University of Strathclyde

Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS)

A model for continuous quality improvement of medication use: Concepts, methods and applications

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A thesis presented in fulfilment of the requirements for the degree of

Doctor of Philosophy (PhD)

2011

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.

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Abstract

Background

Despite the instigation of regulations to ensure that medicinal products entering the market are nontoxic and yield a favourable risk-benefit balance, drug products frequently fail to produce the benefits found in clinical trials and frequently cause harm. The aim of this thesis is to design and operationalise a conceptual framework for monitoring and improving the performance of medication use systems.

Objectives

(1) To contribute to the conceptual understanding of preventable drug-related morbidity (PDRM) and its causes, (2) to identify components of a model for continuous quality improvement of medication use systems, (3) to develop an instrument to measure the quality of medication use for multiple conditions and (4) to test the instrument for its utility within the proposed quality improvement model.

Methods

(1) Concepts used in the pharmaco-epidemiological and pharmaceutical care literature were critically reviewed. (2) A structured literature review was conducted in order to summarise the impact of previously tested quality improvement interventions on medication use processes and patient outcomes. (3) A generic framework for explicit quality assessment of medication use was developed and applied to design a medication assessment tool for multiple cardiovascular conditions (MAT$_{CVC}$). (4) Field testing of the MAT$_{CVC}$ instrument was undertaken by applications in retrospective surveys conducted in German inpatient (A), Scottish outpatient (B) and Dutch primary care settings (C).

Outcomes

(1) The concept of drug therapy failure (DTF) was introduced to address an identified lack of a concept to capture negative drug therapy outcomes that are the consequences of sub-optimally effective medication use. The concepts of pharmaceutical care need (PCN) and drug therapy risk (DTR) were introduced as pre-cursors of negative drug therapy outcomes. (2) A theoretical model for continuous quality improvement of medication use systems was designed, in which the routine assessment of the quality of medication use is exploited to provide decision support at the point of care, to identify patients who are at risk of PDRM for targeted review and to allow quality control at strategic level. (3) The developed MAT$_{CVC}$ comprised of 52 explicit assessment criteria, organised at five hierarchical levels. (4) Field testing of MAT$_{CVC}$ in three settings revealed that data capture for MAT$_{CVC}$ from routine clinical records was reliable (Cohen's Kappa > 0.8) but resource intensive (10 to 20 minutes per patient). It was estimated that samples of between <50 (for MAT$_{CVC}$ as a whole) and > 500 (for individual MAT$_{CVC}$ measures) patients would be required for meaningful assessments of the quality of medication use for a given health care provider. Single quantitative approaches of prioritising specific aspects for medication use improvement were found to miss potentially important quality gaps. The ability of MAT$_{CVC}$ assessment to identify actual opportunities for quality improvement was found to be high in inpatient (PPV = 0.78) and outpatient settings (PPV = 0.81) but lower in the primary care setting (PPV = 0.27).

Conclusion

This thesis has made an attempt to address current controversies around key concepts underpinning the theory and practice of pharmaceutical care. Previous approaches to explicit quality assessment for single diseases have been advanced to a multi-disease approach and positioned within a model to monitor and continuously improve the performance of medication use systems. Methodological

challenges in the design and application of explicit medication assessment instruments for multiple conditions were identified and possible solutions have been proposed. The work presented in this thesis has the potential to inform the definition of collaborative services to address the problem of preventable drug related morbidity.

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Abbreviations

ACE	Angiotensin converting enzyme
ACEI	ACE inhibitor
ACS	Acute coronary syndrome
Act	An activity to address a drug therapy risk
ADE	Adverse drug event
Adherence	Conformance with a practice standard
ADR	Adverse drug reaction
A&F	Audit and feedback
AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality, AHRQ
ARB	Angiotensin receptor blocker
ASHP	American Society of Health-System Pharmacists
BB	Beta blocker
BNF	British National Formulary
CCB	Calcium channel blocker
CCM	Chronic care model
CDSS	Clinical Decision support system
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval (95%)
COPD	Chronic Obstructive Pulmonary Disease
CVC	Cardiovascular condition
DGI	Data gap index
DM	Diabetes mellitus
DTF	Drug therapy failure
DTO	Drug therapy objective
DTP	Drug therapy problem
DTR	Drug therapy risk
DTR EXP	An explained rug therapy risk (DTR MAN or DTR EXE)
DTR POS	An unexplained drug therapy risk
ECG	Electrocardiogram
ECHO	Echocardiography
EF	Ejection fraction
eGFR	Estimated Glomerular filtration rate
ENAI	Explained non-adherence index
F	Female
GER	Germany
GFR	Glomerular filtration rate
GP	General Practitioner
GPASS	General Practitioner Administration System for Scotland
GTN	Glyceryl trinitrate
HbA1c	Glycosylated haemoglobin

HF	Heart failure
HTN	Hypertension
ICD	International classification of diseases
INR	International normalised ratio
IQR	Inter-quartile range
ISDN	Isosorbide dinitrate
ISMN	Isosorbide mononitrate
K	Potassium
LDL	Low density lipoprotein
LFT	Liver function tests
LVSD	Left ventricular systolic dysfunction
M	Male
MAI	Medication Appropriateness Index
MAT	Medication assessment tool
MI	Myocardial infarction
NAI	Non-adherence index
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NL	Netherlands
NNT	Number needed to treat
NSF	National Service Frameworks
NYHA	New York Heart Association
PACT	Prescribing Analysis and Cost
PC	Pharmaceutical care
PCN	Pharmaceutical Care Need
PCNMET	An addressed PCN
PTW	Pharmacotherapy Workup
QI	Quality index
RL- CCB	Rate limiting CCB (verapamil, or diltiazem)
S1	A drug therapy risk pertaining to uncontrolled safety parameters
S2	A drug therapy risk pertaining to unnecessary drug therapy
S3	A drug therapy risk pertaining to high risk drug choice
S4	A drug therapy risk pertaining to high risk dosing
SCO	Scotland
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
TE	Thrombo-embolism, thrombo-embolic
U&E	Urea and electrolytes
UK	United Kingdom
UNAI	Unexplained non-adherence index
US	United States

Publications and presentations

1. Oral presentations

ESCP 36th European Symposium on Clinical Pharmacy 'Implementing Clinical Pharmacy in Community and Hospital Settings: Sharing the Experience', Istanbul, Turkey 25–27 October 2007

Tobias Dreischulte, John J. McAnaw, Steve A. Hudson
Medication assessment tool to assess quality of prescribing in chronic cardiovascular disease (MATCVD). Abstract published in Pharmacy World and Science (2008) 30:649–740

PCNE 7th Working Conference. Innovation in Pharmaceutical Care Research, Vimeiro, Portugal 4-7 March 2009.

T Dreischulte, SA Hudson. Medication Assessment Tool for chronic cardiovascular conditions (MATCVC): A novel approach to evaluating guideline implementation. Abstract published in Pharmacy World and Science, 2009 31(4): 494-508.

2. Poster presentations

ESCP 37th European Symposium on Clinical Pharmacy, Pharmaceutical Care Models, and Therapeutic Innovations, Dubrovnik, Croatia, 21–24 October 2008
Tobias Dreischulte, Steve A. Hudson. Strategies in pharmaceutical care and pharmaceutical public health: quality of cardiovascular drug therapy use. Abstract published in Pharmacy World and Science (2009) 31:246–349

American College of Clinical Pharmacy/ European Society of Clinical Pharmacy International Congress on Clinical Pharmacy April 24–28 2009, Orlando

Tobias Dreischulte, Susanne Frisse, Andrea Liekweg, Thomas Twisselmann, Gerian Groenefeld, Ulrich Jaehde, Stephen A. Hudson. Evaluation of cardiovascular medication use: development and validation of an assessment tool for use in Germany. Abstract published in Pharmacotherapy 2009; (29):36e-176e.

Tobias Dreischulte, Michiel E. Verhulst, Leendert H. Heeres, Erik E. Gerbrands, Jan de Waard, Hugh R. Kruyt, Johan J. de Gier, Stephen A. Hudson. Evaluation of cardiovascular medication use: A novel multidisciplinary approach to guideline implementation in Dutch primary care. Abstract published in Pharmacotherapy 2009; (29):36e-176e.

Acknowledgements

Firstly, I would like to offer my sincerest thanks to my supervisor, guide and friend Professor Steve Hudson, who sadly passed away during the final stages of this PhD. His support and encouragement have given me the confidence to finalise this thesis.

I would like to thank Julienne Johnson, who did not hesitate to step in as my supervisor after Steve Hudson's death and John McAnaw, who has supervised me during the initial stages of this PhD.

For the work carried out in relation to the field testing of the medication assessment tool, I would like to thank all collaborators in each setting, whose names are too numerous to be listed here. Representative of them all, I thank Dr Gerian Groenefeld (German inpatient setting), Steve McGlynn and Carl Fenelon (Scottish outpatient setting), Eric Gerbrandts and Professor Han de Gier (Dutch primary care setting). I am grateful to all students, who have assisted in data collection, namely Susanne Frisse, Joachim Strobel and Michiel Verhulst.

Special thanks go to the Data-driven Quality Improvement in Primary care (DQIP) team, Professor Bruce Guthrie, Dr Aileen Grant and Debby O'Farrell, who have taken on extra work in order to support me during the final stages of this PhD. I would also like to thank my friend and colleague Dr Oliver Schwalbe, who has given me valuable feedback on the final draft of this thesis.

Finally, I would like to thank my family and friends for their moral support over the entire duration of this PhD.

Wie jede Blüte welkt und jede Jugend
Dem Alter weicht, blüht jede Lebensstufe,
Blüht jede Weisheit auch und jede Tugend
Zu ihrer Zeit und darf nicht ewig dauern.
Es muss das Herz bei jedem Lebensrufe
Bereit zum Abschied sein und Neubeginne,
Um sich in Tapferkeit und ohne Trauern
In and're, neue Bindungen sich zu geben.
Und jedem Anfang wohnt ein Zauber inne,
Der uns beschützt und der uns hilft, zu leben.

Wir wollen heiter Raum um Raum durchschreiten,
An keinem wie an einer Heimat hängen,
Der Weltgeist will nicht fesseln uns und engen,
Er will uns Stuf' um Stufe heben, weiten.
Kaum sind wir heimisch einem Lebenskreise
Und traulich eingewohnt, so droht Erschlaffen,
Nur wer bereit zu Aufbruch ist und Reise,
Mag lähmender Gewöhnung sich entraffen.

Es wird vielleicht auch noch die Todesstunde
Uns neuen Räumen jung entgegensenden,
Des Lebens Ruf an uns wird niemals enden…
Wohlan denn, Herz, nimm Abschied und gesunde!

Hermann Hesse

Chapter 1

Defining, quantifying and understanding the quality gap in medication use systems

1. Background

The safety and quality of medicinal products has been a major public concern since the thalidomide tragedy in the 1950s[1]. As a consequence, new approval procedures for pharmaceutical products have been introduced in order to ensure that drug products entering the market are nontoxic and yield a favourable risk-benefit balance. Despite these high demands, however, the inconsistent use of beneficial treatments in eligible patients and the high-risk use of drugs in vulnerable patients is frequently the cause of suboptimal patient outcomes and preventable harm.[2, 3]

Rising profile of the quality gap in medication use

The profile of preventable drug related morbidity (PDRM) has been raised in recent years by a number of policy reports. In 2000, the American Institute of Medicine published *'To Err is human'*[4] and in the same year, the UK Department of Health issued *'An organisation with a memory'*[5]. Both reports have established that medication errors are one of the most common types of errors in health care, substantial numbers of patients are affected each year and that such errors account for a considerable increase in health care costs. The economic implications of drug-related morbidity in patients aged 65 and older have been estimated in 2005[6] at almost $900 million in the ambulatory care setting in the United States, of which the largest component (62%) was attributed to drug-related hospitalisations. The Department of Health has estimated in 2007[7] that drug related hospital admissions to secondary care may cost more than £750 million annually.

The quality gap relates to both safety and effectiveness of medication use

'To Err Is Human' focused on injuries arising as a direct consequence of medical care. Similarly, increasing patient safety has been declared a priority by the World Health Organisation (WHO)[8], health authorities in the US[4] and the UK[5,9]. In view of a growing evidence base supporting drug therapy as a means of preventing and

slowing the progression of long term conditions, such as cardiovascular disease, there is increasing emphasis on the co-existing problem of underutilisation of indicated medication.[10] The importance of making consistent use of preventative and disease-slowing treatments, such as lipid lowering medication in the primary and secondary prevention of vascular events, is underlined by the expected rise in the prevalence of long term conditions, which according to the WHO [11] 'endangers the prosperity of all nations'.

Paradigm shift from practitioner performance to system performance

Errors in the medication use process have been conventionally attributed to the behaviours of individual practitioners or on the play of chance. However, a cultural shift is now seeing preventable adverse drug events less as the result of incompetent or negligent individuals and more as deficiencies in the design of health care delivery *systems*.[4, 12] Consequently, a 'whole systems' response has been advocated[12], which takes into account the interdependencies of different stages of the medication use process and the ways in which professionals collaborate, institutions organise and the wider health care environment supports the delivery of care, respectively.

2. Aims and objectives

The first chapter of this thesis aims to describe the scope of the problem of preventable drug related morbidity (PDRM) in long term care and to contribute to the conceptual understanding of how PDRM arise in current medication use systems. The chapter will provide the basis for the identification of quality improvement strategies, which are the subject of chapter 2. The specific objectives of chapter 1 are:

1. To define 'quality of medication use'
2. To describe the size and spectrum of PDRM and its causes in long term care
3. To critically review terms used in the literature to describe the PDRM problem in relation to undesirable patient outcomes and their causes

4. To propose a theoretical model of the aetiology of PDRM and to identify targets for quality improvement

3. Defining 'quality' in health care and medication use

3.1 The Medication use Process

3.1.1 Process stages

The medication use process can be broadly divided into five sub-processes: medication needs assessment, care planning, care plan validation, care plan implementation and clinical monitoring. The process can be seen to start with a patient consultation or a referral to a health care practitioner, where a *medical problem* (risk factor, symptom or disease) that is potentially susceptible to drug therapy is identified (figure 1.1).

Medication needs assessment. The need for drug treatment is established (*assessment*) in the context of the patients' medical history, current drug therapy, the patient's preferences, cognitive/technical abilities and the likely effectiveness, safety and cost-effectiveness of available drug treatments.

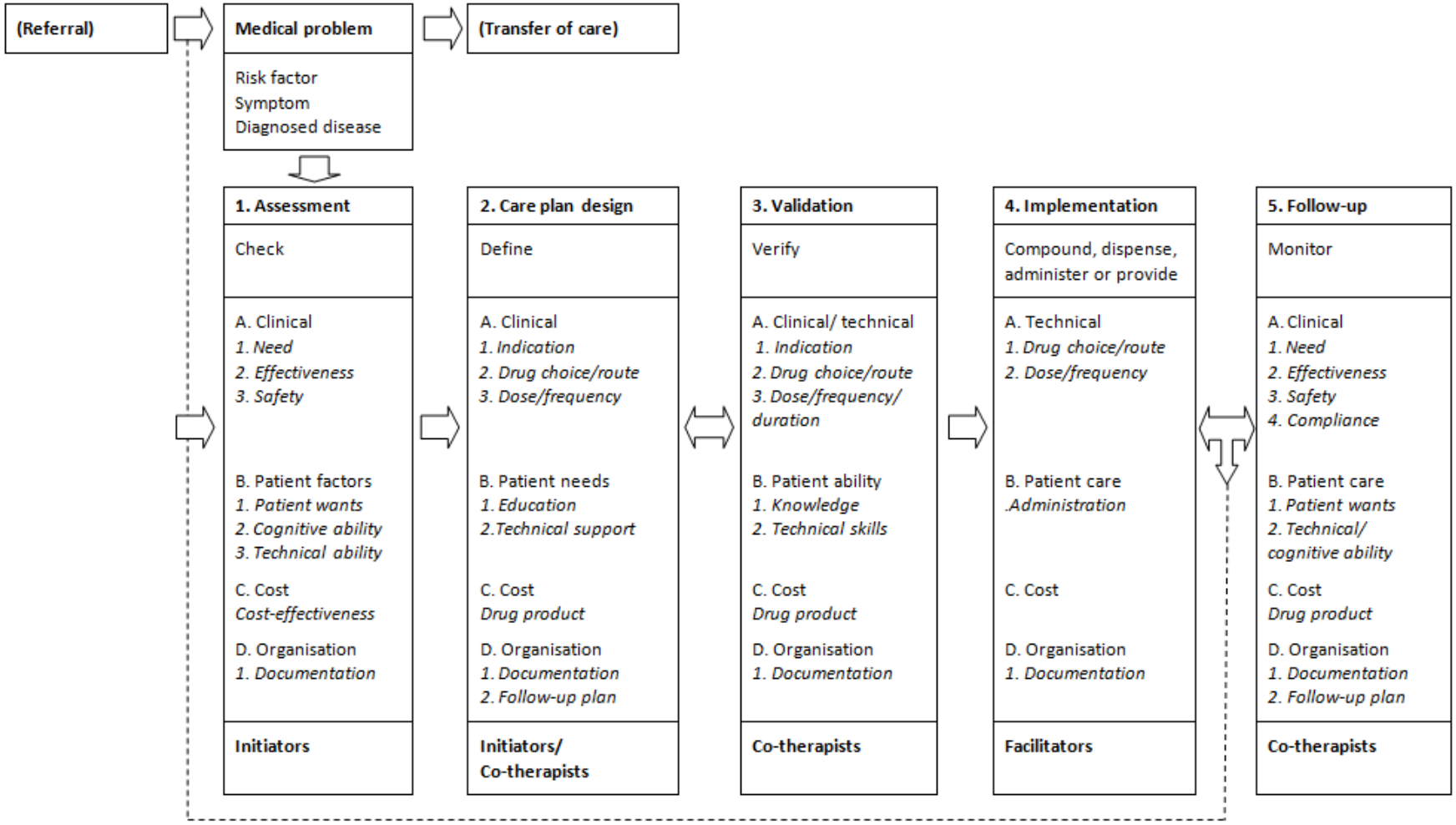
Care plan design. If the decision is made to initiate (or alter) current medication, a treatment strategy (*care plan*) is designed, which specifies the (altered) medication selection, dose and dose frequency and defines a plan for patient follow-up.

Care plan validation. The care plan is validated by verification of adherence to standards of indication, choice, duration, dose/frequency and route (where available), the patient's knowledge about the medication and the patient's ability to administer the medication.

Care plan implementation. The medication is subsequently dispensed and administered.

Clinical monitoring. The continued suitability (in terms of indication, effectiveness, safety and compliance) of the care plan to achieve the goals of therapy is monitored and drug therapy is individualised according to a patient's specific needs within the remits of the care plan. Where adjustments to the care plan are required or a new medical problem is encountered, a review of the patient's medical and/or medication needs is conducted.

Figure 1.1: Stages, activities and functions within the medication use process (inspired by references[12, 13])



The medication use process as described here is to be understood as a response to a specific patient need for medication related care. In patients with multiple needs, therefore, several processes may be active at the same time, and each process may be at a different stage. Furthermore, patients with long term conditions often receive episodes of care from a number of different professionals, including general practitioners, hospital specialists in multidisciplinary settings (as inpatient and/or ambulatory care), community pharmacists and primary care nurses that may include parallel or consecutive medication use processes.

3.1.2 Tasks and functions

The medication use process requires three overlapping functions: (1) prescribing (understood as the initiation of therapy based on medical problem assessment); (2) professional supervision and management; (3) dispensing and administration.[12] Accordingly, practitioners may function as (1) initiators, (2) co-therapists or (3) facilitators.[12] The distinction by function rather than by profession is useful since the professional boundaries in executing these functions are diminishing (e.g. in the UK, prescribing rights have been extended to nurses and pharmacists). Furthermore, one practitioner may fulfil multiple functions. For example, the same practitioner may be responsible for initiating and monitoring therapy (often a physician) or for validating and dispensing therapy (often a pharmacist) or for administering and monitoring therapy (often a nurse).

3.2 Definitions

The United States Institute of Medicine (IOM)[14] defines quality in health care as

> *'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'.*

The concept of quality has been described as consisting of eight dimensions across three perspectives (table 1.1).

In an effort to capture the multi-dimensional nature of health care quality within one single concept, the term 'appropriateness' has found widespread application. A widely cited definition considers health care procedures (in general) 'appropriate' if

> *'for an average patient presenting to an average physician the expected health benefits exceed the risks by a sufficiently wide margin that the procedure is worth doing, excluding cost'.*[15]

Table 1.1: Eight dimensions of quality in health care (adapted from reference [12])

Clinical perspective	
Safety	- Avoiding injury from the care that is intended to help patients - Avoiding physical, social and other hazards
Effectiveness	- Based on scientific knowledge - Providing interventions to all who could benefit (meets need, improves patient's health, prevents disease, is selected and provided correctly)
Humanitarian perspective	
Patient-Centredness	- Providing care that is respectful of and responsive to individual patient references, needs and values - Ensuring that patient values guide all clinical decisions - Ensuring patient information - Encouraging patient participation - Ensuring patient satisfaction
Equity	- Providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socio-economic status
Timeliness	- Reducing waits and sometimes harmful delays for both those who receive and those who give care
Economic/organisational perspective	
Efficiency	- Avoiding waste, including waste of equipment, supplies, ideas and energy
Documentation	- Recording of information about care for purposes of communication, continuity and audit
Continuity	- Coordination of needed care between practitioners, organisations and time

3.2.1 Quality in medication use

The above definition of appropriateness has been criticised for being limited to the clinical or technical perspective.[16] Cribb and Barber therefore define 'appropriate *prescribing*' more broadly as [17]:

> *'A balance between the right technical properties, what patients want and the greater good'*

Cribb and Barber's definition[17] emphasises not only the multidimensional nature of prescribing (technical, humanitarian and society) but also highlights that attaining these dimensions may be in conflict with each other. Tensions may arise between societal and individual needs, such as when small improvements in health status are desirable to individual patients but at perhaps unjustifiable cost to society; or when irrational patient wants (for example antimicrobial agents for viral infections) endanger the greater good (such as risk of antimicrobial resistance). Furthermore, a patient's preference for short term improvements in functional status may be in conflict with scientifically determined long term benefits and risks (for instance in the case of hormone replacement therapy). Even within the clinical dimension, appropriate medication use often forms a compromise between safety and effectiveness, especially in patients with co-morbidities or other risk factors for adverse events, such as old age.

Cribb and Barber's definition accounts for the above described uncertainties of clinical decision making, but with reference to the IOM definition[14], spares the organisational perspective. In order to capture the medication use process in its entirety the following definition of quality in medication use is therefore proposed:

> *'An optimal balance of scientific knowledge, patient preference and patient need in the planning, implementation and monitoring of medication use within the constraints of society'*

3.2.2 Quality deficits in medication use

Undesired patient outcomes

The outcomes of health care in general can be categorised in accordance with the IOM quality dimensions as economic, clinical and humanistic outcomes ('ECHO'). This review focuses on clinical outcomes. The pharmaco-epidemiological literature distinguishes between adverse drug reactions (ADRs) and adverse drug events (ADEs). The term 'adverse drug reaction' (ADR), which is synonymous with 'adverse drug effect' has been defined by the WHO in 1972 as

> *'A noxious, unintended and undesired effect of a drug, which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy'* [18]

A number of authors assert that ADRs are due to the innate toxicity of drugs and are not preventable, by definition.[19,20] Drug safety researchers have therefore coined the term adverse drug events (ADEs) [21] as an expansion to the concept of ADRs. This term includes both ADRs and events that would be preventable by today's standards. The IOM [22] has defined an adverse drug event as

> *'Any injury due to medication'*

In 2004, adverse events that are the consequences of acts of omission, for example *'a recurrent myocardial infarction in a patient without a contraindication, who was not given a beta blocker'* [13] were explicitly included in the IOM definition of adverse events. The same shift in thinking is reflected in the pharmaco-epidemiological literature: while earlier publications on the epidemiology of ADEs and their preventability have focussed on direct injury from drug products only[22], more recently, authors[23] have extended the definition to include under-dosing or failure to prescribe a medication when clearly indicated (under-prescribing).

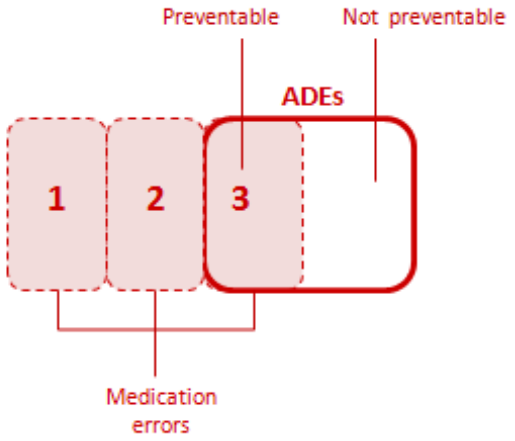
Suboptimal processes

The preventable causes of adverse events in health care in general have been referred to as 'errors' and have been defined by the IOM [4] as

'The failure of a planned action to be completed as intended (i.e. error of execution), or the use of a wrong plan to achieve an aim (i.e. error of planning)'

The reported relationship between adverse drug events (ADEs) and medication errors is shown in figure 1.2. It illustrates that not all medication errors will lead to patient harm. Some errors (1) are so minor that patient harm is not even a reasonable possibility, whereas others (2) may cause harm but do not because of the play of chance or because they have been corrected in due time. (3) When medication errors are identified as the cause of adverse drug events (ADEs), such events are considered to be preventable. Adverse drug events that are not the consequence of medication errors, are considered to be not preventable.

Figure 1.2: Reported relationship between adverse drug events (ADEs) and medication errors (adapted from reference [21])



1 = Medication errors that do not cause harm

2 = Medication errors that potentially cause harm (potential ADEs)

3 = Medication errors that have caused harm (ADEs)

In analogy to the definition of ADEs outlined above, there has been a shift towards including acts of omission into the definition of errors.[10] Applied to drug therapy, errors of commission refer to the use of contraindicated or interacting drugs or overdosing that may directly lead to patient injury. In contrast, errors of omission refer to failures to provide adequate monitoring, not responding to abnormal clinical results (clinical inertia) or not prescribing medication that is of likely benefit to the patient. The following definition of medication error is used by the IOM [13]:

'Any error occurring in the medication use process'

4. The scale and nature of the PDRM problem

4.1 Preventable drug related hospital admissions

Most studies investigating the prevalence or incidence of preventable drug related hospital admissions are prospective observational studies. Typically, investigators identify trigger events and then work backwards in order to identify whether or not the event was attributable to medication use and would have been preventable. Typically, clinical case notes (or summaries) are reviewed by two or more experienced researchers or clinicians, who use more or less implicit methods to assign drug-related causality and preventability of admissions.[25]

Five systematic reviews were identified that had been published since 2000 and their findings are summarised in table 1.2.[2,23,26-28] Four of these reviews have included hospital based observational studies and provide prevalence data.[2, 26-28] From three systematic reviews, the median total prevalence of drug related hospital admissions ranged from 4.9 to 7.1%, while the findings of the individual studies included in these reviews ranged from 0.2 to 41.3%.[26-28] The median absolute prevalence of *preventable* hospital admissions was 3.7 and 4.3%[2,28], respectively, and the relative preventability rate was between 29 and 59%[26,28] of all drug related hospitalisations.

Table 1.2: Systematic reviews of the prevalence and incidence of (preventable) drug related morbidity

Author	No. of studies included	Studies included Setting/ Patients/ Study	Drug related admissions (DRA) (Prevalence (%) except where indicated*	Preventability %	Included causes and definitions
Prevalence studies					
Beijer et al [26] 2002	68	Hospital based All ages	Median: 4.9 (Range 0.2-41.3) Non-elderly: 4 Elderly: 17	Mean (95% CI) from 12 studies: 29 (+/- 0.2) of total Non-elderly (mean): 24 (+/- 0.2) Elderly (mean): 88 (+/- 0.6)	ADRs (WHO definition)* causing hospital admission
Winterstein et al[28] 2002	15	Hospital based All ages	Median: 7.1 (Range 2.5-25)	Median(Range): 4.3 (1.4-15) 58.9 (32 -86) of total	(p)ADEs** causing hospital admission
Howard et al [2] 2006	13	Hospital based Aged ≥ 16	Not reported	Median: 3.7(Range 1.4-15.4)	(p)ADEs (4 studies included ADRs only, others also included undertreatment) causing hospital admission
Kongkaew et al[27] 2008	25	Hospital based All ages	Median: 5.3 (Range 0.2 to 16) Children: 4; Adults: 6 Elderly: 11	Not reported	ADRs causing hospital admission
Incidence studies					
Thomsen et al [23] 2007	29	Hospital (15) Community (14) All ages	*Incidence(range) from 8 studies** Median: 0.45 () /1000 patient months	*Preventability from 1 study:* 6% (95%CI 2 to 10) *Incidence from 1 study:* 4.5 /1000 patient months	(p)ADEs (reference to IOM definition) including errors of omission and treatment failure) causing hospital admission
Thomsen et al [23] 2007	29	Hospital (15) Community (14) All ages	*Incidence(range) from 8 studies** Median: 6 (1 to 10) /1000 patient months	*Preventability from study:* Median: 21 (range 11 to 38)% *Incidence from 1 study:* /1000 patient months	(p)ADEs (reference to IOM definition including errors of omission and treatment failure) causing hospital admission or other undesired outcome

4.2 PDRM managed in primary care

Studies focussing on hospital admissions may underestimate the problem of drug related morbidity in primary care, since many ADEs are managed in primary care. For example, in the review by Thomsen et al [23], the median incidence of ADEs was 14.9 per 1000 persons-months, but only 0.45 ADEs/1000 patient months required hospital admission. The median preventability rate (from 4 studies) was 21%. This equates to 18 out of every 100 patients treated for one year suffering an ADE, of which 3 to 4 are preventable.

4.3 The causes of PDRM in long term care

4.3.1 Prevalence and incidence of medication errors

Errors at the care planning stage

Although care planning involves rather more than prescribing medication, the research literature has focussed on prescribing errors. Two of the systematic reviews on drug-related hospitalisations described above[2,23] have reported the frequency that preventable hospital admissions were caused by prescribing errors. Howard et al[2] found a median of 31% (range 11 to 42) while Thomsen et al[23] found a higher rate of 56% of preventable drug-related hospitalisations, respectively. Table 1.3 shows the drug groups most frequently associated with preventable hospitalisations, where prescribing errors were either the main or an important underlying problem. The vast majority of these prescribing errors were attributed to high-risk prescribing, such as the prescribing of contra-indicated medication or the use of combinations of drugs with cumulative side effects, rather than under-prescribing.

Nevertheless, a number of surveys provide evidence of substantial under-prescribing of effective treatments, particularly for cardiovascular conditions, where inadequate management of risk factors for conditions such as hypertension and coronary heart disease remains an important international challenge. Under-use of treatments for secondary prevention of coronary heart disease or cerebrovascular

disease have been identified in the prescription of antiplatelet agents[29], lipid lowering drugs[30], and the use of beta-blockers after myocardial infarction[31]. Underuse of ACE inhibitors/Angiotensin Receptor Blockers has been reported in patients with heart failure[32,33], and the inadequate use of oral anticoagulation in patients with atrial fibrillation[34].

Table 1.3: Drugs frequently associated with preventable hospital admissions (adapted from[2]), where prescribing was an important underlying cause

Rank	Drug group	Frequency as a cause of preventable hospitalisation (%)	Frequency that cause is preventable ADE* (%)**	Process most likely to improve outcomes
1	Antiplatelets ***	16	97	Prescribing
3	NSAIDs	11	97	Prescribing
5	Opioid analgesics	5	99	Prescribing/ Self-monitoring
6	Beta blockers	5	86	Prescribing
9	Positive inotropes	3	91	Prescribing/ Self-Monitoring
10	Corticosteroids	3	93	Prescribing
11	Antidepressants	3	98	Prescribing
12	Calcium Channel Blockers	3	87	Prescribing

*Directly linked to adverse effects of the drug. ** The proportion of events that is missing from 100% was attributed to patient non-adherence or under-treatment; *** Includes low dose aspirin

Errors at the implementation stage

The research literature on dispensing errors has concentrated on the technical aspect of filling and labelling prescribed medication. Technical dispensing errors are relatively rare events and affect approximately 3% of filled prescriptions in the UK.[35] Errors at the administration stage encompass errors in the technical administration of a drug product by a carer or patient (eg administration of an intravenous infusion or correct use of inhalers) and errors in drug taking (non-adherence to instructions). Unlike other forms of medication error, patient non-adherence has been extensively

studied and recently been systematically reviewed[36]. It is estimated that between 30 and 50%[36] of patients do not take their medication as recommended. Studies have also found that 3% of prescriptions ultimately are not presented at the pharmacy for dispensing (primary non-adherence).[36-38] In systematic reviews on preventable drug related hospitalisations[2,23], adherence problems were the main underlying cause in approximately a third of hospitalisations.

Errors at the monitoring stage

Errors at the monitoring stage comprise failures to review medications or conduct appropriate clinical or laboratory checks at adequate time intervals, or a failure to react to abnormal clinical/laboratory results (clinical inertia[39]).

In one systematic review of preventable drug related hospitalisations[2], monitoring errors accounted for between 22% and 61% of preventable admissions. Table 1.4 shows the drug groups most frequently associated with preventable hospitalisations, where monitoring errors were either the main or an important underlying problem. In a UK study[40], medical record review revealed that in a random sample of 427 patients from fifty general practices, there was no indication in the patient notes that the GP had considered whether to continue medication in the last 15 months in 72% of cases. In addition, failure to intensify treatment in patients whose risk factors continue to be inadequately controlled, has been found to be a common problem in the treatment of hypertension[41], diabetes[42] and hypercholesterolaemia[43].

