQR

of lipid parameters before and after PCSK9i initiation, accompanied by a detailed summary table.

To evaluate lipid target goal attainment, the frequency and percentage of patients achieving their respective targets were calculated at each timeframe, including the baseline period. This was performed by dividing the number of patients who met the target by the total number assessed in that period. A grouped bar chart was used to visually present target achievement across baseline and post-index periods, accompanied by a detailed summary table. These analyses were repeated for each lipid parameter and stratified by overall PCSK9i users, as well as by individual agents: evolocumab and alirocumab. Statistical significance was defined as a p value of <0.05. Notably, the primary analysis in this study focused on lipid changes within the first three months (90 days) following PCSK9i initiation.

5.3.6.3. Factors associated with median changes in LDL-C and non-HDL-C levels using LMM

The LMM enabled comparisons of lipid levels before and after PCSK9i initiation by incorporating fixed effects to estimate overall population-level changes and random effects to account for within-patient repeated measures and between-patient variability. In this model analysis, fixed effects included time (baseline and follow-up), age at the index date, gender, PCSK9i agent, background LLT, all of which measured at the index date. Random effects allowed each patient to have their own baseline lipid level, thereby accounting for intra-individual variability over time.

The model focused on the period from baseline to the first quarter post-index (within 90 days), given that this timeframe included the largest number of patients compared to later follow-up periods.

Time was modelled as a factor variable with two levels (baseline and follow-up). Age was tested as both a continuous and categorical variable (<55 vs ≥55). Model fit was compared using the Akaike Information Criterion (AIC), with the continuous age model yielding a slightly lower AIC (784.08 vs 786.51), indicating a better fit (211). Therefore, the model with age as a continuous variable was retained. While the Likelihood Ratio Test (LRT) is often used to compare nested models, it was not valid in this case due to zero degrees of freedom, confirming that the models were not properly nested. Nevertheless, the AIC remains an appropriate and valid metric for model comparison under such cases (211). Other categorical variables were coded as binary variable (Yes/No), with the category representing the largest subgroup designated as the reference category.

After developing the LMM, residual diagnostics were performed to evaluate the goodness-of-fit (GOF) of the model (**Appendix S5.1**) (203). For both the LDL-C (**Appendix S5.1, Figure S5.1.1**) and non-HDL-C (**Appendix S5.1, Figure S5.1.3**) models, the residuals vs. fitted values plots showed no clear pattern, indicating homoscedasticity and suggesting that the residual variance was constant across fitted values (203). Additionally, normal Q-Q plots were examined to assess whether residuals follow a normal distribution (203). The residuals closely followed the diagonal line, confirming that they were approximately normally distributed and that the linearity assumption was met. Moreover, scale-location plots were performed to further verify the consistency of variance across fitted values, showing no major patterns and no evidence of heteroscedasticity (202). Finally, Cook's distance plots were used to identify influential observations (potential outliers) (212, 213).

In the LDL model, one highly influential outlier (residual > 10) was detected, corresponding to a baseline LDL-C value of 22.0 mmol/L, with a Cook's distance of 1.4 (**Appendix S5.1, Figure S5.1.1**). This unusually high value, as Cook's distance values >1 typically indicate a highly influential point, likely reflected untreated FH. A sensitivity analysis excluding this observation (**Appendix S5.1, Figure S5.1.2**) improved the model fit, with the AIC reducing from 784 to 656 and the residuals showing a more normal distribution.

Similarly, in the non-HDL-C model (**Appendix S5.1, Figure S5.1.3**), two observations with residuals > 10 were detected as potentially influential. Excluding these in a sensitivity analysis (**Appendix S5.1, Figure S5.1.4**) improved the model fit, with the AIC decreasing from 922 to 820 and the residuals showing a more normal distribution.

Models were fit using the lmer function in Rstudio (lme4 package) (214).

5.4. Results

5.4.1. Baseline characteristics of new PCSK9i-treated patients

Over the six-year period (2017-2022), a total of 458 patients were identified as new users of PCSK9is. Among the total cohort, 78.6% of patients (n= 360) initiated treatment with evolocumab, while 21.4% of patients (n= 98) commenced therapy with alirocumab. The baseline characteristics of incident PCSK9i users are depicted in **Table 5.4**.

The mean age ± SD was 55.4 ± 10.9 years overall, with no significant difference between the evolocumab (55.5 ± 11.2 years) and alirocumab (55 ± 9.8 years) groups (p= 0.69). However, age became statistically significant (p <0.05) when analysed as a categorical variable. The majority of patients across both PCSK9i groups were younger than 65 years (80.1%, n= 367/458), including 79.2% of evolocumab users (n= 285/360) and 83.7% of alirocumab users (n= 82/98). Notably, none of the alirocumab-treated patients were aged 75 years or older.

The gender distribution of the cohorts revealed that just over two-thirds (69%, n= 316/458) of the patients were males. Both evolocumab and alirocumab groups had a comparable gender distribution (≈69%) yet statistically insignificant (p= 1). In terms of nationality, the majority of PCSK9i users (98.7%, n= 452/458) were from the Middle East region. This pattern was consistent across both agents, with 99.4% of evolocumab users (n= 358/360) and 95.9% of alirocumab users (n= 94/98) originating from the region.

Regarding background LLTs, 41.5% (n= 190/458) of patients were not receiving any oral LLT during the six-month pre-index period. Although the difference was not statistically significant (p= 0.08), a larger proportion of alirocumab users (53.1%, n= 52/98) were not receiving background LLT compared with evolocumab users (38.3%, n= 138/360). Just over half of the cohort (51.5%, n= 236/458) were observed using statins during this period, and among these, 53.4% (n= 126/236) were receiving HIST.

Examining the background LLTs in more detail, 37.1% (n= 170/458) were observed using statins only, 6.6% (n= 30/458) were using ezetimibe only, and 13.3% (n= 61/458) were observed using both a statin and ezetimibe.

Regarding the initial dose of PCSK9is, the majority of patients in both PCSK9i groups (≈92%) administered their doses Q2W. Among evolocumab users, 90.3% (n= 325/360) received 140mg biweekly, while 8.6% (n= 31/360) used a monthly regimen of three 140mg pens administered as a single dose. In the alirocumab group, 95.9% (n= 94/98) received one pen of 75mg biweekly, and 3.1% (n= 3/98) were dispensed two 75mg pens biweekly. The difference in dosing regimens between the two groups was statistically significant ($p < 0.05$).

5.4.2. Real-world effectiveness of PCSK9i (percentage change in lipids and target goal attainment)

Among the 458 incident PCSK9I users, a total of 115 patients were eligible for the effectiveness analysis, comprising 86 patients on evolocumab and 29 patients on alirocumab. Flowchart of PCK9I users included in the real-world effectiveness analysis is illustrated in **Figure 5.5**.

All 115 eligible patients were assessed across four lipid parameters: non-HDL-C, TG, HDL-C, and TC. The remaining 343 patients were excluded for the following reasons: absence of baseline lipid measurements, absence of post-index lipid values, lack of corresponding baseline-post-index lipid parameter pairs, or post-index values recorded within 12 months of initiation that did not align with the defined criteria for PCSK9i continuation.

Further exclusions were performed for the LDL-C analysis, reducing the cohort to 104 patients (77 on evolocumab and 27 on alirocumab). Eleven additional patients were excluded: 9 patients due to TG levels ≥4.5 mmol/L, which limited the use of the FF for LDL-C calculation, and two due to missing post-index LDL-C measurements (**Figure 5.5**).

Although more than 75% of the initial cohort were not eligible for the effectiveness analysis, the post hoc power analysis demonstrated 100% statistical power for detecting changes in lipid levels (see **section 5.3.6.2**).

The baseline characteristics of the subcohort of 115 patients were also assessed (**Table 5.5**). When compared with the full cohort of 458 patients (**Table 5.4**), no substantial differences were observed, suggesting that the subcohort remained broadly representative of the overall study population.

Table 5.4 Baseline characteristics of new PCSK9i-treated patients (n=458)

Covariates	Total patients (n= 458)	Evolocumab (n= 360; 78.6%)	Alirocumab (n= 98; 21.4%)	p- value (evolocumab vs. alirocumab)
Age, years				
Mean ± SD	55.4±10.9	55.5±11.2	55±9.8	t-test; p= 0.69
Categories, n (%)			Fisher's exact test; **p <0.05***	
<55	197 (43%)	156 (43.3%)	41 (41.8%)	
>=55 - <65	170(37.1%)	129 (35.8%)	41 (41.8%)	
>=65 - <75	76 (16.6%)	60 (16.7%)	16 (16.4%)	
>=75	15 (3.3%)	15 (4.2%)	0	
Gender, n (%)				Pearson's Chi-squared test; p= 1
Male	316 (69%)	248 (68.9%)	68 (69.4%)	
Female	142 (31%)	112 (31.1%)	30 (30.6%)	
Nationality, n (%)				
Middle East	452 (98.7%)	358 (99.4%)	94 (95.9%)	
Others	6 (1.3%)	2 (0.6%)	4 (4.1%)	
Background LLTs, n (%)			Fishers exact test; p= 0.08	
No background LLT	190(41.5%)	138 (38.3%)	52 (53.1%)	
Statin	170(37.1%)	145 (40.3%)	25 (25.5%)	
Ezetimibe	30 (6.6%)	22 (6.1%)	8 (8.1 %)	
Fibrate	2(0.4%)	2 (0.6%)	0	
Statin + ezetimibe	61 (13.3%)	48 (13.3%)	13 (13.3%)	
Statin + fibrate	4 (0.9%)	4 (1.1%)	0	
Statin + ezetimibe + fibrate	1 (0.2%)	1 (0.3%)	0	
Statin Intensity, n (%)				Pearson's Chi-squared test; p= 0.94
HIST	126/236 (53.4%)	105/198 (53%)	21/38 (55.3%)	
MIST	110/236 (46.6%)	93/198 (47%)	17/38 (44.7%)	
PCSK9i dose at initiation, n (%)			Fisher's exact test; **p <0.05***	
Q2W	419 (91.5%)[a]	325 (90.3%)	94 (95.9%)[a]	
	3 (0.6%)[b]	-	3 (3.1%)[b]	
QM	31 (6.8%)[c]	31 (8.6%)[c]	-	
One pen	5 (1.1%)	4 (1.1%)	1 (1.0%)	

***Significant. **SD:** Standard deviation**; LLT**: Lipid-lowering therapy; **HIST:** High-intensity statin therapy; **MIST:** Moderate-intensity statin therapy; **PCSK9i:** proprotein convertase subtilisin/kexin type 9 inhibitors; **Q2W**: Biweekly; **QM**: Monthly. **a**: One pen (75mg) biweekly; **b**: Two pens of 75mg (150mg) biweekly; **c**: Three pens of 140mg (420mg) monthly

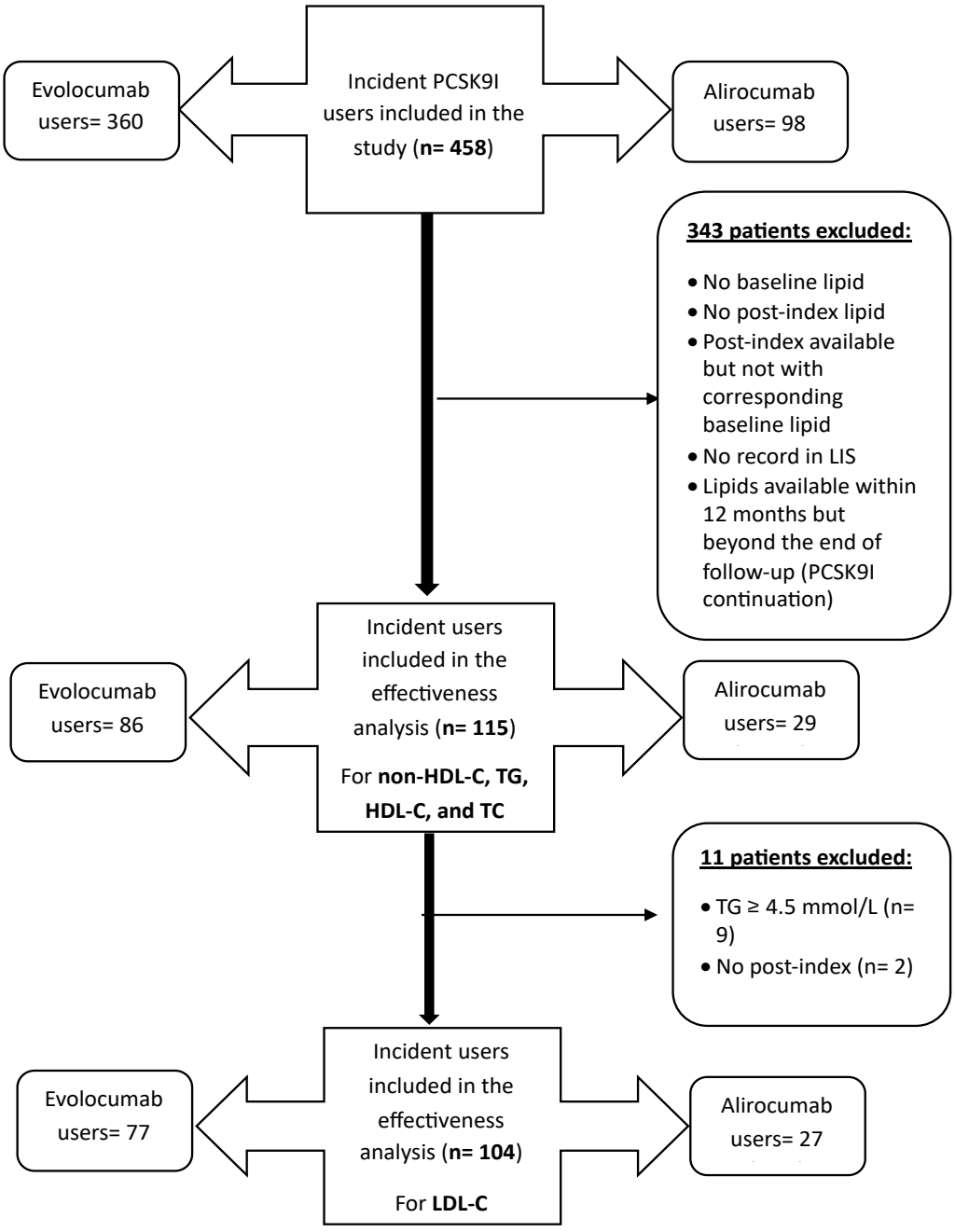

Figure 5.5 Flowchart illustarting the number of patients eligible for the effectiveness analysis of PCSK9is. **LIS**: Laboratory Information System. **PCSK9I:** Proprotein convertase subtilisin/kexin type 9 inhibitors; **Non-HDL-C:** Non-high-density lipoprotein cholesterol; **TGs:** Triglycerides; **HDL-C:** High-density lipoprotein cholesterol; **TC:** Total cholesterol; **LDL-C:** Low-density lipoprotein cholesterol

Table 5.5 Baseline characteristics of incident PCSK9i-treated patients eligible for the effectiveness analysis (n= 115)

Covariates	**Total (n= 115)**	**Evolocumab (n= 86; 74.8%)**	**Alirocumab (n= 29; 25.2%)**	**p-value (evolocumab vs. alirocumab)**
Age, years				
Mean ± SD	54.1±12.1	53.3±12.6	56.6±10.1	t-test; p= 0.69
Categories, n (%)				Fisher's exact test; **p <0.05***
<55	52 (45.2%)	42 (48.8%)	10 (34.5%)	
>=55 - <65	41 (35.6%)	28 (32.6%)	13 (44.8%)	
>=65 - <75	18 (15.6%)	12 (14%)	6 (20.7%)	
>=75	4 (3.5%)	4 (4.7%)	0	
Gender, n (%)				Pearson's Chi-squared test; p= 0.88
Male	68 (59.1%)	50 (58.1%)	18 (62.1%)	
Female	47 (40.9%)	36 (41.9%)	11 (37.9%)	
Nationality, n (%)				
Middle East	115 (100%)	86 (100%)	29 (100%)	
Others	0	0	0	
Background LLTs, n (%)				Fishers exact test; p= 0.24
No background LLT	43 (37.4%)	27 (31.4%)	16 (55.2%)	
Statin	44 (38.3%)	36 (41.9%)	8 (27.6%)	
Ezetimibe	8 (7%)	6 (7%)	2 (6.9 %)	
Fibrate	0	0	0	
Statin + ezetimibe	17 (14.8%)	14 (16.3%)	3 (10.3%)	
Statin + fibrate	3 (2.6%)	3 (3.5%)	0	
Statin Intensity, n (%)				Pearson's Chi-squared test; p= 1
HIST	40/64 (62.5%)	33/53 (62.3%)	7/11 (63.6%)	
MIST	24/64 (37.5%)	20/53 (37.7%)	4/11 (36.4%)	
Calendar year of incident PCSK9i, n (%)				Chi-squared test; **p <0.05***
2017	3 (2.6%)	3 (3.5%)	-	
2018	23 (20%)	20 (23.3%)	3 (10.3%)	
2019	18 (15.7%)	12 (14%)	6 (20.7%)	
2020	19 (16.5%)	11 (12.8%)	8 (27.6%)	
2021	14 (12.2%)	7 (8.1%)	7 (24.1%)	
2022	38 (33%)	33 (38.4%)	5 (17.2%)	

***Significant. **SD:** Standard deviation**; LLT**: Lipid-lowering therapy; **HIST:** High-intensity statin therapy; **MIST:** Moderate-intensity statin therapy; **PCSK9i:** proprotein convertase subtilisin/kexin type 9 inhibitors

The outcomes of the real-world effectiveness of PCSK9is are categorised into median changes in lipid levels following PCSK9i initiation and the attainment of lipid target goal.

5.4.2.1. Lipids changes following PCSK9i initiation

The impact of PCSK9is on lipid parameters is presented, with emphasis on the primary lipid targets, including LDL-C and non-HDL-C, as well as the secondary lipid targets, including TG, HDL-C, and TC. The findings are first reported for the overall PCSK9i cohort, followed by subgroup analyses for evolocumab and alirocumab.

5.4.2.1.1. Primary lipid targets: LDL-C and non-HDL-C

Overall, the median baseline LDL-C for new PCSK9i users (n=104) was 2.95 mmol/L (IQR: 1.96 to 3.83 mmol/L). Within 90 days (months 1-3) of PCSK9is initiation, the median LDL-C (n= 84) decreased to 1.73 mmol/L (IQR: 0.76 to 2.6 mmol/L), corresponding to an absolute reduction of 1.01 mmol/L (IQR: -2.1 to 0 mmol/L) and a relative LDL-C reduction of 41.9% (95% CI: -50.9% to -24.1%). This reduction within the first 90 days was statistically significant (p <0.001) (**Figure 5.6A, Appendix S5.2, Table S5.2.1A**). The LDL-C reduction was sustained at 42.2% (95% CI: -54.1% to -23.5%, n= 55; p< 0.001) through 91-180 days (months 4-6) but declined to 36% (95% CI: -95.5% to -13.3%, n= 4; p= 0.1) by 181-270 days (months 7-9), with no patients identified at 271-360 days (months 10-12) (**Appendix S5.2, Table S5.2.1A**).

In the subgroup analysis, the proportion of patients initiating evolocumab (74%, n= 77/104) was higher than those receiving alirocumab (26%, n= 27/104). However, no statistically significant difference in baseline LDL-C levels was observed between the two agents (p= 0.335).

Following initiation of either evolocumab or alirocumab, both agents demonstrated significant reductions in LDL-C levels. Among evolocumab users, the median baseline LDL-C (n= 77) was 2.85 mmol/L (IQR: 1.9 to 3.8 mmol/L), decreasing to 1.59 mmol/L

(IQR: 0.6 to 2.6 mmol/L; n= 60) within 90 days (months 1-3) of treatment. This represented an absolute reduction of 0.98 mmol/L (IQR: -2.12 to -0.04 mmol/L) and a relative reduction of 45.67% (95%CI: -53.5% to -25.4%), which was statistically significantly (p <0.001) (**Figure 5.6B**, **Appendix S5.2, Table S5.2.1B**). During 91-180 days (months 4-6), the relative reduction in LDL-C was 42.27% (95% CI: -54.87% to 1.29%, n= 38; p= 0.045), while a reduction of 35.98% (95% CI: -95.49% to -13.3%, n= 4; p= 0.1) was observed during 181-270 days (months 7-9) (**Appendix S5.2, Table S5.2.1B**).

For alirocumab, the median baseline LDL-C (n= 27) was 3.39 mmol/L (IQR: 2.25 to 4.11 mmol/L). At 90 days (months 1-3), the median LDL-C (n= 24) decreased to 1.87 mmol/L (IQR: 1.28 to 2.68 mmol/L; n= 24), representing in an absolute reduction of 1.16 mmol/L (IQR: -1.98 to 0.075 mmol/L) and a relative reduction of 37.09% (95% CI: -50.8% to -7.69%). This reduction was statistically significantly (p =0.004) (**Figure 5.6C**, **Appendix S5.2, Table S5.2.1C**). During 90-180 days (months 4-6), the relative LDL-C reduction was 42.35% (95% CI: -74.05% to -20.68%; n= 17; p < 0.001), with no patients identified in the following periods (**Appendix S5.2, Table S5.2.1C**).

Although the reduction was more pronounced among patients receiving evolocumab, the comparison between the two agents did not reveal any statistically significant differences in LDL-C reduction at months 1-3 (p= 0.247) or months 4-6 (p= 0.96).

The key finding for LDL-C was that PCSK9is significantly reduced LDL-C levels by 41.9% (95% CI: -50.9% to -24.1%) within 90 days (months 1-3). Although evolocumab was associated with greater percentage reduction than alirocumab (45.7% vs. 37.1%), this difference was not statistically significant.

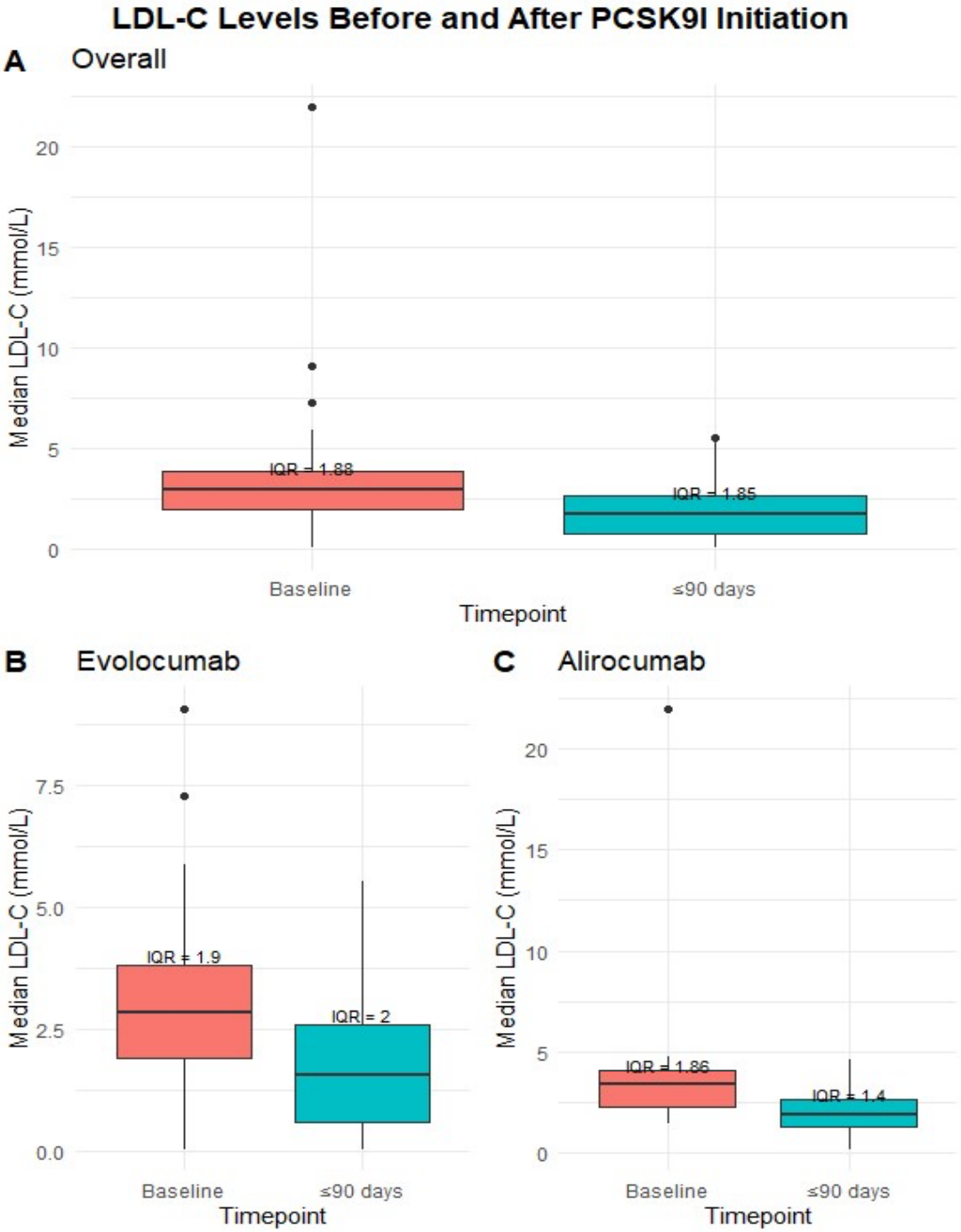

Figure 5.6 Reduction in LDL-C following PCSK9I initiation within 90 days (months 1-3); **A.** Overall (n= 84), **B.** Evolocumab (n= 60), **C.** Alirocumab (n= 24). Values are summarised as median (IQR), mmol/L. **IQR:** Interquartile range; **LDL-C:** Low-density lipoprotein cholesterol; **PCSK9I**: Proprotein convertase subtilisin/kexin type 9 inhibitor

A significant reduction in non-HDL-C levels was also observed. Overall, the median baseline non-HDL-C (n= 115) was 3.94 mmol/L (IQR: 2.85 to 5.16 mmol/L). At 90 days (months 1-3) after initiating PCSK9is, the median non-HDL-C (n= 93) had decreased to 2.38 mmol/L (IQR: 1.52 to 3.27 mmol/L), representing an absolute reduction of 1.36 mmol/L (IQR: -2.46 to -0.3 mmol/L) and a relative reduction of 38.08% (95% CI: -46.53% to -23.88%). This reduction within the first 90 days was statistically significantly (p <0.001) (**Figure 5.7A**, **Appendix S5.2, Table S5.2.2A**). During 91-180 days (months 4-6), the non-HDL-C reduction lessened to 32.99% (95% CI: -45% to -19.03%; n= 63; p < 0.001) and to 36.46% (95% CI: -87.7% to -10.5%; n= 4; p= 0.1) during 181-270 days (months 7-9) (**Appendix S5.2, Table S5.2.2A**).

In the subgroup analysis, the proportion of patients initiating evolocumab (74.8%, n= 86/115) was higher than those receiving alirocumab (25.2%, n= 29/115). However, no statistically significant difference in baseline non-HDL-C levels was observed between the two agents (p= 0.222).

Following initiation of either evolocumab or alirocumab, both agents demonstrated significant reductions in non-HDL-C levels. Among evolocumab users, the median baseline non-HDL-C (n= 86) was 3.72 mmol/L (IQR: 2.77 to 5.14 mmol/L), which decreased to 2.25 mmol/L (IQR: 1.47 to 3.11 mmol/L, n= 68) at 90 days (months 1-3), reflecting an absolute reduction of 1.3 mmol/L (IQR: -2.4 to -0.32 mmol/L) and a relative reduction of 40.7% (95% CI: -50% to -26.05%). This reduction was statistically significantly (p <0.001) (**Figure 5.7B**, **Appendix S5.2, Table S5.2.2B**). During 91-180 days (months 4-6), the relative non-HDL-C reduction was 36.5% (95% CI: -45.6% to -14.98%; n= 44; p= 0.005) and was 36.5% (95% CI: -87.7% to -10.5%; n= 4; p= 0.1) during 181-270 days (months 7-9) (**Appendix S5.2, Table S5.2.2B**).

For alirocumab, the median baseline non-HDL-C (n= 29) was 4.37 mmol/L (IQR: 3.53 to 5.11 mmol/L). Within 90 days (months 1-3), the non-HDL-C level decreased to 2.78 mmol/L (IQR: 1.91 to 3.54 mmol/L; n= 25), representing an absolute reduction of 1.37 mmol/L (IQR: -2.46 to -0.3 mmol/L) and a relative reduction of 30.13% (95%CI: -41.92% to -14.73%). This reduction was statistically significantly (p <0.001) (**Figure 5.7C**, **Appendix S5.2.2, Table S5.2.2C**). During 91-180 days (months 4-6), the relative reduction was 32.59% (95% CI: -52.12% to -13.3%; n= 19; p= 0.001) (**Appendix S5.2, Table S5.2.2C**).

Similar to the findings for LDL-C, the reduction in non-HDL-C was more pronounced among patients receiving evolocumab. However, the comparison between the two agents did not reveal any statistically significant differences in non-HDL-C at months 1–3 (p= 0.23) or months 4–6 (p= 0.96).

The key finding for non-HDL-C was that that PCSK9is significantly reduced non-HDL-C levels by 38.08% (95% CI: -46.53% to -23.88%) within 90 days (months 1-3). Although evolocumab resulted in a greater percentage reduction than alirocumab (40.7% vs. 30.1%), this difference was not statistically significant.