Table 1.4: Drugs frequently associated with preventable hospital admissions (adapted from[2]), where monitoring was an important underlying cause

Rank	Drug group	Frequency as a cause of *preventable* hospitalisation (%)	Frequency that cause is overtreatment (%)*	Process most likely to improve outcomes
2	Diuretics	16	91	Laboratory-/ self- monitoring
4	Anticoagulants	8	97	Laboratory monitoring
5	Opioid analgesics	5	99	Prescribing/ Self-monitoring
7	ACE inhibitors/ ARBs, aldosterone antagonists	4	93	Laboratory monitoring
8	Antidiabetics	4	82	Self-monitoring
9	Positive inotropes	3	91	Prescribing/ Self-Monitoring

* Directly linked to adverse effects of the drug and not due to patient non-adherence or under-treatment

Errors in the transfer of care

In the interest of continuity of care, health care practitioners practising from disjointed locations need to exchange information; which, if incomplete or erroneous, may lead to adverse outcomes. In one systematic review[36], unintentional discrepancies between inpatient records and outpatient or primary care records have been identified in approximately 60% of items prescribed at hospital admission (comparison of GP and hospital record), 11 to 27% of items at hospital discharge (comparison of inpatient prescription and discharge prescription) and 43 to 60% after an episode of hospitalisation (comparison of discharge prescription and GP repeat prescription records). A German study [44] found that in primary care, 8% of the total number of medicines taken by patients with diabetes mellitus, were not recorded in the GP's database, while 7% of all medicines recorded in the general medical practitioner's database were not actually taken by the patients.

5. Critical review of terms used to describe PDRM and its causes

5.1 Preventable drug related morbidity (PDRM)

5.1.1 Limitations of the term adverse drug events (ADEs)

The IOM definition of quality in health care[14] distinguishes in the clinical domain between safety and effectiveness. Safety is defined in terms of avoiding harmful care (non-maleficence) and effectiveness is understood in terms of providing beneficial care (beneficence). It is clear, that it was the IOMs intention to additionally accommodate the indirect consequence of not using drug therapy that is indicated to alter the natural course of disease within the concept of ADEs. This is reflected in the above cited example (non-use of a beta-blocker resulting in recurrent myocardial infarction) that was a direct quotation from the relevant IOM publication[13].

However, the current situation is unsatisfactory, because the definition of an 'ADE' has remained unaltered (*'injury due to medication'*). The terms '*drug event'* in ADE rather than *'drug therapy event'* and '*injury due to medication*' suggest, however, that a direct cause-and-effect relationship between the administration of a drug product and a negative outcome must exist for it to be classified as an ADE. In addition, intermingling events that are the consequence of direct harm (safety) with events that are the consequence of a failure of drug therapy to prevent or cure disease (effectiveness) has disadvantages. This is because establishing a causal relationship between the lack of benefit from drug therapy and omitting indicated treatments is always confounded by the underlying disease process. For example, beta blockers may only prevent a small proportion of myocardial infarctions. In contrast, the relationship between adverse events that are the direct consequences of drug use (rather than the lack of its use) can be established with more confidence. Mixing both types of events within the same concept may diminish the persuasiveness of reports on the current performance of medication use systems.[45]

5.1.2 Need for the term Drug Therapy Failure (DTF)

Introducing a new concept to accommodate the consequences of sub-optimally effective medication use therefore has advantages over including such events in the concept of ADEs. The term *'treatment failure'* has previously been used in this context[12], but has not been formally defined. However, *'treatment failure'* does not reflect the cause of the failure and the term *drug therapy failure* (DTF) is therefore proposed with the following definition:

'A negative clinical outcome due to a medical condition that is preventable or modifiable by drug therapy'

In parallel to pADEs, preventable drug therapy failure (pDTF) is defined as

'Drug therapy failure due to an untreated indication, the selection of a suboptimal drug or the use of lower than indicated intensity of drug treatment'

5.2 Causes of PDRM

5.2.1 Limitations of the term medication error

According to the traditional model (see figure 1.2), medication errors are the only causes of preventable adverse drug events (pADEs), which bears the risk of missing important opportunities for process improvements. Drug related morbidity may be caused by factors that are not attributable to rule violations by practitioners or patients (errors) but rather to an accumulation of unfavourable *'circumstances'*.[12] For example, an asthmatic patient may compensate for worsening asthma symptoms by increasing the use of short acting beta-agonists and a trigger event, such as a respiratory tract infection, may lead to the clinical manifestation of injury that was initially latent.[12] The described scenario would hardly meet the definition of an error (in the sense of violating a rule). It may, nevertheless, have been prevented by closer monitoring of the patient's use of reliever drugs by practitioners or by the patient reporting worsening symptoms. The absence of medication errors does therefore not necessarily imply that such events are non-preventable per se.

5.2.2 Strengths and limitations of the term Drug Therapy Problem (DTP)

As an extension to the term 'medication error' Hepler and Segal[12] have coined the term 'latent injury' to capture a patient 'propensity or predisposition' to PDRM that happens during the treatment process. Latent injuries may be caused by medication errors but coincidental patient exposures to risk factors that are not rule violations are equally captured by this term. Some latent injuries are detectable and therefore correctable and are referred to as *drug therapy problems* (DTPs), defined as

> *'Any circumstance that a competent professional would judge to be inconsistent with achieving the objective of drug therapy'*[12]

Since the concept of DTPs (or drug-related problems[46]) was introduced more than 20 years ago, the definition of the concept and the categorisation of DTPs have been the subjects of extensive debate among researchers.[47-52] A number of definitions and categorisation systems have been proposed and revised over the years with the result that a uniform definition of the concept or its categorisation does not exist. This is perhaps the reason, why DTPs have not obtained status of medical subject headings and have not been added to the International Classification of Primary Care (ICPC) codes, despite a corresponding request from Spain in 2002.[53]

The most recent discussions have circled around the question as to whether the DTP concept should comprise (1) clinically manifest negative outcomes from medication use only, (2) be restricted to the risk of such outcomes or (3) include both.[50-52] Given the central importance of DTPs in the aetiology of preventable drug related morbidity and as key targets for improving the processes and outcomes of medication use, the DTP concept is critically reviewed here in an effort to identify sources of ambiguity and add clarity.

Functions of the DTP concept

Drug therapy problems (or drug-related problems as they were referred to at the time[54]) have been introduced by Hepler and Strand as a cornerstone of the

philosophy and practice of pharmaceutical care. The detection and resolution of DTPs was identified as '*the focus of a professional role that is truly proactive and patient-focused, and contributes to positive patient outcome'*.[54] The declared function of the concept was to *'provide practising pharmacists with a means to [...] focus on the patient and move away from the profession's pre-occupation with the pharmaceutical agent or the technical process employed to understand the agent'*.[46] In addition, the DTP concept has been used by researchers as a process parameter in numerous evaluations of pharmaceutical care services.[55-59]

Current definitions and categorisation systems

Hepler conceives of DTPs as latent injuries that, if unresolved, may lead to negative patient outcomes. The question as to whether DTPs are risks or clinical outcomes therefore seems to be answered: DTPs are identifiable *risks* (latent injuries) that precede undesired clinical outcomes. However, not all current DTP definitions are consistent with this conceptualisation (table 1.5). Table 1.6 shows how the respective terms used in these definitions were interpreted (based on definitions by the Oxford dictionary) in order to determine whether or not outcomes, understood as changes in health status, and/or the risks of such changes are included in respective definitions and corresponding categorisation systems.

Most definitions include terminology that points towards authors perceiving of DTPs as changes in health status (outcomes) *and* the risks of such changes. However, the combination of terminology, such as 'events' and 'experiences', that appears to denote outcomes with the phrase 'interfere with outcomes' or 'objectives of drug therapy' may be a source of ambiguity. If events or experiences are taken to mean 'changes in health status', then it remains unclear what distinguishes them from the 'outcomes of drug therapy' they are said to interfere with. In addition, Hepler's inclusion of ADRs in the DTP categorisation system appears to contradict the author's DTP definition in table 1.5. Similarly, the distinction between 'health problem' as an outcome and 'insufficiently treated 'health problem' as a process parameter in the Granada III categorisation system, suggests that risks are distinct

from outcomes by virtue of their lower severity. Such distinctions are, however, arbitrary.

The use of terms with scarcely specific meaning, such as 'circumstances', 'event', 'experience'[50] and obscured distinctions between risks and outcomes therefore make disagreements in the interpretation of DTPs (at least) understandable.

Table 1.5: Current DTP definitions and categorisation systems

Strand, Cipolle 1990 [54]	Hepler 2003[12]	Strand, Cipolle 2004[60]	PCNE V 5.01 2009[61]	PCNE V 6.02 2010[62]	Granada II 2002/[47] Fernandez-Llimos et al. 2005 [51]	Granada III[49] 2007
Definitions						
'An undesirable patient experience that involves drug therapy and that actually or potentially interferes with desired patient outcomes'	*'Any circumstance that a competent professional would judge to be inconsistent with achieving the objective of drug therapy'*	*'An undesirable event or (risk of an event*) experienced by a patient, which involves, or is suspected to involve, drug therapy, and that interferes with achieving the desired goals of therapy'* [1]	*'An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.'*		*'DRPs/NOM's are health problems, understood as negative clinical outcomes, resulting from pharmacotherapy, that for different causes, either do not accomplish therapy objectives or produce undesirable effects.'*	*'DRPs are elements of process (understood as all that occurs before outcome) which put the patient at greater risk of suffering from an NOM*
Categorisation systems						
1. Unnecessary drug 2. Needs additional drug 3. Ineffective drug 4. Dosage too low 5. ADR 6. Dosage too high 7. Noncompliance 8. Drug-drug interaction	1. Access 2. Wrong drug (E) 3. Wrong dose (E) 4. Wrong drug (S) 5. ADR 6. Wrong dose (S) 7. Unnecessary drug 8. Drug-laboratory interaction	1. Unnecessary drug 2. Needs additional drug 3. Ineffective drug 4. Dosage too low 5. ADR 6. Dosage too high 7. Noncompliance	1. Drug Choice 2. Dosing 3. Interactions 4. ADRs 5. Drug use 6. Other *DRP causes* - Drug/Dose - Drug use process - Information - Patient behaviour - (Pharmacy) logistics - Other	1. Effectiveness 2. ADRs 3. Costs 4. Other DRPs can be: - *Actual* - *Potential* *DRP causes* - Drug selection - Drug form - Dose selection, - Treatment - Duration - Drug admin. - Logistics	1. Untreated health problem 2. Effects of unnecessary drug Non-quantitative ineffectiveness 4. Quantitative ineffectiveness 5. Non-quantitative unsafe 6. Quantitative unsafe	1. Insufficiently treated health problem 2. Contraindication Inappropriate dosage 4. Probability of ADR 5. Non-compliance 6. Duplicity 7. Prescription errors 8. Dispensing errors 9. Interactions 10. Other health problems

[1] * the inclusion of 'risks of events' is inconsistent throughout the publication; NOM = negative outcomes from medication;

Table 1.6: Interpretation of current definitions of drug therapy problems with respect to their respective inclusion of risks and clinical outcomes

Author	**Undesirable outcomes**		**Risk of undesirable outcomes**	
	Included in definition?	*Included in categorisation?*	*Included in definition?*	*Included in categorisation?*
Cipolle/Strand [54, 60]	✓(a,b)	✓ (g)	✓ (c)	✓
Hepler [12]	× (d)	✓ (g)	✓ (c)	✓
PCNE V 5.01 [61]	✓(a,b)	✓ (g)	✓ (c)	✓
PCNE V 6.02 [62]	✓(a,b)	✓ (g)	✓ (c)	✓
Granada II [47]	✓(e)	✓ (all)	×	×
Granada III [49]	× (f)	(×) (h)	✓	✓

Term used		**Definition** (Dictionary unless specified otherwise)	**Interpretation**
a	'Event'	*'A thing that happens or takes place, especially one of importance'*	Outcome
b	'Experience'	*'An event of importance'*	Outcome
c	'Risk/potential'	*'The probability that an event will occur'* [63]	Risk
d	'Circumstance'	*'A fact or condition connected with or relevant to an event or action'*	Risk
e	'Outcome'	*'Negative clinical outcome from drug therapy'*	Outcome
f	'Process'	*'All that occurs before outcome (author's definition)'*	Risk
g	'ADR'	*'Adverse drug reaction'*	Outcome
h	'health problem'	*'insufficiently treated' (author's definition)*	Outcome

6. Proposal of new terms

The ongoing debate and the numerous conflicting definitions and categorisation systems more than 20 years after the introduction of the DTP concept, suggest that the concept has not succeeded in fulfilling the dual functions of (1) shifting the pharmacy *'profession's pre-occupation with the pharmaceutical agent or the technical process employed to understand the agent'*[46] to a patient focussed practice and (2) as a process paramter in the evaluation of pharmaceutical care services. Cipolle and Strand's approach[60] to promoting a patient-centred approach, has been to restrict the DTP concept to (1) undesirable outcomes that are causally related to drug therapy (e.g. an asthma attack due to use of beta blockers) and (2) immediate threats to such outcomes that demand a change in drug regimens (e.g. use of non-steroidal anti-inflammatory drugs in a patient with heart failure).

However, restricting the need for professional action to manifest ADRs or required changes in drug therapy is problematic. Patients may sometimes require drug treatments that are high-risk, because such treatments are the least bad option among possible alternatives. For example, disabling inflammation in a patient with rheumatoid arthritis and heart failure may justify the use of NSAIDs as long as the patient's heart failure symptoms remain stable. In these and other situations, changing a patient's drug regimen is therefore not required at the point of assessment, but nevertheless requires continued monitoring of the patient's condition. Recognising risks to undesirable outcomes and instigating risk management strategies is therefore paramount to preventing ADRs. It is therefore important for practitioners and researchers alike to note that risk identification and mitigation are important contributions of pharmaceutical care services, even if changes in drug therapy are not required.

Nevertheless, when DTPs are used as outcomes in the evaluation of pharmaceutical care services (research), it is desirable to report changes in patient outcomes (i.e. clinically manifest PDRM) and process outcomes (i.e. situations where patients are at risk of PDRM) separately. The most recent PCNE system (V.6.02) and Granada II/III consensus have therefore made attempts to separate such 'problems' in the medication use process. Staying within the concept of DTPs, the PCNE V6.02[62] distinguishes between 'potential' DTPs (risks) and 'actual' DTPs (outcomes). In contrast, Granada II/III[47,49] have introduced the concept of negative clinical outcomes (NOM) to replace the DTP concept and have re-defined DTPs as process ('everything that precedes outcomes').

In view of the fact that there is currently no process in place, which ensures consistency in the use of the DTP concept, different definitions and categorisation systems that are in some cases contradictory are likely to continue to co-exist. An argument is therefore to be made, that new concepts are required in order to distinguish between the following situations:

1. There is clinically manifest evidence of an undesirable outcome (a change in health status) that is either directly attributable to, curable or modifiable by drug therapy.

2. There is NO clinically manifest evidence of undesirable outcomes, but there is a risk of such outcomes that requires a change in prescribing (start, stop or adjust drug therapy) in order to abolish or mitigate the risk.

3. There is NO clinically manifest evidence of undesirable outcomes, but there is a risk of such outcomes that either does not require or cannot be addressed by a change in prescribing, but requires a change in monitoring or drug administration.

Proposal of the concept 'Drug therapy risk (DTR)'

The first situation describes patient outcomes, which have been defined above as ADEs (safety) and DTFs (effectiveness). Since the term 'risk' is a medical subject heading, it seems rational to make use of this term in order to describe situations 2 and 3. 'Risk' has been defined as:

> *'The probability that an event will occur. It encompasses a variety of measures of the probability of a generally unfavourable outcome.'* [50, 63]

In the context of health care, risks that are identified to impede the achievement of therapeutic goals imply the need for professional action in order to prevent negative outcomes. Situations 2 and 3 are distinct by the type of action required but they are not conceptually different in this respect. It is therefore proposed that both situations 2 and 3 be captured under the same concept of *'drug therapy risk (DTR)'*. With reference to the above introduced concepts of ADE and DTF, a '*drug therapy risk (DTR)'* is therefore defined as:

> *'A potential pre-cursor to ADEs or DTFs that requires professional action in order to prevent an ADE or DTF'*

Proposal of the concept 'Pharmaceutical Care need'

In order to identify DTRs, it is necessary to recognise situations that pre-dispose to risk, i.e. risk factors for DTRs that require a DTR *check*. In health care, the process that aims to identify patients with health risk factors is referred to as *screening*. For example, patients between the ages of 60 and 70 are encouraged to conduct faecal occult blood (FOB) tests, because patients in this age range are at increased risk of bowel cancer. If the test is repeatedly positive, an indication for colonoscopy, i.e. health care action, has been identified; if the test is negative, no further action will be necessary until the next test (in this case every 2 years) is due. In this example, the *'situation'* that may or may not require action, is the patient's age.

A further example may illustrate the relevance of these considerations in the context of pharmaceutical care. A clinical pharmacist is employed to cover three general medical wards and does not have the time to interview every patient admitted to these wards. The pharmacist will therefore, as a first cognitive step, employ a *screening* strategy, which aims at identifying factors that pre-dispose the patient to DTRs on the basis of the clinical information at hand. Such pre-dispositions may relate to either the safety or effectiveness of treatment. An example of a risk factor that pre-disposes to adverse drug events (safety) is renal impairment. An example of a risk factor that pre-disposes to drug therapy failure (effectiveness) is chronic heart failure, which requires careful design and timely adjustments of drug regimens. The patient's age (in the bowel cancer screening example), renal impairment (in the safety example) and a diagnosis of chronic cancer pain (in the effectiveness example) can be understood as 'risk factors' or 'pre-dispositions to risk' that trigger further enquiry. In the context of pharmaceutical care delivery, the concept '*Pharmaceutical care need'* is proposed as the result of positive screening tests. It is defined as

'A risk factor of a patient, which pre-disposes to drug therapy risks'

Relationship between introduced and existing concepts

The introduction of new concepts bears the risk of adding to the confusion around existing concepts rather than resolving it, unless the relationships between new and existing concepts are demonstrated. Figure 1.3 therefore aims to clarify the relationships between PCN, DTRs and undesirable outcomes (ADE and DTF) and concepts that have previously been used in the literature to capture the concept of risk: (potential) drug therapy problems and pharmaceutical care issues.

ADEs (preventable or unpreventable) encompass both the negative consequences of harmful treatment and untreated or sub-optimally treated indications for drug therapy. 'Negative clinical outcomes associated with medication (NOM)' and '(preventable) drug-related morbidity ([P]DRM)' are similar in scope. Medication errors cover any shortcomings in the medication use process, irrespective of whether they lead/have the potential to lead to or have already led to undesired outcomes. While the term drug therapy problems (DTP) is perceived by most authors as comprising clinically manifest undesired outcomes *and* the risk of such outcomes[21,54,60-62], attempts have been made to capture these two situations separately by distinguishing 'actual' from 'potential' DTPs[21,61,62] or by restricting DTPs to 'parts of the process'[47,49]. Pharmaceutical care issues (PCIs) encompass potential and actual drug therapy problems[64] but have been used even more broadly, additionally encompassing 'situations in which a question (a potential risk or an identified problem) about drug therapy is identified'[65]. In contrast, the terms Pharmaceutical Care Need (PCN), drug therapy risk (DTR), adverse drug event (in its traditional definition) and drug therapy failure (DTF) are four distinct concepts to describe drug related morbidity and its causes.

Figure 1.3: Relationship between new (PCN, DTR, DTF) and existing (DTP, pharmaceutical care issue) concepts to describe targets within the pharmaceutical care process and its outcomes.

Terms to capture drug related morbidity, its causes and targets for prevention	**Indication for drug therapy/ Patient vulnerability**	**Risk of undesired outcomes**		**Undesired outcomes** (decline in health status)			
		Professional action required:		***Safety***		***Effectiveness***	
		Monitoring	Treatment change	Harmful drug effect		Insufficient effect of treatment	Untreated condition
				Mild	Severe		
Quality Improvement and Pharmaceutical Care literature							
Adverse **D**rug **E**vent[13]				■	■	■	■
Drug **R**elated **M**orbidity[21]				■	■	■	■
Negative **O**utcomes from **M**edication[49]				■	■	■	■
Medication **E**rror[13]				■	■	■	■
Drug **T**herapy (Related) **P**roblem[54, 60]			■	■	■	■	■
Drug **T**herapy(Related) **P**roblem		■	■	■			
- *Potential DTP* [21,61,62]		■	■				
- *Actual DTP* [21,61,62]				■	■	■	■
Pharmaceutical **C**are **I**ssue[64, 65]	■	■	■	■	■	■	■
Proposed set of terms to capture drug related morbidity, its causes and targets for prevention							
Pharmaceutical **C**are **N**eed	■						
Drug **T**herapy **R**isk		■	■				
Adverse **D**rug **E**vent				■	■		
Drug **T**herapy **F**ailure						■	■

7. Theoretical model of the aetiology of PDRM

Figure 1.4 shows a theoretical model of the aetiology of undesirable outcomes of the medication use process, which summarises the points made above and further illustrates the relationships between the introduced concepts of pharmaceutical care need (PCN), drug therapy risk (DTR) and drug therapy outcomes. The model identifies unaddressed PCNs as the causes of DTRs and DTRs as the causes of preventable ADEs and DTFs.

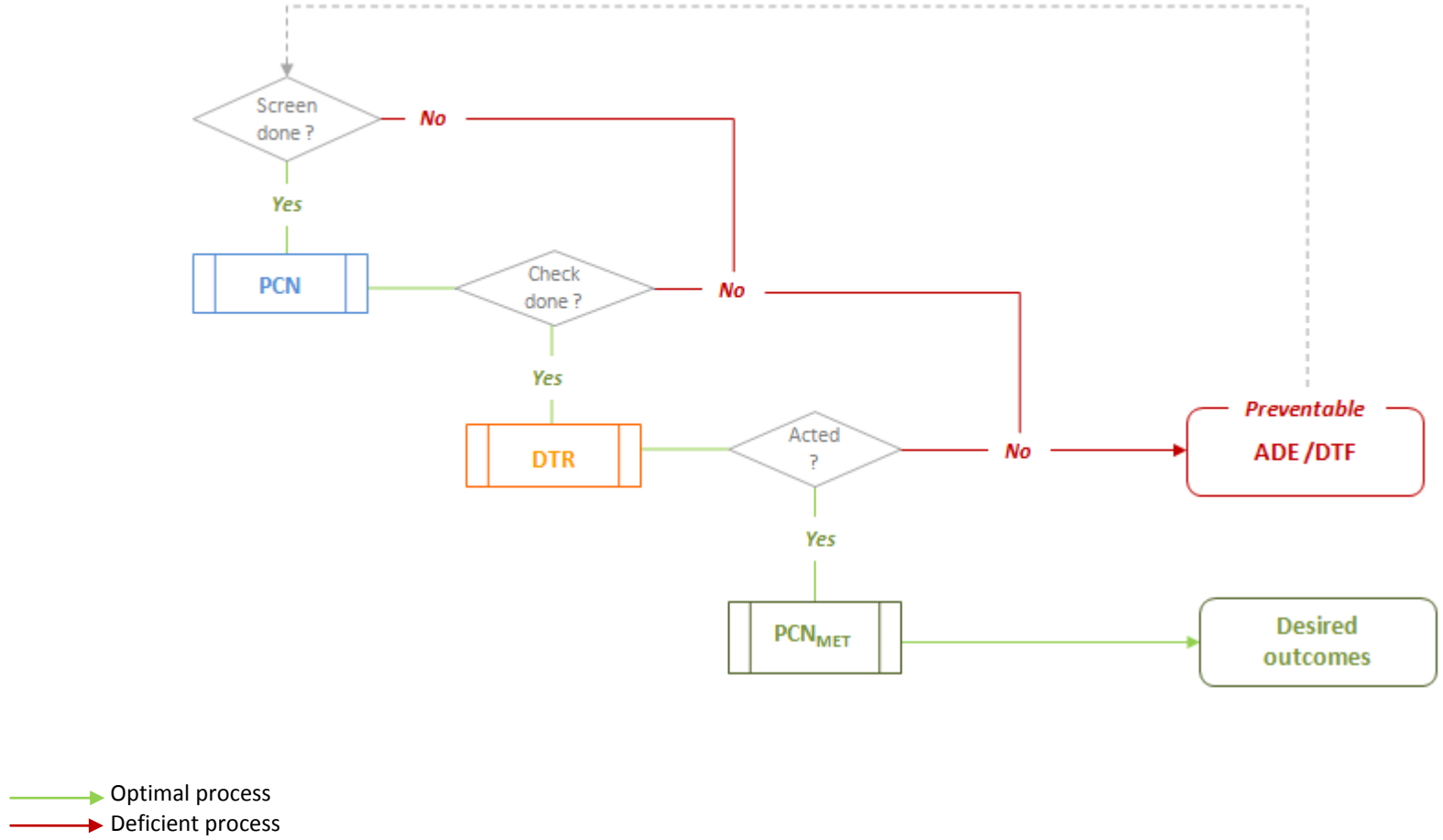
Deficiencies in screening

Deficiencies in screening constitute failures to identify a detectable and addressable PCN. Such PCNs can be one of the following: (1) A known allergy or intolerance to a certain drug or drug class (directly leads to preventable ADE if prescribed) or an acute indication for drug therapy (directly leads to preventable DTF if not prescribed; (2) a medical condition, risk factor (such as age) or existing treatment that makes a patient particularly vulnerable to the use of a certain drug or drug class, (3) a risk factor or medical condition that requires drug therapy for adequate management, (4) an indication for regular monitoring checks to confirm ongoing safety or effectiveness, or (5) an indication for patient education or self-management support.

Deficiencies in checking

Deficiencies in checking constitute failures to identify a detectable and correctable DTR (i.e. an unmet PCN that has not yet led to ADE or DTF). Such DTRs can be one of the following: (1) Drug therapy is not used despite an existing indication, (2) a sub-optimally effective or high risk drug is selected, (3) drug therapy is used at an inadequate intensity in terms of dose or duration, (4) necessary monitoring for medication safety or effectiveness is overdue, (5) necessary patient education or self-management support is overdue.

Figure 1.4: Theoretical model of the aetiology of PDRM including the concepts of pharmaceutical care need (PCN) and drug therapy risks (DTR). ADE stands for adverse drug event and DTF for drug therapy failure.



Deficiencies in acting

Deficiencies in acting constitute failures to correct or otherwise manage an identified DTR. Such action may include (1) to start or stop drug therapy, (2) to switch drug therapy to a more effective or safer alternative, (3) to intensify (increase or reduce the intensity (dose or duration) of treatment, (4) to intensify monitoring or order tests for safety/effectiveness parameters or (5) to provide patient education or self-monitoring support.

Figure 1.4 is a simplified illustration of the aetiology of PDRM, since undesirable outcomes may occur despite an optimal process. Not all pharmaceutical care needs (PCNs) and drug therapy risks (DTRs) are detectable and can be addressed, corrected or managed. In these cases, ADEs and DTFs are considered non-preventable. The pharmaceutical care process continues when a suboptimal outcome occurs (unless the outcome is not repairable), since ADEs and DTFs are best understood as risk factors to future outcomes.

8. Chapter summary

Based on a description of the medication process as comprising of the five consecutive stages of assessment, care plan design, validation, implementation and patient follow-up, quality of medication use was defined as *'An optimal balance of scientific knowledge, patient preference and patient need in the planning, implementation and monitoring of medication use within the constraints of society'*.

It has been demonstrated that deficiencies in the medication use process account for considerable patient harm and unrealised health benefit that is avoidable. Between 1 in 30 and 1 in 40 hospital admissions are drug related and preventable, which places adverse events from medication use as a cause of hospital admission on a par with heart disease from all causes (4%) and higher than ischaemic heart disease (2.1%). These studies are likely to under-estimate the consequences of suboptimal medication use, since morbidity that could potentially be prevented by more consistent use of evidence based therapies was inconsistently considered in the studies included in systematic reviews. Hospitalisation studies have attributed the vast majority of preventable drug related admissions in approximately equal parts to failures in prescribing, patient adherence and monitoring.

The concept of drug therapy failure (DTF) was proposed in order to segregate between undesired outcomes that are the consequences of underuse, sub-optimal selection or intensity of drug therapy (medication effectiveness) from those that constitute direct harm from high-risk medication use (medication safety). It was argued that the concept of medication errors requires an extension to include medication related risks that do not constitute violations of best practice rules. Despite the advantage of the DTP concept in this respect, current definitions and categorisation systems give rise to ambiguity as reflected by ongoing debates about whether DTPs constitute negative clinical outcomes, the risk of such outcomes or both. The concept of drug therapy risk (DTR) was therefore proposed in order to more clearly separate negative outcomes from their precursors. In order to address

an identified lack of a concept that captures patient circumstances (indications for drug therapy or vulnerability to adverse effects), which pre-dispose to risk, the concept of pharmaceutical care need (PCN) was introduced. Based on these newly developed concepts, a revised theoretical model of the aetiology of PDRM was proposed, which forms the foundation for a three step approach to its prevention:

1. *Screening* for pharmaceutical care needs (PCN)
2. *Checking* for drug therapy risks (DTRs)
3. *Acting* on drug therapy risks

The terminology and the theoretical model of the aetiology of PDRM described here provide a theoretical basis for the following chapters.

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Chapter 2

A model for continuous quality improvement of medication use systems

1. Background

1.1 PDRM and long term conditions

Studies into the causes of preventable drug related morbidity in primary care clearly demonstrate that the majority of shortcomings in the medication use process reside in patients with long term conditions.[1-6] In the systematic review by Thomsen et al.[5], agents used in cardiovascular disease, rheumatic disease and diabetes were identified to be responsible for 87% of preventable adverse drug events in ambulatory-based studies. Similarly, in studies included in the systematic review by Howard et al[2], 86% of preventable drug related hospital admissions were attributed to agents used in the management of chronic diseases (cardiovascular 57%, rheumatoid arthritis or chronic pain 20%, diabetes 3%, epilepsy 2%, asthma and chronic obstructive pulmonary disease 1%). Furthermore, although preventable drug therapy failure is typically underrepresented in studies into the prevalence or incidence of PDRM, there is strong evidence for the underuse of evidence based treatments in patients at risk of- or with established cardiovascular conditions.[7-13]

1.2 Root causes of failures in current medication use systems

The majority of patients with long term conditions are managed in primary care. However, most research into the underlying causes of shortcomings in current medication use systems has been conducted in the secondary care setting.[14,15,16] The findings are not necessarily transferable to long term medication use in the primary care setting, since long term care is characterised by the involvement of practitioners working from disjointed locations and a greater role of patient self management.

A qualitative study by Howard et al[17] provides useful insights into the root causes of PDRM in UK primary care. The authors used medical record review and semi-structured interviews with patients, carers, general practitioners and community pharmacists in order to identify weaknesses in the medication use process in

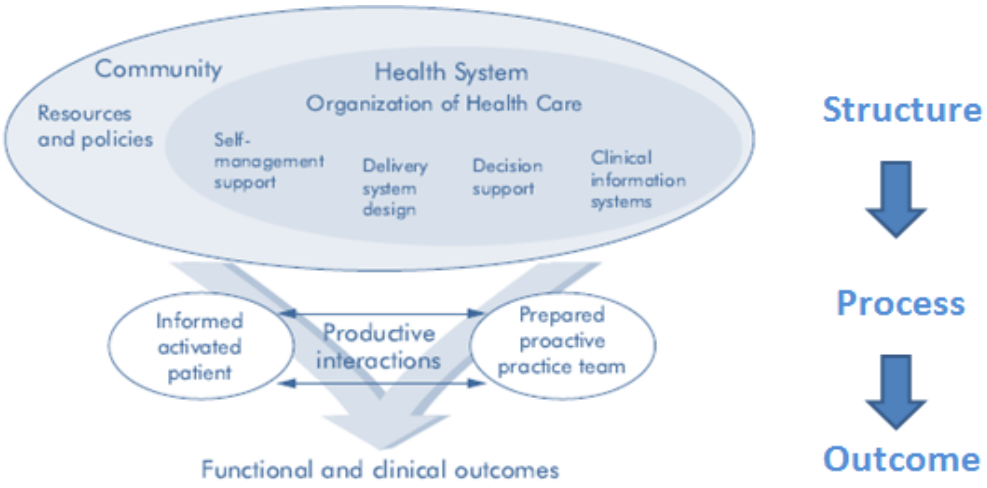
ambulatory care that led to 18 cases of preventable drug related admissions. The authors found that PDRM was often the consequence of failures at multiple stages of the medication use process. Shortcomings in prescribing were mainly the consequences of inaccurate information about patients and lack of pharmaco-therapeutic knowledge by practitioners that were often exacerbated by workload pressures. Deficiencies in professional monitoring were mainly attributed to time constraints and the lack of blurred responsibilities and efficient communication between community pharmacists and general practitioners. Practitioners were often not aware of the potential risks associated with certain drug-drug and drug-disease combinations and therefore failed to employ closer monitoring practices or encourage patients to seek help when problems were encountered. In some cases, community pharmacists recognised drug therapy risks at the dispensing stage but were reluctant to challenge prescribers based on limited patient information. In addition, the authors found that tacit inter-professional barriers described as 'asymmetrical relationships' hindered closer collaboration between community pharmacists and general practitioners.