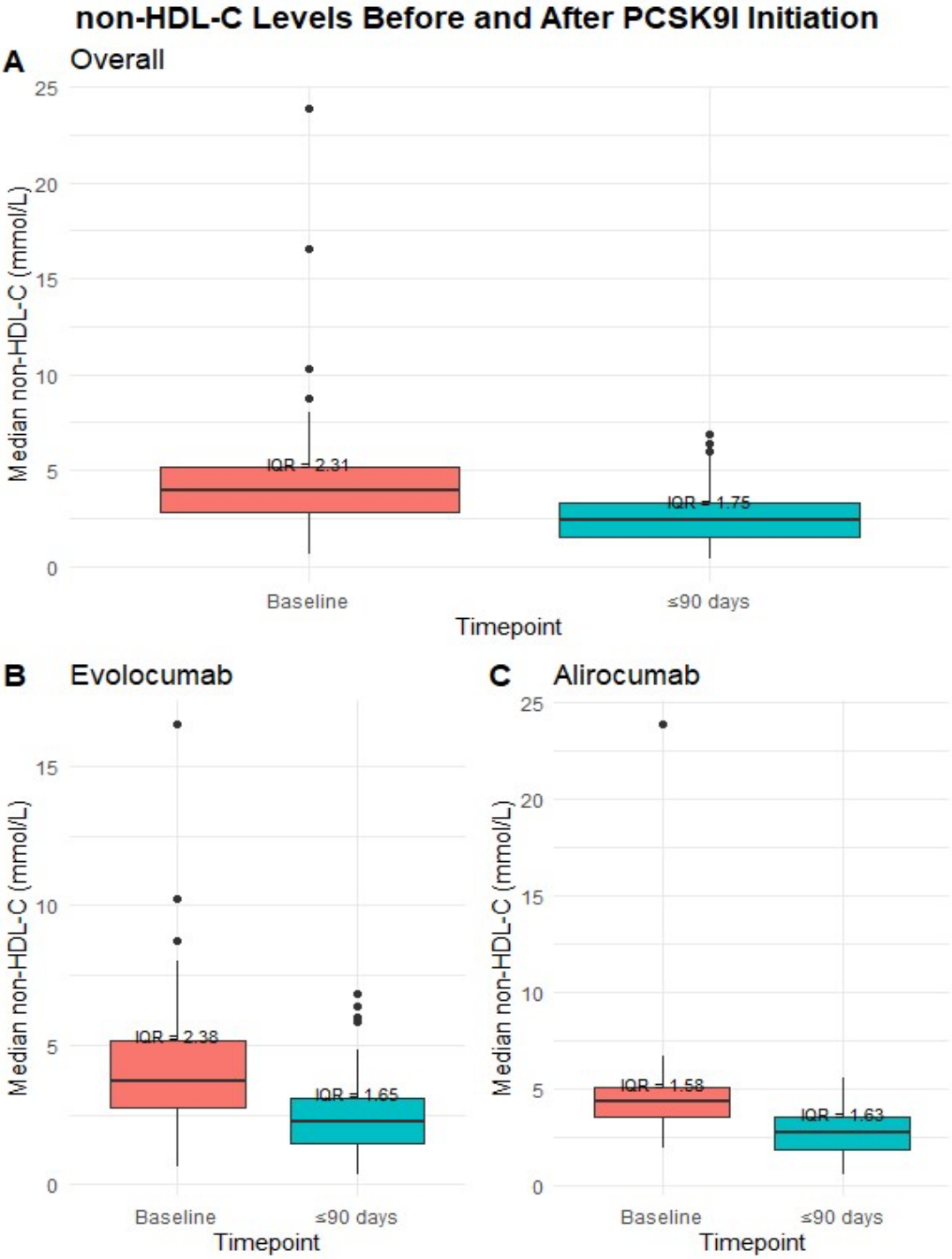

Figure 5.7 Reduction in non-HDL-C following PCSK9I initiation (n= 93) within 90 days (months 1-3); **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). Values are summarised as median (IQR), mmol/L. **IQR**: Interquartile range; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **PCSK9I**: Proprotein convertase subtilisin/kexin type 9 inhibitor

5.4.2.1.2. Secondary treatment targets: TG, HDL-C, and TC

Regarding the effectiveness of PCSK9is on TG levels, the findings indicate a reduction in median baseline TG levels from 1.82 mmol/L (IQR: 1.31 to 2.82 mmol/L; n= 115) to 1.75 mmol/L (IQR: 1.11 to 2.43 mmol/L; n= 93) within 90 days (months 1-3). This corresponds to an absolute reduction of 0.3 mmol/L (IQR: -0.97 to 0.08 mmol/L) and a relative reduction of 14.78% (95% CI: -26.1% to -7.24%). Although the reduction in TG was smaller compared to the primary lipid targets, it remained statistically significant (p <0.001) (**Figure 5.8A, Appendix S5.2, Table S5.2.3A**). During 91-180 days (months 4-6), the relative reduction in TG was 16.23% (95% CI: -31.3% to 1.68%; n= 63), and during 181-270 days (months 7-9), it reached 37.5% (95% CI: -63.19 to -3.55; n= 4) (**Appendix S5.2, Table S5.2.3A**).

In the subgroup analysis, the proportion of patients initiating evolocumab (74.8%, n= 86/115) was higher than those receiving alirocumab (25.2%, n= 29/115). However, no statistically significant difference in baseline TG levels was observed between the two agents (p= 0.347).

Following initiation of either evolocumab or alirocumab, both agents demonstrated significant reductions in non-HDL-C levels. Among evolocumab users, the median baseline TG (n= 86) was 1.76 mmol/L (IQR: 1.3 to 2.63 mmol/L), which decreased to 1.51 mmol/L (IQR: 1.0 to 2.43 mmol/L, n= 68) at 90 days (months 1-3), reflecting an absolute reduction of 0.28 mmol/L (IQR: -1.16 to 0.01 mmol/L) and a relative reduction of 17.3% (95% CI: -28.8% to -7.8%). This reduction was statistically significantly (p <0.001) (**Figure 5.8B, Appendix S5.2, Table S5.2.3B**). During 91-180 days (months 4-6), the relative TG reduction was 13.65% (95% CI: -31.3% to 4.3%; n= 44) and was 37.55% (95% CI: -63.19% to -3.5%; n= 4) within 181-270 days (months 7-9) (**Appendix S5.2, Table S5.2.3B**).

For alirocumab, the median baseline TG (n= 29) was 2.13 mmol/L (IQR: 1.38 to 3.16 mmol/L). By 90 days (months 1-3), it slightly decreased to 2.03 mmol/L (IQR: 1.49 to 2.34 mmol/L; n= 25), representing an absolute reduction of 0.3 mmol/L (IQR: -0.81 to 0 mmol/L) and a relative reduction of 12.14% (95% CI: -23.6% to -0.87%). This reduction was statistically significantly (p= 0.012) (**Figure 5.8C, Appendix S5.2, Table S5.2.3C**). During 91-180 days (months 4-6), the relative reduction was 16.4% (95% CI: -40.5% to 23%; n= 19) (**Appendix S5.2, Table S5.2.3C**).

Similar to the findings for the primary lipid parameters, the reduction in TG was higher among patients receiving evolocumab. However, the comparison between the two agents did not reveal any statistically significant differences in TG reduction at months 1-3 (p= 0.098).

The key finding for TG was that PCSK9is significantly reduced TG levels by 14.78% (95% CI: -26.1% to -7.24%) within 90 days (months 1-3). Although evolocumab resulted in a greater percentage reduction than alirocumab (17.3% vs. 12.1%), this difference was not statistically significant.

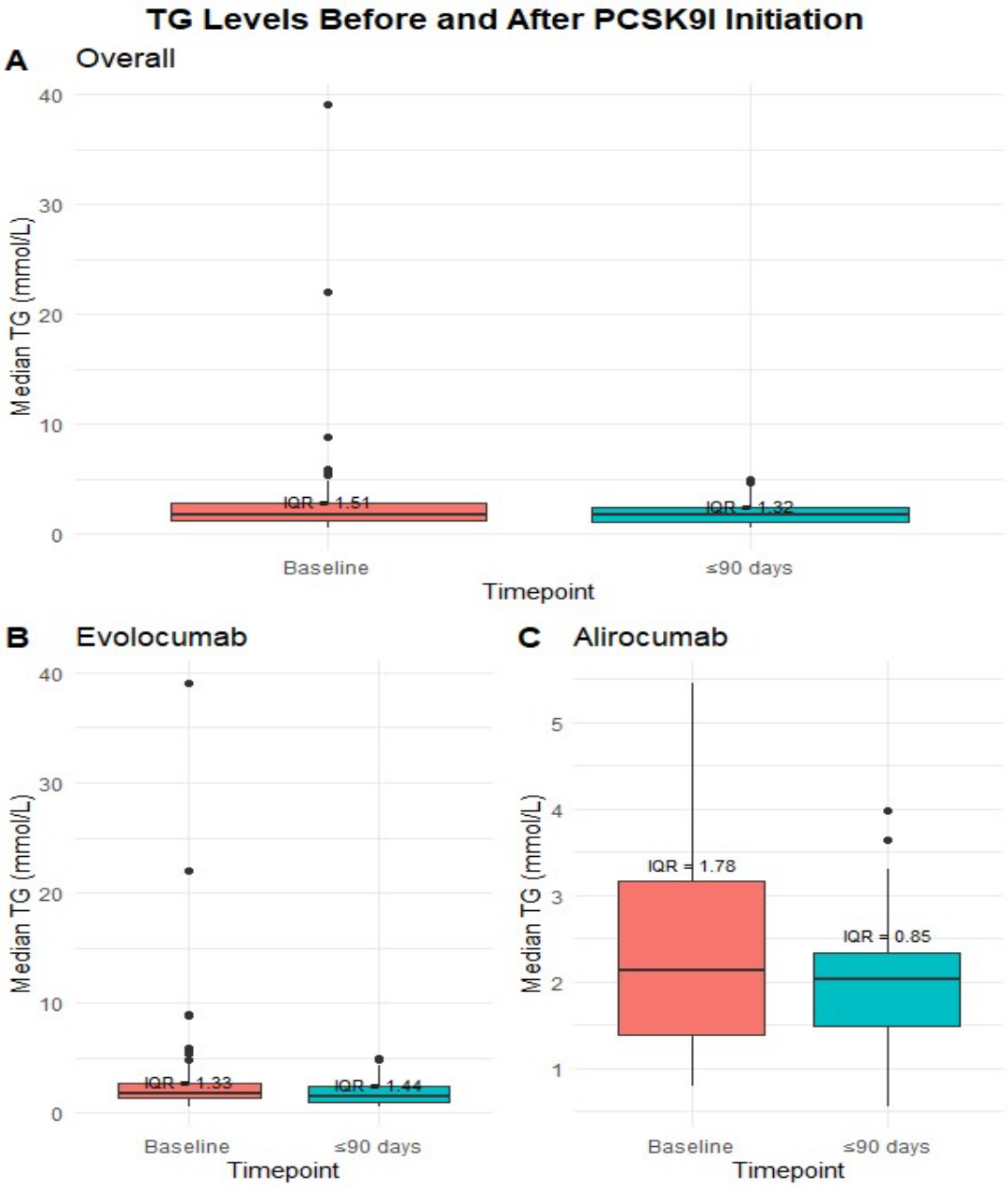

Figure 5.8 Reduction in TG following PCSK9I initiation (n= 93) within 90 days (months 1-3); **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). Values are summarised as median (IQR), mmol/L. **IQR**: Interquartile range; **TG**: Triglycerides; **PCSK9I**: Proprotein convertase subtilisin-kexin type 9 inhibitor

For the HDL-C parameter, where an increase is clinically desirable, the overall results indicated no meaningful change following the initiation of PCSK9is. The median baseline HDL-C was 1.11 mmol/L (IQR: 0.94 to 1.28 mmol/L; n= 115), which was comparable to the post-index value of 1.1 mmol/L (IQR: 0.9 to 1.38 mmol/L; n= 93), during the first 90 days (months 1-3), with no statistically significant difference observed (p= 0.792) (**Figure 5.9A, Appendix S5.2, Table S5.2.4A**). During 91-180 days (months 4-6), the median HDL-C was 1.09 mmol/L (IQR: 0.96 to 1.34 mmol/L; n=63) and during 181-270 days (months 7-9), the median HDL-C was 1.08 mmol/L (IQR: 1.02 to 1.17 mmol/L; n= 4) (**Appendix S5.2, Table S5.2.4A**).

In the subgroup analysis, although the proportion of patients initiating evolocumab (74.8%, n= 86/115) was greater than those receiving alirocumab (25.2%, n= 29/115). Similar to the previously discussed lipid parameters, no statistically significant difference in baseline HDL-C levels was observed between the two agents (p= 0.115).

Unlike other lipid parameters, neither evolocumab (p= 0.463) nor alirocumab (p= 0.368) resulted in a significant change in HDL-C levels during 90 days (months 1-3) (**Figure 5.9B-C, Appendix S5.2, Table S5.2.4B-C**). Consistent with the findings for the other lipid parameters, the comparison between the two agents also showed no statistically significant difference in HDL-C change at months 1-3 (p= 0.655).

The key finding for HDL-C was that median levels remained comparable before and after PCSK9i initiation, with no significant change observed for either agent.

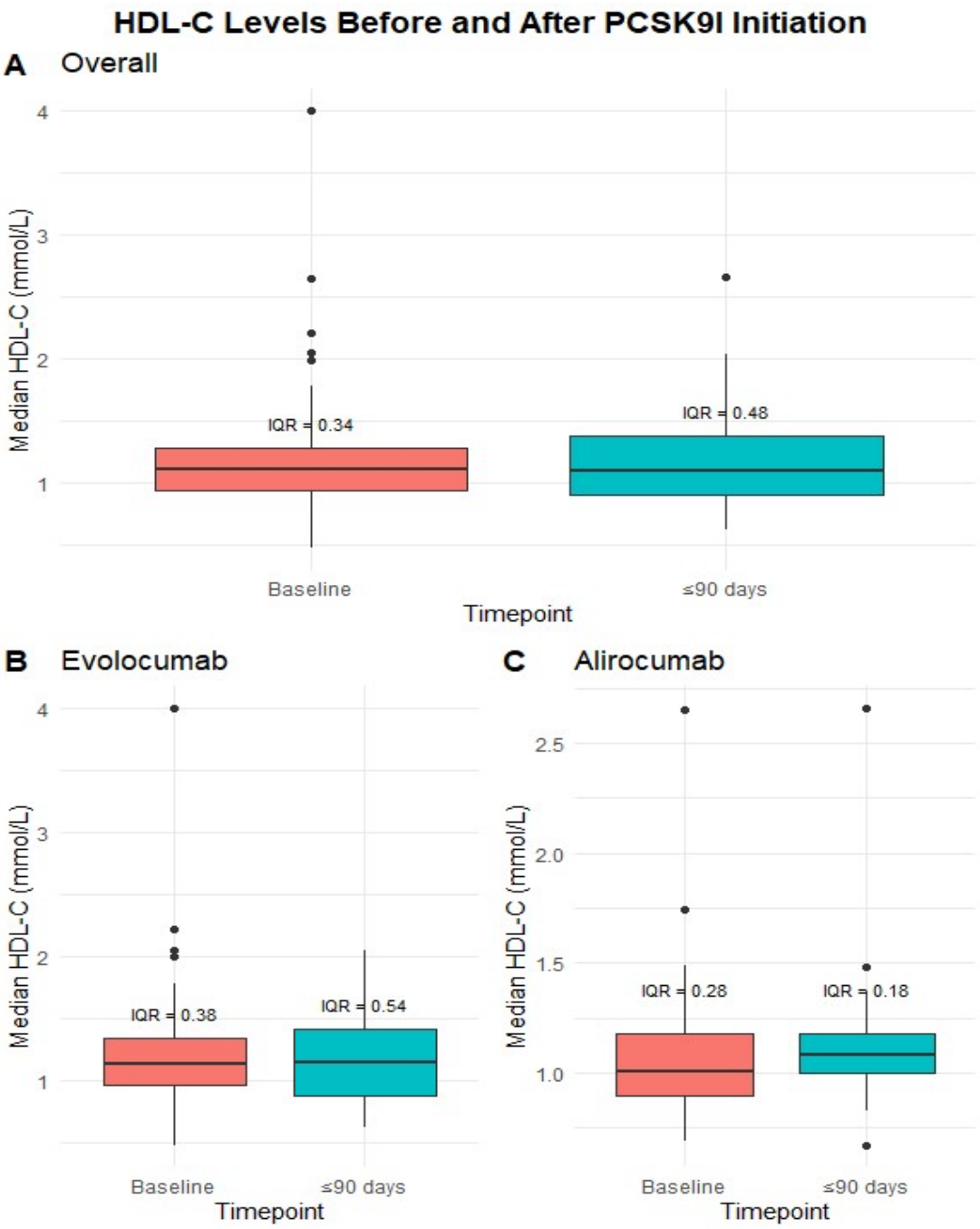

Figure 5.9 Increase in HDL-C following PCSK9I initiation (n=93) within 90 days (months 1-3); **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). Values are summarised as median (IQR), mmol/L. **IQR**: Interquartile range; **HDL-C**: High-density lipoprotein cholesterol; **PCSK9I**: Proprotein convertase subtilisin-kexin type 9 inhibitor

The last lipid parameter included in the analysis was TC in which the findings indicate a reduction in median baseline TC levels from 5 mmol/L (IQR: 3.98 to 6.31 mmol/L; n= 115) to 3.5 mmol/L (IQR: 2.76 to 4.77 mmol/L: n= 93) within 90 days (months 1-3). This corresponds to an absolute reduction 1.46 mmol/L (IQR: -2.54 to -0.32 mmol/L) and a relative reduction of 31.06% (95% CI: -35.7% to -14.87%). This reduction was statistically significant (p <0.001) (**Figure 5.10A, Appendix S5.2, Table S5.2.5A**). Within 91-180 days (months 4-6), the relative reduction in TC was 26.13% (95% CI: -33.1% to -15.07%; n= 63), and during 181-270 days (months 7-9), it reached 25.6% (95% CI: -68.02% to -3.5%; n= 4) (**Appendix S5.2, S5.2.5A**).

In the subgroup analysis, the proportion of patients initiating evolocumab (74.8%, n= 86/115) was greater than those receiving alirocumab (25.2%, n= 29/115). Similar to other lipid targets, the comparison between the two agents did not result in a statistically significant difference in baseline TC levels (p= 0.295).

Following initiation of either evolocumab or alirocumab, both agents demonstrated significant reductions in TC levels. Among evolocumab users, the median baseline TC (n= 86) was 4.82 mmol/L (IQR: 3.96 to 6.31 mmol/L), which decreased to 3.42 mmol/L (IQR: 2.63 to 4.59 mmol/L, n= 68) at 90 days (months 1-3), reflecting an absolute reduction of 1.43 mmol/L (IQR: -2.56 to -0.36 mmol/L) and a relative reduction of 32.57% (95% CI: -39.51 to -18.49%). This reduction was statistically significantly (p <0.001) (**Figure 5.10B, Appendix S5.2, Table S5.2.5B**). During 91-180 days (months 4-6), the relative TC reduction was 25.3% (95% CI: -35.3% to -8.5%; n= 44) and was 25.6% (95% CI: -68.02 to -3.5; n= 4) during 181-270 days (months 7-9) (**Appendix S5.2, Table 5.2.5B**).

For alirocumab, the median baseline TC (n= 29) was 5.25 mmol/L (IQR: 4.58 to 6.4 mmol/L). Within 90 days (months 1-3), it decreased to 4.05 mmol/L (IQR: 2.94 to 5.28 mmol/L; n= 25), representing an absolute reduction of 1.55 mmol/L (IQR: -2.29 to -0.28 mmol/L) and a relative reduction of 23.3% (95% CI: -34.4% to -8.95%). This reduction was statistically significantly (p= 0.001) (**Figure 5.10C, Appendix S5.2, Table S5.2.5C**). During 91-180 days (months 4-6), the relative reduction was 29.03% (95% CI: -42.5% to -12.7%; n= 19).

Similar to the findings for the primary lipid parameters and TG, the reduction in TC was greater among patients receiving evolocumab (p <0.001) compared with those receiving alirocumab (p= 0.001) at months 1-3. However, the comparison between the two agents did not show any statistically significant difference in TC reduction at months 1-3 (p= 0.287).

The key finding for TC was that PCSK9is significantly reduced TC levels 31.06% (95% CI: -35.7% to -14.87%) within 90 days (months 1-3). Although evolocumab was associated with greater percentage reduction than alirocumab (32.6% vs. 23.3%), this difference was not statistically significant.

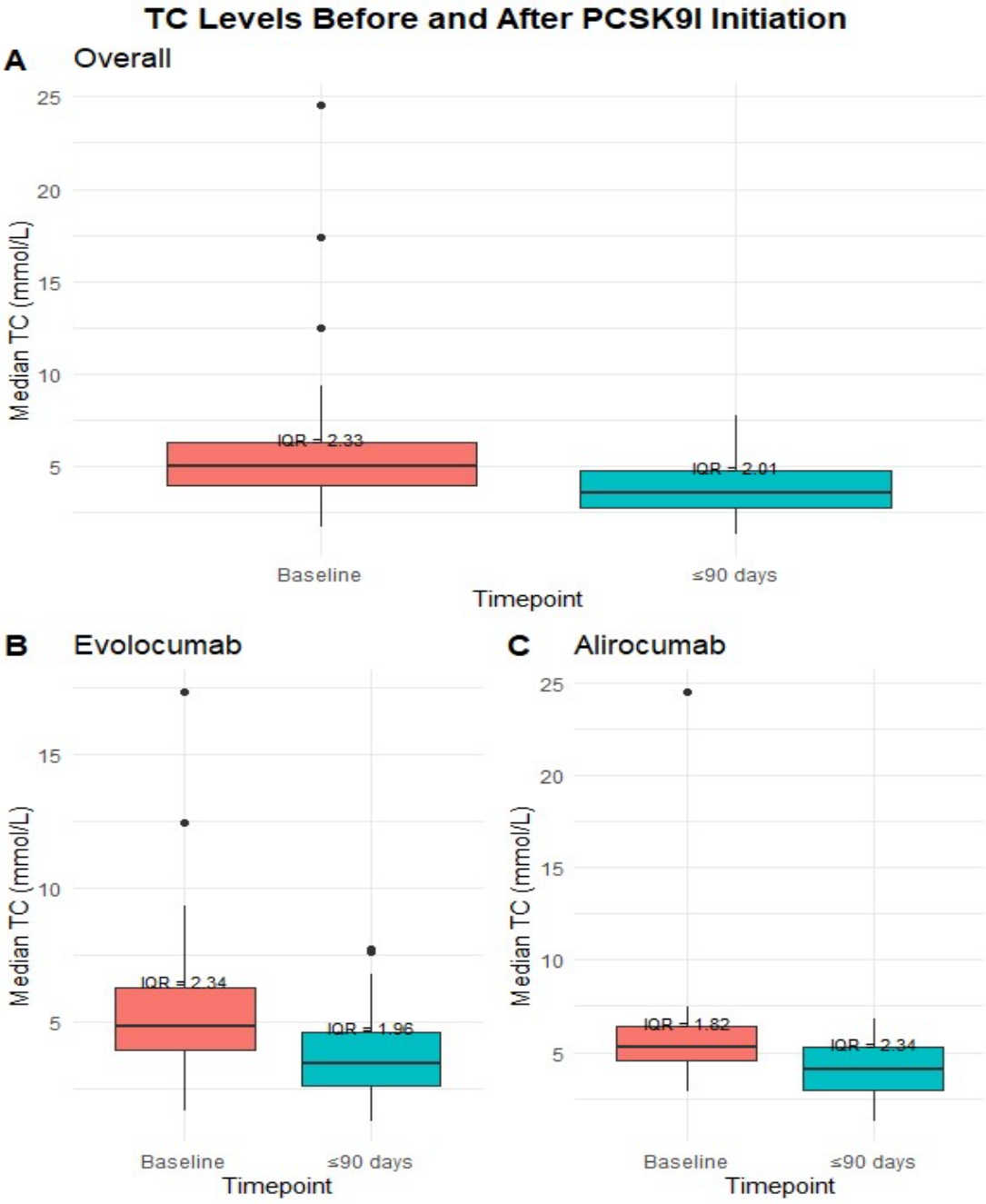

Figure 5.10 Reduction in TC following PCSK9I initiation (n= 93) within 90 days (months 1-3); **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). Values are summarised as median (IQR), mmol/L. IQR: Interquartile range; TC: Total Cholesterol; **PCSK9I**: Proprotein convertase subtilisin-kexin type 9 inhibitor

5.4.2.2. Target goal attainment following PCSK9i initiation

The findings for target goal achievement are presented by starting with primary lipid targets, followed by secondary lipid targets. Results are displayed for overall PCK9is users and further by individual agents (evolocumab and alirocumab).

5.4.2.2.1. Primary treatment targets: LDL-C and non-HDL-C

For the primary threshold of LDL-C <1.4 mmol/L, 8.7% of the overall cohort (n= 9/104) were at target at baseline. Following PCSK9i initiation, the proportion of patients achieving this target increased to 42.9% (n= 36/84) at 90 days (months 1-3) (**Figure 5.11A**, **Appendix S5.3, Table S5.3.1A**). The LDL-C target achievement was 43.6% (n= 24/55) at 91-180 days (months 4-6) and 50% (n= 2/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.1A**).

The subgroup analysis indicated that the proportion of patients achieved LDL-C target before evolocumab initiation was 11.7% (n= 9/77) compared to none had achieved the target before alirocumab initiation (n= 27). Within 90 days (months 1-3) of treatment, 46.7% (n= 28/60) of evolocumab users and 33.3% (n= 8/24) of alirocumab users attained the target. (**Figure 5.11B-C, Appendix S5.3, Table S5.3.1B-C**). During 91-180 days (months 4-6), the target was met by 44.7% (n= 17/38) of evolocumab users and 41.2% (n= 7/17) of alirocumab users (**Appendix S5.3, Table S5.3.1B-C**). It should be noted that the proportion reported for the overall cohort during months 7-9 reflects only evolocumab users, as no alirocumab users had available data during this period.

The sensitivity analysis showed that applying a more stringent LDL-C threshold of <1.0 mmol/L resulted in a lower proportion of patients achieving the target level. At baseline, only 6.7% (n= 7/104) of the overall cohort were at target. Following PCSK9i initiation, the proportion of patients achieving this target increased to 31% (n= 26/84) at 90 days (months 1-3) (**Figure 5.11A, Appendix S5.3, Table 5.3.1A**), 27.3% (n= 15/55) at 91-180 days (months 4-6), and 25% (n= 1/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.1A**). The subgroup analysis showed that 9.1% (n= 7/77)

of patients were at target before evolocumab initiation, while none of had achieved the target before alirocumab initiation (n=27). Within 90 days (months 1-3) of treatment, 36.7% (n= 22/60) of evolocumab users and 16.7% (n= 4/24) of alirocumab users attained the target (**Figure 5.11B-C, Appendix S5.3, Table S5.3.1B-C**). At 91-180 days (months 4-6), the target was met by 28.9% (n= 11/38) of evolocumab users and 23.5% (n= 4/17) of alirocumab users (**Appendix S5.3, Table S5.3.1B-C**).

In contrast, the sensitivity analysis using a more lenient threshold of LDL-C <1.8mmol/L resulted in a higher proportion of patients achieving the target. At baseline, 22.1% (n= 23/104) of the overall cohort were at target. Following PCSK9i initiation, the proportion of patients achieving this target increased to 52.4% (n= 44/84) at 90 days (months 1-3) (**Figure 5.11A, Appendix S5.3, Table S5.3.1A**), 56.4% (n= 31/55) at 91-180 days (months 4-6), and 100% (n= 4/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.1A**). The subgroup analysis showed that 22.1% (n= 17/77) of patients achieved target before evolocumab initiation, while 22.2% (n= 6/27) had achieved the target before alirocumab initiation. Within 90 days (months 1-3) of treatment, 53.3% (n= 32/60) of evolocumab users and 50% (n= 12/24) of alirocumab users attained the target (**Figure 5.11B-C, Appendix S5.3, Table S5.3.1B-C**). At 91-180 days (months 4-6), the target was met by 52.6% (n= 20/38) of evolocumab users and 64.7% (n= 11/17) of alirocumab users (**Appendix S5.3, Table S5.3.1B-C**).

The key finding for LDL-C target achievement was that PCSK9is improved attainment of the <1.4 mmol/L goal within 90 days (months 1-3); however, achievement remained suboptimal, with only 42.9% of patients reaching the target (n= 36/84). Sensitivity analyses demonstrated that these findings varied according to the LDL-C thresholds applied (<1.0 and <1.8 mmol/L), yet target attainment remained suboptimal across all thresholds.

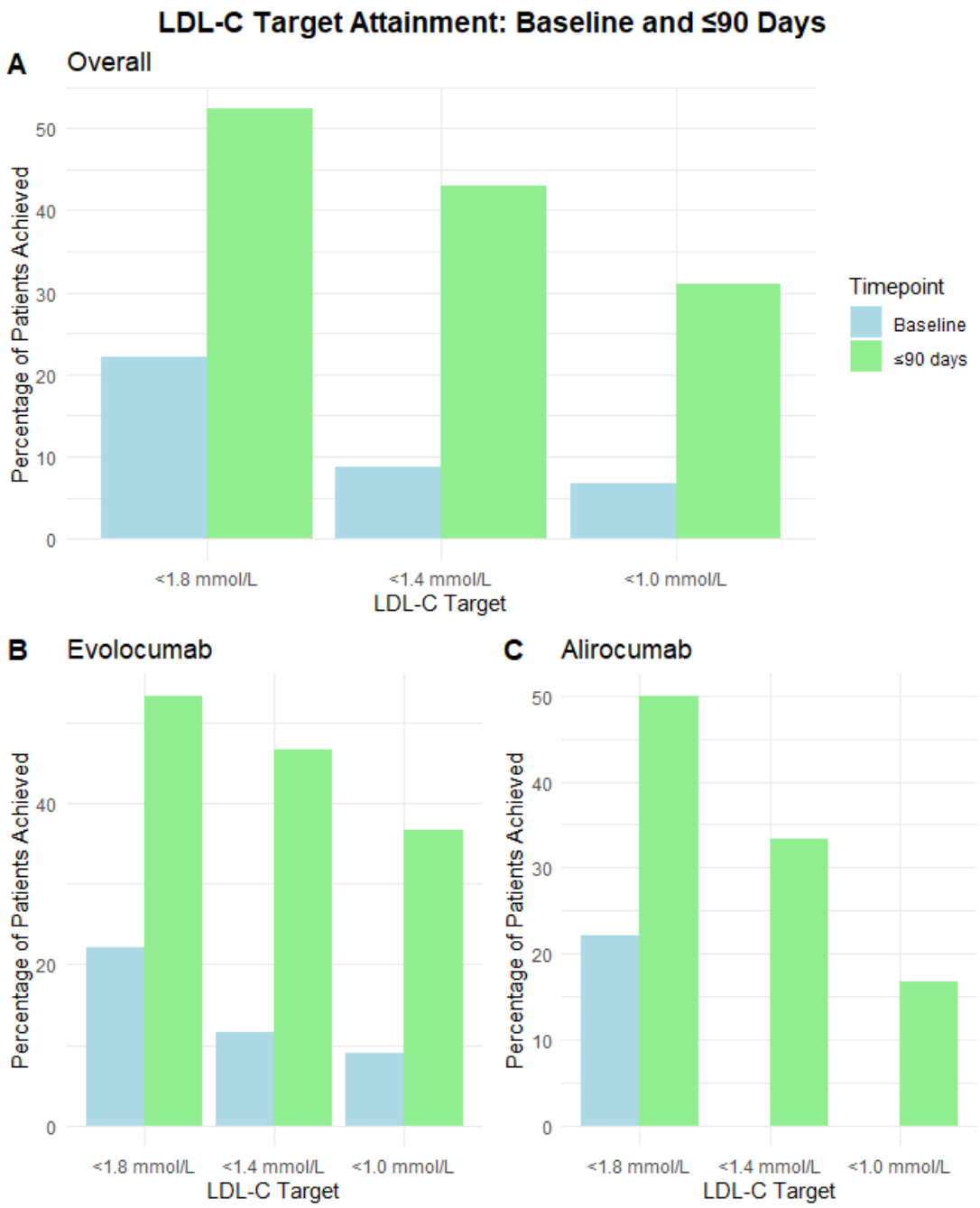

Figure 5.11 Percentage of patients achieving LDL-C target goals within 90 days (months 1-3) at different LDL-C thresholds (1.8, 1.4 and 1.0 mmol/L): **A.** Overall (n= 84)**, B.** Evolocumab (n= 60)**, C.** Alirocumab (n= 24). **LDL-C**: Low-density lipoprotein cholesterol

For the primary threshold of non-HDL-C <2.2 mmol/L, 13.9% of the overall cohort (n= 16/115) were at target at baseline. Following PCSK9i initiation, the proportion of patients achieving this target increased to 45.2% (n= 42/93) at 90 days (months 1-3) (**Figure 5.12A, Appendix S5.3, Table S5.3.2A**), 39.7% (n= 25/63) at months 4-6, and 100% (n= 4/4) at months 7-9 (**Appendix S5.3, Table S5.3.2A**).