With reference to the theoretical model described in chapter 1, the investigated cases of PDRM were therefore the consequences of failures in recognising particular patient vulnerability (screening for pharmaceutical care needs) that led to high-risk prescriptions, failures to identify patients at risk (checking for drug therapy risks) and/or failures to act on identified drug therapy risks before they caused patient harm. The root causes of these failures fell into three categories: (1) insufficient practitioner education (pharmaco-therapeutic knowledge), (2) shortcomings in the organisation of care (inter-professional collaboration) and (3) shortcomings in the underlying infrastructure and conditions of care provision (lack of relevant patient information at the time of decision making and time pressures).

1.3 Quality improvement approaches: The chronic care model

The quality gap in the delivery of health care is not limited to medication use. In view of demographic developments and the corresponding rise in the prevalence of chronic conditions, the need for a paradigm shift in the delivery of health care has been acknowledged internationally. There is widespread agreement that overcoming the growing fragmentation of health care, which leads to discontinuity, inefficiency and limited accountability of practitioners working disjointedly, is central to meeting the increasing demands on health care systems. In response, 'integrated care' has been proposed as a possible solution, defined as a co-ordinated set of services, which are planned, managed and delivered to patients across organisations and by a range of co-operating professionals and informal carers.[18] The perhaps most cited specification of the integrated care approach is the chronic care model (CCM)[19], which provides a framework for health care organisations to accomplish the paradigm shift (figure 2.1).

Figure 2.1: The Chronic care model (reproduced from Wagner et al [19])



The model was initially based on systematic reviews of interventions to improve the quality of diabetes management in primary care [20,21], which found that improving clinical outcomes for patients depends on a comprehensive strategy that combines support for practitioners and patients and is embedded in an overall supportive

environment with adequate funding (resources) and policies. Subsequent reviews of interventions to improve the care for other long term conditions have reached similar conclusions, even for those unrelated to diabetes, such as mood disorders.[22,23] Table 2.1 describes the functions of each system component within the CCM.

Table 2.1: System components and their functions within the CCM

1. Clinical information system

- to provide timely useful data about processes and outcomes of care
- to target/recall patients for review by team members (*see delivery system design)*
- to receive feedback on team's performance
- to use reminder systems (see decision support)

2. Decision support

- to institutionalise guidelines/ prompts
- to educate providers
- to provide access to specialist expertise

3. Delivery system design

Population based care
- to ensure that effective interventions reach all patients who benefit

Evidence based clinical management/ sustained follow-up
- to implement increasingly complex and/or resource intensive interventions by identification or addition of team members*

Treatment planning
- to schedule regular appointments in advance
- to enable pro-active follow up using formal written care plans
- to organise team work by defining clear complementary roles for non-physician team members
- to help patients to manage the complexities of multidisciplinary care

4. Self management support

- to enable patients (and families) to care better for their illness by education and ongoing collaboration between patients and professionals

Implicit in the model is the paradigm that the likelihood of desired health care outcomes *('functional and clinical improvement')* is increased by suitable processes (*'informed, activated patients meeting a prepared, proactive practice team'*), which in turn rely on a supportive infrastructure.[24]

2. Aims and objectives

The identified root causes of PDRM in long term care therefore provide arguments to support the working hypothesis that changes to medication use systems in line with the CCM may be successfully applied to improve medication use for long term conditions and reduce preventable drug related morbidity (PDRM). This chapter aims to substantiate this hypothesis by a structured literature review of the impacts of interventions advocated by the CCM on the quality of long term medication use and patient outcomes. The specific objectives are:

1. To review the research literature reporting the impact of audit and feedback interventions targeting prescribers

2. To review the research literature reporting the impact of clinical decision support interventions (CDSS) targeting prescribers

3. To review the research literature reporting the impact of collaborative models of care including pharmacist-delivered services to patients

The literature review will inform the proposal of a model for continuous quality improvement of medication use.

3. Methods

3.1 Audit and feedback (A&F) interventions

Audit and feedback (A&F) is defined as 'any summary of clinical performance of health care over a specified period of time, given in a written, electronic or verbal format'[25]. It is based on the notion 'that healthcare professionals would be prompted to modify their practice if given feedback that their clinical practice was inconsistent with that of their peers or accepted guidelines'.[25] Performance is typically assessed against specific criteria derived from guidelines or expert consensus.

A Cochrane review[25] of randomised controlled trials (RCTs) of audit and feedback interventions (last updated in 02/2006) suggested that A&F can be associated with improvements in medical practices in general, but did not specifically identify the impact on medication use processes or medication-related patient outcomes. The Cochrane review provides an appendix, where all included studies are briefly described in terms of study design, targeted behaviours and outcome measures. All studies that the review's authors had classified as targeting long-term (rather than one-off) prescribing or where at least one of the reported outcomes was 'prescribing or monitoring practice' were considered for inclusion into this review. Medline, Embase and Cochrane Database of controlled trials were searched to identify studies, which were published between the closing date of the Cochrane review and 03/2010. Since the main interest of this review was to examine whether A&F was effective in principle in targeting different drug therapy risks, only trials comparing audit and feedback (alone or in combination with other intervention components) to inactive controls were included. Where trials reported the impact of interventions on medication underuse, only those pertaining to cardiovascular disease are reported.

3.2 Clinical decision support

Clinical decision support systems (CDSS) have been defined as any electronic or non-electronic system designed to aid directly in clinical decision making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are subsequently presented to clinicians for consideration.[26] A recent systematic review[27] from 2009 included 56 studies evaluating the impact of computerised clinical decision support systems (CDSS) on prescribing and monitoring practices. Since the CDSS review focussed on prescribing only, all studies were eligible for inclusion. Studies targeting acute prescribing, one-off prescribing or dosing only were excluded from this literature review as were interventions with an active control group. Medline, Embase and Cochrane Database of controlled trials were searched to identify studies, which were published between the closing date of the review (11/2007) and 03/2010. Where trials reported the impact of interventions on medication underuse, only those pertaining to cardiovascular disease are reported.

3.3 Collaborative models of care including pharmacists

Two types of services provided by pharmacists to patients can generally be distinguished: (1) Services delivered to patients who are generally considered to be at risk of PDRM (generic approach) and (2) services focussing on the management of patients with a specific condition (disease management).

Generic approach

The generic approach is exemplified by 'medication review' interventions in the elderly, which have recently been systematically reviewed by Holland et al[28]. Medline, Embase and Cochrane Database of controlled trials were searched in order to identify large scale studies, which were published between the closing date of the review (09/2005) and 03/2010 using MEDLINE, EMBASE and the Cochrane controlled trial register.

Disease management approach

In order to summarise current evidence of the effectiveness of pharmacist delivered services in chronic disease management, the findings of two recent systematic reviews on the management of patients with cardiovascular risk factors[29] and those with heart failure[30] are reported.

Since all aforementioned systematic reviews[29-31], were limited to studies reporting patient or therapeutic outcomes (mortality, hospital admissions or cardiovascular risk factor control), the findings of a fourth systematic review[32] summarising the impact of any collaborative services including pharmacists on both medication use processes and outcomes are reported. Table 2.2 summarises the criteria by which relevant studies were identified in the four systematic reviews.[29-32]

Table 2.2: Summary of inclusion criteria of four systematic reviews[29-32] assessing impact of collaborative models of care with pharmacist involvement on medication use processes and outcomes

Pharmacist involvement	Patients	Setting	Outcomes	Study design
Medication review in the elderly (Holland et al[31])				
Led by pharmacist	Mean age > 60 years ≥1 diagnostic category	Ambulatory or secondary care, but follow-up period of 1 month	All-cause hospital admission/ mortality	32 RCTs
Disease management – Heart failure (Koshman et al[30])				
Led by pharmacist or pharmacist as member of a team	Heart failure	Ambulatory or secondary care	All-cause or HF hospital admission/ mortality	12 RCTs
Disease management – CV risk factors (Santschi et al[29])				
Led by pharmacist or pharmacist as member of a team	Cardiovascular risk factors	Ambulatory or secondary care	Any cardio-vascular risk factor	30 RCTs
Any collaborative services involving pharmacists (Chisholm-Burns et al[32])				
Pharmacist as member of a team	Any	Ambulatory or secondary care	Any patient-related outcomes	298 studies with a usual care arm

4. Results

4.1. Description of identified studies

4.1.1 Audit and feedback

In total, 20 comparisons of the impact of A&F interventions on prescribing and monitoring to usual care were identified (see appendix 1 for a more detailed description of included trials). The studies were conducted in the United States (35%), Europe (40%), Canada (15%) and Australia (10%). In the majority (85%) of interventions, feedback was provided to primary care physicians. In 12 comparisons (60%), A&F was combined with an educational intervention component, while A&F was the only intervention component in the remaining 8 comparisons.

4.1.2 Clinical decision support

In total, 41 comparisons of the impact of CDSS interventions on prescribing and monitoring to usual care were identified (see appendix 1 for a more detailed description of included trials). The majority of studies were conducted in the United States (73%), followed by Europe (24%) and Canada (2%). In the majority of interventions, CDSS was implemented in primary care (63%), followed by outpatient (20%) and secondary care (17%) settings. In approximately half of comparisons (51%), CDSS was combined with educational intervention components with the remainder testing CDSS as the only intervention component.

4.1.3 Collaborative care models including pharmacists

Generic approach

A total of 36 studies were identified including four trials that were published after 2005 [33-36] (the closing date of the systematic review by Holland et al[31]). The majority of trials (52%) were delivered in primary care, followed by outpatient clinics (22%), the patient's own home (19%), and nursing homes (6%). Pharmacists had face-to-

face contact with physicians in 18 trials (50%) and telephone or mail contact in 14 trials (39%) and were not described in four trials (13%). Pharmacists generally reviewed patients once or twice and in only two trials (6%) were pharmacists able to enact their recommendations fully.

Disease management – cardiovascular risk factor control

A total of 30 RCTs were included from the systematic review by Santschi et al[29] , in which pharmacists provided services either as key directors of interventions (18 studies) or as part of a multi-disciplinary team (12 studies) in order to improve blood pressure control (19 studies), lipid control (9 studies) or to promote smoking cessation (2 studies). The majority of studies were conducted in the United States (63%) and the remainder in Asia (10%), South America (10%), Europe (7%), Australia (7%) and Canada (3%). Twenty-three (77%) trials were conducted in outpatient clinics, 6 (20%) in community pharmacies and 1 (3%) in patients' homes. Pharmacists provided education to patients in 26 (87%) studies and conducted medication management (defined as medication assessment, monitoring and adjustment or change) in 22 (73%) studies. Mean (range) follow-up was 8 (3 to 24) months. Follow-up was at least three-monthly in 24 (80%) studies, at least monthly in 19 (63%) studies and less frequent or 'as required' in 6 (20%) studies.

Disease management - Heart failure

A total of 12 RCTs were included in the systematic review by Koshman et al[30] , in which pharmacists provided services either as key directors of interventions (7 studies) or as part of a team (5 studies). Studies were conducted in the United States (4 studies), Europe (4 studies), Canada (2 studies), Asia (1 study) and Australia (1 study). Pharmacists' responsibilities in both collaborative and pharmacist-directed interventions included mainly patient education and self-management directions or assistance. Trials were of 6 to 12 months duration. Follow-up was at least 3-monthly in 6 (50%) studies and one-off in two studies (17%). In the remaining 4 (33%)

studies, several follow-up interventions were limited to the initial phases of the trials followed by care as usual.

Any services provided by US pharmacists as part of a multidisciplinary team (based on systematic review by Chisholm et al[32])

A total of 298 controlled studies conducted in the United States were included in the systematic review by Chisholm et al[32], in which US pharmacists provided direct patient care as part of a multidisciplinary team. The majority (65%) of studies were conducted in primary care or outpatient settings. The most frequently reported services provided by pharmacists to patients directly were patient education about medication use (52%), self management directions (36%), adherence interventions (34%), medication review (33%) and chronic disease management (29%).

4.2 Impact of interventions on prescribing and monitoring

The impact of interventions on medication use processes were reported for A&F and CDSS interventions, for pharmacist-directed medication reviews and for studies included in the systematic review of US pharmacists collaborative services[32].

4.2.1 Underuse and suboptimal choice

Table 2.3 shows that across all types of interventions, relatively consistent improvements were achieved in reducing underuse of antiplatelets. Two of four A&F trials also led to significant improvements in a composite endpoint reflecting underutilisation of cardio-preventative treatments and one A&F trial led to significant improvements in the use of antihypertensives. CDSS has additionally been tested as a means of reducing under-prescribing of lipid-lowering treatment, ACE-inhibitors, warfarin, beta-blockers and other antianginals but none of these studies found significant beneficial effects.

4.2.2 High-risk prescribing

Endpoints reflecting high-risk medication use were exclusively reported in A&F and CDSS studies. Cardiovascular agents, non-steroidal anti-inflammatory drugs and agents that should generally be avoided in the elderly were mainly targeted. Table 2.3 shows that five of seven (71%) CDSS interventions and five of eight (63%) A&F interventions led to significant reductions in high-risk prescribing.

4.2.3 Monitoring and treatment adjustment (inertia)

Monitoring and endpoints reflecting timely adjustment of treatment to achieve therapeutic targets were exclusively studied in CDSS trials. Table 2.3 (overleaf) shows that trials of CDSS interventions found significant improvements for one of eight (13%) comparisons targeting inertia and seven of 34 (21%) comparisons targeting monitoring of urea and electrolytes, international normalised ratio and other laboratory tests (see appendix 1 for details).

4.2.4 Drug therapy risk composites

The impact of interventions on composite endpoints reflecting generic categories of drug therapy risks or their causes were exclusively evaluated in studies involving direct patient care by pharmacists. Trials of pharmacist-directed medication reviews in the elderly and US pharmacist collaborative care interventions relatively consistently demonstrate improvements in the use of unnecessary drugs, medication errors and drug therapy problems. US pharmacist collaborative care interventions also achieved relative consistent improvements in composite scores of medication appropriateness.

4.3 Impact of interventions on therapeutic outcomes

The impact of interventions on pharmaco-therapeutic (intermediate) endpoints were reported by included A&F studies, CDSS trials, pharmacist disease management

interventions[31] and by studies included in the systematic review of US pharmacists acting as members of a multidisciplinary team[32].

Table 2.3: Impact of interventions on prescribing and monitoring endpoints

Endpoint	No. of trials with significant improvements/ No. of trials included			
	CDSS	A&F	Pharmacist-directed medication review[31]	US pharmacists collaborative services[32]
Underuse or suboptimal choice (Cardiovascular)				
Lipid-lowering drugs	0/2 [37, 38]	-	-	-
Antihypertensives	2/5 [39-43]	1/1[44]	-	-
Antiplatelets	3/3 [45-47]	-	-	7/8
Warfarin	0/1 [48]	-	-	-
Beta blockers	0/4 [48, 49,50,,51]	-	-	-
ACE inhibitors	0/3 [50-52]	-	-	-
Angina treatments	0/1 [50]	-	-	-
Composite (CVD prophylaxis)	-	3/4 [53-56]	-	-
Subtotal	5/19 (26%)	4/5 (80%)		7/8 (88%)
High-risk choice or dose				
Antihypertensives	-	0/1 [57]	-	-
Lipid-lowering drugs	1/2 [58,38]	-	-	-
Warfarin	1/1 [59]	-	-	-
NSAIDs	-	2/2 [60,61]	-	-
Drugs-to-avoid in elderly	2/3 [62-64]	3/4 [60, 65-67]	-	-
Other	1/1[68]	0/1 [44]	-	-
Subtotal	5/7 (71%)	5/8 (63%)	-	-
Inertia	1/8 (13%)			
Laboratory monitoring	7/34 (21%)			
Drug therapy risk composites				
Unnecessary drugs	-	-	7/9 [36,34]	-
Medication errors	-	-	-	9/11
Drug therapy problems	-	-	4/4	-
Medication appropriateness	-	-	0/1 [35]	13/17
Subtotal	-	-	11/14 (79%)	22/28 (79%)

Table 2.4 shows that beneficial effects were inconsistently achieved by CDSS interventions and are limited to improvements in blood pressure control. Evidence

of beneficial effects of A&F interventions on therapeutic outcomes is limited, with only one trial reporting beneficial effects on blood pressure control. In contrast, both systematic reviews of pharmacist interventions show relatively consistent beneficial effects on lipid, blood pressure and glycated haemoglobin (HbA1c) control. Meta-analyses of studies of pharmacist delivered services demonstrate overall statistically significant beneficial effects for all aforementioned endpoints, although absolute effect sizes were of minor clinical significance for the diastolic blood pressure endpoint. Subgroup analysis of disease management trials[29], in which pharmacist were the key drivers of interventions versus those where pharmacists acted as team members, found no major differences between subgroups with overall statistically significant reductions in blood pressure for both.

Table 2.4: Impact of interventions on therapeutic (intermediate) outcomes

Endpoint	No. of trials with significant improvements/ No. of trials included			
	CDSS	A&F	US pharmacists collaborative services[32]	Pharmacist disease management – CVD risk factor control[29]
Therapeutic/intermediate outcomes (cardiovascular)				
Total cholesterol	0/2 [38,69]	-	-	6/9 Meta analysis: ↑ -17.4 mg/dl
LDL cholesterol	-	-	50/59 Meta analysis: ↑ - 6.3mg/dl	4/7 Meta analysis: ↑ -13.4 mg/dl
Systolic BP	2/4 [40, 41, 43,70]	1/1[71]	10/14 Meta analysis: ↑ -7.8 mmHg	14/19 Meta analysis: ↑ -8.1 mmHg
Diastolic BP	-	-	7/13 Meta analysis: ↑ -2.9 mmHg	11/19 Meta analysis: ↑ -3.8 mmHg
HbA1c	-	-	32/36 Meta analysis: ↑-1.8%	-

↑ = significant change favouring intervention; ↔ = no significant change

4.4 Impact of interventions on patient outcomes

The impact of interventions on clinical or humanistic patient endpoints were reported by included A&F studies, pharmacist-directed medication reviews, by trials included in the systematic review of pharmacist disease management services for patients with heart failure[30] and by studies included in the systematic review of US pharmacist collaborative services[32]. Table 2.5 shows that while evidence of beneficial effects of A&F interventions on patient outcomes are limited to a single trial, the impact of interventions involving pharmacists on clinical or humanistic patient endpoints are available from a larger number of studies, demonstrating mixed results.

Table 2.5: Impact of interventions on patient outcomes

Endpoint	No. of trials with significant improvements/ No. of trials included			
	A&F	Pharmacist directed medication review[31]	US pharmacists collaborative services[32]	Pharmacist disease management-CHF[30]
Drug-related safety events				
ADE	1/1[60]	1/12	22/28 Meta analysis: ↑ (OR = 0.53)	-
ADR	-	-	9/15	-
Health care utilisation				
Hospital admission (all-cause)	-	1/18 [36] Meta analysis: ↔ (RR = 0.99)	18/35	2/11 Meta analysis: ↑ (OR = 0.71)
Hospital admission (CHF)	-	-	-	2/11 Meta analysis: ↑ (OR = 0.69)
Mortality (all cause)	-	0/34 [36 34] Meta analysis: ↔ (RR = 0.96)	13/18	1/12 Meta analysis: ↔ (OR = 0.84)
Humanistic outcomes				
Quality of life	-	0/15 [72,35,34]	5/35	-

↑ = significant change favouring intervention; ↔ = no significant change

Only one of 12 trials (8%) included in the review of pharmacist-directed medication review interventions but 22 of 28 studies (79%) included in the review of US pharmacists collaborative services[32] found significant reductions in adverse drug event rates, with meta-analysis demonstrating that patients receiving these services had approximately half the odds of suffering an ADE compared to control patients. Similarly, meta-analysis of pharmacist-directed medication review interventions found minimal, non-statistically significantly reduced risks of all-cause emergency hospital admission and death, while meta-analysis of studies included in the review of pharmacist heart failure management[30] *did* find significant reductions in mortality, all-cause and heart failure hospital admission, respectively. Beneficial effects on heart failure hospital admission (but not for all-cause admission and mortality) were, however restricted to interventions where pharmacists acted as members of a multidisciplinary heart failure team but not for services principally directed by pharmacists. Studies included in the review of US pharmacist collaborative services[32] demonstrated significant reductions in all-cause hospital admission in over half and significant reductions in all-cause mortality in over three quarters of trials, for which these outcomes had been reported. None of the 15 trials reporting the impact of pharmacist-directed medication review interventions on quality of life found significant improvements, while approximately one third of studies included in the review of US pharmacist collaborative services[32] *did* find significantly beneficial effects.

5. Discussion

5.1 Summary of findings

Audit and feedback (A&F), clinical decision support (CDSS) and US pharmacist collaborative services can be effective in improving under-prescribing of cardio-preventive treatment, but evidence is mainly limited to antiplatelet use. Evidence of beneficial effects of CDSS and A&F trials is strongest for reductions in high-risk prescribing and weak for timely adjustment of drug treatment in response to

abnormal test results (inertia) or laboratory monitoring. Pharmacist delivered services demonstrate relatively consistent beneficial effects on composite endpoints of drug therapy risks and in some cases appropriate prescribing. Therapeutic endpoints were rarely assessed in A&F and CDSS interventions, but there is moderately strong evidence from meta-analyses that disease management services by pharmacists can lead to statistically and clinically significant improvements in cardiovascular therapeutic endpoints (blood pressure, cholesterol, HbA1c control) irrespective of whether pharmacists were the key drivers of interventions or acted as members of a multidisciplinary team. Evidence of beneficial effects on patient outcomes is scarce for A&F and CDSS interventions. Pharmacist delivered services showed mixed results, with only one of 18 trials of pharmacist directed medication reviews demonstrating a significant reduction in all cause hospital admission, but over half of studies evaluating US pharmacist collaborative and meta analyses of pharmacist heart failure management services demonstrating significant reductions in hospital admission and mortality.

The literature review therefore provides some evidence that A&F, CDSS and collaborative services involving pharmacists can improve medication use processes and therapeutic endpoints and collaborative services involving pharmacists have the potential to reduce hospital admissions and mortality. However, across all interventions and endpoints, beneficial effects were inconsistently achieved.

5.2 Possible predictors of effectiveness

In view of the mixed effectiveness of audit and feedback and CDSS trials, a number of authors have attempted to identify the critical features for the success of these interventions.[26,73,74] In one interview series[73] and one meta-analysis[74], five features of A&F interventions have been identified that are likely to promote effectiveness: (1) timeliness of feedback, (2) higher frequency of feedback, (3) identification of specific tasks for improvement, (4) recommendations on how improvement can be achieved and (5) customisability of data presentation to meet practitioners' preferences. The

authors identified the 'actionability' of feedback as the overarching theme that assisted effectiveness. In relation to CDSS interventions, Kawamoto et al[26] found that the following seven features are associated with higher effectiveness: (1) automatic (rather than user-activated) provision of decision support as part of clinician workflow, (2) provision of decision support at the time and location of decision making, (3) provision of recommendations rather than just assessments, (4) computer based decision support (rather than manual chart audits), (5) providing periodic performance feedback (audit), (6) sharing recommendations with patients, and (7) requesting documentation of reasons for not following recommendations.

The features predicting the effectiveness of pharmacist-led medication review interventions on patient outcomes are, however, less clear. For example, the systematic review by Holland et al[28] found no association between the number of pharmacist - patient contacts (<3 versus ≥3 patient contacts) or the type of pharmacist (clinical specialist versus community pharmacist) conducting the review. In addition, subgroup analyses of pharmacist disease management trials have found no major differences in the impact of pharmacist-directed services versus those where pharmacists acted as team members.[29,30] Of note is, however, that evidence of statistically significant improvements in therapeutic and patient endpoints is mainly limited to studies conducted in the United States.[29,32] In Europe, evidence of significant reductions in mortality or hospital admission are limited to two single trials of pharmacist heart failure management.[75,76]

5.3 Implications

The mixed findings for A&F and CDSS interventions and evidence from other systematic reviews suggest that the ways in which audit and feedback is provided and clinical decision support systems are designed are likely to be decisive for the success of these interventions. The features that were identified to be associated with more consistent improvements in medication use[26,73,74] support arguments that synergistic effects may be achievable by a combination of the two approaches.

'Kawamoto' et al[26] found that the effectiveness of CDSS interventions can be enhanced by periodic performance feedback, that is A&F, while Hysong et al[73,74] report that the timeliness and frequency of feedback are crucial in promoting effectiveness of A&F interventions, i.e. features inherent to the CDSS approach. In view of the findings of little impact of pharmacist-led medication reviews on hospital admissions, Holland et al[28] concluded that 'although improvements in patient knowledge and adherence are laudable objectives [...], money may be better spent on cost-effective interventions that have a definite effect on reducing hospital admissions and deaths.' However, a number of limitations in the design and evaluation of interventions suggest that this conclusion may be too absolute.

First, study durations were typically short, giving patients, pharmacists and prescribers little time to gain experience in a service that is likely to have been a substantial change to traditional models of care. Collaboration with prescribers is essential for the effectiveness of such interventions, since pharmacists are usually not able to fully enact their recommendations and several triallists[17,33,77] report that pharmacist recommendations were frequently not implemented by prescribers.

Second, a number of studies raise doubts about the quality of intervention delivery by pharmacists. For example, one study[78] assessed pharmaceutical care plans completed by pharmacists in the MEDMAN trial[33] and found that intervention pharmacists only identified 33% of all 'care issues' (on average) compared to the gold standard (combined assessment by one academic general medical practitioner and one clinical pharmacist).

Third, it is likely that many studies included in the review by Holland et al [28] were underpowered in relation to the chosen outcome measure of all-cause hospital admission and the baseline risk of patients included (see footnote [1]).[33,34]

[1] Most studies have targeted patients that were elderly and the rate of non-elective all-cause hospital admissions in the studies included in the review was approximately 20%. Considering that most interventions have targeted patients with additional risk factors for drug related hospital admissions, a reasonable assumption is that 5% of all emergency admissions may be drug related and preventable, and therefore susceptible to medication review interventions. If a reduction of preventable drug related admissions by 30%[1] would be considered a worthwhile intervention effect, this would correspond to a difference of 20.0% vs 18.8% in *all cause* emergency hospitalisations in intervention vs control groups. The total sample size required in order to detect such a difference with 80% power

Improvements in medication use processes may not directly translate into demonstrable short term benefits in mortality or hospital admission because such outcomes may occur with a time lag (especially for improvements in the underutilisation of preventive treatments) and are confounded by underlying patient morbidity that may not always be controllable by drug therapy. In addition, demonstrable benefits are only likely to be demonstrable if patients, who are truly at risk of preventable drug related morbidity, can be targeted. For example, in the MEDMAN study[33], utilisation rates of cardio-preventive treatments in patients targeted for pharmacist management of coronary heart disease was already high at baseline.

Finally, the vast majority of studies included in this review, which have demonstrated beneficial effects on patient endpoints, have been conducted in the US, where the enhanced role of pharmacists in the delivery of clinical services to patients has a longer tradition in both hospital and ambulatory care settings than in Europe.

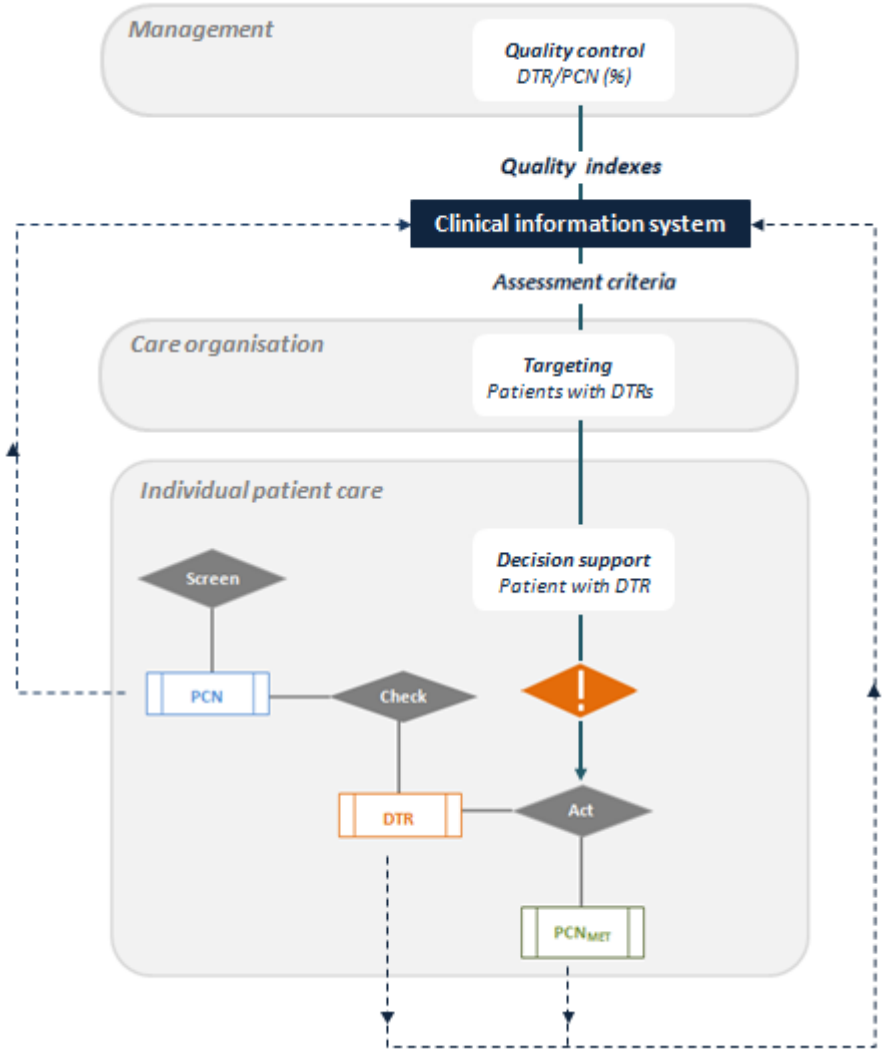
In conclusion, although interventions by pharmacists have relatively consistently shown to improve drug therapy processes, demonstrable benefits on patient outcomes may therefore rely on (1) improved working relationships with prescribers, (2) quality assurance of medication reviews conducted and (3) instruments that allow to more specifically target patients at high risk of preventable drug related morbidity. The health care environment may play a key role in the successful implementation of pharmacist delivered services.

and 95% confidence would be 334 patients (assuming a non-cluster trial). However, 15 (47%) of the trials included in the systematic review by Holland et al. had recruited less than 300 patients and 10 (31%) had enrolled less than 200 study subjects. Nevertheless, it is acknowledged that meta-analysis of trials does possess sufficient power to detect effect sizes of the above magnitude.

6. Components of a model for continuous quality improvement of medication use systems

With reference to the aim of this literature review, it is therefore reasonable to assume that improvements in drug therapy outcomes may be achievable by an integration of audit, clinical decision support and better integration of clinical services provided by pharmacists. The adoption and shared use of clinical information systems can play a key role in this respect. Shared access to systematically recorded patient information and documentation of the care provided by different stakeholders has the key advantage that pharmaceutical care needs (PCNs) and drug therapy risks (DTRs) can be identified and managed in a systematic way and duplication of effort is avoided. In chronic disease management, medication use is in large parts informed by evidence based practice standards (e.g. clinical practice guidelines). Such standards can be operationalised in order to routinely *screen* for PCNs and systematically *check* whether DTRs are present and have been addressed. Where this is not the case, drug therapy risks (DTR) are identified, which require professional *action*. Consistent with the CCM, such systematic assessments may serve three key functions: (1) to provide decision support in the design of care plans for individual patients, (2) to organise patient follow-up by a multidisciplinary team of providers and (3) to enable quality control of the medication use system as a whole. Figure 2.2 illustrates how the chronic care model may be applied to facilitate continuous quality improvement of medication use.

Figure 2.2: A model for continuous quality improvement of medication use with control functions at the level of individual patient care, at organisational and at system level.



6.1 Individual patient care - Decision support

Where clinical information systems contain relevant information in electronic format, practitioners can be assisted in the *screening* and *checking* process by alerts that are generated by the system based on pre-specified rules (*assessment criteria*). When a PCN has been identified (e.g. a diagnosis of heart failure) a rule is employed (check), which alerts practitioners to any existing DTRs, such as an unmet need for drug therapy (e.g. a beta blocker) or any medication that may be detrimental to the control of the condition (e.g. an NSAID). This will trigger 'action' by the prescriber

in the form of correcting (PCN_{MET}) or - if not possible – otherwise managing the DTR, for example, by intensifying monitoring.

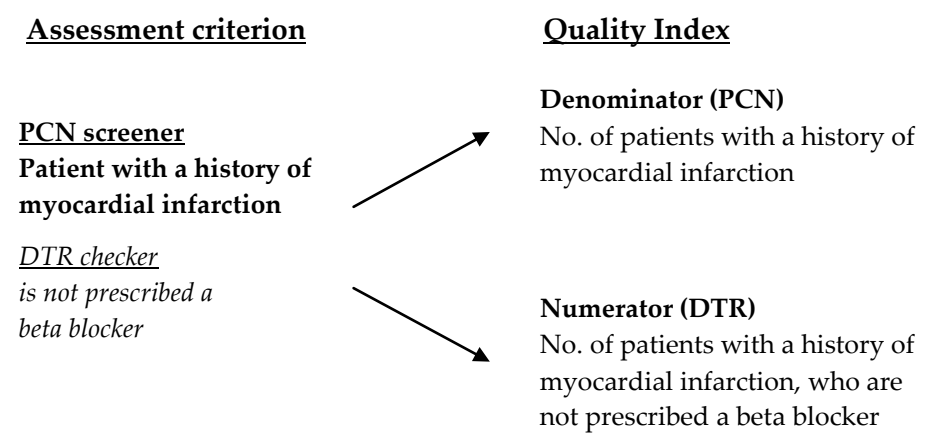
6.2 Care organisation - Patient targeting

At population level, the systematic identification of patients with DTRs allows an estimation of the resources and workforce required in order to meet the needs of the population served by a multidisciplinary team of practitioners and to allocate resources accordingly. For example, a pharmacist with special interest in the management of heart failure may review all heart failure patients, who are not prescribed beta blocker treatment or manage patients with uncontrolled risk factors for cardiovascular disease. This ensures that patients, who have slipped through the system of decision support at the point of patient encounter, are not lost to follow-up and those with apparent opportunities for medication use optimisation can be targeted for review.

6.3 Management - Quality control

Indicators or indexes refer to metrics that are designed to reflect the quality of care at provider level. With reference to the concepts pharmaceutical care need (PCN) and drug therapy risk (DTR), such quality indexes represent the proportion of patients with a particular PCN, the denominator, who do not receive adequate treatment (DTR), the numerator. Indicators are operationalised using assessment criteria, which are applied to individual patients on a case-by case basis. Where electronic clinical information systems are available such assessments can be automated, such as in the Quality and Outcomes Framework (QOF)[79]. Figure 2.3 illustrates the difference between indicators and assessment criteria.

Figure 2.3: Operationalisation of indexes through assessment criteria



The overarching aim of the above described three functions of a clinical information system (supporting individual patient care, care organisation and management) is to enable the implementation of a quality management system for medication use, which routinely exposes weaknesses in the system of pharmaceutical care delivery and facilitates the integration of services provided by different stakeholders in the delivery of pharmaceutical care.

7. Chapter summary

Systematic reviews into the causes of preventable drug related hospital admissions demonstrate that current deficits in the quality of medication use mainly reside in patients with long term conditions. An argument was developed to support the working hypothesis that components of the chronic care model (CCM- an integrated multifaceted approach to the delivery of care for patients with long term conditions), may be successfully applied to improve the performance of medication use systems. A structured literature review of the impacts of interventions advocated by the CCM (audit and feedback, clinical decision support, and collaborative models of care) on the quality of medication use processes and outcomes was conducted in order to substantiate this hypothesis. The literature

review provides evidence to support each strategy as a means to improve medication use processes in principle, but there is a paucity of evidence for beneficial effects of audit and feedback and clinical decision support on therapeutic and patient outcomes and studies of collaborative services involving pharmacists have shown mixed results. A more detailed discussion of studies investigating pharmacist delivered services has identified limitations in patient inclusion criteria, suboptimal choice of outcome measures, questionable quality of intervention delivery and inconsistent pharmacist-prescriber collaboration as factors that may hinder more consistent positive effects. It has been argued that a multi-faceted strategy may be required for improvements in drug therapy outcomes to be achieved. A model for continuous quality improvement of medication use systems has been proposed, which enables quality management by means of medication use assessment against standards of best practice. Within this model, quality assessment serves three functions: (1) to provide decision support through the standardised detection of drug therapy risks, (2) to organise patient follow-up by a multidisciplinary team of providers and (3) to enable quality control of medication use systems through the use of quality indexes (i.e. metrics, which summarise the quality of medication use at provider level). Instruments to assess the quality of medication use for patients at risk of experiencing drug related harm or lack of benefit are therefore a pre-requisite to operationalise the model in clinical practice. The development of a medication assessment tool that has the potential to function within the proposed quality improvement model is therefore the subject of chapter 3.

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Appendix 1: Literature review findings

Table A.1.1 Studies of audit and feedback targeting medication underuse; ↑ = significant change favouring intervention; ↔ = no significant change

Study	Study design/ Country	Setting/ Practitioners	Intervention Experimental arm vs control	Endpoints	Effect		
					Patient outcomes	Intermediate outcomes	Medication use practice
Goff 2003 [53]	RCT/ US	GPs	REM + A&F (comparative) vs usual care	Secondary prevention in CHD (composite)			↔
McCartney 1997 [54]	RCT/ UK	GPs	A&F + gEDU vs usaual care	Secondary prevention in CHD (Aspirin)			↑
Sondergaard 2006 [55]	RCT/ Denmark	GPs	A&F + EOV vs usual care	Secondary prevention in CHD (composite)			↑
Soumerai 1998 [56]	RCT/ US	Community hospital physicians	A&F vs usual care	Secondary prevention in CHD (composite)			↑
Boekeloo 1990	RCT/ US	Secondary care physicians	A&F vs usual care	Lipid lowering therapy			↑
Nilsson 2001[44]	RCT/ Sweden	GPs	A&F + EOV vs usual care	ACEIs and ARBs in antihypertensive Therapy			↑
Dickinson 1981[71]	RCT/ US	GPs	A&F vs usual care	Antihypertensive therapy *BP control*		↑	

Table A.1.2 Studies of audit and feedback targeting high-risk medication use; ↑ = significant change favouring intervention; ↔ = no significant change

Study	Study design/ Country	Setting/ Practitioners	Intervention Experimental arm vs control	Endpoints	Effect		
					Patient outcomes	Intermediate outcomes	Medication use practice
Pimlott 2003 [66]	RCT/ Canada	GPs	A&F + gEDU vs usual care	Benzodiazepines			↔
Smith 1998 [67]	RCT/ US	GPs	A&F + gEDU vs usual care	Benzodiazepines			↑
Pit 2007 [60]	RCT / Australia	Primary care/ GPs	EOV + A&F vs usual care	Benzodiazepines *Falls prev.* *Quality of life*	↑ ↔		↔
Holm 1990 [65]	RCT/ Denmark	GPs	A&F vs usual care	Long term hypnotics			↔
Pit 2007 [60]	RCT/ Australia	Primary care/ GPs	EOV + A&F vs usual care	NSAIDs			↑
Anderson	RCT/	GPs	A&F	Regulated			↑

1996 [61]	Canada		vs usual care	Analgesics			
Herbert 2004 [57]	RCT/ Canada	GPs	A&F + gEDU vs usual care	Antihypertensive therapy (choice)			↔
Nilsson 2001 [44]	RCT/ Sweden	GPs	A&F + EOV vs usual care	PPIs			↔

Table A.1.3 Studies of clinical decision support systems targeting underuse of medication; ↑ = significant change favouring intervention; ↔ = no significant change

Study	Study design/ country	Setting/ practitioners	Intervention Experimental vs control	Endpoints	Effect		
					Patient outcomes	Intermediate outcomes	Medication use practice
Bloomfield 2005 [37]	RCT / US	Primary care/ Physicians, nurses, assistants	*Multi-faceted* vs active vs usual care	Lipid lowering therapy			↔
Cobos 2005 [38]	RCT / Spain	Primary care/ GPs	*Multi-faceted* vs usual care	- Lipid lowering therapy - Lipid control		↔	↔
Fretheim 2006 [39]	RCT / Norway	Primary care/ GPs	*Multi-faceted* vs active vs usual care	BP lowering therapy			↑
Murray 2004 [42]	RCT / US	Secondary care/ Physicians, pharmacists	*Multi-faceted* vs active vs usual care	- BP lowering Therapy - Side effects, QoL	↔		↔
Roumie 2006 [43]	RCT / US	Primary care/ HMO	*Multi-faceted* vs usual care	- BP lowering Therapy - BP control		↑	↔
Montgomery 2000 [41]	RCT / UK	Primary care/ GPs	*Multi-faceted* vs usual care	- BP lowering therapy - CVD risk		↔	↔
Hicks 2009	RCT / US	Outpatient/ Physicians	*CDSS only* vs usual care	- BP lowering therapy - BP control		↔	↑
Dexter 2001 [45]	RCT / US	Secondary care/ Physicians	*CDSS only* vs usual care (CPOE)	Antiplatelet			↑
Filippi 2003 [46]	RCT / Italy	Primary care/ GPs	*Multi-faceted* vs active vs usual care	Antiplatelet			↑
Krall 2004 [47]	RCT / US	Primary care/ HMO	*CDSS only* vs usual care	Antiplatelet			↑
Ansari 2003 [49]	RCT / US	Primary care/ Physicians, nurses	*Multi-faceted* vs Active vs usual care	BBs in CHD ADEs	↔		↔
Demakis 2000 [48]	RCT / US	Primary care/ Physicians	*Multi-faceted* vs active vs usual care	-BB after MI -A.-thrombotic/AF			↔ ↔
Eccles 2002 [50]	RCT / UK	Primary care/ GPs	*CDSS only* vs active vs usual care	CHD indicators (individual)			↔
Apkon 2005 [52]	RCT / US	Primary care/ Physicians,	*CDSS only* vs usual care	ACEI in DM Pt satisfaction	↔		↔

		nurses, assistants					
Overhage 1996 [51]	RCT / US	Secondary care/ physicians	*Multi-faceted* vs usual care	Secondary prevention			↔
Eccles 2002 [50]	RCT / UK	Primary care/ GPs	*CDSS only* vs active vs usual care	Asthma QoL (generic and disease spec)	↔		↔
Tierney 2005 [80]	RCT / US	Primary care/ Physicians, pharmacists	*Multi-faceted* vs active vs usual care	Asthma - HR-QoL - Pt adherence	↔ ↔		↔
Feldstein 2006 [81]	RCT / US	Primary care/ HMO	*Multi-faceted* vs usual care	Osteoporosis prophylaxi			↑
Overhage 1996 [51]	RCT / US	Secondary care/ Physicians	*Multi-faceted* vs usual care (CPOE)	Osteoporosis prophylaxis			↔
Kralj 2003 [82]	RCT / US	Primary care/ Physicians	*CDSS only* vs usual care	Erythropoietin			↑
Safran 1995 [83]	RCT / US	Primary care/ physicians	*CDSS only* vs active vs usual care	- PCP prophylaxis - Zidovudine or didanosine - Health care utilisation - Death	↔ ↔		↑ ↔

Table A.1.4 Studies of CDSS targeting monitoring or inertia

Study	Study design/ country	Setting/ practitioners	Intervention Experimental arm vs control	Target topic or outcomes	Effect: Patient outcomes	Effect: Intermediate outcomes	Effect: Medication use practice
Inertia							
Lester 2006 [70]	RCT/ US	Primary care/ GPs	CDSS only vs Usual care	Inertia/ - BP control - Lipid control		↔ ↑	↔ ↑
Roumie 2006 [43]	RCT/ US	Primary care/ GPs	Multi-faceted vs active vs usual care	Inertia/ - BP			↔
McCowan 2001 [84]	RCT/ UK	Primary care/ GPs	CDSS only vs usual care	- Inertia/ Preventive inhaler - Asthma control	↑		↔
Safran 1995 [83]	RCT/ US	Outpatient/ physicians	CDSS only vs usual care	Inertia/ Zidovudine			↔
Judge 2006 [59]	RCT/ US	Outpatient/ physicians	CDSS only vs usual care	Inertia/ - Diuretics - Phenytoin			↔ ↔
Tierney 2005 [80]	RCT/ US	Outpatient/ physicians	Multi-faceted vs active vs usual care	- Inertia/ Theophylline - HR-QoL - Pt adherence	↔ ↔		↔
Laboratory monitoring							
Feldstein 2006 [85]	RCT/ US	Primary care/ HMO physicians	Multi-faceted vs usual care	Lab test/ - Allopurinol			↑

Palen 2006 [69]	RCT/ US	Primary care/ HMO physicians	Multi-faceted vs usual care	Lab test/ - MTX (LFT) - Others			↑ ↔
Lo 2009	RCT/ US	Outpatient/ physicians	CDSS only vs usual care	Lab test/ Antimanic agents Others (eg ACEI, diuretics, antifungals etc)			↑ ↔
Palen 2006 [69]	RCT/ US	Primary care/ HMO physicians	Multi-faceted vs usual care	Laboratory / - Gemfibrozil - Others			↑ ↔
Demakis 2000 [48]	RCT/ US	Outpatient/ physicians	Multi-faceted vs active vs usual care	Lab test / Warfarin			↔
Feldstein 2006 [85]	RCT/ US	Primary care/ HMO physicians	Multi-faceted vs usual care	Lab test/ - ACEIs - Statins			↑ ↔
Overhage 1997 [86]	RCT/ US	Secondary care/ physicians	Multi-faceted vs usual care	Lab test/ - Heparin, warfarin, digoxin *- Length of hospital stay*		↑	↑
Safran 1995 [83]	RCT/ US	Outpatient/ physicians	CDSS only vs usual care	Lab test/ Zidovudine			↑
Palen 2006 [69]	RCT/ US	Primary care/ HMO physicians	Multi-faceted vs usual care	Lab test / - Isoniazid - Rifampin			↔ ↔

Table A.1.5 Studies of CDSS targeting high-risk or inappropriate medication use

Study	Study design/ country	Setting/ practitioners	Targeted behaviour	Target topic or outcomes	Effect		
					Patient outcomes	Intermediate outcomes	Medication use practice
Cardiovascular							
Martens 2007 [58]	RCT / NL	Primary care/ GPs	*CDSS only vs* Usual care	Statins			↔
Cobos 2005 [38]	RCT / Spain	Primary care/ GPs	*Multi-faceted* vs usual care	Lipid lowering therapy			↑
Judge 2006 [59]	RCT/ US	Outpatient care/ Physicians, nurses, adssistants	*CDSS only vs* Usual car	- Warfarin - Warfarin dose - Other			↑ ↑ ↔
Respiratory							
Kuilboer 2006 [87]	RCT/ NL	Primary care/ GPs	*CDSS only vs* Usual care	- Cromoglycate - Deptropine oral broncho-dilators/ steroids			↑/↔ ↔
Martens 2007 [58]	RCT/ NL	Primary care/ GPs	*CDSS only vs* active vs usual care	Inhaled steroids for COPD - Other			↑ ↔

Tierney 2005	RCT/ US	Secondary care/ physicians	*Multifaceted*	Ipratropium			↔
Davis 2007 [68]	RCT/ US	Primary care/ paediatric clinics	*CDSS only vs* usual care	ENT treatments			↑
Elderly							
Peterson 2007 [62]	RCT/ US	Secondary care/ physicians	*CDSS only vs* Usual care	Composite (Benzodiazepine, NSAIDs etc.)			↔
Tamblyn 2003 [63]	RCT/ Canada	Primary care/ GPs	*CDSS only vs* Usual care	Composite (Benzodiazepine, NSAIDs etc.)			↑
Terrell 2009	RCT/ US	Secondary care/ physicians	*CDSS only vs* Usual care	Composite (Benzodiazepine, NSAIDs etc.)			↑
Other							
Field 2009	RCT/ US	Long term care facility/ physicians	*CDSS only vs* usual care	Renal px: - Dose - Frequency - CI Drugs - Missing information			↔ ↑ ↑ ↑

Chapter 3

Development of a Medication Assessment Tool for multiple chronic cardiovascular conditions (MATCVC)

1. Background

1.1 Quality assessment of medication use – General principles

The generation and analysis of data on the quality and performance of health services by health authorities has become common practice in a number of countries. For example, the '*Bundesgeschaeftsstelle Qualitaetssicherung (BQS)'*[1] in Germany publishes the outcomes of a number of mostly invasive procedures (e.g. in hospital mortality after percutaneous coronary intervention) conducted in German hospitals annually. In the US, the Joint Commission on Accreditation of Health Care organisations[2] requires a specific set of indicators (e.g. for heart failure) to be collected, monitored and certain standards achieved by organisations as a condition for accreditation. The UK has introduced the Quality and Outcomes Framework (QOF)[3] as part of the contractual arrangements between general medical practitioners and the National Health Service, which rewards general practices financially according to their achievements against a range of quality indicators ('pay for performance').

While health authorities use quality assessment in order to ensure that services are of an acceptable minimum standard, quality information is also used by managers, in order to optimise service design/management, and by health care practitioners, in order to optimise the services they provide.[4] A key distinction is between applications which address (1) continuous quality improvement and (2) performance judgement as shown in table 3.1. A further distinction refers to the principle users of quality information, that is between (1) clinicians who deliver health care and (2) those more involved in its management or control.[4] It should be noted, however, that neither of these distinctions is clear-cut in that the same quality measures may fulfil multiple functions and users may fulfil multiple roles.

Table 3.1: Different applications and purposes of quality assessment in healthcare

Application	Purpose
Quality Judgement	
Performance management: o Regulatory processes, such as accreditation o Provide information to the public and/or purchasers about organisational performance o Pay for performance (e.g. QOF)	
Quality Improvement	
1. Audit and quality control: Targeting aspects of care delivery o Highlight to clinicians or managers areas of service delivery in need for reflection/ further enquiry o Evaluating the effects of quality improvement initiatives	
2. Patient targeting o Targeting and prioritising patients with opportunities for better medication use for quality improvement and care delivery design o Inform allocation of professional resources	
3. Decision support: Assisting practitioners at the point of care o Alerting practitioners to pharmaceutical care needs and drug therapy risks at the time of decision making	

1.2 Quality assessment methods

Different methods to assess the quality of medication use can be distinguished according to whether they pertain to the structure, process or outcomes of care and by the extent to which judgement is allowed in their application by assessors.

1.2.1 Process versus outcome assessment

Direct measurements of patient outcomes (such as myocardial infarction) relate directly to health goals. For example, the incidence of recurrent myocardial infarction can be used as a measure to reflect the effectiveness of secondary prevention strategies; and episodes of haemorrhage can be used to reflect the safety of thrombo-embolic prophylaxis. In comparison, process measures evaluate the quality of care by assessing the care provided against implicit or explicit standards

of best practice (see below). For example, process measurement may consider whether or not a patient with uncontrolled blood pressure receives adequate antihypertensive treatment. It is based on the assumption that a good care process increases the likelihood of favourable outcomes but does not consider whether such outcomes have actually been achieved. Similarly, assessment of the care environment (structure), assumes a link between the facilities and resources invested to support the delivery of care and the quality of care provided.

1.2.2 Implicit versus explicit quality assessment

Methods to assess the quality of medication use not only vary according to whether they address structure, process or outcomes of care but also according to the means by which quality information is generated. A key distinction is the extent to which assessment methods allow clinical judgement to be applied by quality assessors. There are purely *implicit* methods which rely on assessors' knowledge and judgements and so allow maximum flexibility to take into account contextual factors and their weighting. In contrast, purely *explicit* methods apply specific criteria that provide operational definitions of the elements within the structure, processes or outcomes of care. Explicit methods are designed to be employed to be as objective as possible by minimising clinical judgement (see table 3.2).

Table 3.2: Illustration of the differences between implicit and explicit quality assessment (adapted from reference[5])

	Implicit Measure	*Example*	**Explicit Measure**	*Example*
Structure	Are resources adequate?	*Are CPD schemes adequate?*	Are resources up to standard?	*Are ≥9 CPD events offered/year?*
Process	Is care process adequate?	*Is treatment appropriate for a particular patient need at the time?*	Did process of care satisfy specific standards?	*Was a patient prescribed a beta blocker post myocardial infarction?*
Outcome	Could better care have improved the outcome?	*Does ADE occur despite an optimal process?*	Did a specific ADE occur?	*Did patient suffer secondary MI?*

1.3 Quality assessment instruments

1.3.1 Implicit instruments

Two approaches to implicit quality assessment are prominent in the literature: the *'Pharmacotherapy work-up'* proposed by Cipolle and Strand (subsequently referred to as the 'PTW' approach)[6], and the *Medication Appropriateness Index* (MAI)[7], which has more recently been supplemented by the '*Instrument for Assessment of Underutilisation of medication (AOU)*'[8].

The PTW system is based on a standardised drug therapy assessment process, which has originally been designed as a framework for the detection of 'drug therapy problems' in the context of pharmaceutical care delivery and has found widespread application as such.[9] According to the authors, the starting point of the assessment process in the PTW is a perceived drug related need from the *patient's* perspective, which is why the presence of the patient is required for assessments to

be employed.[6] In contrast, the starting point of the MAI is a patient's drug regimen in conjunction with clinical notes (see footnote[1]).

The MAI is the only implicit instrument currently available to allow quantification of the appropriateness of prescribing[10] and it has therefore found widespread application in research[32,11-16]. The PTW approach and the corresponding system for DTP categorisation have also been used in numerous studies to demonstrate the added benefit of pharmaceutical care services[17-21], although a validated system for quantifying 'drug therapy problems' (DTP) does not exist in the literature (see chapter 1).

1.3.2 Explicit instruments

Explicit medication assessment instruments have been designed by numerous authors following the publication of the BEERS set[22] in 1991. Table 3.3 shows examples of published instruments.

The BEERS set in its original form listed 'potentially inappropriate' drugs that should generally be avoided in elderly patients. A more recent update of the instrument[23] has, however, added criteria, which restrict the label of 'potential inappropriateness' to elderly patients with specific clinical conditions. A Canadian adaptation of the BEERS' list, the McLEOD's set[24], is also limited to identifying high-risk prescribing practices but additionally includes four criteria referring to drug-drug interactions. The STOPP/START[25,26] further extends BEERS' and McLEOD's approaches by including criteria to detect under-prescribing (START).[25,26] More recently, the Australian BASGER set[27] has been published, which additionally targets medication monitoring (HbA1c) and the achievement of therapeutic targets, such as blood pressure and international normalised ratio (INR).

[1] The 10 domains of the MAI are applied to each individual drug within patients' drug regimen, and each drug is assigned a score on a 3 point scale (A=appropriate, B=marginally appropriate, C=inappropriate). A similar scale is used in the AOU (A=Drug not omitted, B=drug omitted but there is a clinically justifiable reason or patient preference, C=Drug omitted but there is no identifiable reason for the omission). For drugs that are assigned a C-score in the MAI, a weighting scheme assigns between 1 and 3 points for each domain. The points are summed up to result in a composite score (with a maximum of 18 points).

Table 3.3: Overview of identified medication assessment instruments and pharmaceutical care needs (PCNs) targeted

Instrument	Country	PCNs targeted	Care Setting
STOPP /START[26]	UK	Health risk factor (Age)	Hospital
BASGER[27]	Australia	Health risk factor (Age)	Primary care
BEERS[23]	US	Health risk factor (Age)	Nursing home
McLeod[24]	Canada	Health risk factor (Age)	Primary care
ACOVE[28]	US	Health risk factor (Age)	Primary care
PONT[29]	NL	Medical condition (asthma)	Primary care
MARTIROSYAN[30]	NL	Medical condition (diabetes)	Primary care
MAT-DM[31]	UK	Medical condition (diabetes)	Outpatient
MAT-CHD[32]	UK	Medical condition (CHD)	Primary care
MAT-CHF[33]	UK	Medical condition (CHF)	Outpatient
HUANG[34]	Canada	Medical conditions (miscellaneous)	Hospital
QOF[3]	UK	Medical conditions (miscellaneous)	Primary care
PDRM (US)[35]	US	Health risk factor (Age)	Primary care

A further set of explicit quality measures is the 'Assessing care of vulnerable elders' (ACOVE[28]) set, which has been developed in the United States as part of a programme to continuously monitor and improve the quality of care provided to elderly patients. Although this set is not restricted to medication use, a considerable proportion of the 236 measures refer to under-utilisation, suboptimal choice, high-risk choice and medication monitoring.

While all of the aforementioned instruments focus on the elderly in general, a number of authors have also developed instruments for specific diseases, such as asthma (Pont[29]) and diabetes (Martirosyan[30]). At the University of Strathclyde, Medication Assessment Tools (MATs[31-33,36]) have been developed as a means to comprehensively assess adherence of medication use to disease specific guidelines published by the Scottish Intercollegiate Guidelines Network (SIGN), namely MAT_{DM}[31], MAT_{CHD}[32] and MAT_{CHF}[33]. A number of instruments have also been

published, which target miscellaneous (typically long term) conditions, among which, the set of clinical quality indicators used within the Quality and Outcomes Framework (QOF)[3] covers perhaps the widest spectrum. Thirty-four (25%) of the 134 indicators directly relate to medication use for atrial fibrillation, coronary heart disease, chronic heart failure, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, epilepsy, thyroid disease, mental health and chronic kidney disease. A Canadian group (Huang[34]) has developed a smaller set focussing on 'proven interventions' in chronic heart failure (CHF), coronary heart disease (CHD), stroke, diabetes mellitus (DM), osteoporosis and smoking. All of the aforementioned disease-specific instruments place a strong focus on medication underutilisation and effectiveness. Finally, indicators of preventable drug related morbidity (PDRM)[86,88] have been developed in order to link medication use to adverse outcomes.

1.3.3 Limitations of published instruments with respect to applications in continuous quality improvement

The model of continuous quality improvement proposed in chapter 2 of this thesis requires quality assessment methods, which can be implemented routinely in order to provide decision support, to identify patients at risk of preventable drug related morbidity (patient targeting) and to feed back information on the performance of the medication use system to care providers, managers and health authorities.

While implicit medication assessment methods have the advantage of allowing assessors to apply clinical judgement in their assessment of the appropriateness of medication use and allow the assessment of a wide range of therapeutic issues, such approaches are time consuming and require expert judgement, which has obvious disadvantages when quality assessment is to be applied routinely and repeatedly.

Although explicit approaches are usually narrower in scope and are usually limited to identifying prescribing that is *potentially* inappropriate, their key advantage is that such approaches can be applied by non-expert assessors. Explicit methods will

therefore be the only viable approach in a context of continuous quality improvement.

Several developers of explicit instruments have attempted to address the inherent limitation of explicit approaches in relation to the consideration of context factors that hinder compliance of medication use with standards of best practice. However, with the exception of the instrument developed by Huang et al[34], such approaches usually require an element of clinical judgement or the presence of the decision maker (QOF[3], MATs[31-33]) or rely on information that is not easily accessible in medical records (QOF[3], ACOVE[28]) and therefore share the limitations of implicit approaches in this respect. Further limitations of existing instruments are that many instruments cover a rather narrow spectrum of therapeutic aspects, either because of being restricted to targeting medication safety issues (Beers[23], McLeod[24]), the elderly (Beers[23], McLeod[24], START/STOPP[26], Basger[27], ACOVE[28]) or assessing medication use for single diseases (Pont[29], Martirosyan[29], MATs[31-33]). Other instruments, which do cover a larger number of clinical conditions tend to focus only on those aspects of medication use that are relevant to all or the majority of patients with that condition (Huang[34], QOF[3], START/STOPP[26], BASGER[27], ACOVE[28]). In an audit and feedback context, a focus on the most prevalent aspects of medication use for a specific disease is rational, but when the aim is to provide decision support or to target patients with opportunities for treatment optimisation, targeting a broader scope of relevant issues is desirable.

1.4 Rationale for targeting chronic cardiovascular conditions

1.4.1 The burden of chronic cardiovascular conditions

The World Health Organisation estimates that the worldwide burden from chronic disease will rise from 46% in the year 2000 to 60% in 2020.[37] Diseases of the cardiovascular system, particularly coronary heart disease (CHD), cerebrovascular disease, chronic heart failure (CHF) and atrial fibrillation (AF) continue to be the leading contributors to morbidity in the populations of developed countries.[38] In

2005, cardiovascular conditions (CVC)[2] were responsible for 30 % of all causes of death worldwide and 48 % of all deaths in Europe.[39, 40] In 2003, CVC accounted for 18% of the British, 15% of the German, and 11% of the Dutch health care expenditures.[41]

Cardiovascular conditions often co-exist due to a common aetiology. Hypertension and diabetes are major risk factors for the development of coronary heart disease[42], which in turn is the most common cause of heart failure.[43] Over half of all patients with CHF (50% to 60%) have evidence of coronary heart disease[44,] and approximately 40% are estimated to have AF[45]. Reciprocally, over 30% of AF patients are estimated to have CHF.[45]

1.4.2 Pharmacotherapy for chronic cardiovascular conditions

The existing evidence base for the pharmacological management of patients with chronic cardiovascular conditions must be one of the strongest at the current time and has provided a solid scientific foundation for the development of clinical practice guidelines. Table 3.4 summarises current guidance by the European Society of Cardiology (ESC).[43, 46-50]

1.4.2.1 Treatments to control risk factors for vascular events

Coronary heart disease, cerebrovascular disease and peripheral vascular disease share the same aetiology of atherosclerosis. The main risk factors that are amenable to drug therapy are dyslipidaemia, diabetes and hypertension. Preventative strategies therefore include antithrombotic, lipid lowering, blood pressure lowering

[2] The term CVD is sometimes used to describe diseases of the circulatory system collectively. In order to differentiate the term from chronic heart failure and cardiac arrhythmias, in this thesis the term includes only those conditions that directly affect the vasculature, i.e. coronary heart disease, peripheral arterial disease (PAD) and cerebrovascular disease encompassing stroke and transient ischaemic attack (TIA). The term cardiovascular conditions (CVC) is used to encompass risk factors for developing CVD, CVD itself chronic heart failure and atrial fibrillation.

and antidiabetic treatment. In addition, the haemodynamic consequences of atrial fibrillation have been shown to increase the risk of thrombo-embolic stroke 4-5 fold.