The subgroup analysis indicated that the proportion of patients achieved LDL-C target before evolocumab initiation was 16.3% (n= 14/86), while 6.9% (n= 2/29) had achieved the target before alirocumab initiation. Within 90 days (months 1-3) of treatment, 48.5% (n= 33/68) of evolocumab users and 36% (n= 9/25) of alirocumab users attained the target (**Figure 5.12B-C, Appendix S5.3, Table S5.3.2B-C**). During 91-180 days (months 4-6), the target was met by 40.9%% (n= 18/44) of evolocumab users and 36.8% (n= 7/19) of alirocumab users. As no alirocumab users had available data at 270 days, the proportion of achievement at this period reflects only evolocumab users (**Appendix S5.3, Table S5.3.2B-C**).

The sensitivity analysis indicated that using a more stringent threshold of non-HDL-C <1.8 mmol/L resulted in a lower proportion of patients achieving the target. At baseline, only 6.1% (n= 7/115) of the overall cohort were at target. Following PCSK9i initiation, the proportion of patients achieving this target increased to 29% (n= 27/93) at 90 days (months 1-3) (**Figure 5.12A, Appendix S5.3, Table S5.3.2A**), 22.2% (n= 14/63) at 91-180 days (months 4-6), and 50% (n= 2/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.2A**). The subgroup analysis showed that 8.1% (n= 7/86) of evolocumab users were at target at baseline, while none of the alirocumab users (n= 29) had achieved the target. Within 90 days (months 1-3) of treatment, 32.4% (n= 22/68) of evolocumab users and 20% (n= 5/25) of alirocumab users attained the target (**Figure 5.12B-C, Appendix S5.3, Table S5.3.2B-C**). During 91-180 days (months 4-6), the target was met by 22.7% (n= 10/44) of evolocumab users and 21.1% (n= 4/19) of alirocumab users (**Appendix S5.3, Table S5.3.2B-C**).

In contrast, the sensitivity analysis indicated that using a more lenient threshold of non-HDL-C <2.6 mmol/L resulted in a higher proportion of patients achieving the target. At baseline, 18.3% (n= 21/115) of the overall cohort were at target. Following PCSK9i initiation, the proportion of patients achieving this target increased to 53.8% (n= 50/93) at 90 days (months 1-3) (**Figure 5.12A, Appendix S5.3, Table S5.3.2A**), 50.8% (n= 32/63) at 91-180 days (months 4-6), and 100% (n= 4/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.2A**).

The subgroup analysis showed that 19.8% (n= 17/86) of evolocumab users were at target at baseline, while 13.8% (n= 4/27) of the alirocumab users had achieved the target. Within 90 days (months 1-3) of treatment, 58.8% (n= 40/68) of evolocumab users and 40% (n= 10/25) of alirocumab users attained the target (**Figure 5.12B-C, Appendix S5.3, Table S5.3.2B-C**). During 91-180 days (months 4-6), the target was met by 52.3% (n= 23/44) of evolocumab users and 47.4% (n= 9/19) of alirocumab users (**Appendix S5.3, Table S5.3.2B-C**).

The key finding for non-HDL-C target achievement was that PCSK9is improved attainment of the <2.2 mmol/L goal within 90 days (months 1-3).; however, achievement remained suboptimal, with only 45.2% of patients reaching the target (n= 42/93). Sensitivity analyses demonstrated that these findings varied according to the non-HDL-C thresholds applied (<1.8 and <2.6 mmol/L), yet target attainment remained suboptimal across all thresholds.

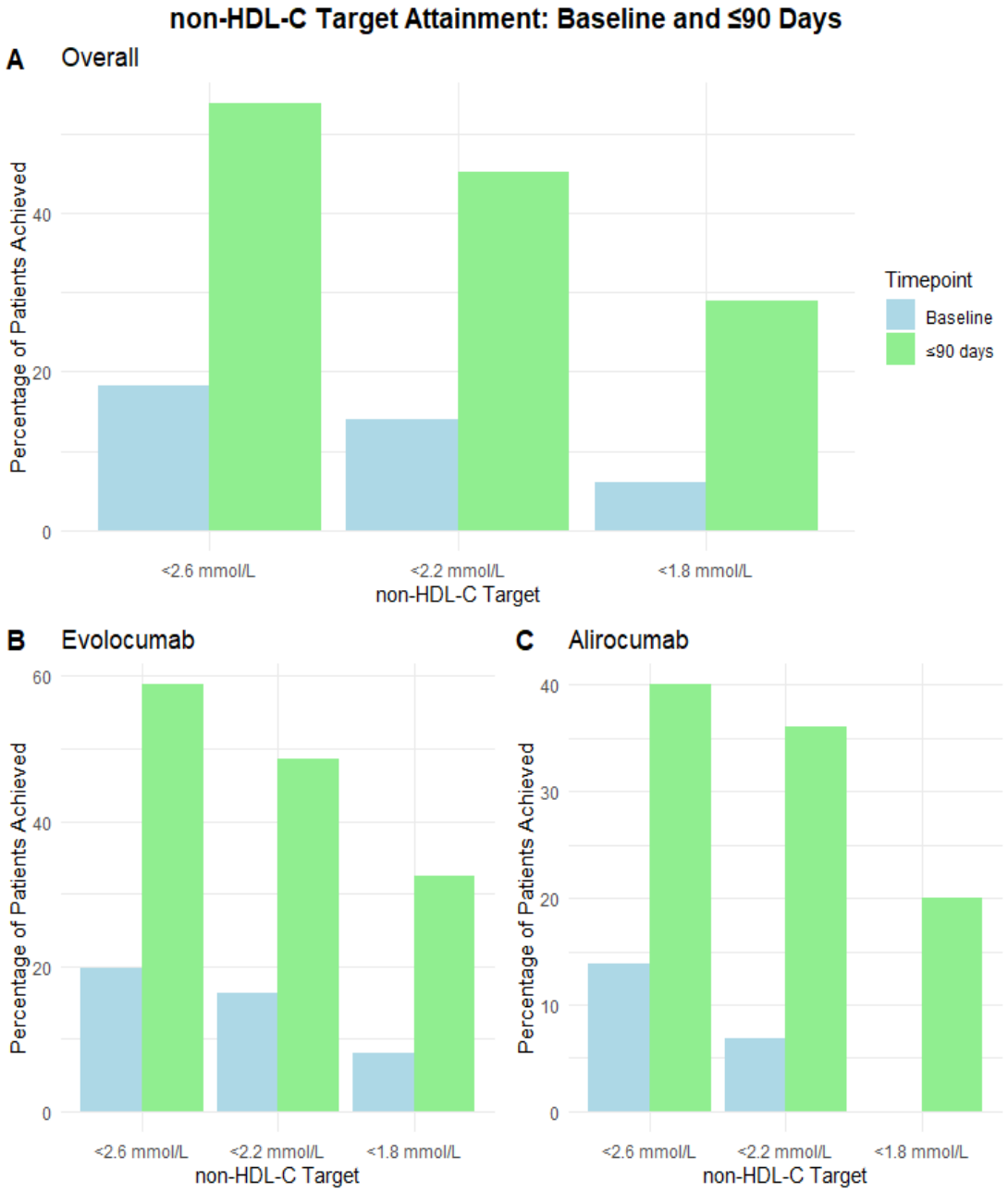

Figure 5.12 Percentage of patients achieving non-HDL-C target goals within 90 days (months 1-3) at different non-HDL-C thresholds (2.6, 2.2 and 1.8 mmol/L): **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). Non-HDL-C: Non-high-density lipoprotein cholesterol

5.4.2.2.2. Secondary treatment targets: TG, HDL-C, and TC

The TG, HDL-C, and TC parameters have a single threshold to achieve, regardless of CV risk category, as supported by the evidence (20, 23).

For TG, where the desirable target is <1.7 mmol/L, 43.5% (n= 50/115) of the overall cohort were at target at baseline. Following PCSK9i initiation, the proportion of patients achieving this target increased to 48.4% (n= 45/93) at 90 days (months 1-3) (**Figure 5.13A, Appendix S5.3, Table S5.3.3A**), 54% (n= 34/63) at 91-180 days (months 4-6), and 100% (n= 4/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.3A**).

The subgroup analysis indicated that the proportion of patients achieved TG target before evolocumab initiation was 47.7% (n= 41/86), while 31% (n= 9/29) of the had achieved the target before alirocumab initiation. Within 90 days (months 1-3) of treatment, 52.9% (n= 36/68) of evolocumab users and 36% (n= 9/25) of alirocumab users attained the target (**Figure 5.13B-C, Appendix S5.3, Table S5.3.3B-C**). At 91-180 days (months 4-6), the target was met by 59.1% (n= 26/44) of evolocumab users and 42.1% (n= 8/19) of alirocumab users (**Appendix S5.3, Table S5.3.3B-C**). Notably, the proportion reported for the overall cohort during months 7-9 reflects only evolocumab users, as no alirocumab users had available data during this period.

The key finding for TG target achievement was that PCSK9is improved attainment of the <1.7 mmol/L goal within 90 days (months 1-3).; however, achievement remained suboptimal, with only 48.4% of patients reaching the target (n= 45/93).

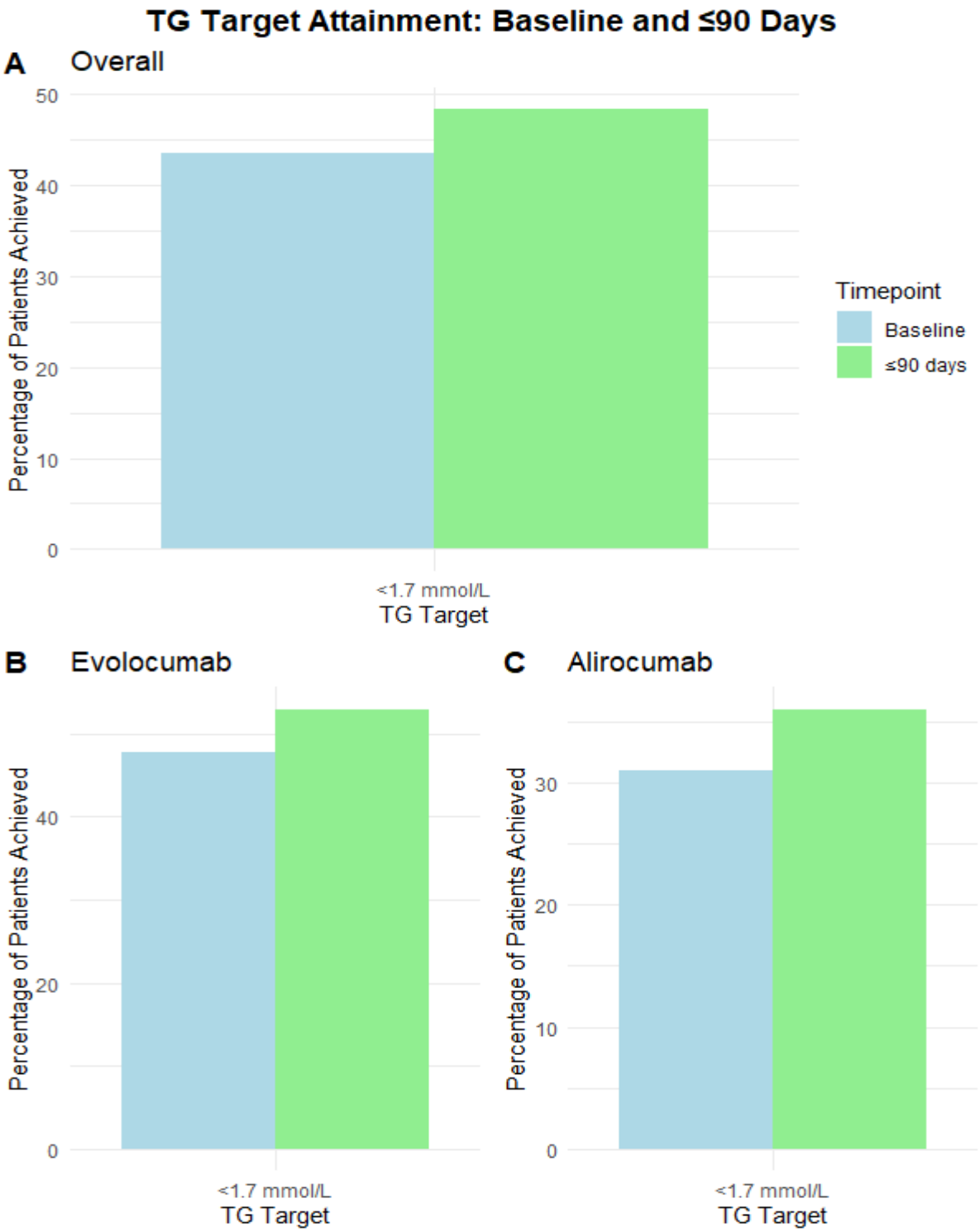

Figure 5.13 Percentage of patients achieving TG target goals within 90 days (months 1-3) at TG <1.7 mmol/L: **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). **TG**: Triglycerides

For HDL-C, where the desirable target is >1.0 mmol/L for males and >1.3 mmol/L for females, 39.1% (n= 45/115) of the overall cohort were at target at baseline. Following PCSK9i initiation, the proportion of patients achieving this target slightly increased to 41.9% (n= 39/93) at 90 days (months 1-3) (**Figure 5.14A, Appendix S5.3, Table S5.3.4A**), 47.6% (n= 30/63) at 91-180 days (months 4-6), and 25% (n= 1/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.4A**).

The subgroup analysis indicated that the proportion of patients achieved TG target before evolocumab initiation was 46.5% (n= 40/86), while 17.2% (n= 5/29) of the alirocumab users had achieved the target. Within 90 days (months 1-3) of treatment, 45.6% (n= 31/68) of evolocumab users and 32% (n= 8/25) of alirocumab users attained the target (**Figure 5.14B-C, Appendix S5.3, Table S5.3.4B-C**). During 91-180 days (months 4-6), the target was met by 52.3% (n= 23/44) of evolocumab users and 36.8% (n= 7/19) of alirocumab users (**Appendix S5.3, Table S5.3.4B-C**). Notably, the proportion reported for the overall cohort during 181-270 days (months 7-9) reflects only evolocumab users, as no alirocumab users had available data during this period.

The key finding for HDL-C target achievement was that PCSK9is improved attainment of the >1.0 mmol/L for males and >1.03 mmol/L goal within 90 days (months 1-3).; however, achievement remained suboptimal, with only 41.9% of patients reaching the target (n= 39/93).

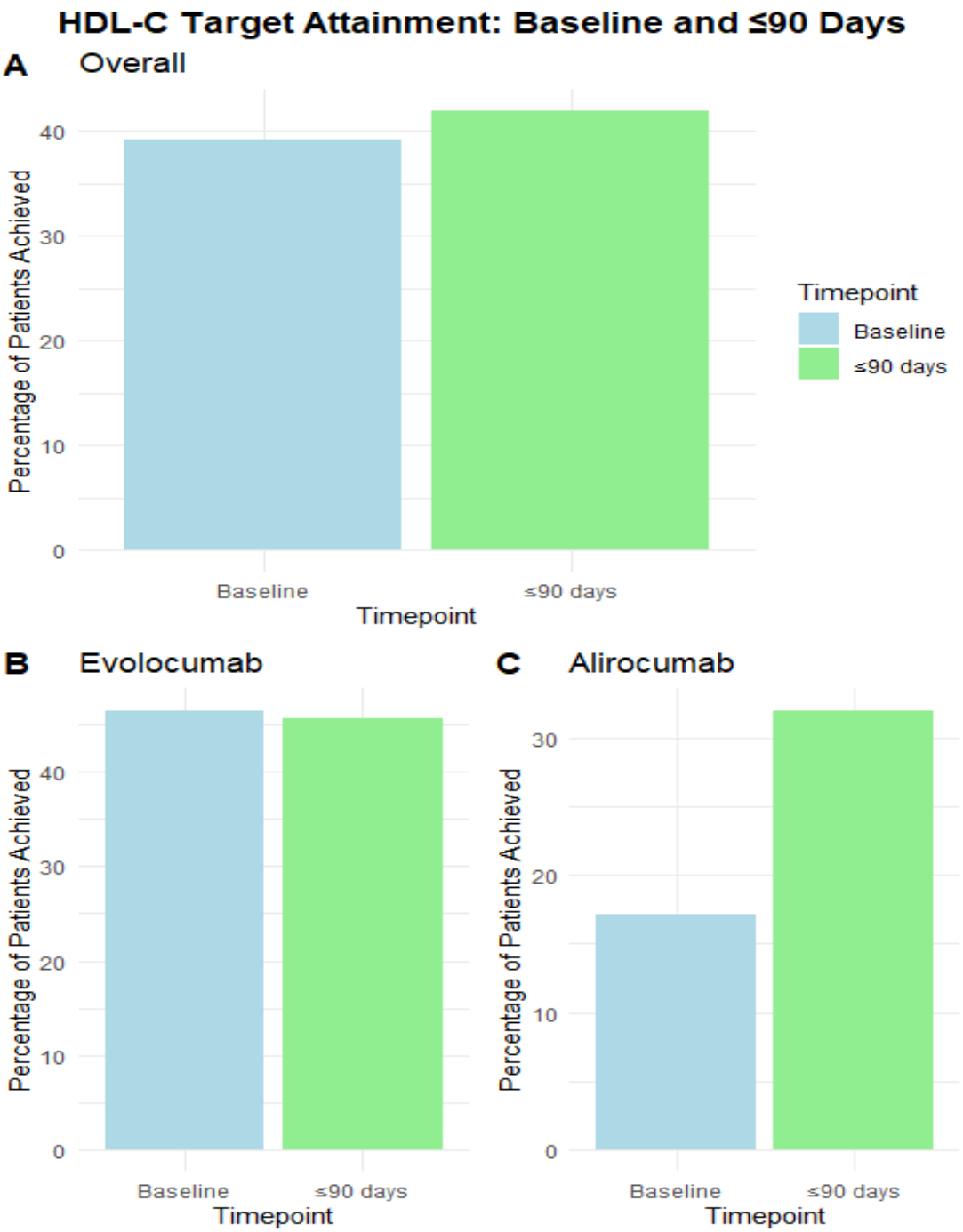

Figure 5.14 Percentage of patients achieving HDL-C target goals within 90 days (months 1-3) at HDL-C >1.0 mmol/L for males and HDL >1.3 mmol/L for females **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). **TG**: Triglycerides

Lastly, for TC, where the desirable target is <5.0mmol/L, 49.6% (n= 57/115) of the overall cohort were at target at baseline. Following PCSK9i initiation, the proportion of patients achieving this target increased to 79.6% (n= 74/93) at 90 days (months 1-3) (**Figure 5.15A, Appendix S5.3, Table S5.3.5A**), 73% (n= 46/63) at 91-180 days (months 4-6), and 100% (n= 4/4) at 181-270 days (months 7-9) (**Appendix S5.3, Table S5.3.5A**).

The subgroup analysis showed that 52.3% (n= 45/86) of evolocumab users were at target at baseline, while 41.3% (n= 12/29) of the alirocumab users had achieved the target. Within 90 days (months 1-3) of treatment, 82.4% (n= 56/68) of evolocumab users and 72% (n= 18/25) of alirocumab users attained the target (**Figure 5.15B-C, Appendix S5.3, Table S5.3.5B-C**). During 91-180 days (months 4-6), the target was met by 72.7% (n= 32/44) of evolocumab users and 73.7% (n= 14/19) of alirocumab users (**Appendix S5.3, Table S5.3.5B-C**). It should be noted that the proportion reported for the overall cohort during months 7-9 reflects only evolocumab users, as no alirocumab users had available data during this period. Notably, the proportion reported for the overall cohort during months 7-9 reflects only evolocumab users, as no alirocumab users had available data during this period.

The key finding for TC target achievement was that PCSK9is improved attainment of the <5 mmol/L goal within 90 days (months 1-3).; however, achievement considered acceptable, with only 79.6% of patients reaching the target (n= 74/93).

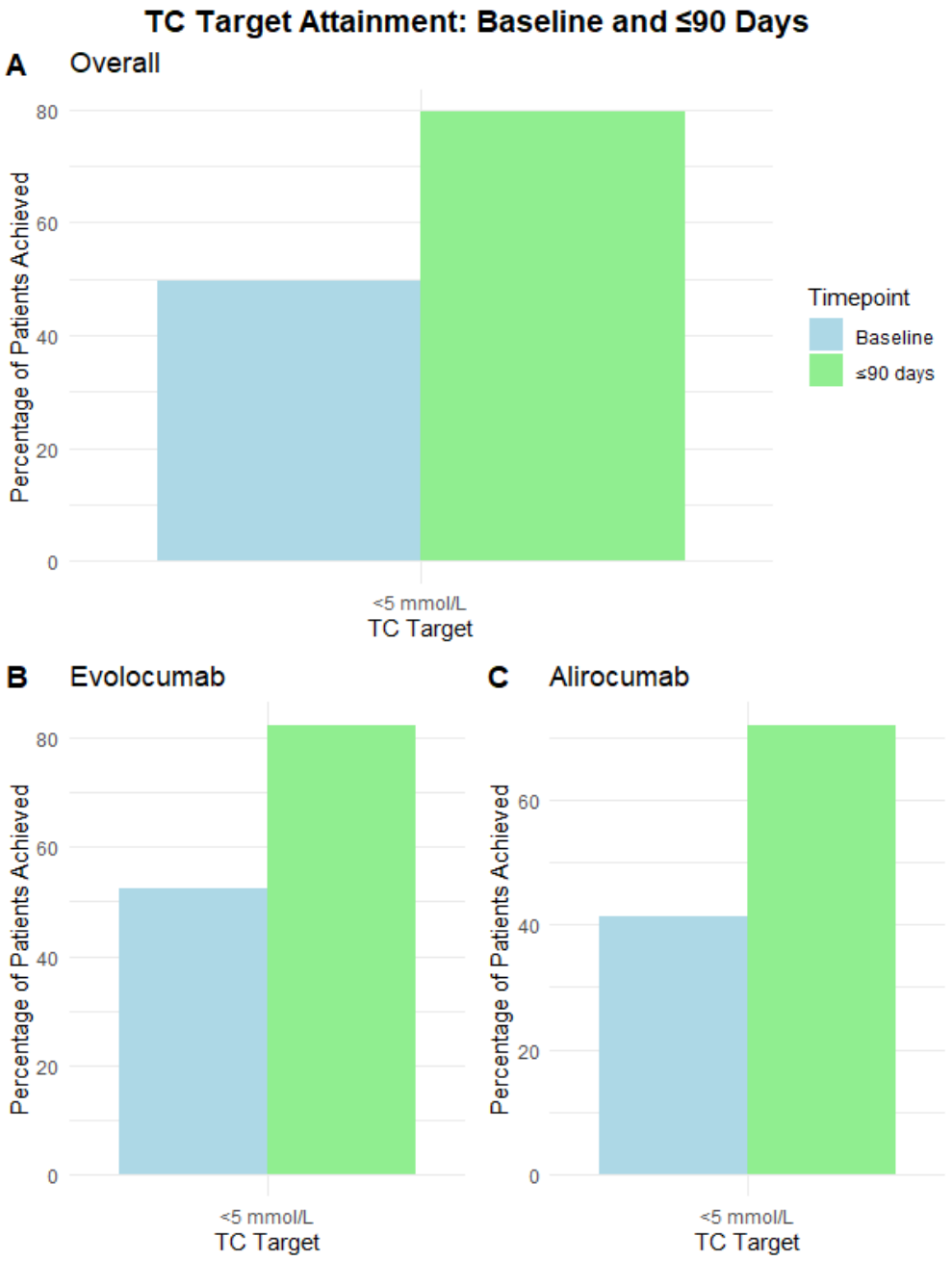

Figure 5.15 Percentage of patients achieving TC target goals within 90 days (months 1-3) at TC <5.0 mmol/L: **A**. Overall (n= 93), **B.** Evolocumab (n= 68), **C.** Alirocumab (n= 25). **TC**: Total cholesterol

5.4.3. Factors associated with LDL-C and non-HDL-C reductions after PCSK9i initiation

The factors included in the LLM were time (before and after PCSK9i initiation), age, gender, type of PCSK9i agent (evolocumab or alirocumab), and background LLTs. A detailed description of the covariates included in the LMM for evaluating changes in LDL-C and non-HDL-C is depicted in **Table 5.6**.

Table 5.6 Summary of covariates included in the LMM

Covariates	**LDL-C**	**Non-HDL-C**
Time	**(Median (IQR), mmol/L)**	**(Median, (IQR), mmol/L)**
Baseline	2.95 (1.96 to 3.83)	3.94 (2.85 to 5.16)
Follow-up at 90 days	1.73 (0.76 to 2.6)	2.38 (1.52 to 3.27)
Age, years	**(Mean ± SD)**	**(Mean ± SD)**
Continuous	54.19 ± 12.3	54.1 ± 12.1
Gender (%, n)	**N= 104**	**N= 115**
Male	(57.7%, 60)	(59.1%, 68)
Female	(42.3%, 44)	(40.9%, 47)
PCSK9i agent type (%, n)	**N= 104**	**N= 115**
Evolocumab	(74%, 77)	(74.8%, 86)
Alirocumab	(26%, 27)	(25.2%, 29)
Background LLTs (%, n)	**N= 104**	**N= 115**
Yes	(61.5%, 64)	(62.6%, 72)
No	(38.5%, 40)	(37.4%, 43)

LMM: Linear-mixed model; **LDL-C**: Low-density lipoprotein cholesterol; N**on-HDL-C:** Non-high-density lipoprotein cholesterol; **IQR**: Interquartile range; **SD**: Standard deviation; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor; **LLT**: Lipid-lowering therapy

The original LMMs for both LDL-C and non-HDL-C demonstrated statistically significant reductions following PCSK9i initiation (p <0.001), with decreases of β= -1.28 mmol/L (95% CI: -1.76 to -0.79) and β= -1.68 mmol/L (95% CI: -2.21 to -1.14), respectively (**Table 5.7**). Both models indicated that older patients experienced slightly greater lipid reductions. Each additional year of age was associated with a further 0.04 mmol/L reduction in LDL-C (95% CI: -0.07 to -0.02; p= 0.001) and a 0.05 mmol/L reduction in non-HDL-C (95% CI: -0.08 to -0.02; p <0.001). Treatment with alirocumab was significantly associated with smaller reductions than evolocumab in both LDL-C (β= 0.73 mmol/L, 95% CI: 0.05 to 1.42; p= 0.036) and non-HDL-C (β= 0.76 mmol/L; 95% CI: 0.02 to 1.51; p= 0.045) (**Table 5.7**).

Other covariates, gender and background LLT use, were not significantly associated with changes in LDL-C or non-HDL-C (**Table 5.7**). Females were associated with a small, non-significant difference in LDL-C (β= 0.07 mmol/L, 95% CI: -0.53 to 0.67; p= 0.817) and a modest non-significant reduction in non-HDL-C (β= -0.1 mmol/L, 95% CI: -0.74 to -0.55; p= 0.772), compared with males. Patients without background LLTs demonstrated greater, but non-significant, reductions in LDL-C (β= -0.2, 95% CI: -1.27 to 0.86; p= 0.708) and non-HDL-C (β= -0.43, 95% CI: -1.63 to 0.77; p= 0.478) than those with background therapy.

Table 5.7 Primary linear-mixed effects model for LDL-C and non-HDL-C (before removing the influential observation)

Covariates	LDL-C		Non-HDL-C	
	Regression coefficients (β, 95% CI)	**p-value**	**Regression coefficients (β, 95% CI)**	**p-value**
Time				
Baseline	1.0 (reference)		1.0 (reference)	
Follow-up	-1.28 (-1.76 to -0.79)	**<0.001***	-1.68 (-2.21, -1.14)	**<0.001***
Age				
Continuous	-0.04 (-0.07, -0.02)	**= 0.001***	-0.05 (-0.08, -0.02)	**<0.001***
Gender				
Male	1.0 (reference)		1.0 (reference)	
Female	0.07 (-0.53, 0.67)	= 0.817	-0.1 (-0.74, -0.55)	= 0.772
PCSK9i type				
Evolocumab	1.0 (reference)		1.0 (reference)	
Alirocumab	0.73 (0.05, 1.42)	**= 0.036***	0.76 (0.02, 1.51)	**= 0.045***
Background LLTs				
Yes	1.0 (reference)		1.0 (reference)	
No	-0.2 (-1.27, 0.86)	= 0.708	-0.43 (-1.63, 0.77)	= 0.478

***p value <0.05. **LDL-C**: Low-density lipoprotein cholesterol; **Non-HDL-C:** Non-high-density lipoprotein cholesterol; **CI:** Confidence interval; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor; **LLT**: Lipid-lowering therapy

The sensitivity analyses revealed similar findings consistent with the primary models, except that the type of PCSK9i was no longer significantly associated with changes in LDL-C and non-HDL-C (**Table 5.8**). Alirocumab was associated smaller, non-significant reductions in LDL-C (β= 0.37 mmol/L, 95% CI: -0.14 to 0.88; p= 0.157) and non-HDL-C (β= 0.39 mmol/L, 95% CI: -0.25 to 1.04; p= 0.23), compared with evolocumab.

Follow up remained strongly associated with lipid reductions, with estimated mean decreases of β= -1.09 mmol/L (95% CI: -1.43 to -0.76; p <0.001) for LDL-C and β = -1.49 mmol/L (95% CI: -1.89 to -1.09; p <0.001) for non-HDL-C. Older age continued to show a significant association with greater lipid reductions, with each additional year associated to reductions of 0.03 mmol/L in LDL-C (95% CI: -0.04 to -0.01; p= 0.007) and 0.03 mmol/L in non-HDL-C (95% CI: -0.06 to -0.01; p= 0.006).

As in the primary models, gender and background LLTs were not significantly associated with changes in LDL-C and non-HDL-C (**Table 5.8**). Females were associated with non-significant, additional reductions in LDL-C (β= -0.16 mmol/L, 95% CI: -0.61 to 0.29; p= 0.474) and non-HDL-C (β= -0.37 mmol/L, 95% CI: -0.92 to 0.19; p= 0.197). Likewise, patients without background LLTs experienced greater, non-significant LDL-C reductions in LDL-C (β= -0.47, 95% CI: -1.27 to 0.33; p= 0.247) and non-HDL-C (β= -0.7, 95% CI: -1.73 to 0.33; p= 0.182) (**Table 5.8**).

Table 5.8 Sensitivity linear-mixed effects model for LDL-C and non-HDL-C (after removing the influential observation)

Covariates	LDL-C		Non-HDL-C	
	Regression coefficients (β, 95% CI)	**p-value**	**Regression coefficients (β, 95% CI)**	**p-value**
Time				
Baseline	1.0 (reference)		1.0 (reference)	
Follow-up	-1.09 (-1.43, -0.76)	**<0.001***	-1.49 (-1.89, -1.09)	**<0.001***
Age	-0.03 (-0.04, -0.01)	**=0.007***	-0.03 (-0.06, -0.01)	**=0.006***
Gender				
Male	1.0 (reference)		1.0 (reference)	
Female	-0.16 (-0.61, 0.29)	=0.474	-0.37 (-0.92, 0.19)	=0.197
PCSK9i type				
Evolocumab	1.0 (reference)		1.0 (reference)	
Alirocumab	0.37 (-0.14, 0.88)	=0.157	0.39 (-0.25, 1.04)	= 0.23
Background LLT				
Yes	1.0 (reference)		1.0 (reference)	
No	-0.47 (-1.27, 0.33)	=0.247	-0.7 (-1.73, 0.33)	=0.182

***p value <0.05. **LDL-C**: Low-density lipoprotein cholesterol; **Non-HDL-C:** Non-high-density lipoprotein cholesterol; **CI:** Confidence interval; **PCSK9i**: Proprotein convertase subtilisin/kexin type 9 inhibitor; **LLT**: Lipid-lowering therapy

5.5. Discussion

The present study evaluated the real-world effectiveness of PCSK9is, including both evolocumab and alirocumab, and examined factors potentially associated with lipid changes at a cardiac care centre in Kuwait between 2016 and 2022.

5.5.1. Key findings

Of the 458 incident users of PCSK9i, 115 patients (25.1%) met the eligibility criteria for inclusion in the effectiveness analysis. These patients were evaluated for changes in non-HDL-C, TG, HDL-C, and TC. However, for LDL-C assessment, the cohort was reduced to 104 patients (22.7%) due to 9 patients having TG levels above 4.5 mmol/L, which limited the application of the FF, and two patients lacking post-PCSK9i LDL-C measurements. Within 3 months of initiation, PCSK9is significantly reduced levels of LDL-C (41.9%), non-HDL-C (38.1%), TG (14.8%), and TC (31.1%) levels (**Figures 5.6-10; Appendix S5.2**). Subgroup analyses showed that evolocumab was associated with greater percentage reductions than alirocumab, including LDL-C (45.7% vs. 37.1%), non-HDL-C (40.7% vs. 30.1%), TG (17.3% vs. 12.1%), and TC (32.6% vs. 23.3%). However, the difference between the two agents was not statistically significant (**Appendix S5.2**).

In terms of lipid target achievement, this study primarily assessed the proportion of patients attaining LDL-C <1.4 mmol/L and non-HDL-C <2.2 mmol/L, based on the assumption that all patients had established ASCVD. Findings indicated suboptimal goal attainment, with only 42.9% (n= 36/84) achieving the LDL-C target (**Figure 5.11**) and 45.2% (n= 42/93) meeting the non-HDL-C goal (**Figure 5.12**).

The adjusted LMM demonstrated significant reductions in both LDL-C and non-HDL-C levels following PCSK9i initiation (**Table 5.7**). Older age and treatment with evolocumab were associated with greater lipid reduction (**Table 5.7**). However, in the sensitivity analyses, the association between the specific PCSK9i agent and lipid reduction was no longer observed (**Table 5.8**).

5.5.2. Real-world effectiveness of PCSK9is and factors potentially associated with lipid reduction

Prior to initiating a PCSK9i, only 9 out of 104 patients (8.7%) had baseline LDL-C levels below the <1.4 mmol/L target (**Figure 5.11**). This wide treatment gap suggests the clinical need for further LLT intensification. However, following PCSK9i initiation, 42.9% (n= 36/84) of patients attained LDL-C <1.4 mmol/L, within 3 months (**Figure 5.11**). During the periods beyond 90 days, a comparable proportion was observed between 91-180 days (4-6 months), during which 43.6% of patients (n= 24/55) met the LDL-C goal (**Appendix S5.3, Table S5.3.1A**). However, between 181-270 days (7-9 months), only 4 patients remained in the cohort with 50% (n= 2/4) attained the target (**Appendix S5.3, Table S5.3.1A**). Given the limited number of patients during the later follow-up period and the application of the LMM to observations within the first 90 days, interpretation of findings beyond this period remains challenging. Therefore, the discussion focuses mainly on the primary analysis during the initial 90 days following PCSK9i initiation.

The initiation of PCSK9is in this cohort was associated with a statistically significant reduction in LDL-C levels, showing a relative median reduction of 42% (95% CI: -50.9% to -24.1%) (**Figure 5.6A**). This observed reduction was reflected in improved rates of target attainment, though still suboptimal (**Figure 5.11**). Further support for this finding was provided by the LMM, which demonstrated a significant LDL-C reduction (β = -1.28 mmol/L, p <0.001) (**Table 5.7**). Moreover, the LDL-C reduction is consistent with the pharmacological mechanism of PCSK9is, which enhance LDL-C clearance by upregulating hepatic LDL receptors (LDLRs), thereby increasing the removal of circulating LDL-C particles (10), as described in **chapter 2; section 2.2.3.3**. Notably, the overall 42% median LDL-C reduction observed in this cohort is lower than the ~60% reductions reported in landmark RCTs. For example, the FOURIER trial (n= 27,564) demonstrated LDL-C reductions of up to 60% with evolocumab (54). Similarly, the ODYSSEY OUTCOMES trial showed a comparable reduction with alirocumab at 150mg Q2W, but a modest reduction of 45% - 48% with the 75mg Q2W dose regimen

(55). This discrepancy may be attributed to several real-world factors that are not typically present in the tightly controlled RCT environment. These include greater heterogeneity in patient characteristics, such as variability in background LLT use (statin and/or ezetimibe), treatment duration, and the burden of comorbidities. In brief, participants in the FOURIER (54) and ODYSSEY OUTCOMES (55) trials (**Appendix 2.7**) were more consistently treated with intensive background LLTs and were managed under conditions of optimal adherence, structured follow-up, regular lipid monitoring, and lifestyle counselling. Accordingly, the following discussion focuses on key real-world factors that may influence LDL-C reduction, including background LLT use, the type of PCSK9i agent, baseline LDL-C, comorbidities, and some demographic factors.

According to the 2019 ESC/EAS guidelines (23) and the 2021 Middle East consensus (20), PCSK9is are recommended as a third-line option for patients who fail to achieve LDL-C goals despite receiving maximally tolerated statin therapy combined with ezetimibe. The synergistic effect of background LLT is well documented. Statins and ezetimibe are known to upregulate PCSK9 expression, thereby increasing the availability of binding target for PCSK9is (215). While statins reduce hepatic cholesterol synthesis via HMG-CoA reductase inhibition, they also stimulate “SREBP-2”, leading to increased expression of LDLRs and PCSK9. This paradox, known as the “statin escape phenomenon”, can limit further LDL-C reductions despite statin titration (215). The addition of PCSK9is prevents LDLR degradation, thereby restoring and enhancing hepatic lipid clearance capacity (215). Ezetimibe, through NPC1L1 inhibition, also increases LDLR activity (215), and its combination with statins and PCSK9is can lead to up to 85% LDL-C reduction, as outlined in the 2019 ESC/EAS guidelines (23).

The finding of the current study showed that 61.5% (n= 64/104) of patients were recorded as receiving background LLT, including statins, ezetimibe, and fibrates (**Table 5.6**). In the LMM, the relatively modest utilisation of background LLT was not significantly associated with changes in LDL-C or non-HDL-C levels (**Table 5.7**). Several factors may explain this lack of association. Initially, background LLT was modelled as a binary variable, which limited the ability to capture differences in statin intensity, use of maximally tolerated statin therapy, and combination with ezetimibe (23). Moreover, the methodology used to identify background LLT relied on dispensing records of the availability of statin and ezetimibe within six-month window of PCSK9i initiation. This approach may not accurately reflect whether background LLTs were taken concurrently with PCSK9i therapy or whether they continued over time, as background LLT was modelled as a fixed variable rather than time-varying variable. In addition, medication adherence represents an important unmeasured confounder, as suboptimal adherence of background LLTs may have attenuated the effect of lipid reduction (157).

Additionally, misclassification of background LLT is also likely to contribute to this finding. The absence of data linkage between the study centre and other healthcare settings may have led to an underestimation of the actual LLT use. Traditional oral LLTs, particularly statins, are commonly initiated and managed in primary care settings. As shown in **chapter 3** (Figure 3.15A & Figure 3.16A-B), the utilisation level of oral LLTs in primary care consistently surpassed those in hospitals. This finding could support the likelihood that background LLT use was not completely captured in this tertiary-care dataset.

Evidence from the FOURIER trial demonstrated that concomitant statin use enhanced the LDL-C lowering effect of evolocumab (54). Similarly, a pooled analysis by Farnier et al. (2016), which included eight ODYSSEY Phase 3 clinical trials, demonstrated that alirocumab achieved greater LDL-C reduction when combined with HIST, reinforcing the role of concomitant use (216).

Several real-world effectiveness studies reinforce the role of background LLT in optimising the LDL-C lowering effect of PCSK9is. Because some studies reported mg/dL as a unit for LDL-C, the values were converted to mmol/L using the standard conversion factor (× 0.026) to ensure consistency. The ZERBINI study conducted in Kuwait (73) included 70 patients, from a tertiary care centre different from this study centre, with 87% had ASCVD, 37.1% had statin intolerance, and 5.7% were diagnosed with FH. Despite a similar baseline LDL-C level (~3 mmol/L), the ZERBINI study reported a 61.7% reduction in LDL-C within six months of using evolocumab, mirroring the clinical trial. This comparable relative reduction could be related to the greater use of background LLT, with 85% of patients on statins and 21% on ezetimibe. Additionally, the prospective design of the ZERBINI study enabled regular monitoring of LDL-C levels and medication adherence, which may have further contributed to the observed lipid reduction.

Further supporting the importance of background therapy and its continued use alongside PCSK9i therapy is the HEYMANS study. This large, prospective registry was conducted across 12 European countries (2015–2021) and involved 1,951 patients on evolocumab, followed up for 30 months (71). Among these, 85% were in secondary CVD prevention, 60% were statin-intolerant, and 45% had FH. A median LDL-C reduction of 58% was achieved within three months, closely mirroring results from the FOURIER trial (54). Notably, patients who maintained consistent background LLT throughout the follow-up period achieved greater LDL-C reductions and higher rates of target attainment. Nevertheless, target achievement remained suboptimal, with only approximately 60% of patients reaching guideline-recommended targets (71).

Similarly, a large multicentre real-world study conducted in Italy included 798 patients, of whom 75.3% were classified as very-high CV risk, 26.7% had FH, and 38.3% were statin-intolerant, reported a sustained LDL-reduction of 64.9% over a follow-up period of up to 57 months (217). Among those who achieved guideline-

recommended LDL-C targets, 83.3% were receiving background statin and/or ezetimibe, compared with only 16.7% who were on PCSK9i monotherapy. These findings reinforce the synergistic benefit of combination therapy in optimising lipid management, improving target attainment, and supporting the importance of sustained use.

Consistent with the importance of combination therapy, Vicente-Valor et al. (2022) applied multiple linear regression using the percentage of median LDL-C reduction as the outcome and found that the absence of concomitant LLT was independently associated with smaller LDL-C reductions (86). The discrepancy between those findings and our findings may be explained by differences in model adjustment, as Vicente-Valor et al. accounted for additional confounders, including medication adherence, variations in intensity of LLT during follow-up, and FH, the role of which is discussed in detail in this section. Importantly, direct comparison should be made with caution due to differences in model type and outcome definitions.

Okada et al. (218) further reported that treatment duration may influence the pharmacodynamic response to LLT. The Okada et al. study showed that while the addition of ezetimibe to statin therapy increased circulating PCSK9 concentrations at 52 weeks, no notable change was observed at 12 weeks (218). This finding suggests a time-dependent effect on PCSK9 regulation and emphasises the need for sustained therapy to maximise clinical benefit. This temporal effect may partly explain the lack of statistical significance observed in the present study, given the relatively short follow-up period of 3 months.

Importantly, although background therapy is recommended in current guidelines unless contraindicated, evidence suggests that the lipid-lowering efficacy of PCSK9is is largely independent of background therapy (23). Accordingly, PCSK9is can still achieve greater reductions in LDL-C, which is consistent with the significant lipid reduction observed in this study, although not fully replicate that reported in trials.

In terms of the type of PCSK9i agent, both the FOURIER (54) and ODYSSEY OUTCOMES (55) trials (**Appendix 2.7**) demonstrated comparable LDL-C percentage reductions with evolocumab 140mg and alirocumab 150mg, whereas smaller reductions was reported with alirocumab 75mg. In the present study, the subgroup analysis showed that evolocumab users achieved a greater median LDL-C reduction (45.7%; 95% CI: -53.5% to -25.4%) (**Figure 5.6B**) compared with alirocumab users (37.1%: 95% CI: -50.8% to -7.69%) (**Figure 5.6C**). However, using the inferential statistics, the difference between the two agents was not statistically significant across all lipid parameters (**Appendix S5.2**). This finding was further corroborated by the LMM in the sensitivity analyses (**Table 5.8**), which demonstrated no independent association between the type of PCSK9i and LDL-C or non-HDL-C levels.

In contrast, the original model indicated that patients receiving alirocumab exhibited significantly smaller reductions in LDL-C and non-HDL-C compared with those treated with evolocumab (**Table 5.7**). This difference may be partly explained by the presence of influential observations among evolocumab users (one in the LDL-C model and two in the non-HDL-C model) (**Appendix S5.1**). Notably, this finding is similar to thate reported by Vicente-Valor et al. in that reported by previously described study from Spain, where multiple linear regression analysis showed that alirocumab use was independently associated with a less pronounced LDL-C reduction compared with evolocumab (86). However, this comparison should be interpretated with caution. In the present study, most patients received the 75mg dose of alirocumab, which is known to achieve smaller LDL-C reductions than the 150mg dose (219). In contrast, the Spanish study did not clearly report the alirocumab dose used. In addition, differences in the adjustment of confounders between the two studies may contribute to the observed discrepancy with the findings of the sensitivity models (**Table 5.8**).

Gargiulo et al. (217) also observed no significant differences in the reduction of LDL-C, TGs, HDL-C, or TC between evolocumab and alirocumab in a study conducted in Italy. Additionally, Devaiah et al. reported a greater LDL-C reduction with evolocumab in their study conducted in Scotland, although this difference was not statistically significant (183). The authors suggested that this observation may be explained by subgroup analyses involving both 150mg and 75mg doses of alirocumab, supported by the evidence from the ODYSSEY data (219).

An additional explanation for the lack of statistical significance in the sensitivity models (**Table 5.8**) is the limited sample size within each group, which may have reduced the statistical power to detect differences. Nevertheless, this comparison was not a primary objective of the study design.

Within the context of PCSK9i agents, the present study showed a higher utilisation of incident evolocumab users (78.6%, n= 360/458) compared with alirocumab users (21.4%, n= 98/458) (**Table 5.4**). This disparity in uptake may be partly explained by differences in dosing regimens between the two agents. Evolocumab is administered at a single standard dose of 140mg, allowing for consistent prescribing and administration in routine practice (47). In contrast, alirocumab is available in two dose strengths (75mg and 150mg), introducing variability in prescribing and requiring dose titration to achieve optimal LDL-C lowering (48). Accordingly, the observed preference of evolocumab may reflect prescriber behaviour towards a simpler, fixed-dose regimen that ensures consistent lipid-lowering efficacy. Additionally, patient preference may have contributed to the greater use of evolocumab. In Kuwait, the higher 150mg dose of alirocumab was only introduced in 2022 (**Appendix S3.1**), and before this, dose intensification required administration of two 75mg injection, which may have negatively influenced patient adherence. Therefore, prescribers may have been less willing to initiate or intensify alirocumab therapy. In support of this interpretation, only 3.1% (n= 3/98) of alirocumab users in the current study received

the 150mg dose, suggesting that suboptimal dosing may have contributed to the lower effectiveness of alirocumab in clinical practice.

Furthermore, the higher uptake of evolocumab may possible be related to its broader approved indications, although this study was not able to investigate underlying medical diagnoses. Evolocumab is indicated for use in both homozygous and heterozygous FH (HoFH and HeFH), whereas alirocumab is approved only for HeFH (47, 48). Although alirocumab has the advantage of being latex free (47), evolocumab was prescribed more frequently. This likely reflects the low prevalence of latex allergy within the cohort, limiting its influence on prescribing decisions. In contrast to this prescribing preference, Blanco-Ruiz et al. found in the Spanish IRIS-PCSK9i study, which included 141 patients recruited between 2016 and 2020 (220), that alirocumab was prescribed more frequently than evolocumab, reflecting potential differences in the national drug supply system or formulary policies.

Regarding baseline LDL-C levels, patients in the current study had relatively higher baseline LDL-C concentrations (**Appendix S5.2, Table S5.2.1A**), which likely contributed to larger absolute reductions in LDL-C. However, the relative reduction in LDL-C, which is more relevant and largely independent of baseline LDL-C levels, was lower than that reported in clinical trials (**Appendix 2.7**), acknowledging differences in the follow-up duration. Blanco-Ruiz et al. reported that their cohort included patients with FH (13.5%), established ASCVD (44%), or statin intolerance (13.5%), with most receiving background statins (66.7%) and ezetimibe (65.2%). A mean LDL-C reduction of 50% at 6 months, with an absolute reduction of 2.2 mmol/L from a baseline LDL-C of 4 mmol/L. Thus, in addition to the high use of background LLT, the higher baseline LDL-C levels are likely to have contributed to the greater absolute LDL-C reduction (220). This provides a plausible explanation for the more modest LDL-C reduction seen in the present study, where baseline LDL-C levels were lower (3 mmol/L in our study vs. 4 mmol/L) and the absolute reduction was smaller (1 in our study vs. 2 mmol/L) (**Appendix S5.2, Table S5.2.1A**).

Although the Kuwaiti ZERBINI study reported a similar baseline LDL-C (~3 mmol/L), its absolute change was higher (1 mmol/L in our stud vs. 1.7), demonstrating in 58% LDL-C reduction within 12 months of using evolocumab compared with 46% within 3 months in the present study. However, differences in background LLT, as mentioned earlier, and the ambispective study design may have contributed to these variations. It should be acknowledged that both the IRIS and ZERBINI studies reported LDL-C as mean values, whereas the current analysis reported LDL-C as medians. This difference can slightly affect comparisons, as mean values tend to be higher than medians in right skewed distribution, with patients having elevated LDL-C, as shown in the Kuwaiti ZERBINI study, which reported the LDL-C baseline in mean ± SD (3.1±1.4 mmol/L) and median (IQR) (2.8 (2.3–3.6) mmol/L) (73).

In terms of comorbidities, PCSK9is are typically prescribed for patients with compelling clinical indications, including established ASCVD, FH, and statin intolerance (47, 48). These patient groups are often those who fail to achieve lipid targets despite receiving maximally tolerated conventional therapies, as they are subject to more stringent LDL-C thresholds (23). Assessing PCSK9i effectiveness within these clinical subgroups would enhance understanding of the variability of lipid responses across different patient populations. However, the absence of detailed comorbidity data in the present study limited the ability to account for these factors, which may have influenced the changes in lipid levels following PCSK9i initiation.

The response to PCSK9is in patients with FH is well-established, highlighting their use in genetically predisposed populations, particularly given the reported high prevalence in Gulf countries (32). The RUTHERFORD-2 trial showed that evolocumab reduced LDL-C by up to 66% in HeFH patients (221), and the ODYSSEY FH I and II trials demonstrated similar reductions with alirocumab (222). Although the present study could not directly identify FH diagnosis, the ZERBINI study conducted in Kuwait reported a 6% prevalence of FH (73), predominantly HeFH. This finding suggests that

FH may also have been present within our cohort, despite the absence of explicit diagnostic criteria. One case in the analysis, with an LDL-C level of 22 mmol/L, may support this possibility, as its exclusion from the LMM improved the overall mode fit. Vicente-Valor et al. reported that FH individuals achieved greater overall lipid reductions; however, HeFH status was not an independent factor of the percentage of median LDL-C reduction in the multivariate analysis (86). The authors explained that PCSK9is were similarly effective in both groups, with comparable reductions observed in patients with HeFH and those without HeFH (61.9% vs. 58.4%, $p > 0.05$).

The PCSK9I-IRIS study reported that 13.5% (n = 19/141) of patients treated with PCSK9is were diagnosed with FH (220). All of these patients were receiving HIST and achieved a mean LDL-C reduction of 45% as a subgroup. This was lower than the reduction observed in patients with CVD (64%) but higher than that seen in statin-intolerant patients (32%). The comparatively lower percentage reduction in the FH subgroup was attributed to the molecular and clinical heterogeneity of the condition, particularly variations in LDLR function, which may affect responsiveness to PCSK9 inhibition (220).

Moreover, statin intolerance (described in **Appendix S2.6**) remains a critical variable influencing the PCSK9i effectiveness and the extent of LDL-C reduction. Patients unable to tolerate statins are less likely to receive HIST. In the HEYMANS study (71), for example, statin-intolerant patients exhibited lower LDL-C reductions than those who could tolerate statins, despite treating with evolocumab. The multi-country ZERBINI study further illustrated the influence of statin intolerance on PCSK9i response (72). Among 578 patients, 35.6% reported statin intolerance, yet the cohort achieved a median LDL-C reduction of 70.2% over 12 months. Patients treated with evolocumab monotherapy achieved a 62.5% reduction, demonstrating that while combination therapy is preferred, PCSK9is remain highly effective even in statin-intolerant individuals when adherence is maintained and therapy is initiated appropriately (72). This finding further supports the lack of a statistically significant

association between background LLT use and lipid reduction in the LMM of the present study (**Table 5.7** and **Table 5.8**).

Broader international data indicate that statin intolerance often coexists with other high-risk indications for PCSK9i use. A cross-sectional analysis conducted between December 2016 and April 2017 across Germany, Spain, and the UK, involving over 3,000 patients with dyslipidaemia, found that PCSK9i users were more likely to have FH, coronary artery disease, ACS, and statin intolerance than non-users (223). A clear understanding of these medical indications could improve the prescribing appropriateness and eventually support the timely optimisation of lipid management. For instance, in patients presenting with ACS who remain above LDL-C targets despite maximally tolerated statin and ezetimibe, early initiation of a PCSK9i during hospitalisation should be considered (224).

In terms of demographic variables, the adjusted LMM demonstrated that increasing age was associated with greater reductions in LDL-C and non-HDL-C (**Table 5.7** and **Table 5.8**). This finding contrasts with evidence from several studies suggesting that age does not significantly influence the lipid-lowering response to PCSK9is. For instance, a post-hoc pooled analysis of 1,257 patients with HeFH combined data from four placebo-controlled ODYSSEY phase 3 trials (ODYSSEY FH I, FH II, LONG TERM, and HIGH FH) examined whether age influenced alirocumab efficacy across predefined age categories (18 to < 45, 45 to < 55, 55 to < 65, and ≥ 65 years) (225). That subgroup analysis reported consistent reductions in LDL-C and non-HDL-C across all age groups, with no statistically significant interaction between age and alirocumab effect (225). As that study focused on patients with FH, the discrepancy between those findings and the present study may be partly explained by residual confounding, particularly related to comorbidities.

Another important, yet unmeasured, confounder that may explain the significant association is the medication adherence. The ODYSSEY pooled analysis also noted that younger participants tended to be less adherence before trial enrolment (225). However, evidence on the association between age and adherence remains mixed. Some studies suggest that older adults are generally more adherent to medications than younger individuals (226), whereas other observational studies, such as the CARhES (CArdiovascular Risk factors for HEalth Service research) cohort, have reported lower adherence with increasing age (227). Other potential explanations may relate to modelling the age as a continuous variable rather than using categorical age groups. However, this modelling choice was informed by the AIC, which indicated improved model fit model when age was treated as a continuous variable.

Notably, the median baseline LDL-C was lower in the older group (2.47 mmol/L) than in the younger group (3.59 mmol/L). However, baseline LDL-C levels were adjusted for in the LMM, and this difference is therefore unlikely to fully explain the association between age and lipid reduction. Moreover, this association is unlikely to be driven by sample imbalance, as the proportions of those aged ≥ 55 years (53.8%, n= 56/104) and <55 years (46.2%, n= 48/104) were comparable.

Additionally, a plausible explanation is that older individuals are more likely to be receiving secondary prevention for established ASCVD, whereas younger patients tend to be in the primary prevention group and may remain asymptomatic. Consequently, those in secondary prevention, often with multiple comorbidities, may be more adherent to LLT to prevent recurrent CV events. This hypothesis warrants further investigation within the Kuwaiti population, using patient-level data that capture comorbidities, CV risk stratification, and medication adherence.

Other factors that may contribute to changes in LDL-C reduction further discussed in **Appendix S5.4.**

5.5.3. Strengths and limitations

While this study is not the first to examine the effectiveness of PCSK9is in the Gulf region, preceded by the ZERBINI studies conducted in Saudi Arabia and Kuwait (73) and by an Emirati study (184), it contributes several distinct strengths to the regional literature. Notably, this study evaluated both evolocumab and alirocumab, thereby assessing all currently available PCSK9i agents, whereas previous Gulf studies focused exclusively on evolocumab.

A further methodological strength is the use of dispensing records rather than prescribing records. In hospitals, medications are typically prescribed for up to six months, but medication are dispensed every two months. Consequently, dispensing data provide a more accurate reflection of actual medication supply and a better approximation of clinical practice. Importantly, this study assessed lipid changes following PCSK9i initiation in relation to therapy continuation. This represents an improvement over the Kuwait ZERBINI study, which evaluated lipid changes over a 12-month period without distinguishing between patients who continued or discontinued therapy (73). In the present study, PCSK9i continuation was assessed using the refill gap method with an appropriate grace period, a widely accepted approach in pharmacoepidemiological research.

The present study also examined a broader range of lipid parameters, including LDL-C, non-HDL-C, TGs, HDL-C, and TC, whereas the ZERBINI study (73) reported only LDL-C. This broader evaluation was particularly valuable given that LDL-C values were available for 104 patients, while the inclusion of additional lipid parameters, especially non-HDL-C, expanded the eligible cohort to 115 patients. Incorporating non-HDL-C reduced reliance on LDL-C alone and was especially important for patients with elevated TGs, for whom LDL-C cannot be calculated using the FF. Furthermore, the study incorporated available covariates to model lipid changes following PCSK9i initiation using LMMs. Model robustness was supported by GOF diagnostics and sensitivity analyses, strengthening the validity of the findings.

Despite its strengths, several limitations should be acknowledged. These limitations are largely inherent to studies based on secondary database analysis and may influence the interpretation of the findings. First, the influence of unmeasured confounders cannot be ruled out. Comorbidity data were unavailable in the dataset, which may have led to misclassification of CV risk categories and, consequently the lipid targets applied. This limitation could have resulted in certain patients being evaluated against threshold that did not accurately reflect their true CV risk category. To mitigate potential misclassification and given that the study was conducted in a specialised tertiary cardiac centre where most patients are manged for established ASCVD (secondary prevention), an LDL-C target of <1.4 mmol/L was applied. To strengthen the robustness of this approach, sensitivity analyses were performed using a more stringent threshold (<1.0 mmol/L) and a more lenient threshold (<1.8 mmol).

The absence of comorbidity data also limited the ability to assess the appropriateness of PCSK9i prescribing. It was not possible to determine whether prescribing followed guideline recommendations, particularly for conditions such as FH, statin intolerance, or persistent suboptimal lipid control despite maximally tolerated oral LLTs. Although background LLT use was examined, the dataset only captured medications dispensed within the tertiary setting. Many patients were likely to have received LLTs in PHCCs, which were not reflected in the tertiary records. Consequently, findings related to background LLT use were interpreted with caution. This was particularly important given that the LMMs showed no statistically significant association between background LLT use and lipid reductions following PCSK9i therapy. However, existing evidence indicates that PCSK9is still achieve greater LDL-C reductions, regardless of background LLT use (23).

Within the lack of integrated hospital records, it was also not possible to confirm whether all included patients were truly newly initiated on PCSK9is at the time of inclusion. Since PCSK9is are not dispensed through primary care in Kuwait, it is likely that most patients began therapy at their designated hospital, either in secondary facility or at tertiary cardiac centre. Nevertheless, it remains possible that some patients had initiated PCSK9is elsewhere at a different hospital, leading to incomplete capture of their treatment history. However, the number of patients included in this study exceeded that of the Kuwait ZEBINI cohort, thereby providing complementary evidence for assessing PCSK9i effectiveness.

Second, the application of eligibility criteria reduced the number of incident PCSK9i users included in the effectiveness analysis, from 458 to 115 patients. Although this reduction could raise concerns regarding statistical power, a post-hoc power analysis was conducted. This power-based approach demonstrated that the study retained sufficient power to detect changes in lipid levels. Moreover, the use of self-controlled (before-and-after) design strengthened statistical power by reducing bias and between-person variability (228), as each individual acted as their own control. Self-controlled approaches are often preferred over comparison group designs in studies using EHRs, provided that key validity assumptions are met (228).