Antithrombotic therapy

Aspirin or other antiplatelet agents, such as clopidogrel, are recommended in all patients at high risk of vascular events unless there are specific contraindications. Clopidogrel has been shown to be similarly effective to aspirin in the prevention of secondary vascular events but is more expensive and is therefore usually reserved for cases where aspirin is not tolerated.[51,52] The combination of aspirin and clopidogrel is superior to aspirin alone in preventing recurrent myocardial infarction, but is also associated with a higher risk of bleeding. Nevertheless, current guidance recommends dual antiplatelet treatment for 9 to 12 months after acute coronary syndromes, when the risk of bleeding is estimated to be outweighed by its benefits.[46,47,50] In patients with non-cardioembolic stroke, the addition of dipyridamole has been shown to enhance the benefits of aspirin treatment.[53] Although warfarin has been demonstrated to be at least as effective in the prevention of vascular events as aspirin, its management is complex and the excess bleeding risk outweighs any benefits in lower risk populations.[54] Its use is therefore mainly restricted to patients with current or previous thrombo-embolism and patients with atrial fibrillation (AF) at moderate to high risk of stroke.[54] The $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes, Stroke (doubled)) score is one way of assessing stroke risk in non-valvular atrial fibrillation and has been advocated as a practical instrument to discriminate AF patients into those who are likely or unlikely to convey overall benefit from warfarin treatment.[55]

Table 3.4: Current guidance by the European Society of cardiology (ESC)

Recommendations by the European Society of cardiology	Strength of evidence
1. General population at risk (without diabetes or hypertension)	
o Statin treatment if markedly elevated cholesterol levels and SCORE 10 year CVD risk >5%	n.a.
2. Patients with diabetes mellitus (with or without established cardiovascular disease)	
o Target HbA1c: <6.5%	I-B
o First line oral antidiabetic: Metformin	IIa-B
o Second line oral antidiabetic: Sulphonylurea	I-B
o Target blood pressure: <130/80 mm Hg or lowest achievable if renal dysfunction	I-A
o Statin treatment	I-A
o ACE inhibitors if micro-albuminuria, proteinuria or hypertension	I-A
3. Patients with hypertension	
3.1 Hypertension without complications (CVD, DM or renal impairment)	
o Blood pressure lowering treatment indicated if BP >140/90mmHg and SCORE 10 year CVD risk ≥5%	n.a.
o Target blood pressure: <140/85 mm Hg	☑
3.2 Hypertension with complications (CVD, DM or renal impairment)	
o Blood pressure lowering treatment indicated if BP >130/80mmHg	n.a.
o Target blood pressure: <130/80 mm Hg	I-A
4. Patients with established cardiovascular disease (CVD)	
4.1 Patients with stable angina	
o Acute acting nitrates as prophylaxis and symptom relief	I-B
o First line antianginal: Beta blocker	I-A
o Second line antianginal: Verapamil or diltiazem	I-A
o Second line antianginal : Regular nitrates	I-C
o Nitrate dosing: Asymmetrical dosing scheme to avoid tolerance	☑
o Dipyridamole or short acting dihydropyridine calcium channel blockers to be avoided	☑

n.a. = not available; CVD = cardiovascular disease; ACE = angiotensin converting enzyme;

Table 3.4 (continued): Current guidance by the European Society of cardiology

Recommendations by the European Society of cardiology	Strength of evidence
4.2 Patients with coronary heart disease without prior Acute Coronary Syndrome (ACS)	
o First line antiplatelet: Aspirin	I-A
o Second line antiplatelet: Clopidogrel	IIa-B
o Statin treatment	I-A
o Statin doses of simvastatin 40mg or equivalent	☑
o Target total cholesterol: <4.5 mmol/L (175 mg/dL)	☑
o First line rate limiting agent: Beta blocker	IIa
o Second line rate limiting agent: Verapamil or diltiazem	☑
o ACE inhibitors/Angiotensin receptor blockers	I-B/☑
4.3 Patients with a history of acute coronary syndrome (ACS)	
o First line antithrombotic: Aspirin *and* clopidogrel for 12 months	I-A
o Second line antithrombotic: Anticoagulants	☑
o Statin treatment	I-A
o Statin doses of simvastatin 40mg or higher (if tolerated)	I-A
o Target LDL cholesterol: <2.5 mmol/L (100 mg/dL) as minimum	I-B
<2.0 mmol/L (70 mg/dL) if possible	IIa-B
o First line rate limiting agent: Beta blocker	I-B [46]
o Second line: Verapamil or diltiazem	I-B [46]
o ACE inhibitors/ARBs	I-A/I-B
4.4 Patients with a history of ischaemic stroke/TIA	
o First line antithrombotic: A combination of aspirin and dipyridamole	I-A
o Second line antithrombotic: clopidogrel	n.a.
o Statin treatment	n.a
o Statin doses of simvastatin 40mg or higher (if tolerated)	n.a
o Target LDL cholesterol: <2.5 mmol/L (100 mg/dL) as minimum <2.0 mmol/L (70 mg/dL) if possible	
4.5 Patients with a history of peripheral vascular disease	
o First line antithrombotic: A combination of aspirin and dipyridamole	n.a
o Second line antithrombotic: clopidogrel	I-A
o Statin treatment	n.a
o Statin doses of simvastatin 40mg or higher (if tolerated)	n.a
o Target LDL cholesterol: <2.5 mmol/L (100 mg/dL) as minimum <2.0 mmol/L (70 mg/dL) if possible	n.a

n.a. = not available; CVD = cardiovascular disease; ACE = angiotensin converting enzyme; DM = diabetes mellitus; LDL = low density lipoprotein; ARB = angiotensin receptor blocker; ISDN = isosorbide dinitrate; NYHA = New York Heart association

Table 3.4 (continued): Current guidance by the European Society of cardiology (ESC)

Recommendations by the European Society of cardiology	Strength of evidence
5. Patients with chronic heart failure due to left ventricular systolic dysfunction	
o Anticoagulants in patients with intra-cardiac thrombus	I-C
o First line RAS inhibitor: ACE inhibitors in all patients with EF < 40%	I-A
o Second line RAS inhibitor: ARBs	IIa-B
o Third line: Hydralazine ISDN if ACEI and ARB intolerant	IIa-B
o NYHA III/IV: Aldosterone antagonist in addition to ACEI or ARB	I-B
o Aldosterone antagonist in patients with post MI heart failure in addition to ACEI or ARB and beta blockers	I-B
o Combination of ACEI *and* ARB in addition to BB if patients remains symptomatic	I-A
o Dose titration of ACEI or ARB to evidence based target doses	☑
o Beta blocker therapy	I-A
o Dose titration of beta blockers to evidence based target doses	☑
o Diuretics for symptom control	☑
o Digoxin for symptom control in addition to ACE inhibitors	I-B
o Drug treatments with negative inotropic effects, those that increase the risk of cardiac arrhythmias and those that cause congestion should be avoided	☑
6. Patients with atrial fibrillation	
o First line antithrombotic if low risk of stroke ($CHADS_2$ ≤1): Aspirin	I-A
o First line antithrombotic if moderate risk of stroke ($CHADS_2$ =1): Aspirin or anticoagulants in patients at	IIa-A
o First line antithrombotic if high risk of stroke ($CHADS_2$ ≥2): Anticoagulant	I-A
o Target INR is 2.0 to 3.0	I-B
o Anticoagulation is not recommended for patients at low risk of stroke ($CHADS_2$ = 0)	I-C
o Rate control is indicated in patients with chronic (persistent or permanent) AF	IIb-C
o First line rate limiting agent: beta-blocker, verapamil, diltiazem, digoxin	I-B/I-C
o Second line: amiodarone	IIb-C
o Digoxin monotherapy should be avoided in paroxysmal AF	III-B

n.a. = not available; CVD = cardiovascular disease; ACE = angiotensin converting enzyme; LDL = low density lipoprotein; ARB = angiotensin receptor blocker; ISDN = isosorbide dinitrate; NYHA = New York Heart association; $CHADS_2$ = Score for stroke risk estimation in AF (Cardiac failure = 1pt; Hypertension = 1pt; Age >75 = 1pt; Diabetes = 1 pt; previous Stroke = 2 pts)

Strength of recommendations	
Class I	Evidence and/or general agreement that a given procedure/treatment is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the procedure/treatment.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful (Use of Class III is discouraged by the ESC)

Lipid lowering therapy

Dyslipidaemia is defined as elevated total or low-density lipoprotein (LDL) cholesterol levels or low levels of high-density lipoprotein (HDL) cholesterol. Statins are central to lipid lowering therapy, inhibiting cholesterol synthesis and increasing hepatic uptake of LDL from the circulation. Evidence from meta-analyses shows that an LDL cholesterol reduction by 1 mmol/l reduces the risk of vascular events by about 21%, which is independent of baseline LDL levels.[56] According to the Joint British Society, there are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total or LDL cholesterol targets in relation to clinical events.[56] The appropriate threshold of risk, at which statin treatment should be instigated, and the target levels to be aimed for are therefore primarily guided by cost considerations.[47,57]

Blood glucose control

Increasing glycaemia (measured as HbA1c) results in increased risk of CVD morbidity and mortality. Each 1% reduction in HbA1c is associated with a 21% (95% CI 15-27%) reduction in the risk of diabetes-related death and specifically a 14% reduction for myocardial infarction (MI) over 10 years. No lower threshold can be demonstrated.[1]

Blood pressure control

The relationship between blood pressure and cardiovascular risk is continuous and treatment targets have been lowered in recent years.[56] In patients with established cardiovascular disease or diabetes, benefits of blood pressure lowering therapy have been demonstrated irrespective of baseline blood pressure. Current guidance recommends blood pressure lowering treatment in patients with sustained systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90mm Hg and clinical evidence of cardiovascular disease.[57] Individuals with established cardiovascular disease, who also have chronic renal disease or diabetes with complications, or

target organ damage may be considered for treatment at the lower threshold of systolic >130 mmHg and/or >80 mmHg.[47,57,56]

1.4.2.2 Management of coronary heart disease

Angina is the clinical syndrome characterised by discomfort in the chest, jaw, shoulder, back, or arms, typically appearing due to exertion or emotional stress. If it is relieved by rest or nitroglycerin, it is called stable angina.[58, 59] Situations where symptoms persist are referred to as acute coronary syndromes (ACS). Cases with and without electrocardiographic (ECG) evidence of myocardial necrosis (ST-elevation) are referred to as ST-elevation ACS (STE-ACS), whereas scenarios where such evidence is lacking are labeled Non-ST-elevation acute coronary syndromes (Non STE-ACS).

Management of angina aims to prevent MI and death offering different pharmacological strategies.[59] Apart from thrombo-embolic prophylaxis and statin treatment (see above), beta blockers remain the first line drugs for the long term prevention of chest pain resulting from CHD.[60-62] Calcium channel blockers (CCB) are generally as effective as beta blockers in reducing angina symptoms[60-62] and mortality benefits have been demonstrated for verapamil in the DAVIT trial.[63] Long acting nitrates (e.g. isosorbide mononitrate) showed no significant difference to beta blockers and CCBs in the control of angina symptoms but mortality benefits have not been demonstrated.[49] Nitrate tolerance may develop when nitrate levels are continuously maintained above a certain threshold level and nitrate free intervals are therefore recommended in order to avoid blunting its effects.[49] Short acting nitrates (e.g. sublingual glyceryl trinitrate or spray) are recommended as situational prophylaxis, if angina symptoms occur or activities expected to cause angina are conducted.[58, 59] Current guidelines recommend that acute acting nitrates be prescribed to all patients with stable angina.[49,64]

ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to reduce mortality and further vascular events post ACS in patients with impaired

ventricular function, diabetes or hypertension, but their benefits in patients without such risk factors is more controversial. Nevertheless, the current SIGN guidelines recommend that '*All patients with stable angina should be considered for treatment with angiotensin converting enzyme inhibitors'*.[64] Similarly, current ESC guidelines recommend ACE inhibitors in '*all patients with stable angina and proven coronary disease'*.[49]

1.4.2.3 Management of chronic heart failure

Chronic heart failure is a clinical syndrome, which is caused by pump failure of the heart and is characterised by fluid retention causing oedema and breathlessness and hypo-perfusion of the tissues causing fatigue. A better understanding of the underlying pathophysiology has caused a shift in the management of heart failure from mainly symptomatic treatment (diuretics and digoxin) to a strategy which additionally aims at pro-longing survival. While diuretics are still indicated and necessary for symptom control (despite the fact that mortality benefits have not been demonstrated), the role of digoxin is diminishing in favour of treatments which are capable of intercepting the vicious circle of increased sympathetic tone and activation of the renin angiotensin system (RAS), namely beta-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs).[65]

Based on a number of trials and meta-analyses demonstrating benefits in reducing hospitalisations and death, current guidelines equivocally recommend the use of ACE inhibitors (ARBs if not tolerated) and beta blockers in all patients with heart failure irrespective of functional status (New York Heart Association [NYHA] status I to IV).[43, 66] Up-titration of doses to those used in randomised controlled trials is advised.[43, 66] In patients, who remain moderately to severely symptomatic (NYHA III to IV) despite optimised treatment with ACE inhibitors (ARBs) and beta blockers should be considered for the addition of aldosterone antagonists (spironolactone or eplerenone).[43, 66] An alternative approach in these patients is the use of ACE inhibitor and ARB combinations, which have been demonstrated to be superior to

ACE inhibitor monotherapy in the CHARM added trial[67]. Digoxin still has a role in the management of heart failure as an adjunct to diuretics, ACE inhibitors, ARBs and beta blockers to control symptoms in all NYHA functional stages and in patients with atrial fibrillation.[66]

1.4.2.4 Management of atrial fibrillation

The estimated prevalence of AF is 0.4% to 1% in the general population, increasing with age.[68] Two forms of AF presentation can be distinguished: 'paroxysmal' (spontaneous return to sinus rhythm) and 'persistent' (arrhythmia is sustained beyond 7 days). In practice, however, these categories are not mutually exclusive in a particular patient, who may have several episodes of paroxysmal AF and occasional persistent AF, or the reverse.[68] AF is an important risk factor for stroke and the mitigation of stroke (and bleeding) risk by risk-stratified use of thrombo-embolic prophylaxis has been discussed above. A second strategy to control stroke risk and AF symptoms is the control of the arrhythmia itself. Two approaches can be distinguished: (1) a 'rhythm control strategy' which aims at restoring sinus rhythm and (2) a 'rate control strategy', which aims at controlling the ventricular rate through suppression of atrio-ventricular node conduction with no commitment to restore or maintain sinus rhythm.[68] It is important to note, however, that neither the clinical presentation of AF nor the selected approach of controlling the arrhythmia (even if sinus rhythm is restored) affects the need for or choice of thrombo-embolic prophylaxis.[68]

Beta blockers, rate limiting CCBs, digoxin and amiodarone are similarly effective in controlling the ventricular rate in AF.[69] Since amiodarone has an unfavourable side effect profile it is reserved for cases, where beta blockers, rate limiting CCBs or digoxin alone or in combination fail to control the heart rate adequately. Digoxin does not control the heart rate effectively during exercise, because its efficacy is reduced in states of high sympathetic tone, which is a possible precipitant of

paroxysmal AF. Digoxin monotherapy is therefore discouraged in patients with paroxysmal AF.[68]

1.4.3 Inconsistent implementation of scientific evidence

Clinical practice guidelines have been developed at local, national and international levels to summarise the scientific evidence and in order to assist practitioner and patient decisions about appropriate health care. Guidelines are intended to facilitate application of up to date therapeutic knowledge to everyday practice and – if implemented successfully - to decrease inappropriate variations in the quality of care.[70] However, the use of preventative and disease slowing drug treatments for chronic cardiovascular conditions remains inconsistent. Recent surveys undertaken in health care settings across Europe have identified substantial scope for improvement: The Euroaspire survey[71] (published in 2001) retrospectively evaluated missed opportunities for primary prevention in patients who had developed coronary heart disease (CHD) in 15 European countries at the point of hospital discharge. While the use of antiplatelets was satisfactory in most countries (90% on average), underuse of beta-blockers (66%), ACE inhibitors (38%) and lipid lowering treatment (43%) and insufficient control of hypertension was common. More recent findings from the EURO Heart survey (published in 2006) have demonstrated shortcomings in the secondary prevention of CHD in patients with stable angina, the treatment of heart failure and atrial fibrillation: only 30% of angina patients achieved recommended blood pressure targets (<140/90 mmHg), lipid lowering treatments were underused and of inadequate intensity in a majority of patients; less than 50% of heart failure patients, who fulfilled the inclusion criteria of landmark clinical trials, received beta blocker treatment and in those treated, recommended target doses were achieved in only 10%.[50,51,53,54,72,73] Finally, antithrombotic prophylaxis was underused in patients with atrial fibrillation and in those treated, the choice of therapeutic agents was frequently not in accordance with stroke risk stratification.[45]

2. Aims and objectives

Aims

The aims of the second part of this thesis are to develop and test methods of quality assessment of medication use in order to allow them to function within the context of the quality improvement model developed in chapter 2. In view of (1) the public health relevance of cardiovascular conditions and the facts that (2) chronic cardiovascular conditions frequently coincide in individual patients and (3) pharmacological strategies for their prevention and treatment substantially overlap, this therapeutic field is ideally suited to study methodological challenges in combining medication assessment approaches for multiple diseases.

The aim of the following chapter 3 is the development and application of a generic framework to facilitate the design of explicit medication assessment instruments for *multiple* conditions, which is intended to fulfil the following key functions:

a) To ensure that drug therapy risks detected by the resulting instrument are aligned with existing frameworks of pharmaceutical care delivery

b) To facilitate the design of mutually exclusive assessment criteria that enable the detection of distinct drug therapy risks at individual patient level

c) To enable the compilation of individual assessment criteria into composite quality indexes

The framework will subsequently be applied to develop a Medication Assessment Tool for the following cardiovascular risk factors and conditions (MAT_{CVC}): (1) diabetes or hypertension (2) coronary heart disease (CHD) (3) chronic heart failure (CHF) and (4) atrial fibrillation (AF).

Objectives

1. To develop a generic framework for explicit quality assessment of medication use based on existing frameworks of pharmaceutical care practice.

2. To identify clinical practice guidelines providing guidance for long term medication use in (1) the primary and secondary prevention of vascular events in patients with diabetes or hypertension and the management of (2) stable angina, (3) chronic heart failure and (4) atrial fibrillation and identify guideline recommendations suitable for explicit quality assessment.

3. To design explicit quality assessment criteria using the framework devised under objective 1 (MAT_{CVC})

4. To define explicit clinical exemption rules for contextualising MAT_{CVC} assessment.

3. Methods

3.1 Generic quality assessment framework

3.1.1 Categorisation of pharmaceutical care needs

In their publication, 'Pharmaceutical care practice: The clinician's guide'[6], Cipolle and Strand define clinical 'situations' (in generic terms) that may trigger enquiries into the effectiveness or safety of current medication use ('pharmacotherapy work-up'). Pharmaceutical care needs have been defined as patient risk factors, which predispose to drug therapy risks (DTRs) and as the starting point for checks which aim to detect or exclude such risks. The 'situations that trigger enquiries' overlap with the PCN concept and were used as the basis for a corresponding categorisation system.

3.1.2 Categorisation of drug therapy risks and outcomes

Chapter 1 has reviewed a range of categorisation systems for drug therapy problems (DTPs) and the system developed by Cipolle and Strand[6] is perhaps the most widely cited and applied system in practice. Although, the concepts of DTRs and DTPs are not identical (discussed in detail in chapter 1), this system formed the basis for the proposal of a categorisation system for drug therapy risks. In order to address the threat that the proposed system, which has not been empirically derived, missed important aspects of pharmaceutical care practice, it was tested by checking whether it allowed the items proposed by previous authors to be exhaustively classified. Adjustments to the proposed system were considered in order to accommodate any missed items.

3.2 Identification of relevant guideline recommendations

The source for the design of the criteria set were the European Society of Cardiology (ESC) guidelines for the management of coronary heart disease, atrial fibrillation and chronic heart failure. The following guidelines published by the European Society of Cardiology were selected:

1) 'Guidelines on cardiovascular disease prevention in clinical practice'[47]
2) 'Guidelines on the management of stable angina pectoris'[49]
3) 'Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes'[74]
4) 'Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation'[50]
5) 'ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008'[43]
6) 'ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation'[68]

All guideline recommendations were eligible for translation into explicit medication assessment criteria if they addressed long term medication use for patients with a history of (1) diabetes or hypertension (2) coronary heart disease with or without a history of vascular events, (3) stroke or transient ischaemic attack, (4) peripheral vascular disease, (5) chronic heart failure and (6) atrial fibrillation. The following exclusion criteria were applied:

1) Recommendation refers to an indication for a drug (group) classified as 'IIb' or unclassified[3] (see table 3.6 for definition of strengths of recommendations)
2) Recommendation refers to an indication or choice of drug treatment but depends on (a) patient preference or (b) prior success or failure of medication
3) Recommendation refers to data that is anticipated to be unfeasible to abstract from routine documentation
4) Recommendation is unspecific or inconclusive
5) Recommendation refers to an aspect of care that is anticipated not to be a relevant problem in practice

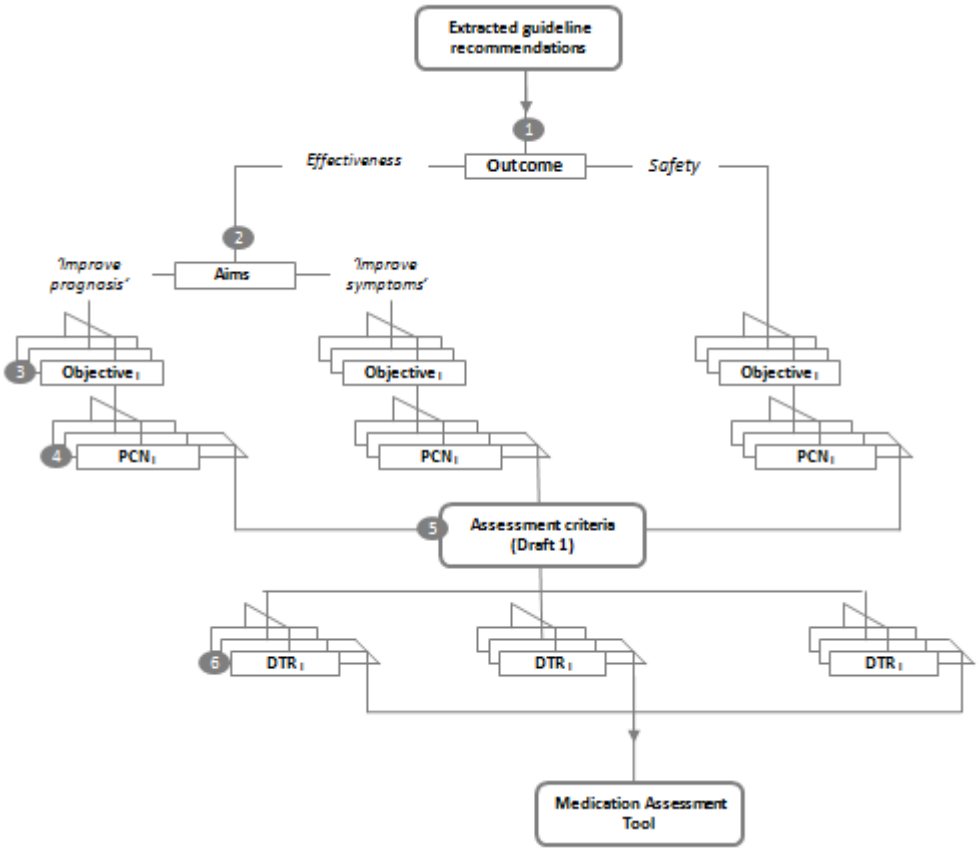
Class III recommendations[4] were considered as safety criteria.

[3] 'Usefulness/efficacy is less well established by evidence/opinion'

3.3 Design of explicit assessment criteria for MATCVC

Figure 3.1 illustrates the six-step process by which extracted recommendations were organised into a hierarchical structure and subsequently translated into draft assessment criteria, which were subsequently further refined to yield the final MAT.

Figure 3.1: Process map for the development of the medication assessment tool (MAT) (see overleaf for explanation)



PCN = Pharmaceutical care need; DTR = Drug therapy risk; DTR i denotes different DTR categories; the interrupted lines illustrate that recommendations may refer to more than one objective or PCN.

[4] 'Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful'

Step 1: Grouping of recommendations by targeted outcome

Eligible guideline recommendations were grouped by the outcome dimension targeted, i.e. medication use *safety* or *effectiveness*. Effectiveness recommendations advised the use, selection or dose of beneficial treatments or referred to the achievement of a therapeutic target associated with better patient outcomes, such as blood pressure. 'Safety' recommendations advised caution or avoidance of high risk medication use, selection or dosing in order to prevent adverse drug events.

Step 2: Drug therapy aims (Prognosis vs symptom control)

Those recommendations targeting effectiveness were further dichotomised into whether the aim was prognosis improvement or symptom control. Where recommended drug treatments fell into both categories, prognosis improvement was prioritised.

Step 3: Drug therapy objectives

Within each cluster obtained in this way, the respective recommendations were subcategorised further into 'drug therapy objectives' (DTO) according to the following rules:

1) Within the prognosis improvement category, DTOs were assigned according to 'physiological target', understood as

   > *'a desired physiological effect that drug therapy aims to achieve in order to prevent disease or improve prognosis'.*

2) Within the symptom control cluster, DTOs were assigned according to which specific symptom each recommendation aimed to address.

3) Within the safety category, DTOs were assigned according to the specific adverse drug event (ADE) that each recommendation aimed to prevent.

Step 4: Pharmaceutical care needs

Recommendations were further subcategorised for each drug therapy objective according to which pharmaceutical care need it referred to according to the following rules:

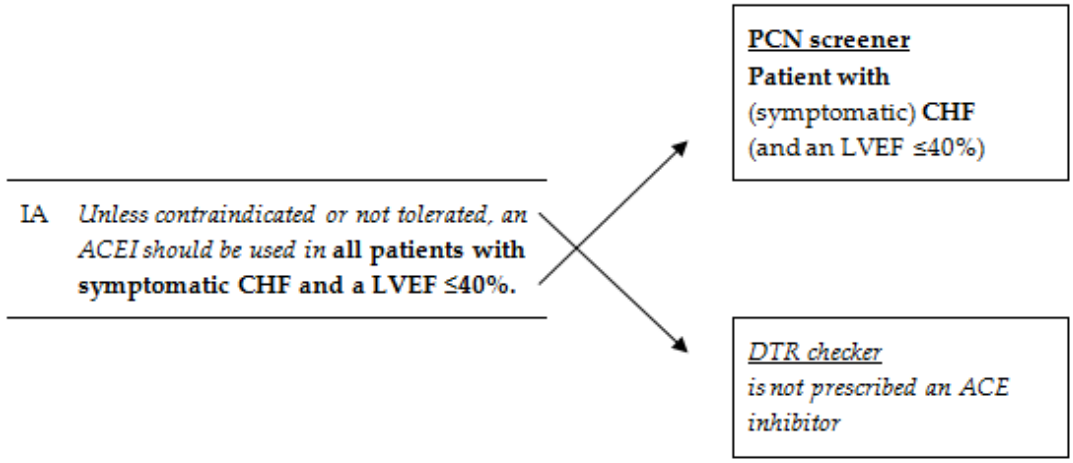
1) For both types of *effectiveness* objectives (prognosis improvement and symptom control), PCNs were assigned according to which medical condition each recommendation referred to.

2) For *safety* objectives, PCNs were assigned according to which drug or drug group each recommendation referred to.

Step 5: Design of draft assessment criteria

Each guideline recommendation was translated into one assessment criterion of standardised format as shown in figure 3.2.

Figure 3.2: Translation of guideline recommendations into draft criteria



Step 6: Refinement of draft assessment criteria to yield MAT_{CVC}

The draft criteria were further processed by the following strategies in order to ensure that each criterion addressed a distinct DTR category:

- Merging draft criteria addressing identical drug therapy risks (illustrated in figure 3.3)
- Splitting draft criteria to match distinct DTR categories in situations, where
    - Recommendations relevant to indication *and* selection of treatment (see figure 3.4)
    - Recommendations relevant to safety *and* effectiveness (see figure 3.5)

Figure 3.3: Merging draft criteria that referred to different subgroups of patients with the same underlying condition but recommended identical treatment. Where guidelines assigned different strengths of recommendations for different patient subgroups the highest grading was adopted for the merged criterion.

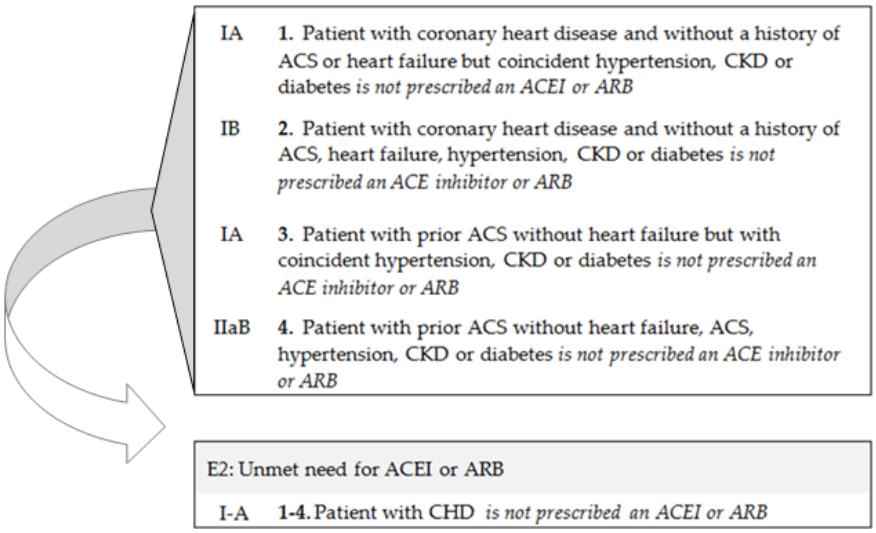


Figure 3.4: Splitting draft criteria that related to indication and drug choice. The example shows the splitting of a draft criterion assessing the use of vitamin K antagonists in AF patients at high risk of stroke into (1) a criterion targeting an unmet need for thrombo-embolic prophylaxis and (2) a criterion targeting suboptimal drug choice.

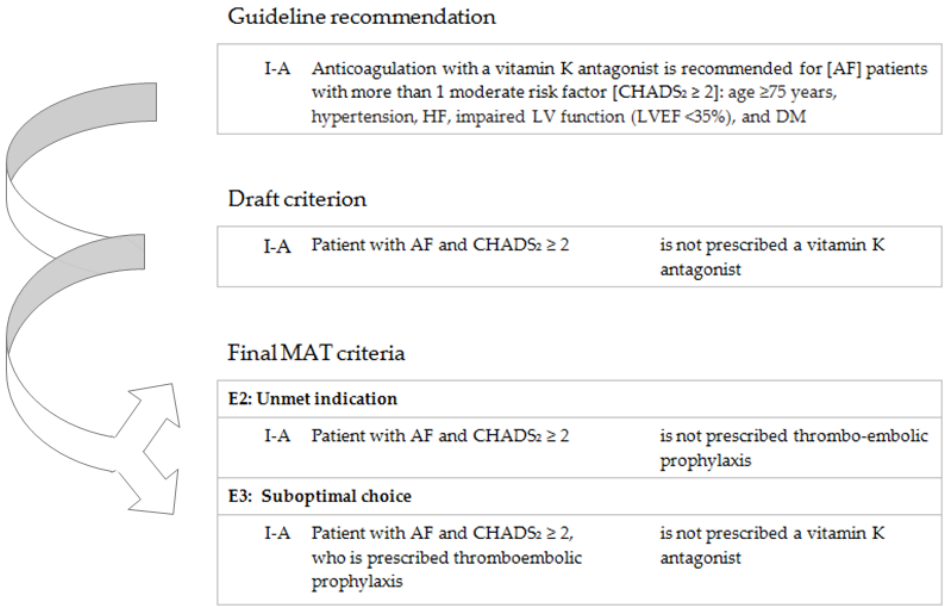
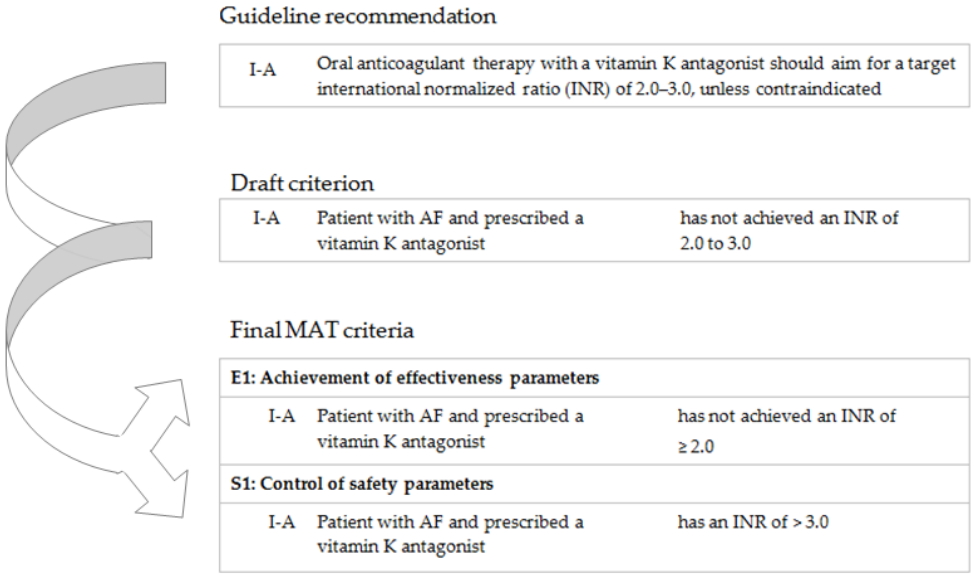


Figure 3.5: Splitting of draft criteria that are relevant to safety and effectiveness. The example shows that a draft criterion assessing the achievement of the target INR range in patients on vitamin K antagonists was split into one criterion assessing over-treatment (safety) and one assessing under-treatment (effectiveness).



A generic template for the design of assessment criteria for each DTR category is shown in table 3.5.

Table 3.5: Template for the design of assessment criteria to match distinct DTR categories

	PCN screener	DTR checker
Effectiveness	**E1: Achievement of therapeutic target**	
	Patient with PCN 'A', who is treated for control of parameter 'B'	has not achieved the 'B' target range to be optimally effective
	E2: Unmet need for drug therapy	
	Patient with PCN 'A' (an indication for drug 'B')	is not prescribed treatment 'B'
	E3: Suboptimal choice of drug therapy	
	Patient with PCN 'A', who is treated for drug therapy objective 'A1'	is not prescribed the optimally effective choice or intensity to achieve drug therapy objective 'A1'
	E4: Suboptimal dose of drug therapy	
	Patient with PCN 'A', who is treated for drug therapy objective 'A1'	is not prescribed the optimally effective dose or dose frequency to achieve drug therapy objective 'A1'
Safety	**S1: Control of drug safety parameter**	
	Patient, who receives drug treatment 'D'	has marker that reflects excessive drug exposition or adverse effects
	S2: Unnecessary drug treatment	
	Patient with PCN 'A'	is prescribed treatment that is known to be ineffective for condition 'A' (and potentially harmful)
	S3: High risk drug choice	
	Patient with PCN 'A'	is prescribed treatment that is known to aggravate condition A
	S4: High risk drug dose	
	Patient, who receives drug treatment 'D'	is prescribed treatment that exceeds a defined maximum dose or dose frequency for B

3.4 Explicit rules for contextualising MATCVC assessment

A panel consisting of four clinical pharmacists (one community pharmacist, one pharmacist working in general practice and two hospital pharmacists specialised in cardiovascular disease) was formed in order to identify valid clinical circumstances, under which the non-use of recommended cardiovascular medication would usually be deemed clinically justified. For each drug (group) included in MATCVC measures that targeted the use of recommended treatments, a list of 'cautions' and 'contraindications' was identified from the British National Formulary (BNF). For each drug group 'X' and each contraindication/caution 'Y' on the list, participants were asked to discuss the following question:

> 'In which clinical scenario would the use of drug (group) X usually be expected to cause more harm than benefit?'

The panel meeting was held at the University of Strathclyde and was moderated by the author of this thesis. The four panel members were informed that the rules under discussion were to be operationalised by research assistants in retrospective audits of guideline adherence in cases, where an explanation for deviations from guideline recommendations was not explicitly documented in routine clinical documentation.

It was emphasised that the context of audits was to facilitate quality improvement rather than placing judgement on the care provided in the settings to be audited and served the purpose of accounting for clinical reasons that hinder the implementation of recommended treatments. During the discussion for each drug (group), the description of the reference patient and the list of 'cautions' and 'contra-indications', which had been identified from the British National Formulary, were displayed.[75] Each drug (group) was discussed with reference to a 'typical' patient, who would be eligible for treatment according to current guideline recommendations:

- The use of antiplatelets, statins, beta blockers and rate limiting calcium channel blockers were discussed with reference to a patient aged 70 years of age with a recent history of ST-segment elevation myocardial infarction.

- The use of ACE inhibitors, ARBs, aldosterone antagonists and digoxin was discussed with reference to a patient aged 75 years with NYHA status III and a ventricular ejection fraction of 35%

- The use of metformin was discussed with reference to an obese patient with diabetes mellitus type II.

4. Results

4.1 Generic quality assessment framework

4.1.1 Draft framework

Table 3.6 shows the proposal of a categorisation system for pharmaceutical care needs, drug therapy risks and undesirable outcomes from medication use. The core of this framework is the categorisation system for drug therapy problems introduced by Cipolle and Strand in 2004.[6] Categories that have been added or reorganised are underlined.

For the concept 'Pharmaceutical care need' (PCN), the category *'medical condition/health risk factor'* was added. This category comprises all diagnosed diseases and risk factors for such diseases that are susceptible to drug therapy. For the concept 'drug therapy risk' (DTR), the categories '*effectiveness/safety parameters not monitored'* and *'effectiveness'* and *'safety parameters uncontrolled'* were added. 'Parameters' constitute measurable items, which are used to monitor or judge the effectiveness or safety of a drug regimen. In order to separate drug therapy risks from outcomes, the category *'adverse drug event (ADE)'* features under outcome in the proposed categorisation system. Since a concept to describe the failure to achieve desired outcomes from drug therapy had not formally been defined in Cipolle and Strand's categorisation system, the category 'drug therapy failure' (DTF) was added.

Table 3.6: Proposal of a categorisation system for pharmaceutical care needs, drug therapy risks and undesired drug therapy outcomes for the purposes of quality assessment

PCNs (to be identified by *screening*)	**DTRs** (to be detected by *checking*)	**Undesired outcomes** (to be prevented by *acting*)
Effectiveness and/or safety 1. Any drug taken by the patient 2. Any drug requiring monitoring and timely adjustment	C: Inappropriate compliance M. Effectiveness or safety parameters not monitored	Adverse drug event (ADE) or Drug therapy failure (DTF)
Effectiveness 1. Laboratory values 2. Medical condition/ Health risk factor 3. Signs and symptoms	M. Effectiveness parameters not monitored E1. Effectiveness parameter uncontrolled E2. Unmet need for a drug E3. Suboptimal drug choice E4. Suboptimal dosing	Drug therapy failure (DTF)
Safety 1. Laboratory values 2. Medical condition/ Health risk factor 3. Signs and symptoms	M. Safety parameters not monitored S1. Safety parameter uncontrolled S2. Unnecessary drug S3. High-risk drug choice S4. High-risk drug dose	Adverse drug event (ADE)

4.1.2 Revised framework

Comparison of DTP and DTR categories

Chapter 1 has summarised six pertinent categorisation systems for drug therapy problems (DTPs).[5,9,76-79] The DTP categories used by different authors overlap substantially. Table 3.7 shows how the categories developed by previous authors were collapsed under the proposed categories for drug therapy risks and outcomes. The category 'cost' and cost-effectiveness' was added.

Table 3.7: Comparison of proposed DTR categories to published DTP categories

Proposed DTR category/ Published DTP categories	Drug therapy outcomes
Compliance (Safety and/or effectiveness) o Noncompliance [6, 80, 77] o Drug use [79]	
Effectiveness E1. Effectiveness parameter uncontrolled - E2. Unmet indication o Needs additional drug [6, 80,] o Access [5] E3. Suboptimal drug choice o Ineffective drug [6, 80] o Wrong drug (Effectiveness) [5] o Drug Choice [79] E4. Suboptimal dose o Dosage too low [80, 6] o Wrong dose (Effectiveness) [5] o Dosing [79] o Inappropriate dosage [77]	Drug therapy failure (DTF) o Effectiveness [78] o Non-quantitative ineffectiveness [76] o Quantitative ineffectiveness [76] o Untreated health problem [76] o Insufficiently treated health problem [77]
Safety S1. Drug safety parameters uncontrolled o Drug-laboratory interaction [5] S2. Unnecessary drug o Unnecessary drug [5,6, 80] o Duplicity [77] S3. High-risk drug choice o Wrong drug (safety) [5] o Drug Choice [79] o Contraindication [77] S4. High-risk drug dose o Dosage too high [80] o Wrong dose (Safety) [5] o Dosage too high [6] o Dosing [79]	Adverse drug event (ADE) o ADR [5, 80, , 78, 79] o Effects of unnecessary drug [76] o Quantitative unsafe [76] o Non-quantitative unsafe [76]
Cost and cost-effectiveness [78] CE. High-cost drug	

4.2 Extraction of guideline recommendations

Eligible recommendations

A total of 112 recommendations were identified that addressed long term medication use for patients with diabetes, hypertension, coronary heart disease, chronic heart failure or atrial fibrillation and were extracted from ESC guidelines [43,46,49,50,68,81,82].

Excluded recommendations

A total of 25 (22%) recommendations met the exclusion criteria (table 3.8). Four items referred to indications or choice of a particular drug (group) and were classified as 'IIb'. A further 17 recommendations were excluded for feasibility reasons, i.e. because they were either anticipated not to be routinely recorded in medical notes (7 recommendations) or depended on patient preference (3 recommendations) or prior success/tolerance of treatment (7 recommendations). A further three recommendations were excluded because guidance was unspecific or inconclusive and one because it was anticipated not to be a relevant problem in practice.

Table 3.8: Excluded recommendations

	1. Low strength of recommendation (n= 4)
IIb-C	Early initiation of insulin may be considered if glucose target cannot be achieved.
IIb-B	In elderly patients with symptomatic chronic HF and systolic dysfunction caused by CAD, statin treatment may be considered to reduce cardiovascular hospitalization.
IIb-B	Fibrate therapy in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome
IIb-C	Fibrate or nicotinic acid in patients with low HDL and high triglycerides at high risk (2% annual CV mortality)
	2. Anticipated not to be routinely recorded in medical notes (n = 7) (questionable data item is underlined)
IIa-B	Supplementation with 1 g of fish oil in patients with a low intake of oily fish
☑	Influenza immunization is indicated in all patients with CAD and thus also in those surviving a STEMI.
IIa-B	High dose statin therapy is recommended in high-risk (>2% CV mortality/year) patients with proven coronary disease
IIa-B	Fibrates and omega-3 supplements should be considered in patients who do not tolerate statins, especially if triglycerides >150 mg/dL (1.7 mmol/L) and/or HDL cholesterol ,40 mg/ dL (1.0 mmol/L)
☑	A recent study showed that the addition of a PPI (esomeprazole 40 mg/day) to aspirin (80 mg/day) was better than switching to clopidogrel for the prevention of recurrent ulcer bleeding in patients with ulcers and vascular disease.
I-B	Diuretics are recommended in patients with HF and clinical signs or symptoms of congestion.
☑	Active counselling, in addition to adjunctive drug interventions (e.g. NRT or bupropione) is necessary.
	3. Dependent on patient preference (n = 3)
I-B	Bupropione and nicotine treatment in patients who keep smoking at follow-up
☑	NRT has proved effective and safe in helping patients with CAD to quit smoking
IIa-C	Patients with clinical depression should be offered treatment with antidepressants
	4. Dependent on prior success/tolerance of treatment (n = 7)
I-A	In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a CCB for symptom control (stable angina)
I-A	Test the effects of a beta-1 blocker, and titrate to full dose for symptom control
I-C	In case of beta-blocker intolerance or poor efficacy attempt long-acting nitrate OR nicorandil
IIa-B	In case of beta-blocker intolerance try sinus node inhibitor
I-B	If the effects of beta-blocker monotherapy are insufficient, add a dihydropyridine CCB
IIa-C	If CCB alone or combined with a BB is unsuccessful, substitute the CCB with a long-acting nitrate or nicorandil.
I-B	If the effects of beta-blocker monotherapy are insufficient, add a dihydropyridine CCB (stable angina)

Table 3.8 (continued): Excluded recommendations

	4. Guidance unspecific or inconclusive (n= 3)
☑	Oral anticoagulants may be given if there is an indication for oral anticoagulation
☑	The optimal antithrombotic dosage of aspirin appears to be 75–150 mg/day
☑	Nitrates continue to be first line therapy for angina pectoris but there is no evidence of impact on prognosis (STEMI)
	5. Anticipated not to be a relevant problem in practice (n = 1)
☑	Aspirin and clopidogrel combination therapy is currently not warranted instable angina pectoris patients without a history of ACS

4.3 Design of explicit assessment criteria for MATCVC

4.3.1 Hierarchical grouping of guideline recommendations

The remaining 87 (78%) recommendations were selected for the design of explicit assessment criteria and grouped hierarchically as described in figure 3.1. The results of this grouping process are shown in appendix 2.

Tables 3.9-11 summarise the counts of recommendations extracted for patient groups with specific conditions. The majority of the 87 included recommendations referred to medication effectiveness (95%), with only 5 (6%) recommendations addressing safety issues. The recommendations were categorised under a total of 11 drug therapy objectives, of which 8 related to medication effectiveness (6 prognosis improvement and 2 symptom control). Recommendations frequently overlapped, because each guideline for the management of a specific condition also included recommendations relating to the management of common cardiovascular co-morbidities. For example, guidelines on the management of patients with ACS specifically addressed drug treatment in patients with heart failure[46,50] and heart failure guidelines gave recommendations for managing patients with coincident atrial fibrillation and vice versa.[43,68]

Table 3.9: Summary of criteria targeting prognosis improvement (effectiveness)

Outcome - Effectiveness **Aim** - Improving prognosis	Recommendation	Draft Criteria	E1	E2	E3	E4	Total E1 - E4
Objective 1 – Thrombo-embolic- prophylaxis							
CVD with or w/o prior events	2	2	-	3	-	-	3
CVD with prior vascular events	10	1			1	-	1
Chronic heart failure (CHF)	1	1	-	1	1	-	2
Atrial fibrillation (AF)	11	5	1	4	2	-	7
Subtotal	24 (30%)	9 (26%)	1 (17%)	8 (36%)	4	-	13 (37%)
Objective 2 - Lipid control							
CVD or DM	3	3	2	4	-	1	7
CHD with prior ACS	6	2					
Subtotal	9 (11%)	5 (15%)	2 (33%)	4 (18%)	-	1 (33%)	7 (20%)
Objective 3 – Diabetes control							
Diabetes mellitus (DM)	2 (3%)	2 (6%)	1 (17%)	1 (5%)	-	-	2 (6%)
Objective 4 – Blood pressure control							
Hypertension	2 (3%)	2 (6%)	2 (33%)	-	-	-	2 (6%)
Objective 5 – RAS inhibition							
CHD or DM	3	2	-	2	-	-	2
CHD with prior ACS	7	3	-	-	-	-	-
Chronic heart failure (CHF)	15	4	-	2	-	1	3
Subtotal	25 (32%)	9 (26%)	-	4 (18%)	-	1 (33%)	5 (14%)
Objective 6 – Heart rate control							
CHD with prior ACS	3	1	-	1	-	-	1
CHD without prior ACS	1	1	-	1	-	-	1
Chronic heart failure (CHF)	5	2	-	1	-	1	2
Atrial fibrillation (AF)	8	3	-	2	-	-	2
Subtotal	17 (22%)	7 (21%)	-	5 (23%)	-	1 (33%)	6 (17%)
Total effectiveness (prognosis improvement)	79 (100%)	34 (100%)	6 (100%)	22 (100%)	4 (100%)	3 (100%)	35 (100%)

CHD = coronary heart disease; ACS = acute coronary syndrome; DM = diabetes mellitus; CVD = cardio-vascular disease comprising coronary heart disease, peripheral vascular disease and cerebrovascular disease

Table 3.10: Summary of criteria targeting symptom control (effectiveness)

Outcome – Effectiveness (continued)							
Aim - Symptom control							
	Recommendation	Draft criteria	E1	E2	E3	E4	Total E1 - E4
Objective 7 – Angina							
Coronary heart disease	2	2	-	1	-	1	2
Objective 8 – Fluid retention							
Chronic heart failure	1	1	-	1	-	-	1
Total (symptom control)	3	3	-	2	-	1	3

Table 3.11: Summary of criteria targeting medication safety

Outcome - Safety							
Aim – Control risk of ADEs							
	Recommendation	Draft criteria	S1	S2	S3	S4	Total S1 to S4
Objective 9 – Preventing haemorrhage							
Antithrombotics	2 (40%)	2 (14%)	1 (7%)	-	1	-	2 (14%)
Objective 10 – Preventing angina exacerbation							
Dipyridamole	1	1	-	-	1	-	1
Short acting CCB	1	1			1		1
Subtotal	2 (40%)	2 (14%)	-	-	2 (17%)	-	2 (14%)
Objective 11 – Preventing heart failure exacerbation							
Antiarrhythmic (class 1)	1	1	-	-	1	-	1
Glitazone		1			1		1
PDE 5 inhibitor		1			1		1
NSAID		1			1		1
Tricyclic antidepressant		1			1		1
Oral steroid		1			1		1
Lithium		1			1		1
Minoxidil		1			1		1
Diltiazem or verapamil		1			1		1
Short acting CCB		1			1		1
Subtotal	1 (1%)	10 (14%)	-	-	10 (83%)	-	10 (71%)
Total safety	5 (100%)	14 (100%)	1 (100%)	-	12 (100%)	-	14 (100%)

CCB=calcium channel blocker; NSAID= non-steroidal anti-inflammatory drug; PDE= phosphodiasterase

4.3.2 Design of assessment criteria

The complete lists of included guideline recommendations and corresponding assessment criteria are listed in appendix 2. Tables 3.9-3.11 summarise the numbers of draft and final (MAT) criteria generated.

Draft assessment criteria

Subsequent to the selection and hierarchical grouping of recommendations, each of the selected 87 guideline recommendations were translated into assessment criteria. Removing of duplicates (i.e. recommendations overlapping between guidelines) yielded a total of 55 draft criteria, of which 34 items addressed the use, selection or dosing of drug therapy to improve prognosis, three criteria targeted symptom control and 18 medication safety issues.

Criteria for MATcvc

Tables 3.9-3.11 show that for the majority of drug therapy objectives, the numbers of draft and final MAT criteria matched, reflecting that no further refinement was necessary. However, for drug therapy objectives 1 ('thrombo-embolic prophylaxis'), 2 ('lipid control'), 5 ('RAS inhibition') and 6 ('heart rate control'), the draft criteria were further processed in order to ensure that the resulting final MAT criteria targeted *distinct* drug therapy risk categories.

This process yielded a total of 52 criteria (see table 3.12), which collectively constituted the Medication Assessment Tool for chronic cardiovascular conditions (MAT_{CVC}). Of these 52 criteria, 35 (67%) related to medication use for prognosis improvement, three (6%) to symptom control and 14 (27%) pertained to medication safety. The highest number of criteria related to drug therapy objective 1 (thrombo-embolic prophylaxis [25%]) followed by drug therapy objectives 2 (lipid control [19%]), drug therapy objective 5 (RAS inhibition [10%]) and drug therapy objective 6 (heart rate control [12%]). Among the categories of drug therapy risks targeted, unmet need for drug therapy was the most pertinent (E2; 46%) followed by high-risk drug choice (S3; 23%) and achievement of effectiveness parameters (E1; 12%).

Table 3.12: Medication assessment tool for cardiovascular conditions (MAT_{CVC})

Outcome – Effectiveness

Aim - Improving prognosis

REC	DTR	No.	**PCN screener/** *DTR checker*
Objective 1 – Controlling risk of thrombo-embolism			
I-A	E1	1	**AF and on an a vitamin K antagonist /** *has achieved the target INR*
I-A	E2	2	**AF and $CHADS_2$ score = 0 and aged ≥60/** *is not prescribed thrombo-embolic prophylaxis*
I-A	E2	3	**AF and $CHADS_2$ score = 1/** *is not prescribed thrombo-embolic prophylaxis*
I-A	E2	4	**AF and $CHADS_2$ score = 2/** *is not prescribed thrombo-embolic prophylaxis*
I-A	E2	5	**AF and $CHADS_2$ score ≥ 3/** *is not prescribed thrombo-embolic prophylaxis*
I-A	E2	6	**Coronary heart disease/** *is not prescribed thrombo-embolic prophylaxis*
n.a.	E2	7	**Peripheral vascular disease/** *is not prescribed thrombo-embolic prophylaxis*
n.a.	E2	8	**Prior stroke or transient ischaemic attack (TIA)/** *is not prescribed thrombo-embolic prophylaxis*
I-C	E2	9	**CHF and prior TE or intracardial thrombus/** *is not prescribed thrombo-embolic prophylaxis*
I-A	E3	10	**History of stroke/TIA or ACS ≤ 12 months ago and on thrombo-embolic prophylaxis/** *is not on dual antiplatelet treatment or a vitamin K antagonist*
I-A	E3	11	**AF and $CHADS_2$= 2 and on TE prophylaxis/** *is not prescribed an vitamin K antagonist*
I-A	E3	12	**AF and $CHADS_2$≥ 3 and on TE prophylaxis/** *is not prescribed an vitamin K antagonist*
I-C	E3	13	**CHF with prior thrombo-embolism or intracardial thrombus and on TE prophylaxis/** *is not prescribed an vitamin K antagonist*
Objective 2 – Controlling dyslipidaemia			
☑	E1	1	**CVD without prior vascular events/ but on a statin/** *has not achieved a TC < 175 mg/dl*
I-A	E1	2	**CVD with prior vascular events and on statin/** *has not achieved an LDL < 100 mg/dl*
I-A	E2	3	**Coronary heart disease (CHD)/** *is not prescribed a statin*
n.a.	E2	4	**Peripheral vascular disease (PVD)/** *is not prescribed a statin*
n.a.	E2	5	**History of stroke or TIA/** *is not prescribed a statin*
n.a.	E2	6	**Diabetes mellitus/** *is not prescribed a statin*
☑	E3	7	**CVD and prescribed a statin/** *is not prescribed simvastatin 40 mg**
Objective 3 – Controlling diabetes			
I-B	E1	1	**DM, who is prescribed anti-hyperglycaemic therapy/** *has not achieved HbA1c < 6.5%*
IIa-B	E3	2	**DM, who is overweight and is prescribed an oral antidiabetic agent/** *is not prescribed metformin*
Objective 4 – Controlling blood pressure			
I-A	E1	1	**HTN and complications (CVD, DM or CKD) who is treated for hypertension/** *has not achieved SBP of ≤ 130mmHg AND DBP ≤80mmHg*
I-A	E1	2	**Uncomplicated HTN (no CVD, DM, or CKD), who is treated for hypertension/** *has ot achieved an SBP of ≤ 140 AND DBP ≤ 85mmHg*
Objective 5 – Controlling the RAS			
I-A	E2	1	**Coronary heart disease/** *is not prescribed an ACEI or ARB*
I-A	E2	2	**Chronic heart failure/** *is not prescribed an ACEI or ARB or H-ISDN*
n.a.	E2	3	**Diabetes mellitus/** *is not prescribed an ACEI or ARB*
I-A	E2	4	**CHF and prior MI or in NYHA III-IV and on a BB, ACEI/ARB and a diuretic/** *is not prescribed an aldosterone antagonist or an ACEI plus ARB*
☑	E4	5	**CHF and on an ACEI or ARB/** *is not prescribed target dose or a documented max. tolerable dose*

Table 3.12 (continued): MAT_{CVC}

Aim - Improving prognosis (continued)			
Objective 6 – Controlling heart rate			
I-A	E2	1	**Chronic heart failure/** *is not prescribed a BB*
☑	E2	2	**Coronary heart disease without prior ACS**/** *is not prescribed a BB or rate limiting CCB*
I-A	E2	3	**Coronary heart disease with prior ACS** */* *is not prescribed a BB or rate limiting CCB*
I-B	E2	4	**Atrial fibrillation/** *is not prescribed a BB or rate limiting CCB or amiodarone*
IIa-B	E2	5	**Paroxysmal AF and on digitalis/** *is not prescribed a BB, a rate limiting CCB or amiodarone*
☑	E4	6	**CHF or LVSD and on a beta blocker/** *has not achieved the recommended target dose*
Aim – Symptom control			
Objective 7 – Controlling angina symptoms			
I--B	E2	1	**Stable angina/** *is not prescribed a short acting nitrate*
IIa-C	E3	2	**CHD and on a regular nitrate/** *is prescribed a dosing regimen, which provokes nitrate tolerance*
Objective 8 – Controlling fluid retention			
IIa-A	E3	1	**CHF and on optimal treatment with ACEI, ARB, aldosterone antagonist and diuretic** *is not prescribed digoxin*
Outcome - Safety			
Objective 9 – Controlling risk of haemorrhage			
☑	S1	1	**AF and on vitamin K antagonist/** *is discharged with an INR >3.0*
III-C	S3	2	**AF and $CHADS_2$= 0/** *is prescribed an oral anticoagulant*
Objective 10 – Preventing drug induced angina symptoms			
☑	S3	1	**Coronary heart disease** / *is prescribed dipyridamol***e**
☑	S3	2	**Patient who is admitted with ACS/** *is prescribed a dihydropyridine CCB without use of a BB*
Objective 11 – Preventing drug induced fluid retention			
IC	S3	1	**Chronic heart failure /** *is prescribed antiarrhytmic class 1 (IC)*
IIb-B	S3	2	**Chronic heart failure /** *is prescribed a glitazone*
☑	S3	3	**Chronic heart failure /** *is prescribed a PDE 5 inhibitor*
☑	S3	4	**Chronic heart failure /** *is prescribed an NSAID*
☑	S3	5	**Chronic heart failure /** *is prescribed a tricyclic antidepressant*
☑	S3	6	**Chronic heart failure /** *is prescribed an oral steroid*
☑	S3	7	**Chronic heart failure /** *is prescribed lithium*
☑	S3	8	**Chronic heart failure /** *is prescribed minoxidil*
☑	S3	9	**Chronic heart failure /** *is prescribed diltiazem or verapamil*
☑	S3	10	**Chronic heart failure /** *is prescribed a short-acting DHP-CCB*

4.4 Explicit rules for contextualising MAT_{CVC} assessment

The clinical exemption rules that were agreed as a group consensus are shown in table 3.13.

Table 3.13: Clinical rules under which the implementation of respective treatments were agreed to be usually inappropriate

Drug (group)	BNF[75] listed contraindication	Agreed rules Scenario when use is considered 'inappropriate'	Time frame of event
1. Thrombo-embolic prophylaxis			
Aspirin/ clopidogrel/ oral anticoagulant	Haemorrhage	Bleeding event requiring acute clinical intervention	Event ≤ 12 weeks ago
Aspirin	History of peptic ulceration (caution)		Event ≤ 12 weeks ago
2. Lipid lowering treatment			
Statins	Active liver disease Persistently abnormal liver function tests	Hepatitis or liver cirrhosis ≥3 times upper end of reference range	Any ≤ 12 weeks ago
3. Antidiabetic treatment			
Metformin	Renal impairment	Chronic kidney disease with eGFR <50ml/min	≤ 12 weeks ago
4. RAS inhibitors			
ACEI/ARB	Hypotension	SBP <90mmHg and symptoms	
	Renal artery stenosis	Bilateral or mono-lateral (if 1 functioning kidney)	Any
Any RAS inhibitor	Hyperkalaemia	Potassium level > 5.5 mmol/l	≤ 1 week ago
5. Rate limiting agents			
Beta blocker	Asthma	Severe asthma or COPD and on SABAs and steroids	≤ 12 weeks ago
RL CCB/ Beta blocker	Hypotension	SBP <90mmHg and symptoms	
RL CCB/ Beta blocker/ Digoxin	Bradyarrhythmia AV block	Heart rate <50/min 2^{nd} or 3^{rd} degree	≤ 2 weeks ago ≤ 12 weeks ago
RL CCB	Heart failure or LVSD	Unconditional	

5. Discussion

5.1 Summary of findings

Building on previous research, which has seen the development of medication assessment tools (MATs) for single cardiovascular diseases from clinical practice guidelines, this chapter has described the extension of the approach to the design of a MATcvc for frequently coinciding cardiovascular risk factors and long term conditions. Evidence based practice guidelines published by the European Society of Cardiology (ESC) served as the template for the development of the MATcvc. The design of the instrument was based on a generic framework for explicit quality assessment of medication use, which subcategorises the three concepts of pharmaceutical care need (PCN), drug therapy risk (DTRs) and drug therapy outcomes that were developed and defined in chapter 1 of this thesis. The instrument comprises of 52 explicit criteria, each defining a pharmaceutical care need and a corresponding check for a specific drug therapy risk. The criteria are organised within a hierarchical framework, within which each item is characterised by (1) the drug therapy outcome, (2) the drug therapy aim, (3) the drug therapy objective, (4) the drug therapy risk category and (5) the pharmaceutical care need it pertains to. For criteria that target unmet indications for recommended drug treatments, explicit clinical exemption rules were defined by a panel of four clinical pharmacists.

5.2 Quality assessment framework

5.2.1 Strengths and limitations of the proposed framework

In parallel to the cognitive process that pharmaceutical care practitioners employ in order to detect drug therapy risks, the operationalisation of explicit assessment criteria has been described in chapter 1 as comprising of a two stage process, namely (1) screening for specific pharmaceutical care needs (PCNs) and (2) checking for drug therapy risks (DTRs). Consequently, if a framework for explicit quality

assessment is to be designed that allows assessment criteria to be integrated into the workflow of practitioners (decision support), devising a categorisation system for PCNs and DTRs was therefore a rational starting point.

The primary aim of the categorisation system proposed here was to inform the design and structuring of explicit medication assessment criteria rather than to propose a system for the categorisation of drug therapy risks in practice. However, the demands placed on categorisation systems for both applications are strongly correlated, since the declared intention was to develop a framework to enable an integration of DTRs detected by explicit assessment criteria into the delivery of pharmaceutical care. Van Mil et al[83] have identified the following desirable attributes of categorisation systems for 'drug therapy problems': (1) the concept to be categorised and the categories within it should be clearly defined, (2) the categorisation system should have a published validation, (3) be usable in practice, (4) have an open hierarchical structure and (5) should have a focus on the drug use process and outcome and (6) separate the problem itself from the cause.

Stipulation (1)[83] can be assumed to be met by the categorisation system proposed here, since all three concepts (PCN, DTR and outcomes) used in the system have been explicitly defined, using terminology that is widely used in the medical literature (see chapter 1). It can also be assumed that the proposed system accommodates the majority of drug therapy risks ('drug therapy problems') encountered in practice, since existing categorisation systems have informed its design (stipulation 4). It has been demonstrated that the majority of previously published categories are either identical or can be understood as subcategories of the ones proposed here. In addition, Cipolle and Strand claim (based on empirical evidence) that the seven categories included in their categorisation system are exhaustive with respect to the scope of pharmaceutical care practice.[6] The proposed categorisation system can also be assumed to meet stipulation (5), since both processes and outcomes have been categorised. Moreover, the processes and outcomes were separated in the proposed categorisation system. According to van

Mil et al[83], the importance of separating causes from problems (stipulation 6) is to provide '*more information on the drug therapy problem*', but the context in which this is relevant is not clear.

A limitation of the categorisation proposed here is that it has neither been formally validated (stipulation 2) nor has its usability been demonstrated in practice (stipulation 3). Further research is therefore required in order to support the proposed framework, both as a means of integrating explicit quality assessment into the delivery of pharmaceutical care and as a categorisation system to be used by practitioners in order to document the care they provide.

5.2.2 Comparison to published categorisation systems for drug therapy problems

Categorisation of pharmaceutical care needs (PCNs)

A categorisation system for pharmaceutical care needs (PCNs) does not exist as such in the literature. However, in their publication 'Pharmaceutical Care Practice', Cipolle and Strand state that the description of deficiencies in medication use ('drug therapy problems') should consist of three components:

1. A description of the patient's condition
2. The drug therapy involved
3. The association between the drug therapy and the patient's condition[6]

Implicit in this description are the three concepts of drug therapy risk (2), the pharmaceutical care need it relates to (1) and the outcome that may be jeopardised (3). While the authors emphasize the importance of the three components in order to facilitate communication between practitioners (typically pharmacists and physicians) in clinical *practice*, it is clear that all three components are also required in order to estimate the added benefit of addressing respective drug therapy risks in quality *evaluations* (audit/quality control and research). However, studies of pharmaceutical care services rarely report the patients' conditions to which detected

drug therapy problems relate.[17, 18, 20, 84-86] Instead, many reports are limited to presenting proportions of different types of drug therapy problems, such as compliance or drug-drug interaction, or actions, such as patient counselling.[17, 18, 84] Reporting the proportions of different categories of 'drug therapy problems' may be valuable in describing the nature of a service but such descriptions on their own do not allow inferences to be made about its relevance to patient outcomes. It also does not allow scrutiny of the comprehensiveness of the screening process applied in such services. For example, if a relatively small proportion of patients with unmet indications for beneficial drug treatments is identified by a pharmaceutical care service, this may either be attributable to a relatively low incidence of under-prescribing or a failure of pharmaceutical care practitioners to detect such underutilisation (deficiencies in screening). Establishing pharmaceutical care needs (PCNs) as a separate entity in the documentation of pharmaceutical care activity has the potential to encourage their reporting and thus facilitate the interpretation of research findings.

E1/S1: Effectiveness/ Safety parameter uncontrolled

Cipolle and Strand's categorisation system has been designed for the purpose of documenting the outcome of the assessment stage of the pharmaceutical care process, where a therapeutic *decision* is agreed with the patient.[6] If an effectiveness parameter, such as blood cholesterol level, is uncontrolled, the practitioner will make a decision (in collaboration with the patient) as to whether the initiation (addition) of a (further) lipid lowering agent (E2), a therapeutic switch (E3) or an increase in dose (E4), is appropriate. Similarly, an uncontrolled safety parameter may lead to the decision to withdraw the causative agent (S2), to change it (S3) or to reduce its dose (S4). The therapeutic *decision* can therefore unequivocally be categorised within the categorisation system proposed by Cipolle and Strand. However, explicit quality assessment can only prompt practitioners to an existing drug therapy risk, but must leave it open for practitioners and patients to decide,

whether and which adjustment of the current drug regimen is the most appropriate in a particular clinical scenario. Hence, this category was necessary.

Monitoring ('M'): 'Effectiveness/safety parameters unknown'

Assessing the effectiveness or safety of medication use in both clinical practice and quality evaluation relies on regular monitoring. For example, in order to verify the effectiveness of lipid lowering treatment, regular blood lipid levels must be available. Similarly, the safety and effectiveness of warfarin treatment requires regular checks of the international normalised ratio (INR). When the intervals between two tests are too long, timely adjustment of drug therapy is not possible. When this or a similar situation is encountered by a practitioner, action is required and, by definition, such situations represent drug therapy risks (see chapter 1).

According to Cipolle and Strand, the existence of a 'drug therapy problem' depends on the presence of either (1) a direct cause and effect relationship between drug therapy and undesirable outcomes or (2) the need for changes in drug therapy.[6] It is therefore understandable that the lack of monitoring is not considered as a separate category in their DTP categorisation system, because the presence of a 'drug therapy problem' would depend on the outcome of the test. However, the definition of *drug therapy risks* as defined in chapter 1 is broader. It is inclusive of situations, where professional action is warranted in order to ensure that desirable outcomes are achieved, which includes monitoring. Hence, this category was added. Although many monitoring tests are performed to confirm the effectiveness *or* safety of drug therapy, the category was separated, since in these cases the monitoring test would serve two distinct purposes.

Exclusion of drug-drug interaction

A number of authors have included the category 'drug-drug interaction' consistent with the first DTP categorisation system developed by Hepler and Strand.[87] However, Cipolle and Strand [9] have abandoned this category in their 2004 system on the grounds that drug-drug interactions constitute scenarios, where either a

'dosage [is] too low' (E4) or a 'dosage [is] too high' (S4). It is therefore proposed that this category not be included in the DTR classification system.

Inclusion of cost and cost-effectiveness

In view of increasing health care expenditure, the cost-effectiveness of pharmacological treatments plays an increasingly important role for health care systems internationally. In many countries, manufacturers must now often demonstrate cost-effectiveness in order to ensure that licensed products are reimbursed in respective countries. While decisions about reimbursement are usually made at policy level, clinicians also have a role to play in ensuring that the likely benefits from drug therapy justify treatment costs. For example, it may not be cost-effective to instigate treatment for primary prevention of vascular events in an elderly patient with limited life-expectancy or to use branded products where less expensive generics are available.

It would, in principle, be possible to assess cost-effective prescribing using explicit assessment methods and the proposed categorisation system may therefore benefit from the addition of this category in the interest of completeness.

Categorisation of outcomes

As discussed in chapter 1, the categorisation system by Cipolle and Strand (and the majority of related categorisation systems) do not[5,6,78,79] or inconsistently[88,76,77] distinguish between outcomes and drug therapy risks. However, from a quality assessment point of view, a conceptual separation is desirable, because undesired outcomes that were preceded by detectable drug therapy risks (DTRs) represent failures of the medication use system. In contrast, drug therapy risks, indicate shortcomings in the process, but their detection does not necessarily imply system failures. Drug therapy risks may in some cases be inevitable and worth taking because the benefits of treatments outweigh the risks.

The Granada II and III systems[76,77] use a total of 9 outcome categories, of which four refer to drug safety and five refer to effectiveness. However, although the proposed

categories are distinct by their causes (that are unaddressed DTRs), the outcomes they categorise are identical to the concepts of ADEs and DTFs. For example, the category untreated health problem defined as *'The patient suffers from a health problem as a consequence of not receiving the medication that he needs'*, combines a DTF (health problem) with DTR category E2 (unmet indication). Since the proposed categorisation system classifies both drug therapy risks (DTRs) *and* outcomes, it is therefore proposed that further sub-categorisations of drug therapy outcomes are unnecessary.

5.3 Strengths and limitations of MATCVC

5.3.1 MATCVC development

Consensus versus guidelines

The key advantage of harvesting expert opinion in the development of quality assessment instruments is to enable quality evaluation in clinical areas that are not well supported by empirical evidence from randomised controlled trials.[89] Most authors of instruments to assess medication use in the elderly have therefore sought formal consensus validation (for example Beers[23], STOPP/START[90], ACOVE[28]). However, this caveat does not apply to most aspects of medication use in the management of chronic cardiovascular conditions. In addition, the guidelines developed by the European Society of Cardiology, which have served as the template for the development of the MATCVC, have been based on both systematic review of the evidence base *and* expert consensus.[91] Similarly, the clinical exemption rules were based on the British National Formulary, which is based on evidence evaluation and advised by expert clinicians in each therapeutic field. The lack of expert involvement in the development of the tool is unlikely to significantly compromise its validity.