Third, the calculation of days of supply relied on standard dosing regimens, which may overestimate or underestimate the actual dosing in routine practice. While dosing assumptions for ezetimibe and fibrates aligned with WHO DDD methodology (**chapter 3**, Table 3.2), statin dosing may vary in clinical practice. To mitigate potential misclassification, a 40-day threshold reflecting routine dispensing practices in Kuwait was applied to estimate days of supply of statins. This approach was further supported through the sensitivity analysis. For PCSK9is, the DDDs for evolocumab and alirocumab assume dosing once Q2W (**chapter 3**, Table 3.2). Although the DDD is expressed as a daily dose, multiplying it by 14 days reflects the usual Q2W dosing schedule applied in this study, with some exceptions applied.

Finally, the evaluation of PCSK9i effectiveness followed the approach used in the Colombian ZERBINI study (201), whereby the post-initiation period was divided into quarterly windows and mean lipid levels were calculated for each window. Although this approach may underestimate lipid value, the Colombian study addressed this through sensitivity analyses using maximum and minimum values. In the current study, lipid measurements were evaluated 4 weeks after initiation to assess therapeutic response, aligning with guideline recommendations. The LMM showed significant reduction in lipid levels, suggesting that the chosen method was unlikely to have influenced the overall findings. Alternative approaches, such as evaluating lipid values at the end of each quarter, as applied in the Spanish study, may be considered in future research.

5.5.4. Conclusion

This single-centre real-world evidence study contributes to the growing body of research on PCSK9is in the Gulf region by offering a Kuwaiti perspective. It affirms the significant lipid-lowering effectiveness of both evolocumab and alirocumab, particularly in reducing LDL-C and non-HDL-C levels. However, despite these reductions, relative reduction remained suboptimal when compared to clinical trial results. This gap between efficacy and effectiveness in the real-world highlights the need for optimised lipid management strategies in routine clinical practice.

Chapter 6. General discussion and implications of the findings

6.1. Summary of the key findings

This chapter presents the key findings derived from the quantitative research conducted across three interlinked healthcare settings within the Ministry of Health (MOH) in Kuwait: the Central Medical Store (CMS), primary healthcare centres (PHCCs), and a tertiary cardiac care centre. The key findings are organised into two related sections addressing lipid-lowering therapy (LLT) utilisation patterns and the quality of lipid control, providing integrated evidence base informed by triangulated data sources. The chapter also explores the potential implications of these findings for policy makers, clinical practice, and future research, based on the reflections and the generalisability of the study results.

6.1.1. Utilisation patterns and trends of LLTs

The overall utilisation of LLTs in Kuwait has increased significantly over the 11-year period (2012-2022), as demonstrated by CMS data (**chapter 3, Figure 3.3A** & **Figure 3.7A**). This upward trend likely reflects increasing recognition of dyslipidaemia as a modifiable risk factor for cardiovascular diseases (CVDs) (63), promoting broader initiation of LLTs, particularly statins, for both primary and secondary prevention (23). Additionally, LLT intensification, through either combination therapy or optimisation of statin dosing, may have further contributed to the increased utilisation.

The increase in LLT utilisation can largely be attributed to the evolution of clinical guidelines for dyslipidaemia management, especially the 2019 ESC/EAS guidelines, which introduced more stringent LDL-C thresholds across CV risk categories (23). Moreover, in the Middle East region, there is increasing emphasis on non-HDL-C as a stronger predictor of CV risk and as a co-primary therapeutic target, particularly in populations with a high prevalence of type 2 diabetes mellitus (T2DM) and other metabolic risk factors (20), which are common in Kuwait. In the present study, this clinical emphasis was reflected in a slight increase in the real-world effectiveness cohort when non-HDL-C was considered in addition to LDL-C (**chapter 5**, **Figure 5.5**).

This occurred because LDL-C could not be assessed in some patients with elevated triglyceride levels, whereas non-HDL-C remained measurable.

Furthermore, recent clinical guidelines have increasingly recommended the use of ezetimibe, particularly following evidence of its CV benefits demonstrated in the IMPROVE-IT trial (44). This was reflected in the substantial increase in ezetimibe utilisation from 2016 onwards (**Figure 3.3A**). Importantly, the introduction of PCSK9is into the national formulary in Kuwait represents a major advancement in lipid management (**Figure 3.3A**), offering further options for intensification, especially in patients very high CV risk.

Aggregated CMS data demonstrated that statins consistently dominated national LLT utilisation throughout the study period (**chapter 3, Figure 3.3A** & **Figure 3.7A**), reinforcing their continued role as the cornerstone of dyslipidaemia management and CVD prevention, as established in pivotal clinical trials and reflected in international guidelines (14, 23, 24, 39, 41, 229). However, stratification of CMS data by healthcare setting revealed contrasting utilisation trends, measure by NSU/TIY, between PHCCs and hospitals. The NSU/TIY for overall LLTs increased in PHCCs but declined in hospital settings (**Figure 3.15A-B**). This pattern likely reflects the expanding role of PHCCs in the long-term management of non-communicable diseases (NCDs), including dyslipidaemia, where LLT is commonly initiated in PHCCs, with statins prescribed as first-line therapy.

In contrast, hospitals primarily manage more complex cases and higher-risk patients, for whom treatment escalation and optimisation are more frequently required. This interpretation is supported by the observation of the upward trends and higher levels of high-intensity statin therapy (HIST) and ezetimibe use observed in hospital settings compared with PHCCs (**Figure 3.15C-D**). Importantly, the exclusive and substantial increase in PCSK9i utilisation within hospitals further highlights the role of hospitals in delivering advanced LLTs for patients requiring treatment intensification. This

pattern is consistent with national regulations in Kuwait, whereby PCSK9is were supplied exclusively through hospital settings during the study period.

However, due to the limitations of aggregated-level data in determining detailed prescribing patterns and quality of lipid control for individuals, studies on patient-level data were performed at both levels of healthcare settings: PHCCs (**chapter 4**) and a hospital, specifically tertiary cardiac centre (**chapter 5**).

The study conducted in PHCCs to describe prescribing patterns of LLTs (**chapter 4**) was a multicentre cross-sectional analysis involving 434 patients receiving LLTs across six governorates. Prescribing patterns showed a clear preference for monotherapy over combination regimens (**Figure 4.1**). Whether this pattern reflects appropriate prescribing in relation to lipid target achievement is discussed in the following section. Statins were the predominant LLT, with 98.9% (n= 429/434) of participants receiving a statin prescription (**Figure 4.2**). Among statin users, moderate-intensity statin therapy (MIST) was most frequently prescribed (90.4%, n= 388/429) (**Figure 4.2**). This prescribing pattern likely reflects conventional dosing practices within PHCCs, as well as the influence of formulary restriction, whereby simvastatin is the only statin included in the Essential Medicine List (EML) (**chapter 2**, **section 2.4, p28**). Notably, 70% of the study participants comprised non-Kuwaiti patients (**Table 4.5**), a group for whom prescribing is largely restricted to medicines listed in the EML. Thus, as simvastatin is categorised only as a MIST (**chapter 2**, **Table 2.3**), this policy largely explains why approximately 70% of participants received MIST (**Figure 4.2**).

In contrast, the hospital-based study (**chapter 5**) focused primarily on the most recent LLT available at the research time, PCSK9is, which are primarily intended for patients with uncontrolled lipid levels despite maximally tolerated statin therapy, as well as for those with statin intolerance or familial hypercholesterolaemia (23). The availability of PCSK9i within hospital settings reflects the ongoing challenges in achieving desired lipid targets among individuals at very-high CV risk who do not

attain adequate control with conventional therapies in PHCCs, particularly given the increasingly stringent thresholds set by recent guidelines (23). The hospital-based study employed a retrospective cohort design of patients newly initiated on PCSK9is, primarily to evaluate their real-world effectiveness in lipid reduction. These findings are discussed in detail s**ection 6.1.2.** While PCSK9is are typically recommended as add-on therapy following statins and ezetimibe, the current findings revealed that 41.5% (n= 190/458) of patients had no recorded background LLT prior to initiating a PCSK9i (**chapter 5**, **Table 5.4**). However, interpretation of this finding should be made with caution. The dataset lacked information on comorbidities, which limits the ability to determine whether conventional LLTs were contraindicated, such as in case of statin intolerance. Furthermore, the absence of record linkage with PHCCs meant that prior prescribing of oral LLTs could not be verified. Consequently, some patients classified as having no background LLT may, in fact, have received earlier LLT outside the study hospital.

6.1.2. Quality of lipid control

The quality of lipid control was examined in two distinct healthcare settings: PHCCs (**chapter 4**) and a tertiary cardiac centre (**chapter 5**), depending on the specific aims of each study. In PHCCs, the assessment focused on the proportion of patients achieving guideline-recommended lipid goals, stratified by CV risk category (**chapter 4**, **Table 4.7**). A cross-sectional design was adopted in PHCCs, based on the WHO STEPS surveillance. Data were collected using a dual approach that combined face-to-face patient interviews with data extracted from the electronic health record system, namely PCIS. A proportional stratified sampling technique was applied, and the required sample size was calculated using a precision-based approach, assuming that approximately 50% of patients would achieve therapeutic lipid goals (**chapter 4, section 4.3.2.3**).

In contrast, the hospital-based evaluation focused on changes in lipid profiles, specifically, the median and percentage change in lipid levels following PCSK9i initiation (**chapter 5, Figures 5.6-10**), as well as the rate of lipid target achievement (**chapter 5, Figures 5.11-15**). As comorbidity data were unavailable to stratify patients by CV risk, it was reasonable to assume that, given the tertiary care setting, all patients had established CVD and were therefore managed under secondary prevention. Accordingly, stringent lipid targets were applied, with an LDL-C target of <1.4 mmol/L and a corresponding non-HDL-C target set 0.8 mmol/L higher, in line with regional recommendations (20). To ensure robustness, sensitivity analyses were conducted using both more stringent (<1.0 mmol/L) and more lenient (<1.8 mmol/L) lipid thresholds. A power-based approach was applied to determine whether the cohort included in the effectiveness analysis was sufficiently powered to detect changes in lipid levels (**chapter 5, section 5.3.6.2**).

Additionally, regression modelling was used to Identify factors associated with lipid control in each healthcare setting. In both models, LDL-C and non-HDL-C were selected as the outcome variables, in agreement with Middle East recommendations from the Middle East consensus guidelines (20), which define these parameters as the primary therapeutic targets. In PHCCs (chapter 4), multivariate binomial logistic regression was employed to identify factors associated with lipid target goal achievement, with lipid parameters modelled as categorical variables (**Table 4.8** & **Table 4.9**). In the hospital setting (chapter 5), linear mixed-effects models (LMMs) were applied to identify factors associated with changes in lipid levels following PCSK9i initiation, with lipid parameters modelled as a continuous variables (**Table 5.7** & **Table 5.8**).

Overall, both studies demonstrated a persistent gap between guideline-recommended lipid targets and real-world achievement. This suboptimal lipid control may partially contribute to the continued burden of CVD mortality in Kuwait (8, 106). The interpretation of this key finding is discussed further for each study.

The key findings from the PHCC study (**chapter 4**) indicated suboptimal lipid control across all CV risk categories (**chapter 4, Table 4.7**). Only 20.4% (n= 65/336) of patients achieved their LDL-C targets, and 26.6% (n = 84/336) reached the non-HDL-C targets. Target attainment was particularly low among patients classified at extreme CV risk, with only 8% (n= 9/113) meeting the LDL-C target and 13.8% (n= 16/116) achieving the non-HDL-C goal (**Figure 4.4A**). These findings were supported by the adjusted multivariate logistic regression analysis, which identified CV risk category as an independent factor significantly associated with achievement of both LDL-C and non-HDL-C target (global p-value= 0.0001) (**Table 4.8** & **Table 4.9**). While therapeutic regimen (monotherapy vs. combination therapy) and statin intensity (MIST vs. HIST) were included in the models, neither showed a statistically significant association with lipid target attainment. This suggest that other factors may have contributed to the suboptimal lipid control. A plausible explanation relates to the clinician-related factors, particularly limited adherence to guideline recommendations, including the application of more stringent lipid thresholds advocated for primary prevention in recent guidelines (20, 23). Inaccurate CV risk classification may lead to an underestimation of true CV risk, resulting in patients being assigned to lower CV risk categories than appropriate. Consequently, less stringent lipid targets may be applied, leading to an overestimation of lipid control. This misclassification may contribute to therapeutic inertia and reluctance to intensify LLT (165). Other potential factors that may have contributed to suboptimal lipid control are discussed in detail in **section 4.5**.

While the key findings from the tertiary cardiac centre (**chapter 5**) indicated a statistically significant reduction in LDL-C (41.9%; 95% CI: -50.9% to -24.1%) (**Figure 5.6A**) and non-HDL-C of 38.08% (95% CI: -46.53% to -23.88%) (**Figure 5.7A**) within 90 days following PCSK9i initiation. The LMM further confirmed lipid reductions following PCSK9i initiation (**Table 5.7** & **Table 5.8**). Although lipid reductions observed were statistically significant, the magnitude did not fully replicate the reductions reported in pivotal clinical trials, such as FOURIER for evolocumab (54) and ODYSSEY OUTCOMES for alirocumab (55), where LDL-C reductions of up to 60% were reported. Additionally, several real-world studies have reported reductions comparable to those trials (71, 72, 86), indicating a discrepancy with the present study.

This difference may be partly attributable to the use of routinely collected secondary data and potential misclassification of incident PCSK9i users, particularly due to the lack of record linkage across healthcare settings. Additionally, the relatively limited use of background LLT could explain the more modest lipid reductions than trials. However, background LLT use was not significantly associated with changes in LDL-C or non-HDL-C in the LMM (**Table 5.7** & **Table 5.8**). This lack of statistical significance could be related to the suboptimal LLT intensification or limited use of combination therapy rather than simple availability. Moreover, the absence of detailed comorbidity data in the model may have resulted in residual confounding. Although background LLT was optimised in the PCSK9i clinical trials (54, 55) and is recommended in clinical guidelines (20, 23) prior to PCSK9i inhiation, with several real-world studies reinforcing this approach (71, 72, 86), existing evidence indicates that PCSK9is can still achieve substantial lipid reductions irrespective of background LLT use (23). Potential factors contributing to this finding are discussed in detail in s**ection 5.5**.

Lastly, this research demonstrated that utilisation of LTTs was largely consistent across the six governorates (**chapter 3**, **Figures 3.18-20**). Similarly, adjusted logistic regression analyses showed that lipid target achievement was not significantly influenced by governorate (**chapter 4**, **Table 4.8** & **Table 4.9**). The absence of regional disparities suggests a strong central role of the MOH in ensuring equitable access to LLTs and uniform delivery of healthcare services across Kuwait. However, this uniformity does not necessarily indicate optimal use or appropriate optimisation of LLTs at the individual level.

6.2. Implications of the research findings

This thesis comprises three quantitative studies conducted across three distinct healthcare settings, providing a comprehensive and integrated perspective on the current practice of LLTs in Kuwait. By utilising real-world data, the research aimed to generate high-quality, valid, and reliable evidence to inform policymakers, guide clinical practice, and support future lipid and more broader CV epidemiological research. Collectively, these efforts seek to promote the optimal and efficient use of medicines within the healthcare system.

6.2.1. Implications for policymakers

The findings of this research have important implications for policymakers in terms of improving electronic health record (EHR) databases and optimising data integration within governmental healthcare system. The challenges encountered during data collection across healthcare settings highlight key areas where strategic improvements could strengthen national health data infrastructure and support evidence-based decision-making.

Starting with the CMS, this system is a valuable resource for assessing medication utilisation and expenditure trends over time, as it maintains comprehensive records of all medicines supplied across healthcare settings (Further on CMS in **chapter 3, section 3.3.1**) (76). However, during data retrieval, coordination with the designated pharmacist was required to obtain datasets classified by drug name and corresponding strength. Although the study protocol focused on a limited number of LLT classes (four in total) and discussions were held to ensure that all agents used over 10-year period were captured within each class, this approach carries several drawbacks. Without the clinical experience of the researcher or the designated pharmacist, certain drugs could be overlooked, particularly those that had been discontinued for extended periods. This challenge would become even more pronounced in studies involving a larger number of drug classes or broader therapeutic categories, such as all CV medications. Moreover, relying on drug names

introduce the risk of errors and inconsistencies, particularly when drugs have multiple brand names for a chemical substance, formulations, and strengths.

This method of identification is not aligned with international standards for medication classification. Consequently, it is strongly recommended that the CMS adopts an internationally standardised coding system for medicines, such as the WHO anatomical therapeutic index (ATC)/defined daily dose (DDD) classification (104) ATC/DDDs discussed further in **chapter 3, section 3.3.4.1, p45**). Implementing this system would not only facilitate the retrieval and analysis of medication data but also allow for cross-national comparisons (CNCs) and evaluation against international trends. In addition to reducing reliance on individual expertise, adopting the coding system would facilitate data integration and merging with datasets from other healthcare setting, such as PHCCs and hospitals.

The CMS database is not yet fully integrated with healthcare settings (PHCCs and hospitals). Establishing such record linkage would enable comprehensive tracking of medication use throughout all levels of care (primary, secondary, and tertiary). Ultimately, linking CMS data with prescription/dispensing records could facilitate real-time monitoring of prescription patterns and help identify potential underuse, misuse, or overuse of medications. Moreover, in consistent with international practice, Kuwait could strengthen transparency by routinely publishing national prescribing, dispensing, and expenditure data in publicly accessible and regularly updated reports. For instance, the National Board of Health and Welfare in Sweden publishes open-access statistical databases covering health, medical, and social services, including pharmaceuticals (230). These pharmaceutical databases include information on all prescribed drugs filled at pharmacies between 2006-2024 (the time of this research), excluding OTC and in-hospital medications. Data can be explored by ATC classification, either annually or monthly, and stratified by age, gender, and Swedish region. The system allows for direct calculation of utilisation measures, such as dispensations per 1,000 inhabitants (230).

Another example of publicly available datasets is the Prescription Cost Analysis (PCA) in the UK, which provides aggregated-level data on all medications prescribed and dispensed in primary care settings, classified according to the British National Formulary (BNF) (231). These open-access data sources offer valuable examples that could inspire similar initiatives in Kuwait. Although, a comprehensive national formulary has not yet been published, a regional or international formulary could be adopted temporarily until the local one is officially released. Furthermore, the CMS should be encouraged to develop and publish detailed documentation outlining its structure, roles, responsibilities, and procedures, with regular review and updates by designated personnel. Making this information publicly available on the MOH website would enhance transparency, improve understanding of the CMS system, and support its use as a credible evidence source for research.

Second, at the PHCCs, it was feasible to retrieve prescription data through the unified Primary Care Information System (PCIS). This system is accessible across all PHCCs via the Advanced Technology Centre, which houses the Information System Management unit within Specialised Sabah Region. The centre was able to provide prescribing/dispensing data at the patient-level at the time of the research. Nevertheless, I was informed that the retrieval would no longer be available from this centre, as such requests would be handled by another centre. Although, the prescribing data from the PCIS could address several research questions, the primary objective of obtaining these data in this project was to evaluate the quality of lipid control. A key limitation, however, was the inability to link the PCIS prescription records with laboratory data, including lipid profiles. To overcome this issue, a nationwide cross-sectional study design using a primary data collection approach was adopted to achieve the aim of this study (**chapter 4**). Moving forward, integrating centralised prescribing records with laboratory databases would enable large-scale retrospective cohort studies, offering deep understanding of real-world practice across various therapeutic areas.

Third, in secondary and tertiary hospital settings, the absence of a unified EHR system remains a major barrier to generating comprehensive datasets that can support informed clinical decision-making. The PCSK9i effectiveness study presented in this thesis (**chapter 5**) was conducted at a single tertiary centre, relying on routinely collected dispensing data. However, there was no linkage between the pharmacy system and either prescribing records or laboratory results. Consequently, although it is possible to manually extract both prescribing and laboratory data, the process is time-consuming and resource-intensive. The absence of linkage between prescribing, dispensing, and laboratory systems significantly constrained the ability to obtain a complete and reliable overview of treatment decisions and patient history. These challenges highlight the urgent need for a unified electronic platform that integrates pharmacy, prescribing, and laboratory records within hospital settings. While some secondary hospitals have internal linkages allowing for data integration within the same facility, a centralised cross-hospital linkage remains lacking.

Although achieving a fully integrated electronic system is complex, leveraging existing digital platforms offers an opportunity toward gradual digital transformation. One such platform is 'Sahel', a government application developed by the Public Authority for Civil Information (PACI), which facilitates access to a wide range of e-services across government sectors. Within the healthcare context, 'Sahel' already provides notifications related to medication dispensing, prescribing details, blood tests, and diagnostic reports, positioning it as a potentially valuable tool for clinical data collection and coordination (Instagram account: Sahel). While 'Sahel', holds promise for enhancing data accessibility, its effective use for research or quality improvement requires careful attention to data integrity, governance, and ethical considerations. It is essential to establish clear national guidelines to define the scope of accessible data, protect patient confidentiality, and ensure responsible data usage by healthcare providers and researchers.

To support this digital evolution, there is a pressing need to establish dedicated research units or data management departments within healthcare facilities. These units would play a vital role in organising, standardising, and facilitating secure access to anonymised clinical data for the purposes of research, audit, and quality improvement. Investing in such infrastructure would not only support researchers in generating timely and relevant evidence but would also contribute to building a learning health system capable of informing evidence-based policies and enhancing patient care across Kuwait.

6.2.2. Implications for clinical practice

The findings of this research offer several important implications for clinical practice, particularly in enhancing CV risk reduction through the optimisation of LLT management.

The first study in this thesis (**chapter 3**) demonstrated that the utilisation of PCSK9is has increased significantly over time since their introduction (**chapter 3, Figure 3.3A**), suggesting their growing incorporation into lipid management and a shift towards more intensive therapeutic strategies. This trend was particularly evident in the absence of lipid threshold restriction (120) or financial barrier to prescribing, compared to other countries. In this context, establishing a local quality registry for PCSK9i users would be highly valuable and essential (232). The registry would enable longitudinal monitoring of PCSK9i effectiveness and safety in real-world practice, especially given the current lack of data linkage or system integration across healthcare levels.

This initiative is essential given the stricter lipid thresholds introduced in recent international guidelines and the approval of additional LLTs beyond PCSK9is, including inclisiran (siRNA), bempedoic acid, and icosapent ethyl (23), which became available after the study period. Therefore, with the increasing diversity of LLT options beyond the traditional LLTs (statins, ezetimibe, and fibrates), a registry would facilitate research and generate robust real-world evidence on their patterns, effectiveness, safety, and adherence. Support for this initiative is reinforced by the findings of the real-world effectiveness study of PCSK9is (**chapter 5**), which included 458 incident users from a single tertiary cardiac centre. However, only 115 patients were included in the effectiveness analysis due to incomplete lipid profile across the required baseline/follow-up periods. Establishing a registry would overcome such limitations by including all PCSK9i users and capturing relevant sociodemographic and clinical variables, including lipid profiles.

Moreover, this proposed registry would not be the first in the lipid therapeutic area. For example, the Gulf familial hypercholesterolaemia (FH) registry, which includes Kuwait, was established to estimate the prevalence of FH across the region (32). Leveraging such regional experience, cardiologists and lipidologists in Kuwait could take a leading role in developing a national PCSK9i registry, in collaboration with pharmacists, laboratory specialists, and administrative teams across hospitals. Internationally, several countries, including Denmark and Italy (120, 233), have been conducted PCSK9i research using registry-based cohort. This emphasises the value and necessity of developing a national registry to support evidence-based practice.

Evidence-based practice in optimising lipid management in Kuwait remains challenging, particularly in the light of the findings from the cross-sectional study (**chapter 4**), which demonstrated that despite the widespread use of statins, suboptimal lipid control persisted across all CV risk categories. The challenge lies not only in the use of LLTs but in their optimal utilisation to achieve guideline-recommended lipid targets. Achieving this requires the involvement of multiple stakeholders, including healthcare providers (HCPs) (234). It should be acknowledged, however, that suboptimal lipid control or limited intensification is a multifactorial issue, involving patients, healthcare systems, and regulatory factors (234). Nevertheless, the implications discussed here are limited in scope to HCPs-related factors.

Prescribers must adhere to clinical guidelines by tailoring lipid target for each individual and accurately assessing the CV risk using validated calculators. Subsequently, the choice of LLT should be guided by the required extent of lipid reduction. Inadequate implementation of clinical guidelines is likely a key contributor to suboptimal lipid control observed in the cross-sectional study, particularly for LDL-C (20%) and non-HDL-C (26%) (**Table 4.7**). This potential explanation is supported by the adjusted multivariate analyses for LDL-C (**Table 4.8**) and non-HDL-C (**Table 4.9**), which showed that individuals in higher CV risk categories exhibited lower odds of

achieving their respective lipid targets. This indicates that patients classified within the extreme CV risk category were less effectively manged, despite requiring the most intensive lipid-lowering regimens.

A local cross-sectional study, though somewhat outdated, conducted between 2015 and 2016, surveyed 279 physicians from PHCCs and hospitals to assess adherence to lipid guidelines and to identify barriers to adherence related to knowledge, attitude, and behaviour (235). The study revealed a considerable gap between physicians' self-reported knowledge of lipid guidelines and their actual knowledge when assessed through guideline-based clinical scenarios, as 65% of physicians scored poorly (≤25%). The survey also reported variations in the selection of lipid guidelines and CV risk assessment tool. The findings imply that reliance on multiple guidelines concurrently may contribute to misinterpretation and inconsistency in clinical decision-making, largely driven by knowledge and behavioural barriers (235). A more recent cross-sectional, multicentre audit of 460 patient medical records was conducted across six secondary and tertiary healthcare facilities in Kuwait between 2019 and 2020 to evaluate the adherence to ESC/EAS and ACC/AHA guidelines for the secondary prevention of coronary heart disease. Overall, the study reported an intermediate level of adherence. Importantly, LDL-C levels ≥1.8 mmol/L were significantly associated with low adherence to guideline recommendations, suggesting suboptimal lipid control and inadequate LLT intensification (236).

Within the context of the two case studies presented in Kuwait, effective implementation of clinical guidelines is essential. Emphasis should be placed on adopting a single, clearly defined guideline to mitigate confusion and variation in clinical practice. Therefore, this thesis recommends the adoption of the updated Middle East consensus recommendations (20), which are informed by the ESC/EAS and ACC/AHA guidelines but tailored to the regional population. The consensus provides clear recommendations on selecting an appropriate CV risk assessment tool, such as QRISK, and specifies the lipid targets to be achieved. Importantly, the

consensus emphasises the significance of monitoring both LDL-C and non-HDL-C, the latter being a particularly strong predictor of CV risk (21). Enhancing the knowledge and awareness of clinicians for the value of assessing non-HDL-C alongside LDL-C could represent another key step in optimising lipid management. Even when non-HDL-C values are not provided in laboratory reports, clinicians should be familiar with how to calculate them using the formula: non-HDL-C= total cholesterol – HDL-C. Practitioners should also recognise that the non-HDL-C target is typically 0.8 mmol/L higher than the corresponding LDL-C target. This practice seems to be crucial for improving lipid management, especially as LDL-C levels may appear controlled while non-HDL-C remains elevated (20).

Moreover, the 2022 consensus statement from the European Association of Preventive Cardiology (EAPC) provided comprehensive guidance on optimising adherence to guideline-directed medical therapy in the secondary prevention of CVDs (234). The statement outlined five key dimensions presenting barriers to adherence: the patients, the disease, the therapy, the healthcare system, and the HCP. The consensus stated that poor guideline implementation and delayed adoption of new evidence into clinical practice contribute to clinical inertia, which defined as the failure to initiate or intensify therapy when target are not achieved (234).

To address this, the consensus proposed several strategies aims at reducing therapeutic inertia and improving guideline accessibility. Rather than relying on traditional continuing education, which has shown limited effectiveness, the statement recommends implementing “education outreach visits”, which are face-to-face sessions led by trained educators who provide direct feedback on HCP performance (234). Given the increasing digitalisation of healthcare communication, authors also emphasised on the importance of expanding access to guidelines through digital platforms, such as smartphone applications (234). Additionally, to enhance accountability, the consensus encourages the establishment of system-level quality improvement programmes that integrate “feedback metrics”, such as

interactive dashboards, allowing clinicians to track and compare their performance indicators against peers (234), such as lipid target achievement.

These interventions could be feasibly applied in PHCCs across Kuwait, as all PHCCs operate under the Central Directorate of Primary Health Care (CDPHC) (129). Therefore, it would be feasible to propose such initiatives and to evaluate the most cost-effective approaches for optimising CV outcomes. Most importantly, efforts should focus on fostering a culture that supports the uptake of evidence-based interventions to improve patient outcomes. According to the EAPC consensus, the application of "implementation science" is essential for supporting HCPs in effectively integrating research findings into clinical practice (234). It should be acknowledged that several PHCCs in Kuwait have implemented quality improvement projects. The Quality and Accreditation Directorate in Kuwait (Instagram account: qad_kw) organises the annual Safety Star Award, which recognises projects conducted across healthcare settings and promotes collaboration through poster presentations on real-world practices. Additionally, the annual Kuwait Primary Health Care Conference and the annual Kuwait International Family Medicine Conference provide platforms for presenting research conducted in PHCCs. These events also recognise outstanding contributions, offering HCPs opportunities to engage with emerging evidence and remain up to date with the latest clinical guidelines that inform practice.

Another key intervention, suggested by EAPC, is the adoption of "multidisciplinary (MDT)-based care models", which have demonstrated effectiveness in reducing CV risk factors (234). A vital feature of such models is the use of "guideline-based algorithmic approach" (234), which is a structured, flowchart frameworks that guides stepwise clinical decision-making, helping to translate evidence into practical actions for medical education and patient care (237, 238). Integrating pharmacists, nurses, laboratory technicians, dietitians within MDTs is a crucial step towards improving the CV risk classification and, ultimately, achieving lipid targets.

In the USA, a retrospective pre-post study evaluated a multidisciplinary lipid clinic (MDLC) during its first year of implementation in 2019, using the RE-AIM implementation science framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) (239). The MDLC found high "effectiveness" in decreasing LDL-C levels, enhancing guideline-adherence, and improving diagnosis. However, "reach" and "adoption" were low, "implementation" was modest, and to improve "maintenance", the MDLC transitioned from in-person follow-up to telehealth consultations. Overall, the MDLCs showed a substantial lipid optimisation, although challenges related to system-level integration were indicated, particularly in its early stages (239). Adopting a similar MDT-based approach in Kuwait could optimise LLT use and improve lipid control, highlighting the importance of ensuring service continuity, sustainability, and resilience to overcome implementation challenges.