Selection of guidelines

The obvious strength of selecting European guidelines for the development of MATCVC is that the resulting assessment criteria set is likely to have relevance to a wider European community than if the instrument had been based on national guidelines. Not all European countries regularly issue and update guidelines and it is rational to assume that in these countries, guidelines developed by the European Society of Cardiology would be a suitable point of reference. Furthermore, since medication use for chronic cardiovascular conditions is based on a solid evidence base that leaves little room for subjective interpretation, fundamental differences between guidelines are scarce.

Nevertheless, a number of criteria may require adaptation to local circumstances when used in a national or local context in order to maintain face validity among stakeholders, especially in areas where guidance is driven more by economic considerations than empirical evidence of efficacy. One example is the recommended target level for cholesterol control. The European guidelines recommend a total cholesterol target of 4.5 mmol/L[47], whereas SIGN recommends lower targets (5.0mmol/l).[57] Although the authors of the respective SIGN guideline acknowledge the fact that patients may benefit from further cholesterol reduction, it is stated that *'reducing this target to 4.5 or 4.0 mmol/l would have major resource implications for NHS Scotland'* and therefore argue that current targets are maintained pending further evidence of cost-effectiveness of a strategy that aims at lower targets. Adaptation of the respective criterion to local guidance would therefore be warranted before it is used to inform quality improvement initiatives.

Identification of 'suitable' recommendations

The selection of suitable recommendations was based on explicit exclusion criteria and the specific guideline recommendations that were not considered have been specified. This rigorous approach makes the criteria development process both transparent and reproducible, which may partially compensate for the potential

limitation that expert opinion has not been considered in the development of the MATcvc. Restricting the design of assessment criteria targeting 'unmet need (E2)' to those, where expert opinion or trial evidence is at least in favour of efficacy (guideline recommendations classified as IIa or higher) is likely to support the face and content validity of the instrument. The rationale for including a lower strength recommendation for the design of assessment criteria targeting medication safety was to account for the fact that the evidence base for detrimental drug effects is rarely based on randomised controlled trials, since exposing an intervention group to treatments that are suspected to do more harm than good is usually unethical. It may therefore be justifiable, that recommendations referring to medication safety were selected at a lower threshold than those referring to effectiveness.

5.3.2 Scope and content of MATcvc

MATcvc comprises an extensive list of medication assessment criteria for patients with one or more common cardiovascular conditions. It can, however, not claim to be comprehensive with respect to covering the range of drug therapy risks that patients with long term cardiovascular conditions may encounter. This is mainly attributable to the limitations of explicit approaches in general that are intended for application to routine clinical documentation. For example, inferring the presence or absence of heart failure symptoms in patients who had an indication for but were not treated with diuretics was considered not to be feasible by retrospective review. A further example are recommendations regarding primary prevention of cardiovascular events in patients without diabetes (apart from blood pressure control), since it was anticipated that accurate cardiovascular risk estimation would not be feasible from routine documentation.

Table 3.14 compares the scope of MATcvc to similar explicit medication assessment instruments. The table lists the numbers of criteria that relate to medication use in the management of patients with at least one of the conditions targeted by the MATcvc. Beers'[23] and McLeod's[24] criteria sets are not considered here since these

instruments exclusively target medication safety in the elderly and therefore have a different focus. The table shows that MATcvc covers a comparably broad range of drug therapy risk categories among the reviewed instruments, and includes the highest number of criteria within the 'unmet need (E2)' and 'suboptimal dose' categories. The comparison to similar instruments, however, also shows that the scope of the MATcvc is limited with respect to medication use safety issues. Although a number of items included in previously published instruments require prospective application, such as *'use of aspirin to treat dizziness not clearly attributable to cerebrovascular disease'* in the STOPP criteria set[26], others would principally allow retrospective assessment. Examples of high risk drug choice (S3) criteria that are not considered in the MATcvc are the '*use of aspirin in patients with a history of peptic ulcer without gastro-protection'*, *'digoxin doses in excess of 125µg/ day in the elderly, 'combined use of beta blockers and rate limiting calcium channel blockers'* and use of the 'triple whammy'[92] combination *'NSAIDs, diuretics and RAS inhibitors'*.[26, 27]

The relative under-representation of medication safety issues in the MATcvc reflects the fact that the templates for the design of the instrument were evidence based guidelines. Such guidelines typically have a strong focus on the effectiveness of drug therapy, since medication safety issues are rarely supported by a strong evidence base. High risk medication use that does neither involve cardiovascular medication nor is expected to cause adverse *cardiovascular* effects is also usually not addressed by guidelines addressing the management of these conditions.

Table 3.14 Comparison of target patients and scope of MATcvc to similar explicit medication assessment instruments targeting patients with risk factors for or manifest chronic cardiovascular conditions

Tool		Scope of DTRs targeted												
		Compliance	*E1: E-parameters*	*E2: Underuse*	*E3: Choice*	*E4: Dose*	*S1: S-parameters*	*S2:Unnecessary*	*S3: Choice*[5]	*S4: Dose*	*Cost*	*Monitoring*	*DTF*	*ADE*
STOPP/ START[93]	Elderly	-	-	8	-	-	-	-	15	2	-	-	-	-
BASGER[27]	Elderly	-	1	9	-	1	-	-	15	1	-	-	-	-
ACOVE[28]	Elderly	-	-	18	1	-	-	-	16	-	-	14	-	-
HUANG[34]	DM, CHD, CHF, AF	-	-	13	-	-	-	-	1	-	-	-	-	-
MART[30]	DM	-	-	7	4	-	-	-	-	-	-	3	-	-
MAT-DM[31]	DM	-	3	15	-	1	-	-	-	2	-	-	-	-
MAT-CHD[32]	CHD	-	8	12	-	-	-	-	-	2	-	-	-	-
MAT-HF[36]	CHF	-	-	12	-	2	-	-	2	1	-	-	-	-
MATcvc	DM, HTN, CVD, CHF, AF	-	6	24	4	4	1	-	12	-	-	-	-	-
QOF[3]	Mixed	-	10	11	-	-	-	-	-	-	-	10	-	-
PDRM[35]	Mixed	-	-	2	-	-	-	-	7	-	-	5	2	12

The number of items may exceed the number of distinct items in each instrument, as items pertaining to multiple domains are listed more than once.

5.3.3 Explicit rules for contextualising MATcvc assessment

The clinical exemption rules that were developed for the MATcvc are intended to allow the reliable extraction of context factors in cases where explanations for non-adherence are not explicitly stated in case notes. Panellists were asked to define situations where the balance of benefit and risk is likely to speak against the implementation of usually recommended treatments. The involvement of experts in

[5] The distinction between unnecessary and unsafe can be ambiguous. Drugs to be avoided, for example can be both unnecessary and unsafe.

this part of the MATCVC development process was necessary, since (1) clinical decision making in exceptional clinical circumstances is not well informed by empirical evidence and (2) guidance (from the BNF) was not sufficiently specific to be translated into rules for use in retrospective audit.

A number of explicit quality assessment instruments have been designed to take into account factors that may justify deviation from practice standards (QOF[3], ACOVE[28], Huang[34], MATs[31-33]). A decisive distinction between the different approaches is that some instruments (ACOVE[28], previous MATs[31-33]) allow flexibility on the part of assessors as to how such context factors are operationalised, whereas others provide specific definitions of contraindications that assessors need to consider and record in each case (Huang[34]). In the former cases, the approach of accounting for context factors is consistent with implicit approaches and therefore shares the same advantages in terms of *validity* but also the same disadvantages with respect to *reliability* and *feasibility*. Consistent with Huang's approach and in contrast to previously developed MATs, an emphasis was placed for the MATCVC on the latter two attributes. The resulting list of clinical exemption rules therefore has the potential to contribute to the validity of routine quality assessment whilst maintaining the advantages of explicit instruments with respect to feasibility and reliability.

5.3.4 Anticipated utility of MATCVC in a quality improvement context

Decision support

Little is known about the features that promote or impede the utility of explicit decision support instruments in clinical practice and the desirable features are likely to depend on the context of their use. If such instruments are to be applied manually, that is non-automated, the ease of their deployment to routine documentation will, however, be a pre-requisite. The time required to apply the START/STOPP set has been reported to be 90 (± 35) seconds per patient, which appears to support its routine use as a decision support tool. Since START and

STOPP consist of 22 and 65 criteria respectively, approximately 1 second per criterion seems ambitious.[94] However, the categorisation of criteria by medical condition (START criteria) and drug indication (STOPP criteria) may accelerate the assessment process, because it facilitates the identification of criteria that are irrelevant to an individual patient (for example those relating to conditions the patient does not have or medications the patient is not prescribed).

The hierarchical structure of the MATCVC may have limitations in this respect because its organisation by drug therapy objective, as the prominent level of criteria organisation, relies on users being able to identify which objective is relevant to each patient. However, in the case of the MATCVC, the majority of objectives are relevant to all patients with established cardiovascular conditions. In view of the fact that these conditions also often coincide in one patient, the organisation by drug therapy objective may save the user duplication of effort. For example, if a patient had heart failure, coronary heart disease and atrial fibrillation, organisation by underlying condition would imply that medication use for heart rate control would have to be considered for each condition separately.

Organisation by drug therapy objective may have the additional advantage of exposing overlaps and conflicts between medication use for different conditions. For example, when considering the choice of thrombo-embolic prophylaxis in a patient with recent myocardial infarction (dual antiplatelet therapy is recommended), who also is at high risk of stroke from AF (warfarin is recommended), the decision as to which treatment choice is appropriate for this particular patient needs to be made in light of all indications for antithrombotic therapy. If coronary heart disease and atrial fibrillation were addressed in different sections of the same instrument, the risk is that such overlaps would be missed. The organisation by drug therapy objective may therefore be of particular relevance for patients with co-morbidities, which require similar and potentially conflicting management.

The structure of the MATCVC may therefore require a higher level of pharmaco-therapeutic knowledge in order to identify relevant criteria than comparable

instruments but it may facilitate a more holistic approach to patient care. It is possible that these features make the MATcvc approach an attractive framework for the design of computerised clinical decision support systems, where the identification of relevant criteria based on patients' medical diagnoses or prescribed drugs (PCN screening) is automated and the ways in which any detected drug therapy risks (DTRs) are presented to the user becomes more decisive.

Audit and quality control

A general limitation of explicit quality assessment instruments is that they are restricted in scope *(content validity)*, since it is usually not possible to design and implement specific criteria for all clinical situations that may put patients at risk of undesirable outcomes and increasing the number of criteria may be constrained by the communicability of the resulting criteria set, especially in audit and quality control applications. One approach to enhance communicability of an extended set of assessment criteria is the use of composite quality indexes, which summarise similar aspects of care and therefore contain their number.[95] A pre-requisite to this approach is, however, that aggregate measures can be defined, which are sufficiently meaningful to inform the selection of targets for quality improvement initiatives. Practitioners seeking to reflect on and improve the care they deliver may place a high emphasis on the 'actionability' of process measures, implying that indexes need to point to specific tasks ('actions') to be targeted for improvement. In contrast, managers primarily require quality information in order to inform improvements in the infrastructure and organisation of care. In order to be useful to managers, quality indexes therefore need to point to remediable shortcomings in care patterns, which allow a process-structure link to be established. Users, whose responsibility is the oversight of health care systems, such as health authorities, will place a high emphasis on the process – outcome link of quality indexes.

The hierarchical grouping of the criteria within the MATcvc set has key advantages in this respect: Each criterion is characterised with respect to (1) the outcome it

targets (effectiveness versus safety), (2) whether it is relevant to improving prognosis or symptom control, (3) which drug therapy objective it refers to, (4) which drug therapy risk category it targets and (5) which underlying condition it pertains to. This characterisation enables to define quality indexes at each level of the hierarchy and thus allows feedback of quality information to be customised to the needs and preferences of different users.

Patient targeting

While it may be desirable that all patients who are identified to have unaddressed drug therapy risks are followed up eventually, this may not always be feasible. This implies that the utility of medication assessment tools in patient targeting applications relies on the capability of such instruments to allow meaningful patient prioritisation. An obvious approach to identifying patients, who would benefit most from a medication review would be to estimate the clinical relevance of drug therapy risks detected by individual assessment criteria, where patients affected by these measures would be targeted first. However, this strategy is complicated by the fact that the effect sizes of different drug treatments observed in clinical trials cannot always be extrapolated to the patients seen in clinical practice. In addition, head to head comparisons of different beneficial strategies are rare in the clinical trial literature, which implies that assigning *relative* clinical importance to different treatments is constrained by the fact that the patient populations included in different trials are variable with respect to baseline risk. Furthermore, clinical relevance depends on clinical circumstances and patient preferences, which cannot always be accounted for by explicit quality assessment methods. Alternative approaches are therefore required and will be explored in chapter 4.

6. Chapter summary

The aim of this chapter was the development and application of a generic framework to facilitate the design of an explicit medication assessment instrument for *multiple* conditions, which has the potential to function within the model of continuous quality improvement proposed in chapter 2 of this thesis.

The core of the framework is a categorisation system for drug therapy risks, where each DTR category (achievement of therapeutic targets, indication for drug therapy, drug selection and drug dose, cost) is linked to a drug therapy outcome category (effectiveness, safety, cost). The outcome categories provided a structure for the initial grouping of guideline recommendations and the DTR categories provided a template for the subsequent design and refinement of explicit assessment criteria. Within each outcome category, the criteria were further clustered by the dominant aim (prognosis improvement or symptom control) drug therapy objective and pharmaceutical care need (either a specific clinical condition for effectiveness criteria or a drug or drug group for safety assessment criteria). It is anticipated that the structure of the resulting MATcvc is generic and open to the addition of further assessment criteria relating to other therapeutic areas.

The MATcvc covers almost 80% of recommendations relating to the pharmacological management of patients with chronic cardiovascular conditions from six evidence based clinical practice guidelines by the European society of cardiology. Nevertheless, a number of guideline recommendations were not translated into assessment criteria since it was anticipated that their application to data routinely documented in medical notes would not be feasible. In addition, comparison to previously developed instruments has highlighted a relative under-representation of medication safety assessment criteria, attributable to the fact that the guidelines on which the development of the MATcvc was based, primarily focussed on medication effectiveness.

A number of key advantages of the MATcvc in comparison to previously developed medication assessment instruments have been identified in relation to its routine

application within a context of continuous quality improvement. First, in contrast to the majority of previously developed instruments that have attempted to take into account context factors that may hinder the adherence of medication use to standards of best practice, explicit clinical exemption rules were validated that have the potential to increase the validity of MATcvc assessment without unduly compromising its reliability and feasibility. Second, the multiple ways in which MATcvc criteria are characterised may allow the design of composite criteria which have the potential to inform the selection of targets for quality improvement initiatives (in audit/quality control applications) and to facilitate the integration of drug therapy risks detected by MATcvc into the workflow of pharmaceutical care practitioners (in decision support applications). The application of the MATcvc within the model of continuous quality improvement proposed in chapter 2 of this thesis will be explored in the following chapter 4.

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Appendix 2: From Guideline recommendations to MATCVC

Effectiveness

Aim - Improving prognosis

Drug therapy objective 1: Thrombo-embolic prophylaxis

Included recommendations

		Patients with CVD
A1 [47]	I-A	Aspirin remains the cornerstone of pharmacological prevention of arterial thrombosis. Aspirin 75 mg daily is recommended in all patients without specific contraindications (i.e. active GI bleeding, aspirin allergy, or previous aspirin intolerance)
A2 [47]	IIa-B	Clopidogrel is an alternative antiplatelet agent in patients with stable angina who cannot take aspirin (e.g. aspirin allergic). Clopidogrel is more expensive than aspirin, but may be considered in aspirin-intolerant/allergic patients with significant risks of arterial thrombosis.
		Patients with CHD and with a history of ACS
B1[50]	I-A	In patients with STEMI aspirin should be given forever.
B2[50]	I-A	All patients with STEMI should be treated with aspirin and a thienopyridine.
B3[50]	☑	In patients with STEMI the optimal duration of clopidogrel on top of aspirin treatment after STEMI has not been determined. Treatment duration of 12 months is recommended whether or not a stent has been placed.
B4[50]	☑	Oral anticoagulants may also be considered in patients with STEMI who do not tolerate aspirin or clopidogrel
B5[50]	☑	The combination of aspirin and oral anticoagulation at INR 2–3 [...] seems to be a reasonable treatment in STEMI survivors who have a high risk of thrombo-embolic events.
B6[50]	☑	In some patients with STEMI, there is an indication for dual antiplatelet therapy and oral anticoagulation (e.g. stent placement and AF). Oral anticoagulants plus a short course of clopidogrel might be an alternative in patients with a higher risk of bleeding.
B7[46]	I-A	Aspirin is recommended for all patients presenting with NSTE-ACS without contraindication
B8[46]	I-B	For all patients with NSTE-ACS and with contraindication to aspirin, clopidogrel should be given instead
B9[46]	I-A	For all patients with NSTE-ACS, clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding
B10[46]	I-A	The aspirin maintenance dose is 75–100 mg
		Patients with AF
C1[68]	I-A	Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications.
C2[43]	I-A	Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, unless contraindicated.
C3[43]	IIa-A	In patients with HF and AF who do not have any additional moderate risk factors (see above), therapy with either aspirin (81–325 mg daily) or a vitamin K antagonist is reasonable for primary prevention of thromboembolism.
C4[68]	IIa-A	For primary prevention of thromboembolism in patients with non-valvular AF who have just 1 of the following validated risk factors, antithrombotic therapy

		with either aspirin or a vitamin K antagonist is reasonable,: age greater than or equal to 75 y (especially in female patients), hypertension, HF, impaired LV function, or diabetes mellitus.
C5[68]	IIa-B	For patients with non-valvular AF who have 1 or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonists reasonable for prevention of thromboembolism: age 65 to 74 y, female gender, or CAD
C6[68]	I-A	Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation.
C7[43]	I-A	Anticoagulation is recommended for patients with 1 or more moderate risk factors: age ≥75 years, hypertension, HF, impaired LV function (LVEF <35%), DM
C8[68]	I-A	For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist.
C9[68]	I-A	Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor: age ≥75 years, hypertension, HF, impaired LV function (LVEF <35%), and DM
C10[43]	I-A	Oral anticoagulant therapy with a vitamin K antagonist should aim for a target international normalized ratio (INR) of 2.0–3.0, unless contraindicated
C11[68]	I-B	The dose should be adjusted to achieve the target intensity INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, TIA, or systemic embolism) and rheumatic mitral stenosis. For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5.
		Patients with heart failure
D1[43]	I-C	Anticoagulation is also recommended in patients with intra-cardiac thrombus detected by imaging or evidence of systemic embolism

Assessment criteria (draft)

The numbers in the left column denote the recommendations on which each criterion was based

		Patients with CVD
A 1,2 B 1,2	I-A	1 Patient with CVD *is not prescribed aspirin or clopidogrel*
		Patient with CHD with prior ACS
B3-10	I-A	2 Patient with a history of ACS (with or without ST-elevation) in the last 12 months *is not prescribed a combination of aspirin/clopidogrel or an antiplatelet plus oral anticoagulant*
		Patients with AF
C1-9	I-A	3 Patient with AF and $CHADS_2$ score= 0 and ≥ 1 of: valve disease, aged>60 (but <75), female gender, CHD *is not prescribed antithrombotic prophylaxis*
C1-9	I-A	4 Patient with AF and $CHADS_2$ score= 1 *is not prescribed an antiplatelet*
C1-9	I-A	5 Patient with AF and $CHADS_2$ score =2 *is not prescribed an oral anticoagulant*
C1-9	I-A	6 Patient with AF and $CHADS_2$ score ≥3 *is not prescribed an oral anticoagulant*
C10,11	I-A	7 Patient with AF prescribed an oral anticoagulant *has achieved an INR of 2 to 3*
		Patients with heart failure
D1	I-C	8 Patient with heart failure or LVSD and intra-cardiac thrombus *is not prescribed an oral anticoagulant*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E1: INR below target

7	I-A	1 Patient with AF or CHF and on an oral anticoagulant *has NOT achieved the target INR*

E2: Unmet need for thrombo-embolic prophylaxis

1,2	I-A	2 Patient with CHD *is not prescribed thrombo-embolic prophylaxis*
	n.a.	3 Patient with PVD *is not prescribed an antiplatelet or oral anticoagulant*
	n.a.	4 Patient with prior stroke or TIA *is not prescribed an antiplatelet or oral anticoagulant*
3	I-A	5 Patient with AF and $CHADS_2$ score = 0 *is NOT prescribed thrombo-embolic prophylaxis*
4	I-A	6 Patient with AF and $CHADS_2$ score = 1 *is NOT prescribed thrombo-embolic prophylaxis*
5	I-A	7 Patient with AF and $CHADS_2$ score = 2 *is NOT prescribed thrombo-embolic prophylaxis*
6	I-A	8 Patient with AF and $CHADS_2$ score ≥ 3 *is NOT prescribed thrombo-embolic prophylaxis*
8	I-C	9 Patient with CHF and prior TE or intracardial thrombus *is NOT prescribed thrombo-embolic prophylaxis*

E3: Suboptimal choice of thrombo-embolic prophylaxis

2	I-A	10 Patient with ACS ≤ 12 months ago and is on an antithrombotic *is not prescribed dual antiplatelet treatment or an oral anticoagulant*
5	I-A	11 Patient with AF and $CHADS_2$=2 who is on an antithromboitic agent *is NOT prescribed an oral anticoagulant*
6	I-A	12 Patient with AF and $CHADS_2$≥3 who is on an antithrombotic *is NOT prescribed an oral anticoagulant*
8	I-C	13 Patient with CHF and prior TE or intracardial thrombus who is on an antithrombotic *is NOT prescribed an oral anticoagulant*

Drug therapy objective 2: Lipid control

Included recommendations

		All patients with vascular disease or diabetes
E1 [47]	I-A	Statin therapy is recommended for all patients with vascular disease (CHD, history of stroke, PVD) or diabetes
E2 [47]	☑	Therapy should aim at statin dosages documented to reduce morbidity/mortality in clinical trials: simvastatin 40 mg, pravastatin 40 mg, and atorvastatin 10 mg.
E3 [47]	☑	Aim for current European prevention guidelines targets: <4.5 mmol/L (175 mg/dL) for total cholesterol and <2.5 mmol/L (96 mg/dL) for LDL cholesterol
		CHD with prior ACS
E4[46]	I-B	Statins are recommended for all patients with Non-STE ACS irrespective of cholesterol levels
E5[50]	I-A	Statins in all STEMI patients irrespective of cholesterol levels, and continued forever.
E6[46]	IIa-B	Intensive lipid-lowering therapy with target LDLc levels <70 mg/dL (<1.81 mmol/L) is advisable
E7[46]	I-B	The aim is to achieve LDLc levels <100 mg/dL (<2.6 mmol/L)
E8 [50]	I-A	An LDL cholesterol of <100 mg/dL (2.5 mmol/L) should be aimed for
E9[50]	IIa-B	Further reduction of LDL cholesterol to achieve 80 mg/dL (2.0 mmol/L) should be considered in high-risk patients

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived

		Patients with or without prior ACS
E1,4,5	I-A	1 Patient with CVD *is not prescribed a statin*
		Patients without prior ACS
E2	☑	2 Patient with stable angina pectoris prescribed a statin *is not prescribed one of the following statin doses: simvastatin 40mg, pravastatin 40mg, atorvastatin 10mg*
E3	☑	3 Patient with stable angina pectoris who is prescribed a statin *has not achieved levels of <4.5 mmol/L (175 mg/dL) for total cholesterol and <2.5 mmol/L (96 mg/dL) for LDL cholesterol*
		Patients with prior ACS
E7,8	IA	4 Patient with previous ACS (with or without persistent ST elevation) *has not achieved an LDL cholesterol of <100 mg/dL (2.5 mmol/L)*
E6,9	IIa-B	5 Patient with previous ACS (with or without persistent ST elevation) *has not achieved an LDL cholesterol of <70 mg/dL (2.0 mmol/L)*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E1: Achievement of TC/LDL target		
3,4	☑	1 Patient with CVD but WITHOUT a history of vascular events, who is prescribed a statin *has not achieved a TC < 175 mg/dl*
5	IA	2 Patient WITH a history of vascular events, who is prescribed a statin *has not achieved LDL < 100 mg/dl*
E2: Use of statin		
1	IA	3 Patient with CHD *is not prescribed a statin (3)*
	n.a.	4 Patient with PAD *is not prescribed a statin (3)*
	n.a	5 Patient with stroke/TIA *is not prescribed a statin*
	n.a	6 Patient with DM *is not prescribed a statin(3)*

E3: Achievement of target dose statins		
2	☑	7 Patient with CVD, who is prescribed a statin is not prescribed a statin dose of simvastatin 40 mg, pravastatin 40 mg or atorvastatin 10 mg

Drug therapy objective 3: Control of hyperglycaemia

Included recommendations

			CHD patients with prior ACS
F1	20 [50]	I-B	Lifestyle changes and pharmacotherapy to achieve HbA1c < 6.5%
			CHD patients without prior ACS
F2	5[49]	☑	In patients with established diabetes, the aim is to achieve HbA1c levels <6.5%
F3	5[46]	☑	In patients with established diabetes, the aim is to achieve HbA1c levels <6.5%.
			Patients with CHF
F4	HF31[43]	IIa-B	Metformin should be considered as a first-line agent in overweight patients with type II DM without significant renal dysfunction (GFR .30 mL/min).
F5	30[43]	IIa-A	Elevated blood glucose should be treated with tight glycaemic control.
F6	33[43]	IIb-C	Early initiation of insulin may be considered if glucose target cannot be achieved.

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived.

		All patients with DM
F1	IIa-B	1 Patient with DM, who is treated with an oral antidiabetic *is NOT prescribed metformin*
F2-6	I-B	2 Patient with DM *has not achieved an HbA1c of < 6.5%*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E1: HbA1c target not achieved

2	I-B	1 Patient with DM, who is prescribed antihyperglycaemic therapy *has not achieved HbA1c < 6.5%*

E2: Suboptimal choice of first line oral antidiabetic

1	IIa-B	2 Patient with DM, and is prescribed an oral antihyperglycaemic agent *is not prescribed metformin*

Drug therapy objective 4: Blood pressure control

Included recommendations

			Patients with HTN
G1	28[43], 2[46]	☑	The goal is to achieve blood pressure <140/90 mmHg in non-diabetic patients without chronic renal dysfunction.
G2	29[43]	I-A	Target BP: (i) should be reduced to at least below 140/90 mmHg (systolic/diastolic), and to lower values if tolerated (ii) should be 130/80 mmHg in diabetics, those with evidence of target organ damage (stroke, MI, renal dysfunction, proteinuria).
G3	4[49]	☑	Patients with concomitant diabetes and/or renal disease should be treated with a blood pressure goal of <130/80 mm Hg.
G4	3[49]	☑	The Task Force report on CVD prevention suggests considering a lower threshold for institution of pharmacological therapy for hypertension (130/85mmHg) for patients with established CHD (which would include patients with angina and non-invasive or invasive confirmation of coronary disease)
G5	19 [50]	I-A	Lifestyle changes and pharmacotherapy to achieve BP <130/80 mmHg
G6	3[46]	☑	The goal is to achieve blood pressure <130/80 mmHg in patients with diabetes
G7	4[46]	☑	The goal is to achieve blood pressure <130/80 mmHg in patients with chronic renal dysfunction.

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived

		All patients with HTN
G1,2	I-A	1 Patient with documented hypertension, who is treated with blood pressure lowering agents *has achieved a blood pressure of SBP<140 and DBP< 85 mmHg*
G3-7	I-A	2 Patient with documented hypertension, who is treated with blood pressure lowering agents and has target organ damage (STEMI, stroke, renal dysfunction) has not achieved an SBP of <130 and DBP of <80mmHg

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E1: BP target not achieved

1	I-A	1 Patient with HTN and complications (CVD, DM or CKD) who is treated for hypertension *has not achieved SBP of ≤ 130mmHg AND DBP ≤80mmHg*
2	I-A	2 Patient with uncomplicated HTN (no CVD, DM, or CKD), who is treated for hypertension *has ot achieved an SBP of ≤ 140 AND DBP ≤ 85mmHg*

Drug therapy objective 5: RAS inhibition

Included recommendations

		CHD or diabetes in patients without prior ACS
H1-3[49]	I-A	ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as heart failure, hypertension, CKD or diabetes is recommended
H4[49]	I-B/ ☑	ACE-inhibitor therapy in all patients with angina and proven coronary disease to improve prognosis ARB treatment may be appropriate therapy for the treatment of heart failure, hypertension, or diabetic renal dysfunction in patients with angina when ACE-inhibition is indicated but not tolerated, but there is no indication for ARB therapy in patients with preserved ventricular function without diabetes as a secondary preventive agent to improve prognosis
H5[47]	n.a.	ACE-inhibitor therapy in patients with diabetes to lower blood pressure, reduce cardiovascular events and nephropathy
		CHD patients with prior ACS
J1[46]	I-A	ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction or diabetes is recommended to improve prognosis
J2[46]	IIa-B	ACE inhibitors should be considered for all patients to prevent recurrence of ischaemic events
J3[50]	☑	Use of ACE-inhibitors should be considered in all patients with atherosclerosis, but, given the relatively modest effect, their long term use cannot be considered to be mandatory in post-STEMI patients who are normotensive, without heart failure or compromised systolic LV function.
J4[46]	I-B	ARBs should be considered in patients who are intolerant to ACE inhibitors and/or who have heart failure or MI with LVEF <40%
J5[7]	☑	ARBs should be considered in patients without a history of heart failure or LVEF <40% who are intolerant to ACE inhibitors
J6	IIa	ACE inhibitor agents of proven efficacy (ramipril and perindopril) are recommended
J7[46]	IIa-C	Evidence based target doses of ramipril or perindopril *should be aimed for*
		Patients with CHF
K1[43]	I-A	Unless contraindicated or not tolerated, an ACEI should be used in all patients with symptomatic HF and a LVEF ≤40%. In hospitalized patients, treatment with an ACEI should be initiated before discharge.
K2[43]	I-A	Agents with documented effects on morbidity and mortality such as ACEIs, b-blockers, ARBs, and diuretics confer benefit at least comparable with that demonstrated in non-diabetic HF patients.
K3 [50]	I-A	At discharge and in the absence of contra-indications, patients with significant LV dysfunction, an ACE-inhibitor (or an ARB) should be added and continued forever.
K4[46]	I-A	ACE inhibitors are indicated long-term in all patients with LVEF <40%
K5[49]	I-A	ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes is recommended to improve prognosis
K6[50]	I-B	ARB (valsartan) in all patients with heart failure or LV dysfunction without contraindications who do not tolerate ACE-inhibitors
K7[43]	IIa-B	An ARB is recommended as an alternative in patients intolerant of an ACEI. In hospitalized patients, treatment with an ARB should be initiated before discharge.
K8[43]	IIa-B	In symptomatic patients with an LVEF <40%, the combination of H-ISDN may be used as an alternative if there is intolerance to both an ACEI and an ARB.

		Treatment with H-ISDN in these patients may reduce the risk of death, reduces hospital admission for worsening HF, improves ventricular function
K9[43]	I-B	Unless contraindicated or not tolerated, the addition of a low-dose of an aldosterone antagonist should be considered in all patients with an LVEF ≤35% and severe symptomatic HF, i.e. currently NYHA III or IV.
K10[46]	I-B	Aldosterone blockade should be considered in patients after MI who are already treated with ACE inhibitors and beta-blockers and who have an LVEF <40% and either diabetes or heart failure, without significant renal dysfunction or hyperkalaemia
K11[50]	I-B	Aldosterone antagonists in patients with heart failure or LV dysfunction if EF ≤40% and signs of heart failure or diabetes if creatinine is <2.5 mg/dL in men and <2.0 mg/dL in women and potassium is <5.0 mmol/L
K12[43]	I-A	Unless contraindicated or not tolerated, an ARB is recommended in patients with HF and an LVEF <40% who remain symptomatic despite optimal treatment with an ACEI and b-blocker, unless also taking an aldosterone antagonist.
K13[43]	☑	Consider ACEI dose titration to evidence-based target dose: Captopril 6.25 t.i.d. 50–100 t.i.d.; Enalapril 2.5 b.i.d. 10–20 b.i.d., Lisinopril 2.5–5.0 o.d. 20–35 o.d., Ramipril 2.5 o.d. 5 b.i.d.Trandolapril 0.5 o.d. 4 o.d.
K14[43]	☑	Consider ARB dose titration to evidence-based target dose: Candesartan 4 or 8 o.d. 32 o.d. ; Valsartan 40 b.i.d. 160 b.i.d.
K15[43]	☑	Consider dose up-titration of the aldosterone antagonise after 4–8 weeks and aim for target dose—spironolactone 50 mg o.d. or eplerenone 50 mg o.d.

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived.