Several PHCCs in Kuwait operates a Medication Therapy Management (MTM) clinic led by pharmacists, who play a vital role in medication reconciliation, patient education, and adherence support. In October 2025, the Pharmaceutical Services Administration (PSA) announced through its official Instagram account (psa.mohkw) the establishment of a Pharmacist-led Medication Counselling & Education (PCE) training programme. This initiative aims to strengthen pharmaceutical care within PHCCs by standardising counselling and education practices using evidence-based recommendations, delivered by experienced pharmacists. Building on this advancement in pharmaceutical care, there is an opportunity to establish a committee within this framework to develop MDT lipid clinic, integrated with MTM service, to optimise lipid management and thereby enhance adherence to evidence-based guidelines. Within MDT lipid clinic, pharmacists could collaborate closely with general practitioner or family medicine physicians to refer patients attending NCD clinics to the MDT lipid clinic. This collaboration would ensure accurate CV risk assessment, optimisation of LLTs, and reinforcement of treatment adherence, though was not assessed in the present research. Pharmacist could also coordinate

with laboratory technicians to ensure the timely provision of complete lipid profile and to facilitate continuous monitoring. Furthermore, pharmacists, in discussions with physicians, could participate in referral decisions for patients requiring advanced therapy, such as PCSK9is. Pharmacists in Kuwait currently cannot prescribe or request lipid profile; therefore, this service would rely on effective collaboration and communication with clinicians.

In hospital settings, a similar model could be implemented through clinical pharmacy units by establishing an MDT-based lipid clinic. PCSK9is are available exclusively in hospitals, and require comprehensive patient counselling, as PCSK9is are self-administered injections that must be stored at cold temperatures. Although the PCSK9i study (**chapter 5**) showed significant lipid reductions, the relative reductions were lower than those reported in trials. This could plausibly be explained by suboptimal LLT utilisation or adherence, which were not evaluated in this study. Other contributing factors may also exist and warrant further research, as discussed in the following section (**chapter 6**, **section 6.2.3**).

A prospective pre–post intervention study conducted in the UK at a specialised hospital centre demonstrated that a pharmacist-led clinic, managed by independent prescribing clinical pharmacists, achieved substantial improvements in LLT utilisation and lipid control (240). The proportion of patients receiving HIST increased from 39% to 76% (OR ≈ 4.89; 95% CI 3.06–7.82) and the proportion achieving non-HDL-C target increased from 19% at baseline to 67% post-optimisation (OR ≈ 8.67; 95% CI 5.30–14.20) (240). This study reinforces the crucial role of integrating pharmacists into lipid management and achieving treatment targets.

Another important implication is related to the quality of the PCIS used in PHCCs. The cross-sectional study (**chapter 4**) employed a dual-source data collection approach, combining face-to-face patient interviews with information extracted from the PCIS to capture all variables required for CV risk calculation. This approach proved more effective than relying on the PCIS alone. Although the PCIS alone allows faster data extraction and could yield larger patient samples, observations during data collection revealed that several variables necessary for CV risk scoring was either outdated or incomplete. Consequently, HCPs were often unable to calculate CV risk accurately using PCIS alone, which could contribute to inaccurate CV risk classification and, eventually, suboptimal lipid control. Therefore, it is essential that physicians ensure accurate documentation and regular updating of EHRs within the PCIS. This would not only facilitate calculating CV risk appropriately but also enhance the quality of PCIS data for research purposes, enabling faster and more comprehensive analyses in the future.

6.2.3. Implications for future research

This thesis has addressed important gaps in the existing literature by providing a comprehensive evaluation of LLT utilisation and expenditure, alongside the quality of lipid target attainment across multiple healthcare settings in Kuwait. Through leveraging multiple data sources and adapting to practical constraints related to data accessibility and time, this research demonstrates the feasibility of conducting real-world pharmacoepidemiological studies in Kuwait healthcare context. Building on this foundation, several research questions warrant further investigating to expand and enrich the current evidence base.

The first study in this thesis **chapter 3**, which quantified LLT utilisation trends, is the first of its kind, to the best of my knowledge, in the Gulf region. The design of this study can serve as a foundation for similar research in other Gulf countries, creating opportunities for valuable CNCs. This is particularly relevant as one of the utilisation metrics employed in the CMS study was DDD/TID. The same dataset could also be utilised to address additional research questions. For instance, an interrupted time series (ITS) analysis could be performed over the 11-year period (2012-2022) to evaluate the impact of 2019 ESC/EAS guidelines, which introduce stricter lipid thresholds, by comparing LLT utilisation before and after their publication, similar to Yew PY et al., 2024 study (241). Another potential intervention point could be the COVID-19 pandemic, allowing examination of whether lockdown influenced LLT utilisation, similar to Dale CE et al., 2023 study (242).

Moreover, the CMS study provides a methodological framework for conducting drug utilisation research across other therapeutic areas, such as antidiabetic medications. The introduction of newer agents, including GLP-1 receptor agonists, could present a timely opportunity to examine utilisation and expenditure trends of antidiabetic therapies over the past decade. Although the analysis is based on aggregate-level data, it nonetheless contributes a foundational perspective on current practices.

In the cross-sectional study (**chapter 4**), the participants were recruited from NCD clinics and were required to be on at least one LLT at the time of recruitment. Future nationwide cross-sectional study could expand this approach by including patients attending PHCCs, whether form NCD or GP clinics, and regardless of their current LLT use. This would allow for the assessment of lipid target attainment among a broader patient populations and enhance understanding of the appropriateness of LLT utilisation in achieving lipid target, similar to Bayram F et al., 2020 (162).

While this cross-sectional study adopted the Middle East consensus recommendations for CV stratification using the QRISK tool (20), future research could extend these findings by applying alternative risk prediction models. For instance, the SCORE algorithm, which estimates the 10-year risk of fatal CV events and is recommended in the 2019 ESC/EAS guidelines (23), or the newer SCORE2 and SCORE2-OP risk algorithms endorsed in the 2025 focused update of the 2019 ESC/EAS guidelines, which estimate the 10-year risk of both fatal and non-fatal CV events (243). Applying different risk tools would enhance generalisability and allow assessment of whether variations in risk classification influence lipid target attainment on the same population.

Since all PHCCs use the same EHR system (PCIS), conducting a retrospective cohort study of patients using LLTs over a defined period would be feasible. However, such an approach would have certain limitations, including the absence of linkage with other healthcare records and the lack of integration of laboratory data. Nevertheless, the prescribing dataset alone could still be used be possible to address several research questions. For example, it could support investigation of the association between statin intensity and adherence, persistence, and discontinuation in PHCCs, similar to the retrospective cohort study conducted in Scotland (188). The selection of this research question is informed by the findings of suboptimal lipid control observed in PHCCs (**chapter 4**) and less-than-expected lipid reductions following

PCSK9i use (**chapter 5**), where LLT adherence may have played a potential factor but could not feasible to assess within the scope of the current research.

Therefore, utilising secondary prescribing data would enable understanding of adherence patterns over time. for better understanding of the underlying reasons for non-adherence and patients' perception of LLT, qualitative research would be required to complement these quantitative findings.

Furthermore, this thesis employed the Friedewald formula (FF) to estimate LDL-C levels in both **chapter 4** and **chapter 5**, consistent with routine laboratory practice in Kuwait. However, evidence has highlighted several limitations of the FF, particularly in patients with elevated triglycerides levels. Alternative equations, such as the Martin-Hopkins method, have been proposed to improve LDL-C estimation accuracy (178, 244). The Martin-Hopkins equation divides TGs by an adjustable factor derived from the patient's non-HDL-C and TG levels. Given that FF is not recommended when TGs exceed 4.5 mmol/L (23, 244, 245), this raises important considerations for laboratory technicians and health administrators. Future research comparing the FF with newer estimation methods could help guide evidence-based updates to current practice. Such efforts would ultimately improve clinical decision-making and adherence to treatment guidelines.

A recent Portuguese study, published in 2024, compared the FF and Martin-Hopkins equations among LDL-C-controlled patients (178). The authors found that substituting the Martin-Hopkins equation for the FF reclassified over 20% of patients from the controlled to non-controlled category. Accordingly, they recommended using the Martin-Hopkins equation or direct LDL-C measurement when LDL-C <1.8 mmol/L. Importantly, both equations are invalid when TG > 4.5 mmol/L due to the accumulation of chylomicrons, which alter the relationship between TG and VLDL (24). Therefore, direct LDL-C measurement is preferred in these cases. Interestingly, Martins et al. (2023) reported that the extended Martin-Hopkins equation may be applied with TG levels up to 9 mmol/L (246). It is also important to note that direct

LDL-C measurement also has limitations, including potential systematic bias and inaccuracy, especially with high TG levels.

The two studies conducted in Kuwait have contributed to understanding the real-world effectiveness of PCSK9is: the ZERBINI study (73) and the retrospective cohort study presented in this thesis (**chapter 5**). Although the retrospective cohort design enables the inclusion of a large number of patients and allows for long-term follow-up, it has certain limitations compared with a prospective design. Based on the experience from the retrospective study (**chapter 5**), which was limited by the available variables in the secondary database, a prospective design, such as in the ZERBINI study (73), would be preferable in future research, particularly for real-world effectiveness studies. The prospective design would enable the collection of more comprehensive data, including comorbidities, background LLT use, and concomitant medications. Ultimately, establishing a quality register, as proposed in **section 6.2.1**, would provide a more robust source of data for monitoring and evaluating the real-world effectiveness of PCSK9is across Kuwait.

The ZERBINI study was limited to a single centre and focused solely on evolocumab (73), thereby narrowing its generalisability. A more comprehensive, longitudinal prospective study could be designed to include multiple hospitals across Kuwait, or at minimum, all tertiary cardiac centres. This can be achieved through collaboration with cardiologists, lipidologists, laboratory technicians, and pharmacists. Such a study could involve the collection of demographic and clinical data over a period of more than two years, allowing for the evaluation not only of lipid-lowering effectiveness and safety (as done in ZERBINI), but also of major adverse cardiovascular events (MACE). This approach would be especially timely and relevant in light of the recent approval and availability of newer lipid-lowering agents, including fixed-dose statin/ezetimibe combinations and emerging therapies such as bempedoic acid and inclisiran. Prioritising this type of collaborative, prospective research would significantly enhance the evidence base for optimising dyslipidaemia management in Kuwait. In an ideal scenario, target trial emulation (TTE) using a comparator group

would provide stronger causal inference and help minimise confounding and immortal time bias (247). Such a model would require a comprehensive registry of patients receiving PCSK9is across hospitals in Kuwait.

Moreover, the LMM presented in **chapter 5** revealed that older patient experienced greater lipid reduction following PCSK9is (**Table 5.7** & **Table 5.8**). Although previous studies have not identified a significant impact of age on PCSK9i response, the findings from this study appear to differ. It remains unclear whether this finding reflects a true effect or residual confounding. Future research examines PCSK9i users by age group could help clarify this association.

6.3. Conclusions

This thesis demonstrates a sustained increase in the utilisation trends of LLTs in Kuwait, reflecting growing recognition of dyslipidaemia as a key modifiable CV risk factor and an increasing reliance on pharmacological interventions to manage lipid disorders and, ultimately, reduce CV mortality. Despite this positive trend, achievement of guideline-recommended lipid targets remains suboptimal. This persistent gap highlights the need for more proactive, patient-centred, and targeted interventions to lipid management that are aligned with contemporary clinical guidelines.

By integrating multiple data sources across primary care, hospital setting, and the national medication procurement system, this thesis provides valuable real-world evidence on lipid management in Kuwait. The findings offer important insights to inform health policy, identify opportunities to improve clinical practice, and establish a strong methodological foundation for future pharmacoepidemiological research in the region.

7. References

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8. Appendices

Appendix S1.1. Overview of the burden of non-communicable diseases (NCDs) in the Middle East and North Africa (MENA) region

The development of NCDs is driven by a complex interplay of genetic, physiological, metabolic, and behavioural factors (6). While certain risk factors, such as genetic predisposition, are non-modifiable, modifiable behavioural risk factors, such as tobacco use, physical inactivity, and unhealthy dietary patterns, play a major role in the onset and progression of disease. In parallel, metabolic risk factors, including obesity, hypertension (HTN), diabetes mellitus (DM), and dyslipidaemia, further increase susceptibility to NCDs (6).

Notably, the MENA region has observed significant improvements in key health indicators, including increased life expectancy and reductions in infant and mortality rate (248), although variations persist across different countries. Concurrently, while communicable diseases have declined, the epidemiological transition has shifted towards NCDs (248). Key risk factors contributing to this shift include obesity, HTN, smoking, and elevated blood glucose. The rapid rise in NCD prevalence has also been closely linked to the rapid urbanisation, a trend projected to continue, including in Kuwait (248). Moreover, several MENA countries are affected by ongoing conflicts and wars, further exacerbating health disparities and negatively impacting overall health outcomes (248). Furthermore, the MENA region has experienced substantial demographic changes, with a 3.7-fold population increase between 1950 and 2000, which was the highest rate of population growth rate globally during that period (249).

Manla and Almahmeed (2023) addressed the growing burden of coronary heart disease (CHD) in the MENA region, highlighting that the region has the highest age-standardised incidence and prevalence rates of CHD globally (250). In 2019, CHD ranked as the leading cause of death in the MENA, responsible for a quarter of all-cause mortality. This was largely attributable to metabolic risk factors (high systolic blood pressure (SBP), high low-density lipoprotein cholesterol (LDL-C), high fasting

plasma glucose (FPG), and high body-mass index (BMI), in addition to behavioural factors (unhealthy diet, tobacco use, and physical inactivity) and environmental factors (air pollution and suboptimal temperature) (250).

Populations in the MENA region exhibits unique demographic characteristics in relation to CVD. For instance, evidence from the INTERHEART study, a large international case-control study conducted between 2000 and 2002 across 52 countries, including Middle East countries, provides important insights into these differences (251). The study enrolled 15,152 cases of acute myocardial infarction (MI) and 14,820 controls to examine the importance of risk factors to coronary heart disease globally (251). Despite being outdated, the study provided compelling evidence that the first MI occurred approximately a decade earlier in the MENA region, with a mean age of 51 years compared with 63 years in Western populations. Moreover, the proportion of individuals aged ≤40 years presenting with MI in MENA was nearly threefold higher (11%) than that observed in North America (4%) and Western Europe (3%) (251).

Additionally, a pooled analysis of 15,532 patients with ST-segment elevation MI (STEMI) from seven MENA countries (including Gulf countries and Yemen) between 2005 and 2017 reported a worse prognosis in younger women (252). Women under 65 years were significantly less likely than men to receive guideline-recommended therapy. Even after adjusting for clinical variables, younger female sex remained independently associated with higher in-hospital mortality compared to younger males (252).

Moreover, analysis of the Global Burden of Diseases (GBD) 2019 data, which quantified the impact of metabolic risk factors in the MENA region between 1990 and 2019, showed that population exposure to all four major metabolic risk factors (high SBP, high FPG, high LDL-C, and high BMI), increased over the past three decades.

Notably, although the disease burden attributable to high BP and LDL-C decreased over time, the burden associated with high FPG and high BMI continued to rise (253). Further evidence from the MENA region indicates that the Gulf countries, comprising Kuwait, Saudi Arabia, Qatar, Bahrain, Oman, and the United Arab Emirates (UAE), face a substantial burden of CVD, accounting for up to 45% of all mortalities (91). Data from the Gulf Registry of Acute Coronary Events (Gulf RACE-2) further demonstrated that individuals in the Gulf countries present with acute coronary syndrome at a younger age compared to their counterparts in Western populations (254).

Appendix S1.2. Lipoprotein structure

Lipoproteins are complex particles composed of a central hydrophobic core containing non-polar lipids, primarily cholesterol esters and triglycerides (TGs). This core is surrounded by a hydrophilic membrane surface layer made up of phospholipids, free cholesterol, and apolipoproteins. These apolipoproteins act as a structural role, ligands for lipoprotein receptors, and enzyme activators or inhibitors (**Figure S1.1**) (12). Lipoproteins play a crucial role in lipid metabolism by absorbing and transporting dietary from the small intestine, delivering lipids from the liver to peripheral tissues, and mediating reverse cholesterol transport, which involves returning excess cholesterol from peripheral tissues to the liver and intestine for excretion (12).

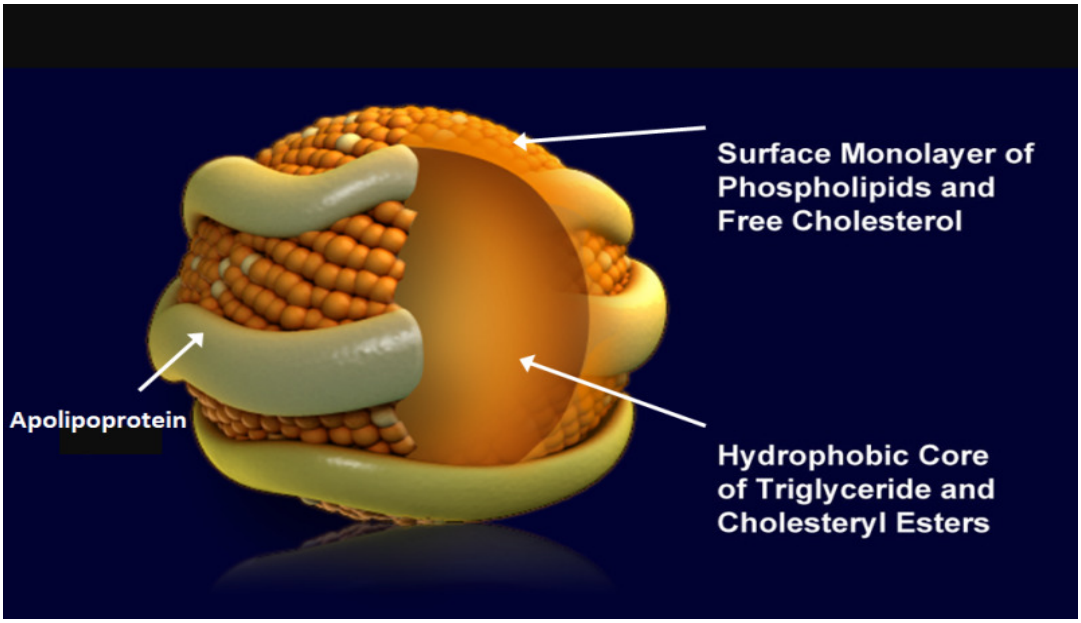

Figure S1.1 Lipoprtien strcture, adapted from Feingold et al. (12)

Appendix S1.3. Lipoprotein classes

Plasma lipoproteins are divided into seven classes: chylomicrons, chylomicrons remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein (a) [Lp (a)]. These classes differ in particle size, lipid content, and apolipoprotein type (**Figure S1.2**).

Among these lipoproteins, a subgroup known as triglyceride-rich lipoproteins (TRLs) is mainly responsible for transporting triglycerides (TGs) and cholesterol in the bloodstream. TRLs include chylomicrons, which are produced by the intestinal mucosa to carry dietary TGs and cholesterol from the gastrointestinal tract to peripheral tissues and the liver, as well as VLDL and IDL, which are derived from the liver and carry lipids synthesised within the body (12, 21).

Chylomicrons are the largest and most TRLs but are short-lived, appearing mainly in the postprandial state. Once their TGs are hydrolysed in peripheral tissues, chylomicrons are converted into smaller, cholesterol-enriched, known as chylomicron remnants. These remnants are pro-atherogenic due to their ability to contribute to arterial plaque formation. In contrast, the liver produces VLDL particles to transport endogenous TGs. These particles are smaller than chylomicrons but also rich in TGs. As VLDL particles lose their TG content through lipoprotein lipase (LPL) action in muscle and adipose tissue, they are converted into IDL, which carry more cholesterol and serve as precursors to LDL, the primary cholesterol-carrying lipoprotein in circulation (12, 21). Lp (a) is a lipoprotein particle consisting of an LDL-like core bound to a unique apolipoprotein (a). Structurally similar to LDL-C, Lp (a) can be incorporated into arterial plaques, promoting the development of atherosclerotic lesions. Elevated plasma levels of Lp (a) are associated with a heigh risk of atherosclerosis and are considered pro-atherogenic, pro-inflammatory, pro-thrombotic, and anti-fibrinolytic (255).

Parameters	Chylomicrons	VLDL	IDL	LDL	Lp(a)	HDL
Size (nm)	~75-1000	30-80	25-35	18- 25	~30	5-12
Density (g/ml)	<0.95	0.950- 1.006	1.006- 1.019	1.019- 1.063	1.055- 1.085	1.063- 1.210
TG Content (%)	~85-90	~50-65	~20-30	~5-10	~5	~5-10
Cholesterol Ester Content (%)	~3-5	~10-15	~30-35	~35-48	~35-40	~12-30
Major Apo-proteins	Apo B-48	Apo B-100	Apo B-100	Apo B-100	Apo (a); Apo B-100	Apo A I-II

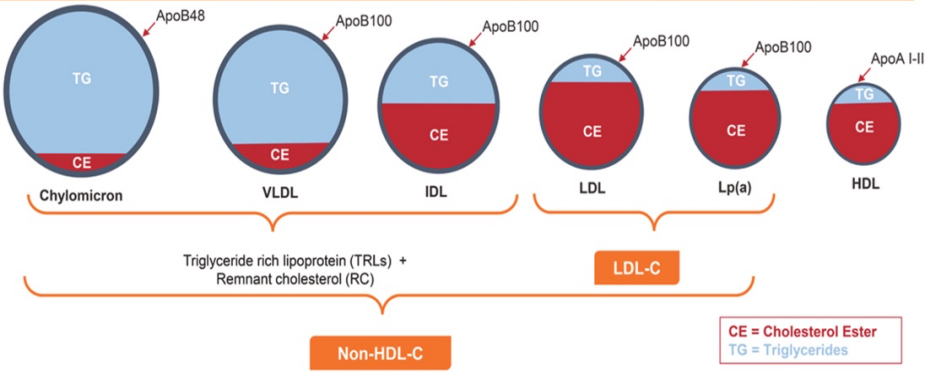

Figure S1.2 Key physical characteristics of the blood lipid particles. Adapted from Raja et al. (21).

Another important marker is apolipoprotein B100 (ApoB100), which is the main structural protein of VLDL, IDL, and LDL. ApoB100 is the primary ligand for the LDL receptor and plays a central role in the hepatic clearance of atherogenic lipoprotein particles, including LDL, IDL, and VLDL remnants (12). ApoB100 is considered a robust and reliable marker for quantifying all atherogenic lipoproteins and assessing overall cardiovascular risk (256). Accordingly, ApoB100 is recommended as a secondary treatment target in international guidelines (23, 24), as well as in the Middle East consensus (20). Data from UK Biobank analyses suggest that LDL-C and non-HDL-C together capture the majority of variability in ApoB100 levels (approximately 92%). This implies that, in routine clinical practice, ApoB100 may provide limited additional predictive value for atherosclerosis cardiovascular risk (ASCVD) beyond that provided by non-HDL-C alone (257). However, non-HDL-C remains a practical alternative to ApoB100 in clinical settings due to its simplicity, accessibility, and cost-effectiveness (21). This understanding is particularly important when examining the role of TGs in ASCVD, as growing evidence suggests that the associated risk is primarily mediated by the number of circulating ApoB-containing lipoprotein particles, rather than the TG content itself (23).

Appendix S1.4. Atherogenic dyslipidaemia

In type 2 diabetes mellitus (T2DM), insulin resistance leads to increased hepatic production of very-low-density lipoprotein (VLDL) (258). Impaired clearance of VLDL results in the accumulation of triglyceride-rich lipoprotein remnants, which are highly atherogenic and contribute to plaque formation in blood vessels. These remnants are further processed into small dense LDL (sdLDL), a highly atherogenic LDL subtype that is more susceptible to oxidation and has greater arterial wall penetration, thereby increasing cardiovascular (CV) risk (258).

In parallel, elevated VLDL levels disrupt the function of high-density lipoprotein (HDL) through a process of cholesterol exchange, whereby HDL particles exchange cholesterol esters for triglycerides (TGs) with VLDL. This process results in triglyceride-rich, dense HDL particles that are cleared more rapidly from circulation and exhibit reduced capacity for reverse cholesterol transport, a critical anti-atherogenic mechanism responsible for removing excess cholesterol from the arterial walls (258). As a result, non-HDL-C, which encompasses the atherogenic apolipoprotein B-containing lipoproteins, including VLDL, LDL, and sdLDL provides a more accurate marker for CV risk than LDL-C alone. This is particularly relevant in diabetic dyslipidaemia, where LDL-C levels may appear normal despite a high concentration of atherogenic particles and elevated residual CV risk. Accordingly, aggressive management of TGs and TC is crucial to reduce non-HDL-C and sdLDL levels and thereby lower CV risk (258).

Obesity, characterised by excessive adiposity, is a major contributor to insulin resistance and T2DM. Obesity promotes hepatic overproduction of VLDL and leads to the formation of TG-rich, dysfunctional HDL particles, resulting in impaired HDL function and reduced efficiency of reverse cholesterol transport. Consequently, these disturbances contribute to atherogenic dyslipidaemia and increased CV risk (258).

Appendix S1.5. Comparison of the 2019 ESC/EAS guidelines and the Middle East consensus on cardiovascular risk categories

Table S1.5.1 Comparison of 2019 ESC/EAS guidelines and Middle East consensus for ASCVD risk classification (20, 119)

Risk category	**2019 ESC/EAS guidelines criteria**	Middle East **consensus using QRISK2 criteria**
Extreme	-	• ASCVD either clinical or equivocal (established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease). • Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL • Diabetes plus microvascular end organ damage (nephropathy, retinopathy, neuropathy), or CKD stage 3–4, or FH with established clinical ASCVD. • QRISK2 score >20% score 2–10%.

Table S1.5.1 Comparison of 2019 ESC/EAS guidelines and Middle East consensus for ASCVD risk classification (20, 119)

Risk category	**2019 ESC/EAS guidelines criteria**	Middle East **consensus using QRISK2 criteria**
Very-high-risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. • DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). • Severe CKD (eGFR <30 mL/min/1.73 m2). • A calculated SCORE >_10% for 10-year risk of fatal CVD. • FH with ASCVD or with another major risk factor.	• Diabetes plus microvascular end organ damage. (nephropathy, retinopathy, neuropathy), or CKD stage 3–4, or FH – PLUS 1 or more risk factor(s) (20). • QRISK2 score 10–20%.

Table S1.5.1 Comparison of 2019 ESC/EAS guidelines and Middle East consensus for ASCVD risk classification (20, 119)

Risk category	**2019 ESC/EAS guidelines criteria**	Middle East **consensus using QRISK2 criteria**
High-risk	People with: • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP >_180/110 mmHg. • Patients with FH without other major risk factors. • Patients with DM without target organ damage, with DM duration >_10 years or another additional risk factor. • Moderate CKD (eGFR 30_59 mL/min/1.73 m2). • A calculated SCORE >_5% and <10% for 10-year risk of fatal CVD.	• ≥2 risk factors (20) • Diabetes plus microvascular end organ damage. (nephropathy, retinopathy, neuropathy), or CKD stage 3–4, or FH – with no other risk factors. • Young patients with diabetes (typ1 <35 and type 2 < 50) • Metabolic syndrome. • QRISK2 score 2–10%.
Moderate-risk	• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. • Calculated SCORE >_1 % and <5% for 10-year risk of fatal CVD.	• ≤2 risk factors (20) • QRISK2 score <2%.
Low-risk	• Calculated SCORE <1% for 10-year risk of fatal CVD.	• No risk factors.

ASCVD: Atherosclerotic cardiovascular disease; **ACS**: Acute coronary syndrome; **BP**: Blood pressure; **CABG**: Coronary artery bypass graft surgery; **CKD**: Chronic kidney disease; **CT:** Computed tomography; **CVD**: Cardiovascular disease; **DM**: Diabetes mellitus; **eGFR**: estimated Glomerular filtration rate; **FH**: Familial hypercholesterolaemia; **LDL-C**: Low-density lipoprotein cholesterol; **MI**: Myocardial infarction; **PCI**:

Table S1.5.1 Comparison of 2019 ESC/EAS guidelines and Middle East consensus for ASCVD risk classification (20, 119)

Risk category	**2019 ESC/EAS guidelines criteria**	Middle East **consensus using QRISK2 criteria**
Percutaneous coronary intervention; **SCORE**: Systematic Coronary Risk Estimation; **T1DM**: Type 1 DM; **T2DM**: Type 2 DM; **TC**: Total cholesterol; **TIA**: Transient ischaemic attack. Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.		

Appendix S1.6. Additional details on statins

Statins are generally well tolerated; however, some individuals may experience side effects that prevent them from continuing treatment, a condition referred to as statin intolerance (142). The most common manifestation is muscle-related symptoms, known as statin-associated muscle symptoms (SAMS). These typically present as myalgia, which includes muscle aches, weakness, or cramps, without an accompanying rise in creatine kinase (CK) levels, and can affect up to 15% of statin-treated patients (142). Although these symptoms are often mild, they may lead to treatment discontinuation, which is a concern given that non-adherence significantly increases the risk of cardiovascular events. Importantly, the development of severe complications such as rhabdomyolysis is rare, occurring in approximately 1 in 23 million people taking atorvastatin (142).

Before deciding to discontinue statin therapy altogether, it is crucial to explore other options. These may include reintroducing the same or a different statin at a lower dose, using a long-acting statin like rosuvastatin on an intermittent basis (e.g. two to three times per week), or combining a statin with ezetimibe to enhance lipid-lowering while minimising statin exposure. Statin intolerance is typically categorised as partial, where some statins at certain doses are tolerated, or complete, in which case non-statin therapies are required (142).

However, it is worthy to mention that true statin intolerance is less common than perceived (259), as this may be partly explained by the nocebo effect, where symptoms arise due to negative expectations rather than the drug itself. The GAUSS-3 trials demonstrated that a substantial proportion of muscle-related complaints also occurred among patients receiving placebo (260).

Appendix S1.7. Comparison of the Fourier and ODYSSEY OUTCOMES trials evaluating PCSK9is

Table S1.7.1. Comparison of the Fourier and ODYSSEY OUTCOMES trials, adapted from (261-264)

Characteristics of study and participants	**FOURIER** (54)	**ODYSSEY OUTCOMES** (55)
Date of publication	May 4, 2017	November 29, 2018
Trial design	Randomised, double-blinded, placebo-controlled	Randomised, double-blinded, placebo-controlled
Drug regimens	Evolocumab 140 mg every 2 weeks or 420 mg monthly	Alirocumab 75 or 150 mg every 2 weeks (dose adjusted to meet LDL-C target of 25–50mg/dL)
Sample size	27,564	18,924
Median follow-up	2.2 years	2.8 years
Mean age of participants	62.5 ± 9.1 (evolocumab) 62.5 ± 8.9 (placebo)	58.5 ± 9.3 (alirocumab) 58.6 ± 9.4 (placebo)
Percentage of male participants	75.4% evolocumab 75.5% placebo	74.7 (alirocumab) 74.9 (placebo)
Inclusion criteria	Age >40 years <85 years	Age >40 years
	ASCVD (MI, stroke, or PAD)	Hospitalised with ACS 1–12 months before randomisation
	LDL-C ≥ 1.8 mmol/L (70 mg/dL)	LDL-C ≥1.8 mmol/L (70 mg/dL)
	Or non-HDL-C ≥ 2.6 mmol/L (100 mg/dL) on optimal therapy	Or non-HDL-C ≥2.6 mmol/L (100 mg/dL) or apolipoprotein B ≥ 80 mg/dL
	High-intensity statin (69.3%)	High-intensity atorvastatin/rosuvastatin (88.9%)
	Moderate-intensity statin (30.4%)	Low-/moderate-intensity atorvastatin/rosuvastatin (8.5%)
	Low intensity/no data (0.03%)	Other statins (0.25%) No statin (2.4%)
	Ezetimibe (5.3%)	Ezetimibe (2.9%)
Primary endpoint	MACE: composite of cardiovascular death, MI, stroke, hospitalisation for UA or coronary revascularization	MACE: composite of death from CHD, nonfatal MI, fatal/nonfatal ischaemic stroke or UA requiring hospitalisation

Table S1.7.1. Comparison of the Fourier and ODYSSEY OUTCOMES trials, adapted from (261-264)

Characteristics of study and participants	**FOURIER** (54)	**ODYSSEY OUTCOMES** (55)
Primary endpoint HR (95% CI) vs. placebo	0.85 (0.79–0.92); p<0.001	0.85; (0.78–0.93); p<0.001
Primary endpoint relative reduction	15%	15%
Baseline LDL-C	2.39 mmol/L (92 mg/dL)	2.39 mmol/L (92 mg/dL)
Target LDL-C	No	Yes (25–50mg/dL)
Mean percentage of LDL-C reduction	59% at 48 weeks	62.7% at 4 months; 61.0% at 12 months; 54.7% at 48 months

MI: Myocardial infarction; **PAD**: Peripheral arterial disease; **ACS**: Acute coronary syndrome; **LDL-C**: Low-density lipoprotein cholesterol; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **MAC**E: Major adverse cardiac events; **UA**: Unstable angina; **CHD**: Coronary heart disease; **HR**: Hazard ratio; **CI**: Confidence interval

Appendix S1.8. Ethical approval obtained from the Ministry of Health, Kuwait

https://drive.google.com/file/d/12x3zyo3HwXPD2mWq7g-h5uEchXECzAj5/view?usp=drivesdk

Appendix S3.1. Time points for initiation (after January 2012), suspension (during the study period), and discontinuation (before December 2022) of LLTs in the CMS dataset

Table S3.1.1. Time points for initiation, suspension, and discontinuation of LLTs in the CMS

Drug name & strength	Initiation time	Suspension for a period	Discontinuation time
Atorvastatin 40 mg	July 2014		
Simvastatin 40mg	March 2012	November 2018	
Rosuvastatin 10 mg	December 2013		
Rosuvastatin 20 mg	December 2013		
Pitavastatin 2 mg	January 2017	July-November 2020	January 2021-end of study
Pitavastatin 4 mg	January 2017	November-December 2018 February 2022	April 2022
Fenofibrate 145 mg	February 2014		
Gemfibrozil		August 2021	
Bezafibrate			July 2018
Ezetimibe 10 mg	December 2013		
Evolocumab 140mg	December 2016		
Alirocumab 75mg	February 2017	June-December 2017 June 2022 & September 2022	
Alirocumab 150mg	March 2022		

LLTs: Lipid-lowering therapies; **CMS:** Central Medical Store

Appendix S3.2. Absolute, relative, and average annual changes in in LLT utilisation (NSU/TIY & DDD/TID) and expenditure (CSU/TIY) at the national level over the study period from 2012 to 2022

	A. NSU/TIY		B. DDD/TID		C. CSU/TIY	
	Absolute change (relative % change)	**Annual average change**	**Absolute change (relative % change)**	**Annual average change**	**Absolute change (relative % change)**	**Annual average change**
All LLTs	71,839 (52%)	7365**	62 (119%)	6.2*	30,627 (136%)	3290*
All Oral LLTs	71,606 (52%)	7342**	61 (116%)	6.1*	15,396 (68%)	1470*
Statins	54,501 (41%)	5800*	53 (102%)	9.6*	10,555 (47%)	968**
• Atorvastatin	-24,260 (-23%)	-3394*	0	-0.3*	-6,343 (-32%)	-898*
• Simvastatin	9,408 (33%)	1,402**	6 (59%)	0.5**	105 (4%)	-4
• Rosuvastatin	65,170 (1,558%)	7,890*	44 (1,500%)	4.9**	15,823 (1,634%)	1901*
• Pitavastatin	-121 (-21%)	-26				
Cholesterol Absorption Inhibitor (Ezetimibe)	10,619 (49,238%)	1221*	5.3 (50,126%)	0.6*	4,119 (49,531%)	474*
Fibrates	6,465 (134%)	420	2.8 (343%)	0.25**	714 (388%)	66**
• Fenofibrate	3,860 (52%)	483**	1.3 (58%)	0.15**	239 (36%)	31
• Gemfibrozil	-737 (-92%)	-65*	-0.2 (-92%)	-0.01**	-21 (-93%)	-2**
• Bezafibrate	-3,286 (-82%)	-616	-0.5 (-84%)	-0.09	-134 (-83%)	-45**
PCSK9is	231 (8,787%)	37*	1.3 (7,116%)	0.2*	14,877 (4,195%)	2468**
• Evolocumab	179 (6,799%)	28*	1.2 (8,803%)	0.19*	10,953 (3,088%)	1831
• Alirocumab	52 (45,135%)		0.06 (439%)		3,909 (31,729%)	

Notes: *Indicates p-value < 0.0001; ** Indicates p-value < 0.05, obtained from the linear regression analysis; **NSU/TIY**: Number of supplied units per 1,000 inhabitants per year; **DDD/TID**: Defined daily doses per 1,000 inhabitants per day; **CSU/TIY**: Cost of supplied units per 1,000 inhabitants per year: **PCSK9is**: Proprotein convertase subtilisin/kexin type 9 inhibitors.

Appendix S4.1. Sample size calculation

Each governorate represented as a separate stratum, resulting in a total of six strata. For each stratum (governorate), the sample size was calculated based on its proportion of the total population size of Kuwait. The proportion was determined by dividing the total population size of the governorate by the overall population of Kuwait. The resulting proportion was then multiplied by the total study sample size (385 participants) to determine the number of participants required from each governorate. This proportional allocation ensured that recruitment was representative of population density, with more participants assigned to densely populated governorates and fewer to less populated ones. The same process was applied across all six governorates.

Subsequently, proportional sampling was further applied to stratify by nationality Kuwaiti vs. Non- Kuwaiti, ensuring a more accurate estimation of nationality distribution within each governorate. The sample size for Kuwaiti participants in each stratum (governorate) was calculated by dividing the total Kuwaiti population in that governorate by the total population size of the same governorate. This proportion was then multiplied by the total sample size for the corresponding stratum, which has been derived from the previous calculation. Similarly, the sample size for non-Kuwaiti participants was determined by applying the same proportional calculation using the total non-Kuwaiti population as the numerator or by subtracting the Kuwaiti sample size from the total sample size for the given stratum, as both values had already been calculated. This proportional sampling approach ensured that the study accurately represented both governorate-level and nationality-based distributions, thereby allowing for robust estimations. See **Table S4.1** for the minimum sample size required for each stratum (governorate), further stratified by nationality. The proportional allocation calculations are demonstrated in **Equations S4.1** and **S4.2**, with an example provided for the CAP governorate, where highlighted values distinctly illustrate each step of the process.

Table S4.1 Minimum sample size required for each of the six governorates, stratified by nationality (Kuwaiti and non-Kuwaiti), proportionally calculated from the population size using PACI data (75)

Governorate	Total population	Kuwaiti	Non-Kuwaiti	Total sample	Kuwaiti sample	Non-Kuwaiti sample
CAP	657,773	310,041	347,732	54 (14%)	26 (21.1%)	28 (10.7%)
HAW	839,179	149,018	690,161	68 (17.7%)	12 (9.8%)	56 (21.4%)
AHM	1,023,994	338,246	685,748	83 (21.6%)	27 (22%)	56 (21.4%)
JAH	570,441	193,201	377,240	46 (11.9%)	15 (12.2%)	31 (11.8%)
FAR	1,200,641	255,448	945,193	98 (25.5%)	21 (17.1%)	77 (29.4%)
MBK	440,085	271,318	168,767	36 (9.4%)	22 (17.9%)	14 (5.3%)
Total	**4,732,113**	**1,517,272**	**3,214,841**	**385**	**123 (31.9%)**	**262 (68.1%)**

CAP: Capital; **HAW**: Hawalli; **AHM**: Al-Ahmadi; **JAH**: Al-Jahra; **FAR**: Al-Farwaniyah; **MBK**: Mubarak Al-Kabeer; **PACI**: Public Authority for Civil Information.

Equation S4.1: Total sample size in CAP =

$$\frac{\text{Total population size in a CAP}}{\text{Total population size in Kuwait}} \times 385$$

Equation S4.2: Kuwaiti sample size in CAP =

$$\frac{\text{Total Kuwaiti population in a CAP}}{\text{Total populaton size in a CAP}} \times \text{Total sample size in a CAP}$$

Appendix S4.2. PHCC selection from each governorate

In four governorates, HAW, AHM, JAH, and FAR, a PHCC was selected from the nominated centres. In JAH, an additional factor that supported the selection was the previous experience of the centre to conduct research related to lipid management (161). in MBK, both nominated PHCCs were unwilling to participate, so an alternative PHCC was chosen based on its previous involvement in similar research, which ensured familiarity with the study design (161, 265). For the CAP, while the nominated PHCCs met the necessary characteristics, the final selection was made based on convenience factors such as existing rapport with staff, familiarity with the centre, and logistical ease for the research team.

All selected PHCCs had established NCD clinics equipped with nursing facilities for routine physical measurements, such as height, weight, fasting blood glucose, and blood pressure (BP), both systolic (SBP) and diastolic (DBP). These centres also operated based on scheduled follow-up appointments, which facilitated better estimation of patient flow prior to enrolment. Geographical distribution and demographic characteristics were also considered, as ach governorate comprises multiple residential areas, with one or more PHCCs serving each area depending on population density. Therefore, the selection of PHCCs was guided by the distribution of the population, particularly the balance between Kuwaiti and non-Kuwaiti residents. For example, governorates such as FAR tend to have a higher density of expatriates due to the concentration of high-rise commercial buildings, whereas CAP is considered more residential. Despite these demographic patterns, most PHCCs serve both Kuwaiti nationals and expatriates, as many Kuwaiti households employ domestic workers (e.g. drivers, housemaids, or cookers) who attend the same PHCC as their sponsors. Hence, the selection process focused on residential rather than purely commercial areas. Although alternative PHCCs with comparable characteristics were available across governorates, the selected centres fulfilled essential requirements: provision of NCD services, demographic representation, logistical feasibility, ease of access, and willingness of physicians to cooperate.

Appendix S4.3. Documents needed to conduct the cross-sectional study

A. **The structure and content of the questionnaire used in the cross-sectional study**

https://drive.google.com/file/d/13-qPZBsqtU5LpizWgzYLoXNfVbTbApGS/view?usp=drivesdk

B. **Consent form (Arabic)**

https://acrobat.adobe.com/id/urn:aaid:sc:AP:21d96ffd-c0dc-404a-b298-73244a8e7bd8

C. **Consent form (English)**
https://acrobat.adobe.com/id/urn:aaid:sc:AP:a65a5053-fcbc-4de3-86b7-b2f0bc2b76b4

D. **Invitation letter to the heads of PHCCs (Arabic)**

https://acrobat.adobe.com/id/urn:aaid:sc:AP:6fda94d2-d725-479f-883f-802542c0cf32

Appendix S4.4. Number and proportion of patients in different CV risk categories achieving lipid targets

Table S4.4.1 Number and proportion of patients in **extreme, very-high, and high** CV risk categories with available measurements and target achievements, stratified by total, monotherapy, and combination therapy.

		A. Extreme CV risk			B. Very-high CV risk			C. High CV risk		
Lipid parameter		**Total patients (n= 122)**	**Monotherapy (n= 100)**	**Combination therapy (n= 22)**	**Total patients (n= 111)**	**Monotherapy (n= 98)**	**Combination therapy (n= 13)**	**Total patients (n= 101)**	**Monotherapy (n= 95)**	**Combination therapy (n= 6)**
LDL-C	Available measurements	113 (92.6%)	95 (95%)	18 (81.8%)	106 (95.5%)	94 (95.9%)	12 (93.3%)	97 (96%)	91 (95.8%)	6 (100%)
	Target Met	9 (8%)	7 (7.4%)	2 (0.1%)	27 (25.5%)	25 (26.6%)	2 (16.7%)	29 (29.9%)	26 (28.6%)	3 (50%)
Non-HDL-C	Available measurements	116 (95.1%)	97 (97%)	19 (86.4%)	102 (91.9%)	89 (90.8%)	13 (100%)	96 (95%)	90 (94.7%)	6 (100%)
	Target Met	16 (13.8%)	13 (13.4%)	3 (15.8%)	35 (34.3%)	34 (38.2%)	1 (7.7%)	33 (34.4%)	31 (34.4%)	2 (33.3%)
LDL-C + Non-HDL-C	Available measurements	111 (91%)	94 (94%)	17 (77.3%)	101 (91%)	89 (90.8%)	12 (92.3%)	95 (94.1%)	89 (93.7%)	6 (100%)
	Target Met	7 (6.3%)	6 (6.4%)	1 (5.9%)	26 (25.7%)	25 (28.1%)	1 (8.3%)	25 (26.3%)	23 (25.8%)	2 (33.3%)

Table S4.4.1 Number and proportion of patients in **extreme, very-high, and high** CV risk categories with available measurements and target achievements, stratified by total, monotherapy, and combination therapy.

		A. Extreme CV risk			B. Very-high CV risk			C. High CV risk		
Lipid parameter		**Total patients (n= 122)**	**Monotherapy (n= 100)**	**Combination therapy (n= 22)**	**Total patients (n= 111)**	**Monotherapy (n= 98)**	**Combination therapy (n= 13)**	**Total patients (n= 101)**	**Monotherapy (n= 95)**	**Combination therapy (n= 6)**
TG	Available measurements	116 (95.1%)	97 (97%)	19 (86.4%)	106 (95.5%)	93 (94.9%)	13 (100%)	97 (96%)	91 (95.8%)	6 (100%)
	Target Met: <1.7 mmol/L	66 (56.9%)	61 (62.9%)	5 (26.3%)	69 (65.1%)	63 (67.7%)	6 (46.2%)	59 (60.8%)	58 (63.7%)	1 (16.7%)
HDL-C	Available measurements	116 (95.1%)	97 (97%)	19 (86.4%)	106 (95.5%)	93 (94.9%)	13 (100%)	98 (97%)	92 (96.8%)	6 (100%)
	Target Met: >1.0 for M and >1.3 for F	64 (55.2%)	57 (58.8%)	7 (36.8%)	50 (47.2%)	43 (46.2%)	7 (53.8%)	57 (58.2%)	53 (57.6%)	4 (66.7%)
TC	Available measurements	120 (98.4%)	99 (99%)	21 (95.5%)	105 (94.6%)	92 (93.9%)	13 (100%)	98 (97%)	92 (96.8%)	6 (100%)
	Target Met: <5 mmol/L	77 (64.2%)	65 (65.7%)	12 (57.1%)	80 (76.2%)	73 (79.3%)	7 (53.8%)	70 (71.4%)	66 (71.7%)	4 (66.7%)
All	Available measurements	111 (91%)	94 (94%)	17 (77.3%)	101 (91%)	89 (90.8%)	12 (92.3%)	95 (94.1%)	89 (93.7%)	6 (100%)
	Target Met	2 (1.8%)	2 (2.1%)	-	10 (9.9%)	9 (10.1%)	1 (8.3%)	14 (14.7%)	13 (14.6%)	1 (16.7%)

Table S4.4.1 Number and proportion of patients in **extreme, very-high, and high** CV risk categories with available measurements and target achievements, stratified by total, monotherapy, and combination therapy.

	A. Extreme CV risk			B. Very-high CV risk			C. High CV risk		
Lipid parameter	**Total patients (n= 122)**	**Monotherapy (n= 100)**	**Combination therapy (n= 22)**	**Total patients (n= 111)**	**Monotherapy (n= 98)**	**Combination therapy (n= 13)**	**Total patients (n= 101)**	**Monotherapy (n= 95)**	**Combination therapy (n= 6)**

LDL-C: Low-density lipoprotein cholesterol; **Non-HDL-C**: Non-high-density lipoprotein cholesterol; **TG**: Triglycerides; **HDL-C**: High-density lipoprotein cholesterol; **TC**: Total cholesterol. **M**: males; **F**: females.

Appendix S4.5. Summary of sociodemographic and clinical characteristics among patients achieving lipid targets

Variables		LDL-C (n= 65)	Non-HDL-C (n= 84)
Age (years)	Mean ± SD	52 ± 8.9	53.2 ± 8.5
Gender, n (%)	Male	28 (43.1%)	33 (39.3%)
	Female	37 (56.9%)	51 (60.7%)
Nationality, n (%)	Kuwaiti	14 (21.5%)	24 (28.6%)
	Non-Kuwaiti	51 (78.5%)	60 (71.4%)
Education level, n (%)	No formal schooling	12 (18.5%)	16 (19%)
	Primary school	12 (18.5%)	13 (15.5%)
	Intermediate-high school	36 (55.4%)	45 (53.6%)
	College/University	5 (7.7%)	10 (11.9%)
Marital status, n (%)	Single	5 (7.7%)	7 (8.3%)
	Married	50 (76.9%)	64 (76.2%)
	Divorced	1 (1.5%)	1 (1.2%)
	Widowed	9 (13.8%)	12 (14.3%)
Occupation, n (%)	Unemployed	7 (10.8%)	13 (15.4%)
	Government	3 (4.6%)	4 (4.8%)
	Non-government	7 (10.8%)	8 (9.5%)
	Domestic workers	41 (63.1%)	47 (56%)
	Retired	7 (10.8%)	12 (14.3%)
Family history of CVD, n (%)	No	49 (75.4%)	63 (75%)
	Yes	16 (24.6%)	21 (25%)
Smoking status, n (%)	Lifelong non-smoker	49 (75.4%)	64 (76.2%)
	Ex-smoker	7 (10.8%)	8 (9.5%)
	Current	9 (13.8%)	12 (14.3%)
Alcohol consumption, n (%)	No	64 (98.5%)	84 (100%)
	Yes	1 (1.5%)	-
Diet (Fruits), median (IQR)	Number of days/week	3 (5)	3 (5)
	Number of servings/day	2 (2)	2 (1)
Diet (Vegetables), median (IQR)	Number of days/week	7 (3)	7 (2.25)
	Number of servings/day	2 (2)	2 (2)
Physical activity, n (%)	None	35 (53.8%)	51 (60.7%)
	Moderate-intensity	24 (36.9%)	28 (33.3%)
	Vigorous-intensity	6 (9.2%)	5 (6%)
	No	19 (29.2%)	22 (26.2%)

Variables			LDL-C (n= 65)	Non-HDL-C (n= 84)
History of HTN, n (%)	Yes		46 (70.8%)	62 (73.8%)
History of DM, n (%)	No		5 (7.7%)	7 (8.3%)
	Yes		60 (92.3%)	77 (91.7%)
History of CVD, n (%)	No		61 (93.8%)	78 (92.9%)
	Yes		4 (6.2%)	6 (7.1%)
History of MetS, n (%)	No		40 (61.5%)	48 (57.1%)
	Yes		25 (38.5%)	36 (42.9%)
BMI (Kg/m^2)	Median (IQR)		29 (7.2)	29.3 (7.2)
BP (mmHg), SBP <130 + DBP <80, **n (%)**	No	46 (70.7%)	59 (70.2%)	
	Yes	19 (29.2%)	25 (29.8%)	
eGFR	Mean ± SD		95.9 ± 21.1	93± 20.4
CV risk category, n (%)	Extreme		9 (13.8%)	16 (19%)
	Very-high		27 (41.5%)	35 (41.7%)
	High		29 (44.6%)	33 (39.3%)
	Moderate		-	-
Therapeutic regimen, n (%)	Mono		58 (89.2%)	78 (92.9%)
	Comb		7 (10.8%)	6 (7.1%)
Statin intensity, if used, n (%)	HIST		6 (9.5%)	5 (6%)
	MIST		57 (90.5%)	78 (94%)
Governorate, n (%)	FAR		23 (35.4%)	24 (28.6%)
	HAW		11 (16.9%)	11 (13.1%)
	CAP		13 (20%)	15 (17.9%)
	AHM		5 (7.7%)	13 (15.5%)
	MBK		6 (9.2%)	7 (8.3%)
	JAH		7 (10.8%)	14 (16.7%)

SD: Standard deviation; **IQR**: Interquartile range; **M:** Male**; F:** Female**; K:** Kuwaiti**; NK:** Non-Kuwaiti**; CVD**: Cardiovascular disease; **HTN**: Hypertension; **DM**: Diabetes mellitus; **MetS**: Metabolic syndrome; **BMI**: Body mass index; **BP**: Blood pressure; **RFT**: Renal function test; **eGFR**: Estimated glomerular filtration rate; **LFT**: Liver function test; **Comb**: Combination; **Mono**: Monotherapy; **HIST**: High-intensity statin therapy; **MIST**: Moderate-statin therapy; **CAP**: Capital; **HAW**: Hawalli; **AHM**: Al-Ahmadi; **JAH**: Al-Jahra; **FAR**: Al-Farwaniyah; **MBK**: Mubarak Al-Kabeer.

Appendix S4.6. Further discussion points on factors potentially associated with suboptimal lipid control

Patient-related factors may have contributed to suboptimal lipid control. Notably, medication adherence could have played a critical role in lipid control outcomes. Poor adherence to statin therapy is well-documented and has been associated with significant increase in cardiovascular (CV) events (266). A systematic review covering the period 2000–2020, which included 47 observational studies, identified several key determinants of non-adherence to LLT; notably, younger age (≤50 years), female sex, and smoking (267). In parallel with these findings, approximately half of the participants in the present study were under 55 years of age, and half were female, which may plausibly explain the suboptimal lipid control observed.

Another potential contributor to suboptimal control is adverse drug reactions (ADRs) associated with statin use. A review of data from Latin America reported that the frequency of statin-related ADRs ranged from 0% to 35.1% in RCTs and 0% to 28.4% in observational studies, with the most common being muscle-related symptoms, including myalgia and elevated creatine kinase (CK) levels (268). This may help explain the relatively low use of HIST in the current study (36.6%, n = 41/112). It is plausible that some patients may have declined intensified treatment due to concerns about tolerability.

However, a retrospective cohort study from Scotland (2010–2015) involving 66,248 newly initiated statin users assessed the relationship between statin intensity and adherence (188). Using a proportion of days covered (PDC) ≥80% as a proxy, the study found that overall adherence was just 52.6%, but with the highest adherence observed among users of HIST (63.7%) (187). These findings suggest that concerns about reduced adherence with higher-intensity regimens may be overstated and that intensifying statin therapy could still be feasible. However, the Scottish study lacked ADR data, limiting interpretation regarding tolerability. It is also worth noting that the HIST classification in the Scottish study included atorvastatin 20–80mg and

simvastatin 80mg, whereas the current study defined HIST more conservatively as atorvastatin 40–80mg only (**chapter 2**, Table 2.3).

In addition to medication adherence, genetic background may also contribute to suboptimal lipid control. A meta-analysis of 8 statin trials involving 38,153 patients with coronary artery disease (2009-2011) assessed the variability in lipid marker reduction achieved with statin therapy. The findings highlighted notable interindividual variation in the reduction of LDL-C, non–HDL-C, and ApoB, when patients were treated with a fixed statin dose (269). Remarkably, over 40% of participants failed to achieve LDL-C levels <1.7 mmol/L, despite being treated with HIST (269). These results suggest that genetic factors may limit the lipid-lowering response, even when intensive regimens are used. Nonetheless, further optimisation of lipid control may still be achieved through the addition of non-statin therapies (23). Additionally, findings from the VOYAGER meta-analysis, which assessed variability in LDL-C reduction among 32,258 patients receiving atorvastatin (10-80mg), rosuvastatin (5-40mg), and simvastatin (10-80mg), demonstrated considerable interindividual differences in treatment response (270). The percentage change in LDL-C varied widely among patients across all doses, with between 5% and 53% of patients exhibiting a suboptimal response, defined as a reduction less than 30% in LDL-C levels (270). Therefore, patient-centred care approach is profound in optimising lipid management, including timely treatment intensification or combination therapy.

Importantly, this study did not measure the duration of diabetes, which is a well-established predictor of CV risk (20, 24, 271, 272). A systematic review and meta-analysis, including 26 observational cohort studies, involving more than 1.3 million individuals from 30 countries (272), aimed to investigate whether earlier age of T2DM onset is independently associated with a greater lifetime risk of death and vascular diseases. the findings revealed that longer exposure to hyperglycaemia is a major contributor to increased risks of mortality, microvascular, and macrovascular complications influencing with age at diagnosis of T2DM, and early-onset T2DM is not only a marker of severity but also a predictor of longer disease exposure, which leads to higher lifetime risk of complications and mortality. Notably, newly diagnosed patients with T2DM should also be considered at high CV risk (272). This is particularly relevant in the present study, as the majority of patients had T2DM.

A recent large nationwide cohort study from Denmark (271), which included 142,587 individuals newly diagnosed with T2DM between 2006 and 2013, demonstrated that these patients had a significantly increased 10-year CVD risk. The onset of CVD occurred up to a decade earlier in younger age groups with diabetes, compared to the general population. Specifically, men with newly diagnosed T2DM reached high CVD risk levels by approximately 35 years of age, and women by 45 years. Authors also revealed that patients diagnosed before age 40, despite having a high prevalence of obesity, were less likely to receive statins or other preventive treatments. These findings imply the need for earlier and intensified interventions, including statins for CVD prevention, in younger individuals with T2DM to mitigate long-term CVD risk. Based on this study, it appears that many participants, which most of whom had T2DM, may not receive early, timely, and appropriately intensified preventive therapy for CV disease, including statins and antihypertensive medications.

Additionally, the Danish study (271) noted that although Denmark is a HIC with universal healthcare and is categorised as a low-risk population by the WHO, authors noted that patients still reached high CVD risk at a young age. This suggests that in countries with higher baseline CVD risk, such as Kuwait, individuals may reach high-risk status even earlier. Although the 2021 Middle East consensus (20) adopted the UK QRISK tool for CV risk estimation, which classifies individuals with T2DM aged under 50 as being at high CV risk, these findings highlight the need for a region-specific or specialised risk assessment tool. Such a tool would better account for local epidemiological patterns and support earlier identification of high-risk individuals in Middle East populations. Therefore, the duration of T2DM and the age-onset would be potential reasons for suboptimal control.

Moreover, variations in physician adherence to lipid-lowering guidelines, as well as differences in the frequency of lipid testing and follow-up appointments, could impact LDL-C control across governorates, even if medical resources are evenly distributed. Data from Sweden (2007–2014) (273) on adherence to guidelines for prescribing LLTs in T2DM patients revealed suboptimal adherence, with treatment often guided more by individual CVD risk than strict adherence to LDL-C thresholds. A local study conducted in Kuwait (2015–2016) (235), which surveyed 279 physicians, found that 77% of respondents claimed that they to consistently used lipid clinical guidelines. However, several barriers to guideline implementation were identified, including time constraints and limited access to guidelines resources.

Appendix S5.1. Residual diagnostics of the linear mixed-effects model for LDL-C and non-HDL-C reduction

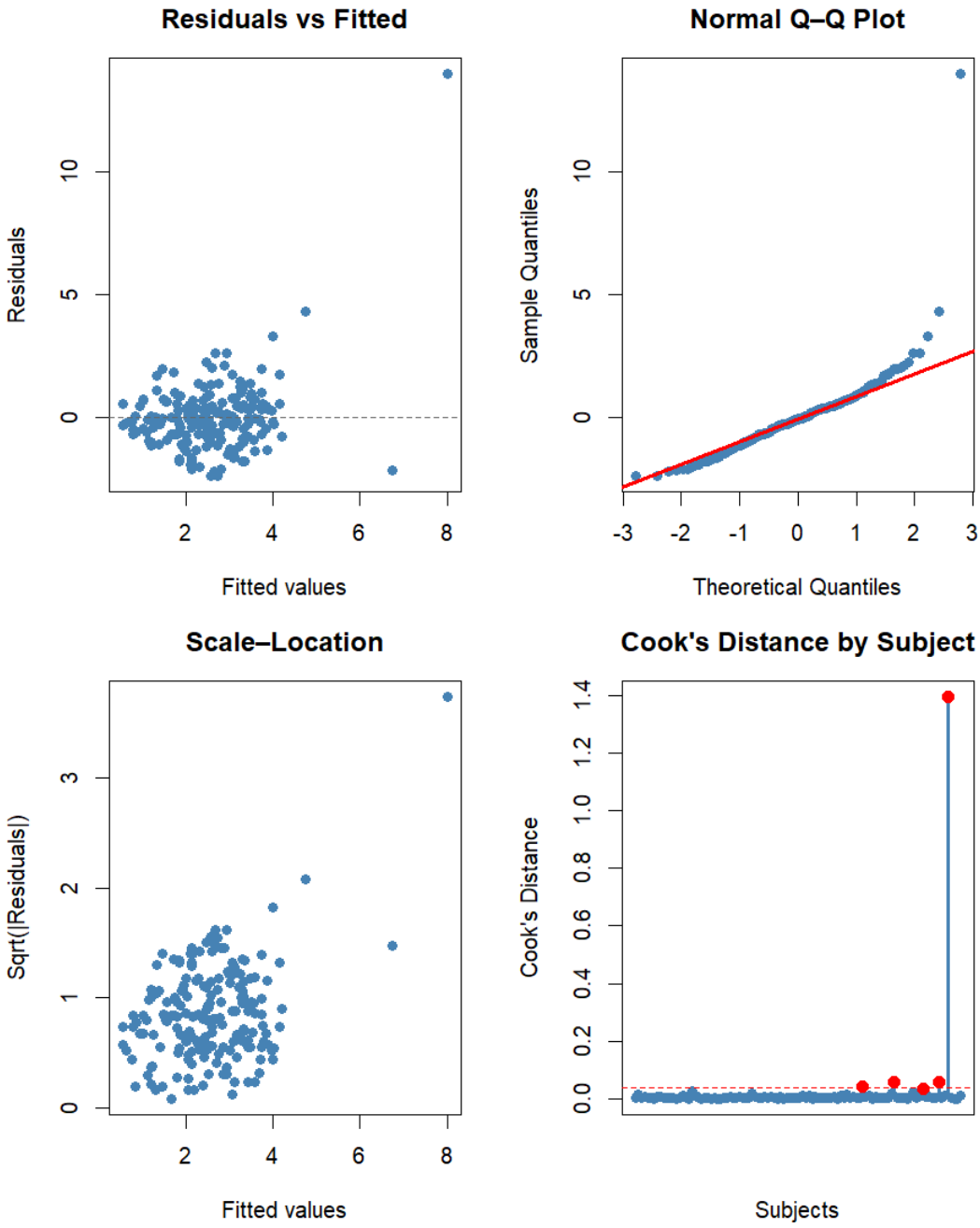

Figure S5.1.1. Residual diagnostics plots (residuals–fitted, normal Q–Q, scale–location, and Cook's distance) of the linear mixed model for **LDL-C** reduction (original model).

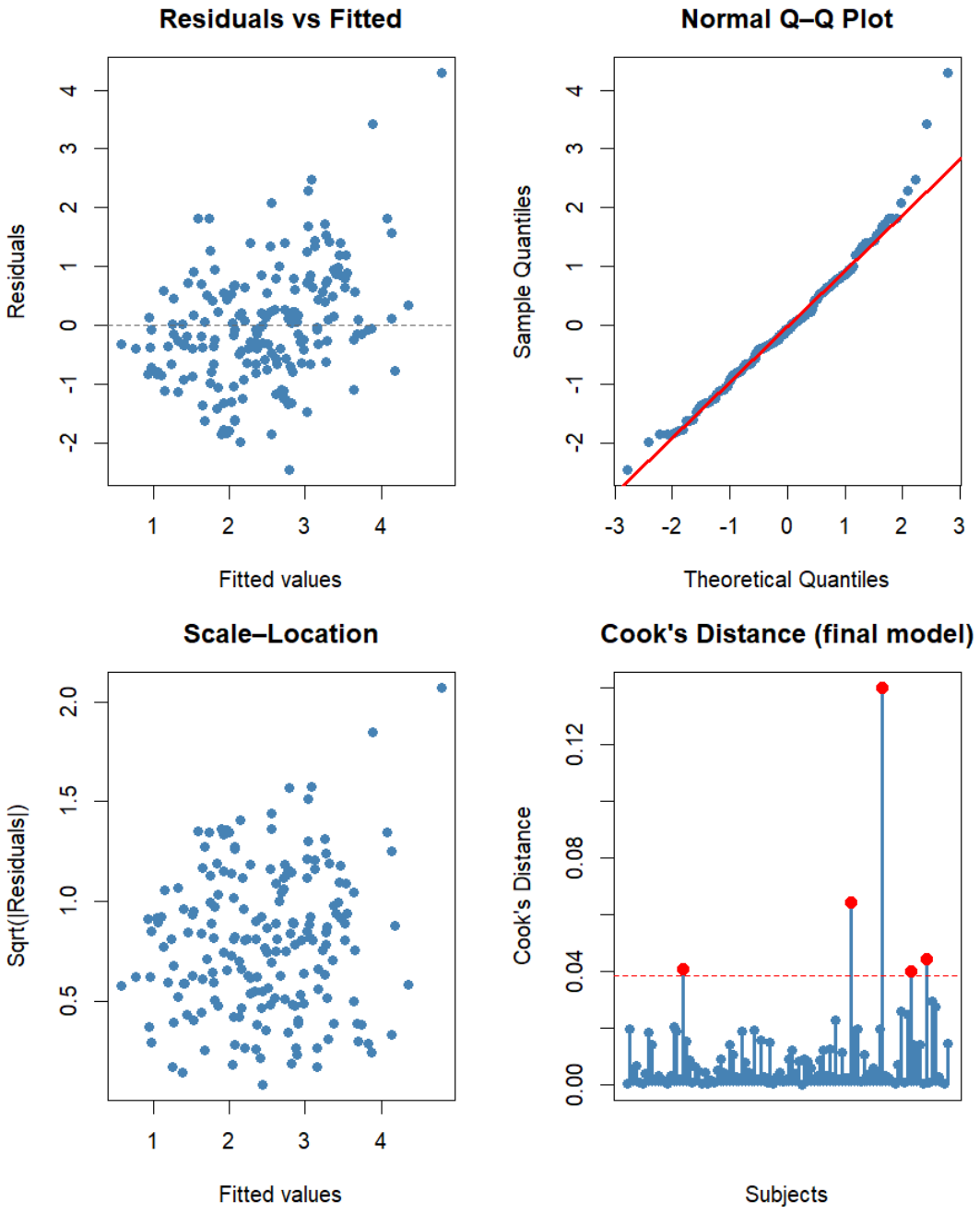

Figure S5.1.2. Residual diagnostics plots (residuals–fitted, normal Q–Q, scale–location, and Cook's distance) of the linear mixed model for **LDL-C** reduction (sensitivity model).

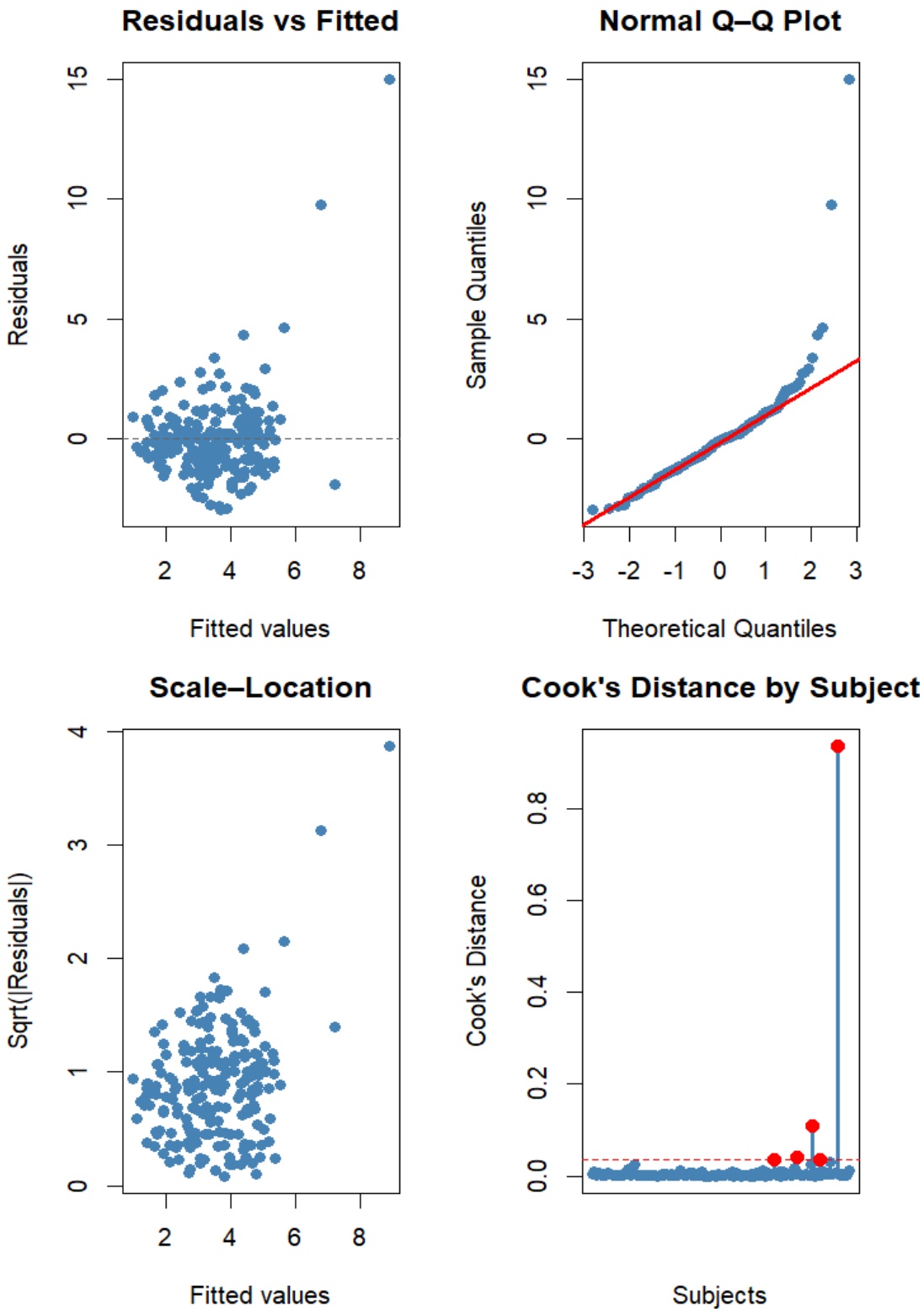

Figure S5.1.3. Residual diagnostics plots (residuals–fitted, normal Q–Q, scale–location, and Cook's distance) of the linear mixed model for **non-HDL-C** reduction (original model).

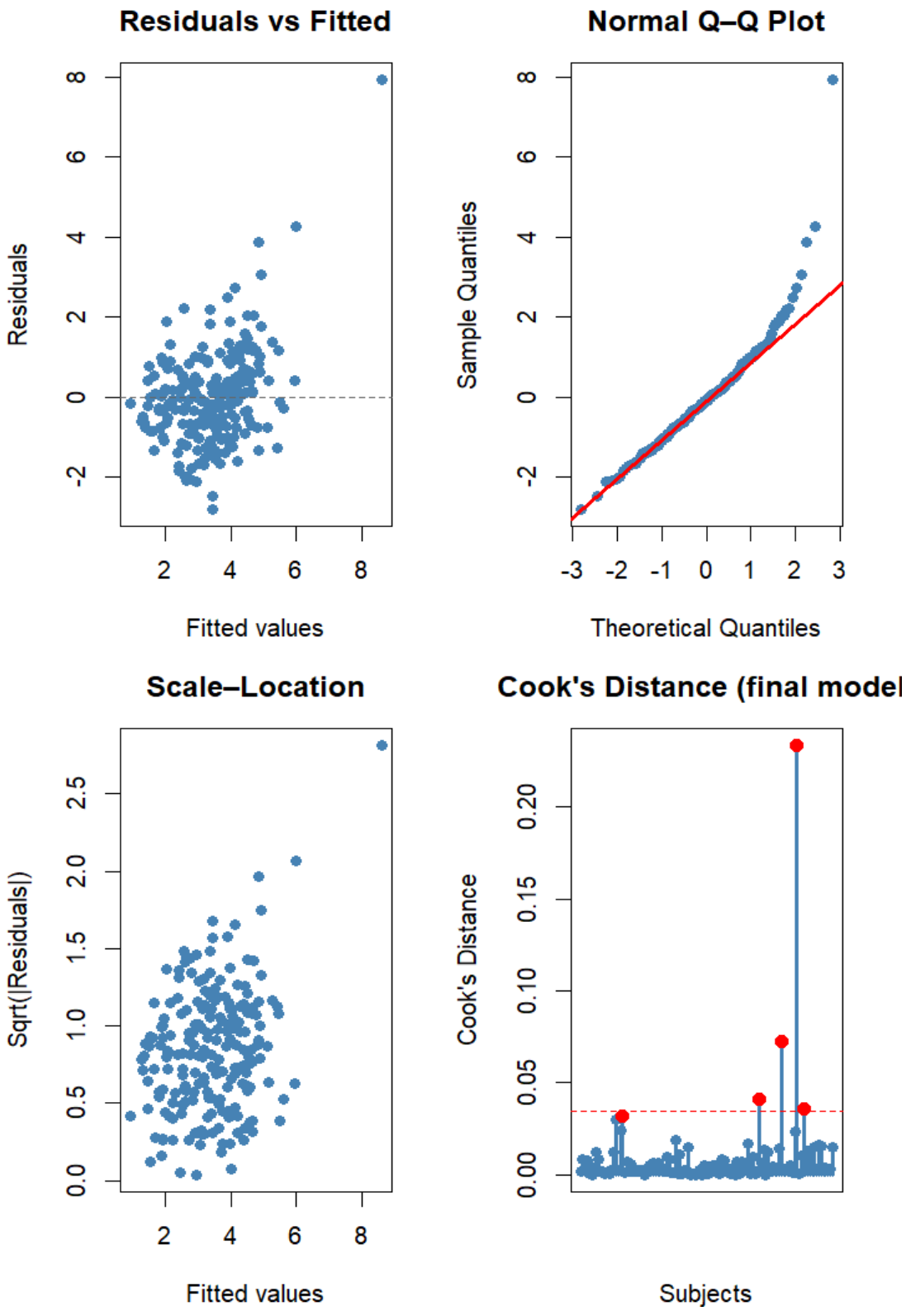

Figure S5.1.4. Residual diagnostics plots (residuals–fitted, Q–Q, scale–location, and Cook's distance) of the linear mixed model for **non-HDL-C** reduction (sensitivity model)

Appendix S5.2. Lipid values at baseline and following initiation of PCSK9i therapy

Table S5.2.1 LDL-C levels at baseline and over time, including number of patients, absolute median differences, relative percentage changes, and p-values for overall PCSK9I users, and by subgroups (evolocumab and alirocumab).

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	104	84	55	4
LDL-C, median (IQR)	2.95 (1.96 to 3.83)	1.73 (0.76 to 2.6)	1.73 (0.97 to 2.63)	1.37 (0.96 to 1.5)
Absolute median difference (IQR)	-	-1.01 (-2.1 to 0)	-1.1 (-1.94 to 0.21)	-1.07 (-2.05 to -0.24)
Relative median percentage % (95% CI)	-	-41.9 (-50.9 to -24.1)	-42.4 (-54.1 to -23.5)	-35.98 (-95.5 to -13.3)
P-value pre-post	-	<0.001	<0.001	0.1
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	77 (74%)	60 (71.4%)	38 (69.1%)	4 (100%)
LDL-C, median (IQR)	2.85 (1.91 to 3.81)	1.59 (0.6-2.6)	1.63 (0.96-2.81)	1.37 (0.96-1.5)
Absolute median difference (IQR)	-	-0.98 (-2.12 to -0.04)	-1.03 (-1.6 to 0.55)	-1.65 (-2.05 to -0.24)
Relative median percentage % (95% CI)	-	-45.67 (-53.5 to -25.4)	-42.27 (-54.87 to 1.29)	-35.98 (-95.49 to -13.3)
P-value pre-post	-	<0.001	0.045	0.1
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	27 (26%)	24 (28.6%)	17 (30.9%)	0
LDL-C, median (IQR)	3.39 (2.25 to 4.11)	1.87 (1.28 to 2.68)	1.74 (1.14 to 2.24)	-
Absolute median reduction (IQR)	-	-1.16 (-1.98 to 0.075)	-1.48 (-2.57 to -0.83)	-

Relative median percentage reduction % (95% CI)	-	-37.09 (-50.8 to -7.69)	-42.35 (-74.05 to -20.68)	-
p-value pre-post		=0.0035	<0.001	-
p-value (evolocumab vs alirocumab)	= 0.3351	= 0.2467	0.96	-

Table S5.2.2 Non-HDL-C levels at baseline and over time, including number of patients, absolute median differences, relative percentage changes, and p-values for overall PCSK9I users, and by subgroups (evolocumab and alirocumab).

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
Non-HDL-C, median (IQR)	3.94 (2.85 to 5.16)	2.38 (1.52 to 3.27)	2.52 (1.91 to 3.39)	1.87 (1.35 to 2.09)
Absolute median difference (IQR)		-1.36 (-2.46 to -0.3)	-1.3 (-2.15 to 0.15)	-1.5 (-2.77 to -0.31)
Relative percentage reduction % (95% CI)		-38.08 (-46.53 to -23.88)	-32.99 (-45 to -19.03)	-36.46 (-87.7 to -10.5)
p-value pre-post	-	<0.001	<0.001	0.1
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
Non-HDL-C, median (IQR)	3.72 (2.77 to 5.14)	2.25 (1.47 to 3.11)	2.43 (1.93 to 3.37)	1.87 (1.35 to 2.09)
Absolute median difference (IQR)	-	-1.3 (-2.4 to -0.32)	-1.29 (-2 to 0.29)	-1.5 (-2.77 to -0.31)
Relative percentage reduction % (95% CI)	-	-40.7 (-50 to -26.05)	-36.5 (-45.6 to -14.98)	-36.5 (-87.7 to -10.5)
p-value pre-post	-	<0.001	0.005	0.1
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
Non-HDL-C, median (IQR)	4.37 (3.53 to 5.11)	2.78 (1.91-3.54)	2.62 (1.95-3.66)	-
Absolute median difference (IQR)	-	-1.37 (-2.46 to -0.3)	-1.46 (-2.8 to -0.42)	-

Relative percentage reduction % (95% CI)	-	-30.13 (-41.92 to -14.73)	-32.59 (-52.12 to -13.3)	-
p-value pre-post		<0.001	0.001	-
p-value (evolocumab vs alirocumab)	= 0.2223	= 0.2301	= 0.964	NA

Table S5.2.3 TG levels at baseline and over time, including number of patients, absolute median differences, relative percentage changes, and p-values for overall PCSK9I users, and by subgroups (evolocumab and alirocumab).

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
TG, median (IQR)	1.82 (1.31-2.82)	1.75 (1.11-2.43)	1.61 (1.15-2.37)	1.1 (0.85-1.27)
Absolute median difference (IQR)	-	-0.3 (-0.97 to 0.08)	-0.25 (-1.0 to 0.39)	-0.67 (-1.29 to -0.16)
Relative percentage reduction % (95% CI)	-	-14.78 (-26.1 to -7.24)	-16.23 (-31.3 to 1.68)	-37.5 (-63.19 to -3.55)
p-value pre-post	-	<0.001		
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
TG, median (IQR)	1.76 (1.3-2.63)	1.51 (1.0-2.43)	1.51 (1.08-2.31)	1.075 (0.85-1.27)
Absolute median difference (IQR)	-	-0.28 (-1.16 to 0.01)	-0.23 (-0.7 to 0.31)	-0.67 (-1.29 to -0.16)
Relative percentage reduction % (95% CI)	-	-17.3 (-28.8 to -7.8)	-13.65 (-31.3 to 4.3)	-37.55 (-63.19 to -3.5)
p-value pre-post		<0.001		
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of pts	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
TG, median (IQR)	2.13 (1.38-3.16)	2.03 (1.49-2.34)	1.81 (1.38-2.44)	-
Absolute median difference (IQR)	-	-0.3 (-0.81 to 0)	-0.31 (-1.1 to 0.42)	-

Relative percentage reduction % (95% CI)	-	-12.14 (-23.6 to -0.87)	-16.4 (-40.5 to 23.0)	-
p-value pre-post		=0.01242		
p-value evolocumab vs alirocumab	= 0.347	= 0.09874		

Table S5.2.4 HDL-C levels at baseline and over time, including number of patients, absolute median differences, relative percentage changes, and p-values for overall PCSK9I users, and by subgroups (evolocumab and alirocumab).

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
HDL-C, median (IQR)	1.11 (0.94-1.28)	1.1 (0.9-1.38)	1.09 (0.96-1.34)	1.08 (1.02-1.17)
Absolute median difference (IQR)	-	-0.02 (-0.14 to 0.14)	0.02 (-0.1 to 0.17)	0.23 (0.14 to 0.23)
Relative median percentage % (95% CI)	-	-1.59 (-5.5 to 4.2)	1.56 (-5.55 to 6.14)	23.74 (-8.7 to 31.9)
p-value pre-post		= 0.7924		
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
HDL-C, median (IQR)	1.14 (0.96-1.34)	1.14 (0.89-1.41)	1.22 (0.97-1.44)	1.08 (1.02-1.17)
Absolute median difference (IQR)	-	-0.03 (-0.17 to 0.14)	0.05 (-0.09 to 0.21)	0.23 (0.14 to 0.23)
Relative median percentage % (95% CI)	-	-1.82 (-7.69 to 2.95)	4.8 (-4.9 to 17.6)	23.74 (-8.7 to 31.9)
p-value pre-post		= 0.4629		
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
HDL-C, median (IQR)	1.01 (0.9-1.18)	1.08 (1-1.18)	1.05 (0.92-1.19)	-
Absolute median difference (IQR)	-	0.01 (-0.08 to 0.14)	-0.06 (-0.11 to 0.025)	-
Relative median percentage % (95% CI)	-	0.38 (-3.03 to 14.1)	-6.1 (-9.9 to -0.83)	-
p-value pre-post		=0.368		

p-value evolocumab vs alirocumab	= 0.1153	= 0.6554

Table S5.2.5 TC levels at baseline and over time, including number of patients, absolute median differences, relative percentage changes, and p-values for overall PCSK9I users, and by subgroups (evolocumab and alirocumab).

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
TC, median (IQR)	5 (3.98-6.31)	3.5 (2.76-4.77)	3.53 (2.94-5.09)	2.97 (2.4-3.25)
Absolute median difference (IQR)	-	-1.46 (-2.54 to -0.32)	-1.22 (-2.04 to 0.095)	-1.39 (-2.53 to -0.29)
Relative median percentage % (95% CI)	-	-31.06 (-35.7 to -14.87)	-26.13 (-33.1 to -15.07)	-25.6 (-68.02 to -3.5)
p-value pre-post	-	<0.001		
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
TC, median (IQR)	4.82 (3.96-6.31)	3.42 (2.63-4.59)	3.4 (2.9-5.1)	2.97 (2.41-3.25)
Absolute median difference (IQR)	-	-1.43 (-2.56 to -0.36)	-1.14 (-1.9 to 0.5)	-1.39 (-2.53 to -0.29)
Relative median percentage % (95% CI)	-	-32.57 (-39.51 to -18.49)	-25.3 (-35.3 to -8.5)	-25.6 (-68.02 to -3.5)
p-value pre-post		<0.001		
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
TC, median (IQR)	5.25 (4.58-6.4)	4.05 (2.94-5.28)	4 (2.93-4.96)	-
Absolute median difference (IQR)	-	-1.55 (-2.29 to -0.28)	-1.53 (-2.7 to -0.47)	-
Relative median percentage % (95% CI)	-	-23.3 (-34.4 to -8.95)	-29.03 (-42.5 to -12.7)	-

p-value pre-post		= 0.001185
p-value evolocumab vs alirocumab	= 0.2953	= 0.2865

Appendix S5.3. Lipid target attainment rates among PCSK9i users

Table S5.3.1 Percentage of patients achieving **LDL-C target** goals over time at different LDL-C thresholds, stratified by CV risk category for overall PCSK9I users, as well as for the evolocumab and alirocumab subgroups.

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	104	84	55	4
LDL-C <1.8 mmol/L[a]	23 (22.1%)	44 (52.4%)	31 (56.4%)	4 (100%)
LDL-C <1.4 mmol/L[b]	9 (8.7%)	36 (42.9%)	24 (43.6%)	2 (50%)
LDL-C <1.0 mmol/L[c]	7 (6.7%)	26 (31%)	15 (27.3%)	1 (25%)
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	77 (74%)	60 (71.4%)	38 (69.1%)	4 (100%)
LDL-C <1.8 mmol/L[a]	17 (22.1%)	32 (53.3%)	20 (52.6%)	4 (100%)
LDL-C <1.4 mmol/L[b]	9 (11.7%)	28 (46.7%)	17 (44.7%)	2 (50%)
LDL-C <1.0 mmol/L[c]	7 (9.1%)	22 (36.7%)	11 (28.9%)	1 (25%)
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	27 (26%)	24 (28.6%)	17 (30.9%)	0
LDL-C <1.8 mmol/L[a]	6 (22.2%)	12 (50%)	11 (64.7%)	-
LDL-C <1.4 mmol/L[b]	-	8 (33.3%)	7 (41.2%)	-
LDL-C <1.0 mmol/L[c]	-	4 (16.7%)	4 (23.5%)	-

a: LDL-C <1.8 mmol/L corresponds to high/very-high CV risk; **b:** LDL-C <1.4 mmol/L corresponds to extreme CV risk; **c:** LDL-C <1.0 mmol/L reflects two vascular events within two years

Table S5.3.2 Percentage of patients achieving **non-HDL-C target** goals over time at different thresholds, stratified by CV risk category for overall PCSK9I users, as well as for the evolocumab and alirocumab subgroups.

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
N-HDL-C <2.6 mmol/L[a]	21 (18.3%)	50 (53.8%)	32 (50.8%)	4 (100%)
N-HDL-C <2.2 mmol/L[b]	16 (13.9%)	42 (45.2%)	25 (39.7%)	4 (100%)
N-HDL-C <1.8 mmol/L[c]	7 (6.1%)	27 (29%)	14 (22.2%)	2 (50%)
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
N-HDL-C <2.6 mmol/L[a]	17 (19.8%)	40 (58.8%)	23 (52.3%)	4 (100%)
N-HDL-C <2.2 mmol/L[b]	14 (16.3%)	33 (48.5%)	18 (40.9%)	4 (100%)
N-HDL-C <1.8 mmol/L[c]	7 (8.1%)	22 (32.4%)	10 (22.7%)	2 (50%)
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
N-HDL-C <2.6 mmol/L[a]	4 (13.8%)	10 (40%)	9 (47.4%)	-
N-HDL-C <2.2 mmol/L[b]	2 (6.9%)	9 (36%)	7 (36.8%)	-
N-HDL-C <1.8 mmol/L[c]	0	5 (20%)	4 (21.1%)	-

a: non-HDL-C <2.6 mmol/L corresponds to high/very-high CV risk; **b:** non-HDL-C <2.2 mmol/L corresponds to extreme CV risk; **c:** non-HDL-C <1.8 mmol/L reflects two vascular events within two years. **N-HDL-C**: non-HDL-C

Table S5.3. 3 Percentage of patients achieving **TG target** goals over time at <1.7 mmol/L for overall PCSK9I users, as well as for the evolocumab and alirocumab subgroups.

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
TG <1.7 mmol/L	50 (43.5%)	45 (48.4%)	34 (54%)	4 (100%)
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
TG <1.7 mmol/L	41 (47.7%)	36 (52.9%)	26 (59.1%)	4 (100%)
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
TG <1.7 mmol/L	9 (31%)	9 (36%)	8 (42.1%)	-

Table S5.3. 4 Percentage of patients achieving **HDL-C target** goals over time for overall PCSK9I users, as well as for the evolocumab and alirocumab subgroups.

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
HDL >1.0 mmol/L (M), HDL >1.3 mmol/L (F)	45 (39.1%)	39 (41.9%)	30 (47.6%)	1 (25%)
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
HDL >1.0 mmol/L (M), HDL >1.3 mmol/L (F)	40 (46.5%)	31 (45.6%)	23 (52.3%)	1 (25%)
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
HDL >1.0 mmol/L (M), HDL >1.3 mmol/L (F)	5 (17.2%)	8 (32%)	7 (36.8%)	

Table S5.3. 5 Percentage of patients achieving **TC target** goals over time at <5 mmol/L for overall PCSK9I users, as well as for the evolocumab and alirocumab subgroups.

A. Overall	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	115	93	63	4
TC <5.0 mmol/L	57 (49.6%)	74 (79.6%)	46 (73%)	4 (100%)
B. Evolocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	86 (74.8%)	68 (73.1%)	44 (69.8%)	4 (100%)
TC <5.0 mmol/L	45 (52.3%)	56 (82.4%)	32 (72.7%)	4 (100%)
C. Alirocumab	**Baseline**	**Months 1-3**	**Months 4-6**	**Months 7-9**
N of patients	29 (25.2%)	25 (26.9%)	19 (30.2%)	0
TC <5.0 mmol/L	12 (41.3%)	18 (72%)	14 (73.7%)	

Appendix S5.4. Further discussion points on real-world effectiveness of PCSK9is

Other potential factors may help explain variations in LDL-C reduction following PCSK9i use. Although the LMM in this study did not identify a significant association between gender and LDL-C reduction, evidence from a real-world Spanish cohort identified female sex as an independent predictor of LDL-C response (86). Similarly, in the ODYSSEY LONG TERM trial (274), Robinson et al. (2015) reported that women experienced approximately 12% lower LDL-C reductions with alirocumab than men, despite comparable baseline characteristics and treatment regimens. These findings may be attributed to higher circulating PCSK9 levels in women, potentially influenced by oestrogen levels, which may reduce the binding efficiency of PCSK9 inhibitors (86).

Furthermore, previous literature has explored potential mechanisms underlying an unusually poor response to PCSK9i, often referred to as hyporesponsiveness or resistance. Hyporesponsiveness is typically defined as an LDL-C reduction of less than 30%, a threshold considered more reflective of real-world clinical expectations. A more stringent definition has also been proposed, whereby a reduction of less than 15% is used, based on the minimum LDL-C reduction required for regulatory approval of PCSK9is (261).

Several mechanisms have been proposed that may contribute for inadequate therapeutic response and subsequent hyporesponsiveness. These include poor adherence to therapy, the development of anti-drug antibodies (ADAs), particularly with humanised monoclonal antibodies such as bococizumab (now discontinued), as well as genetic factors such as mutations in the LDL receptor or PCSK9 gene (275). Structural changes resulting from such mutations may impair the binding and function of PCSK9is. While some authors have proposed diagnostic tools to identify underlying causes of poor response, their practicality is limited in many settings, including Kuwait. For example, plasma PCSK9 level testing may be useful, as a twofold increase following injection suggests proper drug entry and may help detect ADA-related resistance. Such assessments are ideally performed before or after the third

injection, approximately one month after initiation. In cases of persistently suboptimal response, clinicians are advised to investigate potential causes, including adherence, immunogenicity, and genetic factors, before considering discontinuation of therapy (275). However, the present study demonstrated a reduction exceeding 40%, thereby excluding the likelihood of hyporesponsiveness.

Interestingly, a small subset of patients (8.7%; n = 9) in this study had already attained LDL-C below 1.4 mmol/L prior to PCSK9i initiation. It is plausible that these individuals had either accessed PCSK9is through other healthcare facilities and maintained this target or had achieved it with conventional therapies but required to add/switch due to side effect or adherence challenges. Some may also have sought more aggressive lipid lowering, aiming for LDL-C <1.0 mmol/L, particularly in the case of recurrent ASCVD events (23). Similarly, 6.7% of patients (n = 7/104) had LDL-C levels below 1.0 mmol/L at baseline, which could reflect the same considerations, including intolerance or adherence issues with conventional therapies necessitating PCSK9i use. Therefore, uncertainty regarding whether all include patients were true PCSK9i users may have influenced the extent of LDL-C reduction. Strengthening EHR system or conducting large prospective studies would improve data completeness and quality, allowing for more accurate evaluation of the real-world effectiveness.