A. Patient with CHD or DM without prior ACS

H1-3,4	I-A	1 Patient with coronary heart disease and without a history of ACS or heart failure but coincident hypertension, CKD or diabetes *is not prescribed an ACEI or ARB*
H5[49]	n.a.	2 Patient with diabetes *is not prescribed an ACEI or ARB*

B. Patient with CHD with prior ACS

J1[46], J4[46]	I-A	3 Patient with prior ACS without heart failure but with coincident hypertension, CKD or diabetes *is not prescribed an ACE inhibitor or ARB*
J2,3[46],5[4][6]	IIa-B	4 Patient with prior ACS without heart failure, ACS, hypertension, CKD or diabetes *is not prescribed an ACE inhibitor or ARB*
J6,7[46]	IIa-C	5 Patient with prior ACS and prescribed ramipril or perindopril *has achieved the recommended target dose*

C. Patients with heart failure

K1-8[6]	I-A	6 Patient with heart failure or LVSD *is not prescribed an ACE inhibitor, ARB or H-ISDN*
K9-12[6]	I-A	7 Patient with heart failure or LVSD , who is in NYHA III to IV despite treatment with a diuretic, an ACEI or ARB and a beta blocker *is not prescribed an aldosterone antagonist or a combination of an ACEI and ARB*
K13,14[6]	☑	8 Patient with heart failure or LVSD prescribed an ACE inhibitor or ARB *has not achieved the recommended target dose* Captopril 6.25 t.i.d. 50–100 t.i.d., Enalapril 2.5 b.i.d. 10–20 b.i.d. Lisinopril 2.5–5.0 o.d. 20–35 o.d., Ramipril 2.5 o.d. 5 b.i.d., Trandolapril 0.5 o.d. 4 o.d.
K15[6]	☑	9 Patient with heart failure or LVSD who is prescribed an aldosterone antagonist *has not achieved the target dose of aldosterone antagonist*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E2: Unmet need for ACEI or ARB

1-5	I-A	1 Patient with CHD *is not prescribed an ACEI or ARB*
6-9	I-A	2 Patient with CHF *is not prescribed an ACEI or ARB or H-ISDN*
	n.a.	3 Patient with DM *is not prescribed an ACEI or ARB*

E2: Unmet need for aldosterone antagonist or ACEI/ARB combination in advanced CHF

13-14	I-A	4 Patient with CHF and a history of MI or in NYHA III-IV prescribed optimal doses of a BB and ACEI/ARB and is prescribed a diuretic *is not prescribed an aldosterone antagonist or an ACEI plus ARB*

E4: Suboptimal dose of ACEI/ARB

15-16	☑	5 Patient with CHF, who is prescribed an ACEI or ARB *is not prescribed target dose or a documented max. tolerable dose*

Drug therapy objective 6: Rate limiting therapy

Included recommendations

			CHD patients with prior ACS
L1	10,11[50]	I-A	At discharge and in the absence of contra-indications, all patients should be treated with a beta-blocker continued forever. Evidence from all available studies suggests that b-blockers should be used indefinitely in all patients who recovered from a STEMI and do not have a contraindication.
L2	16 [46]	☑	In other patients (without reduced LV function), beta-blockers may be useful, but evidence of their long-term benefit is not established. Meta-analysis and registry data have shown that long-term treatment with beta-blockers in patients suffering from NSTE-ACS may lead to a significant risk reduction for death.
L3	12 [50]	☑	Trials with verapamil and diltiazem have suggested that they may prevent reinfarction and death in patients with prior STEMI but without heart failure. The use of verapamil and diltiazem may be appropriate when b-blockers are contraindicated, especially in obstructive airways disease. Caution must be exercised in the presence of impaired LV function. Trials with dihydropyridines have failed to show a benefit in terms of improved prognosis; they should, therefore, only be prescribed for clear clinical indications such as hypertension or angina.
			CHD patients without prior ACS
L4	21[49]	☑	Beta blockers should be used as first line agents to prevent angina
			Patients with CHF
M1	20[49]	IIa-A	Oral beta-blocker therapy is recommended in patients post-MI or with heart failure to improve prognosis
M2	15[46]	I-A	Beta-blocker therapy should be initiated in all patients and maintained indefinitely in the case of reduced LV function, with or without symptoms of heart failure, unless formal contraindications exist. Beta-blockers should be given to all patients with reduced LV function
M3	35[43]	☑	The majority of patients with HF and COPD can safely tolerate b-blocker therapy.
M4	7[43]	I-A	Unless contraindicated or not tolerated, a b-blocker should be used in all patients with symptomatic HF and an LVEF ≤40%.
M5	8[43]	☑	Visits every 2–4 weeks to up-titrate the dose of b-blocker (slower dose up-titration may be needed in some patients).dose. Bisoprolol 1.25 o.d. 10 o.d.; Carvedilol 3.125 b.i.d. 25–50 b.i.d. Metoprolol succinate 12.5/25 o.d. 200 o.d.; Nebivolol 1.25 o.d. 10 o.d.

Included recommendations (continued)

		Patients with AF
N1[68]	I-B	Measurement of the heart rate at rest and control of the heart rate using pharmacological agents (either a beta blocker or non-dihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent AF.
N2[68]	IIb-C	When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF using a beta blocker, non-dihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate.
N3[68]	III-B	Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.
N4[68]	IIa-B	A combination of digoxin and either a beta blocker or non-dihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise in patients with AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia.
N5	I-B	A b-blocker or digoxin is recommended to control the heart rate at rest in patients with HF and LV dysfunction.
N6	IIa-C	In patients with HF and preserved LVEF, a non-dihydropyridine calcium channel antagonist (alone or in combination with digoxin) should be considered to control the heart rate at rest and during exercise.
N7	☑	A combination of digoxin and a b-blocker may be considered to control the heart rate at rest and during exercise.
N8	I-C	Digoxin is effective following oral administration to control the heart rate at rest in patients with AF and is indicated for patients with HF, LV dysfunction or for sedentary individuals.

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived.

A. Patient with CHD with prior ACS

L1,2,3	I-A	1 Patient with a history of ACS *is not prescribed a beta blocker*
L2	☑	2 Patient with CHD and without a history of ACS *is not prescribed a beta blocker or rate limiting CCB*

B. Patients with AF

N1,2,5-7	I-B	3 Patient with permanent AF *is not prescribed a rate limiting agent (beta blocker, digoxin, diltiazem, verapamil) or amiodarone*
N3,4	IIa-B	4 Patient with paroxysmal AF without heart failure (NYHA II-IV) *is prescribed digoxin without co-prescription of a further rate limiting agent (beta blocker, digoxin, diltiazem, verapamil, amiodarone, ibutilide)*
N8		5 Patient with persistent or permanent AF without heart failure, who is prescribed a rate limiting agent (beta blocker, digoxin, diltiazem, verapamil, amiodarone, ibutilide) is not prescribed a beta blocker, diltiazem or verapamil

C. Patients with heart failure

M1 to 4[43]	I-A	6 Patient with heart failure or LVSD *is not prescribed a beta blocker*
M5[43]	☑	7 Patient with CHF or LVSD and prescribed a beta blocker *has not achieved the recommended target dose*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E2: Unmet need for a beta-blocker or alternative

1,2	☑	1 Patient with CHD and without prior ACS *is not prescribed a BB or a rate limiting CCB*
1,2	I-A	2 Patient with CHD and a *history of ACS* *is not prescribed a BB or rate limiting CCB*
3,5	I-B	3 Patient with PERSISTENT AF *is not prescribed a BB, rate limiting CCB or Amiodarone*
4	IIa-B	4 Patient with PAROXYSMAL AF who is prescribed digitalis *is not prescribed a BB, a rate limiting CCB or amiodarone*
6	I-A	5 Patient with CHF *is not prescribed a BB*

E3: Target dose beta blocker not achieved

7	☑	7 Patient with CHF or LVSD and prescribed a beta blocker *has not achieved the recommended target dose*

2. Symptom control

Drug therapy objective 7: Control of angina symptoms

Included recommendations

O1[49]	I-B	1 Provide short-acting nitroglycerin for acute symptom relief and situational prophylaxis, with appropriate instructions on how to use the treatment
O2[49]	☑	5 Be careful to avoid nitrate tolerance

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived

O1	I-B	1 Patient with stable angina pectoris *is not prescribed a short acting nitrate*
O2	IIa-C	2 Patient with CHD prescribed a regular nitrate *is prescribed a dosing regimen, which provokes nitrate tolerance*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

E2: Unmet need for short acting nitrate

1	I-B	1 Patient with stable angina pectoris *is not prescribed a short acting nitrate*

E4: Suboptimal dosing of regular nitrates

2	IIa-C	1 Patient with CHD prescribed a regular nitrate *is prescribed a dosing regimen, which provokes nitrate tolerance*

Drug therapy objective 8: Control of fluid retention

Included recommendations

			Patients with CHF
P1	13[43]	IIa-B	In patients in sinus rhythm with symptomatic HF and an LVEF ≤40%, treatment with digoxin (in addition to an ACEI) improves ventricular function and patient well-being, reduces hospital admission for worsening HF, but has no effect on survival.

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived.

P1	IIa-B	1 Patient with CHF or LVSD and symptoms of heart failure despite treatment with an ACE inhibitor and diuretic *is not prescribed digoxin*

Assessment criteria (MAT_{CVC})

The numbers in the left column are the recommendations from which each criterion has been derived.

1	IIa-B	1 Patient with CHF or LVSDand symptoms of heart failure despite treatment with an ACE inhibitor and diuretic *is not prescribed digoxin*

Safety

Drug therapy objective 9: Controlling risk of haemorrhage

Included recommendations

A1	III-C	Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 y without heart disease (loneAF) or any risk factors for thromboembolism. (Level of Evidence:C) When cardioversion is contemplated and the duration of AF is unknown or exceeds 48 h, patients who do not require long-term anticoagulation may benefit from short-term anticoagulation
C11[68]	I-B	The dose should be adjusted to achieve the target intensity INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, TIA, or systemic embolism) and rheumatic mitral stenosis. For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5.

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived

1	III-C	1 Patient with AF and $CHADS_2$= 0 *is prescribed an oral anticoagulant*
2	I-A	1 Patient with AF or CHF and on an oral anticoagulant *has an INR >3.0*

Assessment criteria (MAT_{CVC})

The numbers in the left column denote the recommendations on which each criterion was based

S3: Choice of oral anticoagulants when antiplatelet therapy may suffice

1	III-C	1 Patient with AF and $CHADS_2$ = 0 *is prescribed an oral anticoagulant*

Drug therapy objective 10: Controlling risk of angina exacerbation

Included recommendations

O5	19[49]	☑	Dipyridamole is not recommended for antithrombotic treatment instable angina due to poor antithrombotic efficacy and the risk of worsening angina symptoms due to coronary steal phenomena
O6		III-B	Nifedipine, or other dihydropyridines, should not be used unless combined with beta-blockers

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived

O5	1 Patient with stable angina pectoris *is prescribed dipyridamol*
O6	2 Patient, who is admitted with ACS is prescribed a dihydropyridine without co-prescription of a BB

Assessment criteria (MAT_{CVC})

The numbers in the left column are the recommendations from which each criterion has been derived

S3: High risk choice of drugs in patients with coronary heart disease

1	1 Patient with stable angina pectoris *is prescribed dipyridamol*
2	2 Patient, who is admitted with ACS *is prescribed a dihydropyridine without co-prescription of a BB*

Drug therapy objective 11: Controlling risk of heart failure exacerbation

Included recommendations

P1[43]	I-C	In patients with AF and HF and/ or depressed LV function, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone.
P2[43]	IIb-B	Thiazolidinediones are contraindicated in HF patients with NYHA functional class III–IV, but may be considered in patients with NYHA functional class I–II with careful monitoring for fluid retention.
P3	☑	PDE5 – inhibitors are not recommended in advanced heart failure. Patients in class II are at intermediate and patients in class III-IV at high risk of cardiac decompensation triggered by sexual activity.
P4	☑	The following drugs should be used with caution when co-prescribed with any form of heart failure treatment or avoided: NSAIDs (including COX II inhibitors), diltiazem, verapamil, short-acting dihydropyridine CCBs, tricyclic antidepressants, corticosteroids, lithium, minoxidil

Assessment criteria (draft)

The numbers in the left column are the recommendations from which each criterion has been derived

P1	I-C	1 Patient with CHF or LVSD *is prescribed antiarrhytmic class 1 (IC)*
P2	IIb-B	2 Patient with CHF or LVSD *is prescribed a glitazone*
P3	☑	3 Patient with CHF or LVSD *is prescribed a PDE 5 inhibitor*
P4	☑	4 Patient with CHF or LVSD *is prescribed an NSAID*
P4	☑	5 Patient with CHF or LVSD *is prescribed a TCA*
P4	☑	6 Patient with CHF or LVSD *is prescribed an oral steroid*
P4	☑	7 Patient with CHF or LVSD *is prescribed lithium*
P4	☑	8 Patient with CHF or LVSD *is prescribed minoxidil*
P4	☑	9 Patient with CHF or LVSD *is prescribed diltiazem or verapamil*
P4	☑	10 Patient with CHF or LVSD *is prescribed a short-acting DHP-CCB*

Assessment criteria (MAT_{CVC})

The numbers in the left column are the recommendations from which each criterion has been derived

P1	I-C	1 Patient with CHF or LVSD *is prescribed antiarrhytmic class 1 (IC)*
P2	IIb-B	2 Patient with CHF or LVSD *is prescribed a glitazone*
P3	☑	3 Patient with CHF or LVSD *is prescribed a PDE 5 inhibitor*
P4	☑	4 Patient with CHF or LVSD *is prescribed an NSAID*
P4	☑	5 Patient with CHF or LVSD *is prescribed a TCA*
P4	☑	6 Patient with CHF or LVSD *is prescribed an oral steroid*
P4	☑	7 Patient with CHF or LVSD *is prescribed lithium*
P4	☑	8 Patient with CHF or LVSD *is prescribed minoxidil*
P4	☑	9 Patient with CHF or LVSD *is prescribed diltiazem or verapamil*
P4	☑	10 Patient with CHF or LVSD *is prescribed a short-acting DHP-CCB*

Chapter 4

Field testing of a Medication Assessment Tool for chronic cardiovascular conditions (MATCVC): Retrospective surveys in inpatient, outpatient and primary care settings

1. Background

1.1 Desirable attributes of explicit quality assessment

Instruments designed to assess the quality of health care processes, such as MATCVC require filed testing for desirable measurement attributes before any wider implementation can be attempted. However, a standard framework against which such instruments may be field tested is currently not available. Nevertheless, a number of authors have conducted work to describe methodological requirements for process of care measures. Four recent publications [1-4] were identified, which have addressed measurement attributes for explicit assessment criteria that are intended for use in a quality improvement rather than performance judgement context. Thirty-five attributes were extracted from these references[1-4] and 16 attributes remained after removing redundancies. Table 4.1 shows these 16 parameters, categorised under the key concepts of reliability, validity and utility.

1.1.1 Reliability

The *reliability of measurements* (precision) refers to the consistency of measurements across time (reproducibility), individuals (inter rater agreement) and contexts (objectivity). Reliability can be compromised by systematic and/or random error. An example of systematic error is the omission of relevant diagnostic codes when identifying patients with a particular disease for quality assessment. In contrast, random errors may occur as a result of inconsistencies in documentation or data abstraction or by the oversights of assessors. Although the explicit nature of assessment criteria included in the MATCVC supports their reliable application in practice, this requires empirical confirmation.

Table 4.1: Summary of desirable attributes of quality assessment methods (adapted from references[1, 3-7])

Attribute	Parameters
Reliability (precision)	
Reliability of measurement	o Application should be as independent of subjective judgement as possible [1,3] o Accurate and consistent data is available[1,3] o Reproducible findings when administered by different raters (inter-rater reliability)[1]
Reliability of discrimination	o Prevalence of patients which measures refer to is sufficiently high to allow reliable comparison[1]
Validity (accuracy)	
Face validity	o Key stakeholders must see that doing well on the quality measure represents better quality care[1,4]
Content validity	o Based on a systematic review of research evidence[4] o Relevance to patient outcomes[4]
Criterion validity	o Measure concurs with gold standard (concurrent validity)[2] o Improvements in the measure predict health outcomes (predictive validity)[3,4,] o Measure should be context free or important context factors should be accounted for (contextual validity*)[1,3]
Utility	
Feasible	o Data should be collected for routine clinical or organisational reasons and be available quickly with minimum extra effort or cost[2,3]
Interpretable	o The results of quality assessments should be capable of ready interpretation[1,4]
Communicable	o The results of quality assessments can be easily explained and understood by key target audiences[1,3,4,]
Actionable	o The results of quality assessments should point to actionable areas for improvement that are likely to bring about change[1]
Remediable	o Improvement is achievable by those assessed[3] o Quality indexes can reflect changes in quality of care[3, 6]

1.1.2 Validity

The *face and content validity* of instruments to measure the quality of medication use are determined by the ways in which instruments are developed.[8] Face validity is a property which (if present) confirms that an instrument appears (at face value) to measure what it intends to measure whereas content validity characterises the clinical relevance of an instrument, judged by the rigour of empirical evidence supporting it and/or the extent of expected clinical benefits. The development of the MAT$_{CVC}$ was based on guidelines by the European Society of Cardiology and is therefore likely to have strong face and content validity in care settings which use these sources as the primary reference for the care they provide. However, guidelines have also been developed at national levels and the extent to which adaptations are necessary for valid assessment of guideline adherence in different care contexts is currently unknown.

Criterion validity refers to the extent, to *which the results of quality* assessment accurately reflect the quality of care provided. *Predictive* validity is the extent to which measurements correlate with future patient outcomes, while c*oncurrent validity* refers to the consistency of one instrument rating quality similarly to a (reference) method applied to the same data source. The relevance of concurrent validity in a context of continuous quality improvement is that if quality assessment instruments, such as MAT$_{CVC}$, identify large numbers of patients without actual opportunities for medication use optimisation, this is likely to have negative implications for practitioners' commitment. Related to concurrent validity is *contextual validity*[i], which is defined as the extent to which quality assessment takes factors that may justify deviations from what is usually considered to be best practice into account. In order to enhance the contextual validity while maintaining feasibility and reliability of MAT$_{CVC}$ assessment, specific clinical exemption rules

[i] The term 'contextual validity' has not previously been used in the literature (to the knowledge of the author of this thesis). The term adjustability has been used before to capture a similar concept, but has mainly been applied to statistically adjust quality measures relating to patient outcomes (rather than processes) by patient level variables at provider level (case mix).

were designed to be deployed without clinical judgement. The relevance of such exemptions in retrospective evaluations of guideline adherence is, however, currently unknown.

1.1.3 Utility

Feasibility refers to the practical manageability of the resources required to obtain accurate and reliable data and conduct quality assessments (see under reliability above). In addition, the sample size (i.e. the numbers of patient records that need to be screened to identify those individuals to whom a specific measure is relevant) is one among other variables that determine whether it is feasible to use that measure to discriminate between 'high' and 'low' quality as reflected by respective quality indexes. Such discrimination may be desirable when comparing quality indexes to benchmarks or when assessing changes in quality over time.[9] The prevalence of patients to whom specific MAT$_{CVC}$ measures are relevant and the resources required to identify such patients is therefore an important variable to determine their suitability for comparative quality assessment.

'*Actionability*' refers to the extent to which specific tasks for improvement can be identified from data fed back to practitioners.[10,11] MAT$_{CVC}$ comprises of 52 individual criteria pertaining to multiple conditions, drug therapy objectives, drug therapy risk categories and pharmaceutical care needs. Such a large number of measures has the potential to overload potential users of quality information generated by the instrument in quality control and audit applications. In addition, the fact that individual measures frequently overlap with respect to the specific drug therapy risks they target and the actions required to address those risks has obvious limitations in patient targeting applications. Approaches of data presentation that allow (1) patients and (2) prescribing patterns to be targeted and prioritised are therefore key to the utility of MAT$_{CVC}$ for applications within the model of continuous quality improvement of medication use proposed in chapter 2.

1.2 Pharmaceutical care for patients with chronic cardiovascular conditions

Patients with cardiovascular conditions or risk factors often receive care from a number of practitioners in general and specialist settings. Increasingly, the team of practitioners providing care to these patients is multidisciplinary, comprising of medical specialists, medical general practitioners, pharmacists and nurses. Although the aim is to manage long term conditions in the community, patients with long term cardiovascular conditions are also frequently hospitalised, e.g. for acute vascular events or exacerbation of heart failure. The principal distinctions are between practitioners providing ongoing care for these patients (primary care) and those, who provide episodes of care in acute situation (inpatient settings) or as a consultation service (outpatient specialist settings).

1.2.1 Primary care

The majority of patients with long term cardiovascular conditions are managed in the primary care. In patients with manifest cardiovascular conditions the aim is to slow or arrest disease progression and to control symptoms and prevent exacerbations. An important role of primary care is also the prevention of cardiovascular conditions by timely control of cardiovascular risk factors, such as diabetes and hypertension.

1.2.2 Outpatient care

In health systems, where medical care in the community is exclusively provided by general practitioners, hospitals often run outpatient clinics in order to provide specialist expertise in the clinical management of patients with complex conditions. One example is heart failure clinics, which are increasingly run by a multidisciplinary team of practitioners as a consequence of accumulating evidence to support their added benefit to patients.[12,13] Heart failure patients frequently have cardiovascular co-morbidities, among which coronary heart disease (CHD) and atrial fibrillation (AF) are the most common. A multi-disease MAT$_{CVC}$, which

assesses drug therapy use for all three of these conditions is therefore of particular relevance to these patients.

1.2.3 Specialist Inpatient care

Hospitalisations provide an opportunity to optimise care plans for patients with chronic cardiovascular conditions, since cardiology specialists are readily available and patients can be monitored closely.[14] In addition, cardiology specialists may play a role in the overall implementation of evidence based practice guidelines as 'local opinion leaders' in the field.[15]

1.2.4 Inter-sectoral collaboration

In order to avoid preventable harm and realise potential benefits from drug therapy, collaboration between practitioners across settings is essential. A pre-requisite for this collaboration is a set of shared standards that practitioners at each stage contribute to attain, thereby increasing the likelihood that optimal health outcomes are achieved. Assessment against these standards at each stage of the process therefore has the potential to provide a basis for informing continuous quality improvement within each practice setting and to serve as a means of quality surveillance of the medication use system as a whole.

2. Aims and Objectives

Primary aims

1. To test the feasibility, reliability and validity of MAT$_{CVC}$ assessment

2. To identify and model strategies of using MAT$_{CVC}$ in audit, quality control and patient targeting applications

Secondary aim

3. To characterise the status quo of guideline implementation in selected inpatient, outpatient and primary care settings.

Objectives

1. To recruit a hospital inpatient setting (A), a hospital outpatient setting (B) and a primary care setting (C) for participation in retrospective surveys using MAT$_{CVC.}$

2. To identify and characterise patient samples with manifest cardiovascular conditions (CVD, CHF and AF) in each setting (patient samples A, B and C1) and a patient sample with diabetes or hypertension without cardiovascular conditions in the primary care setting (patient sample C2).

3. To summarise the findings of MAT$_{CVC}$ assessment in each setting with respect to limitations in the data sources used and the prevalence and nature of explained and unexplained non-adherence to guideline recommendations.

4. To identify and model approaches of using the MAT$_{CVC}$ in order to identify targets for quality improvement in quality control, audit and patient targeting applications in each setting.

5. To estimate the patient sample sizes required for different MAT$_{CVC}$ composite indexes for applications in quality control.

6. To test inter rater reliability of data capture for MAT$_{CVC}$ assessment.

7. To assess the relevance of extracted explanations for non- adherence to guideline recommendations to quality measurement using MAT$_{CVC.}$

8. To test the concurrent validity of MAT$_{CVC}$ assessment in the detection of truly unexplained non-adherence to MAT$_{CVC}$ measures in each setting.

3. Ethical approval and data protection

3.1 Inpatient setting

According to Hamburg hospital law (Hamburger Krankenhausgesetz (HmbKHG) §12), patient data may be transferred to third party researchers without formal approval by an ethics committee, if patient data is anonymised and does not allow patients to be traced back. This was achieved in this retrospective research by the following procedures:

a) Unanonymised data in both electronic and paper based formats was kept within hospital premises
b) Anonymisation of extracted patient demographics by replacing names and hospital IDs by randomly assigned study IDs
c) Extraction of minimum data sets (including replacing date of birth by patient age)

Formal ethical approval was therefore not sought. The author of this thesis and the research assistant, who assisted in data capture, were employed by the respective hospital, where this study was conducted and routinely had access to medical notes. The medical director of the hospital and the head of the cardiology department gave their consent to the conduct of this study.

3.2 Outpatient setting

The NHS research ethics committees[16] have issued guidance to researchers as to whether ethical approval is required. According to this guidance, studies that use existing data only and are designed and conducted to measure care delivery against standards and produce information to inform delivery of best care do not require formal ethical approval.[16] All of the aforementioned criteria were met by this study. The research in the participating outpatient clinic was conducted in collaboration and under the close supervision of a resident clinical pharmacist, who ensured data handling was undertaken within local practice guidelines for conducting clinical

audits. Confidentiality of patient data was maintained at all times. Formal ethical approval was therefore not sought.

3.3 Primary Care setting

The study was approved by the community pharmacists and general practitioners, who participated in the study. Patients registered with the participating general practitioners (GPs) and community pharmacies (CPs) had signed a service level agreement, which allowed GPs and CPs to exchange medication related patient information. Data collection was undertaken by a research assistant (RA), who held an honorary contract with the participating community pharmacies. The RA had signed a data confidentiality agreement before commencing data collection. The RA had access to community pharmacy patient records but did not have access to the medical notes. All relevant diagnostic information from medical records was extracted, anonymised and subsequently transmitted to CPs by the participating GPs. All data were stored in anonymised form within the premises of one of the community pharmacies. Formal ethical approval was therefore not sought.

4. Methods

4.1 Identification of settings and of patient target groups

In order to ensure the practical relevance of this research programme, the guiding principle was to test models of patient sampling and data capture that were practical and thus potentially sustainable in each setting.

Consistent with these general considerations, the intention was to identify (A) a specialist cardiology inpatient setting, (B) an outpatient heart failure setting and (C) a primary care setting. Within this sampling frame, the geographical location of practice settings was guided by logistic considerations. Three settings, one inpatient setting located in northern Germany, one outpatient setting located in Scotland and one primary care setting located in the north-eastern part of the Netherlands were identified as eligible and invited to participate. In each setting, the responsible physician(s) and one resident pharmacist were approached.

A. Hospital inpatients

Patients admitted to the participating cardiology wards were eligible for inclusion into the survey if they were discharged to primary care within a specified time period of 6 weeks.

B. Hospital outpatients

All patients attending the heart failure outpatient clinic within the 3 months time period between 01/10/2007 and 31/12/2008 were eligible for inclusion into this survey.

C1. Primary care patients with manifest cardiovascular conditions

All patients who were registered with enrolled community pharmacies and GP practices were eligible for inclusion into the survey.

C2. Primary care patients at cardiovascular risk

All patients who were registered with the enrolled community pharmacies and GP practices were eligible for inclusion into the survey.

Inclusion and exclusion criteria for all three settings are specified in table 4.2.

Table 4.2: Inclusion and exclusion criteria for patient samples A, B, C1 and C2

Eligibility criteria	A. Inpatient sample	B. Outpatient sample	C1. Primary care with CVC	C2. Primary care w/o CVC
CHD	Included	Included	Included	Excluded
Stroke/TIA	Included	Included	Included	Excluded
PVD	Included	Included	Included	Excluded
CHF	Included	Included	Included	Excluded
AF	Included	Included	Included	Excluded
Hypertension				Included
Diabetes mellitus				Included
Treated for palliation	Excluded	Excluded	*	*
Patients admitted for <24h	Excluded	N/A	N/A	N/A
Age < 18 years	Excluded	Excluded	Excluded	Excluded

CHD = coronary heart disease, TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; * It was not possible to identify and exclude patients who were treated for palliation only (in contrast to the hospital in-and outpatient settings), since this information was not available in this setting.

The sample size in each setting was chosen based on available resources and the time frame over which each survey had to occur.

4.2 Patient enrolment

Eligible patients were identified retrospectively using different data sources in each setting as specified in table 4.3.

Table 4.3: Data sources used in the three settings to identify eligible patients

	Data sources	Description
A. Hospital inpatients	Local data base for reimbursement from third party payers	Patient diagnoses entered by clinicians using ICD-10 codes either as: 'Hauptdiagnose' (reason for hospital admission) or 'Nebendiagnose' (co-morbidities)
B. Hospital outpatients	ATHENA™ data base	Data base used by resident clinicians to systematically record patient information that was relevant to heart failure management.
C. Primary Care	MEDICOM™	Contains diagnostic information in the form of ICPC (International Classification of Primary Care) codes.[26]

4.2.1 Patient demographics

Data analysis was performed using SPSS statistical software (SPSS, Inc., version 14.0). Patients were characterised in terms of age, gender and relevant medical histories. Continuous variables were reported as means (standard deviation) when normally distributed and medians (IQR) when distributions were skewed.

Comparison of patient samples to internal and external reference populations

The extent to which the enrolled patient samples were consistent with the populations of cardiology inpatients, heart failure outpatients and primary care patients at large was assessed by comparisons to external 'reference populations' (where available). In order to assess the extent to which enrolled patient samples were consistent with the general population of patients served *within* each setting, the demographics of sample populations were compared to a larger sample of

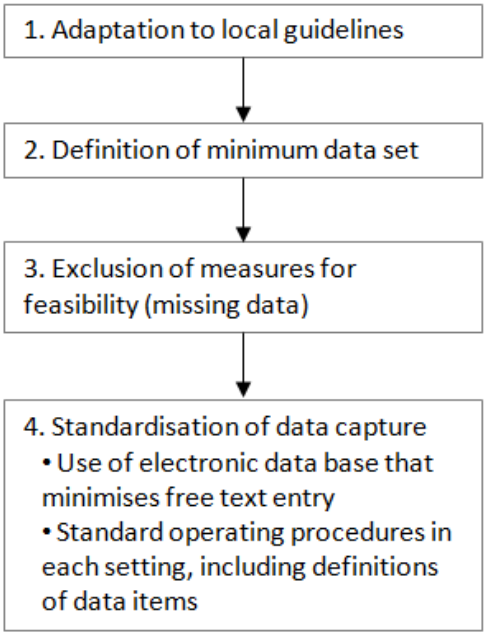
patients served within each setting.[ii] The demographics of subgroups of patients with vascular disease (CVD), chronic heart failure (CHF) and atrial fibrillation (AF) enrolled into inpatient, outpatient and primary care surveys were compared separately. Differences between means were tested for statistical significance using independent t-tests and differences between medians using the Mann-Whitney-U test. Differences between proportions were tested using z-tests.[17]

4.3 MATCVC assessment

4.3.1 Operationalisation of MATCVC

MATCVC was operationalised in each setting in a four step process as shown in figure 4.1 and described below.

Figure 4.1: Four-step approach to operationalising MATCVC assessment



[ii] Comparison to internal reference populations was relevant to the inpatient setting and outpatient setting only, since in the primary care setting *all* patients with relevant cardiovascular conditions served by participating practices and community pharmacies were enrolled into the survey.

Step 1: Adaptation of MAT$_{CVC}$ to local practice guidelines

MAT$_{CVC}$ measures were assessed against guidance by the Scottish Intercollegiate guidelines network (SIGN) for the Scottish hospital outpatient setting and against drug therapy standards recommended by the 'Nederlands Huisartsen Genootschap (NHG)' for the Dutch primary care setting. Differences between guidelines were identified by the main investigator and their relevance discussed within the research team. Where differences were considered to pose a threat to the validity of MAT$_{CVC}$ within each setting, MAT$_{CVC}$ measures were amended.

Step 2: Minimum data set

A minimum data set (MDS) comprising of relevant patient diagnoses, drug therapy prescribed and relevant laboratory data was defined.

Step 3: Exclusion of MAT$_{CVC}$ measures for feasibility

Before data capture for the retrospective surveys in each setting was commenced, the minimum data set (MDS) for MAT$_{CVC}$ assessment (see below) was presented to resident clinicians in each setting. Clinicians were asked to identify data items within the MDS that were perceived to be either (1) not feasible to obtain or (2) inconsistently documented in the selected data sources. Measures that relied on information that was classified as 'unfeasible to obtain', were excluded a priori. Where inconsistent documentation was anticipated, the use of assumptions was considered in consultation with resident clinicians.

Step 4: Design of MAT$_{CVC}$ data base

The MDS served as the basis for the design of an MS ACCESS™ database, of which screenshots are shown in appendix 3. The design of the database followed the following principles:

- Free text data entry avoided where possible.
- Tick boxes for dichotomous data (e.g. presence/absence of diagnosis)

- Drop down boxes for more complex data items, i.e. those with more than two possible answer categories, drop down boxes were designed (e.g. for time frames of biochemical investigations).
- Integration of definitions of data items (e.g. 'antihypertensive therapy'), specifications (e.g. time frame for cholesterol measurements) and explicit operational rules (e.g. pre-specified explanations for non-adherence to guidelines)

4.3.2 Data capture

Subsequent to a training phase, the MATcvc data base was populated by research assistants (pre-registration pharmacists), who abstracted the minimum data sets for patients enrolled into each survey using defined data sources in each setting. In all three settings, data capture was retrospective and was based on patient information routinely recorded by practitioners. Once the relevant information for patients enrolled into each survey was assembled in the MATcvc database, each patient case was assigned a study ID code. A data linkage file was created, which contained the list of case numbers linked to the corresponding study IDs. The original patient case numbers were subsequently deleted from the MATcvc data base. The data linkage file was stored on a separate computer within the premises of each setting.

Table 4.4: Data sources used in inpatient, outpatient and primary care surveys

	Data sources			
	Demographics	Diagnoses	Medication	Laboratory results
A. Hospital inpatients	----------Patient discharge letters----------			Local system
B. Hospital outpatients	----------ATHENA™ data base----------			Local system
C. Primary Care	PHARMACOM™	MEDICOM™	PHARMACOM™	MEDICOM™

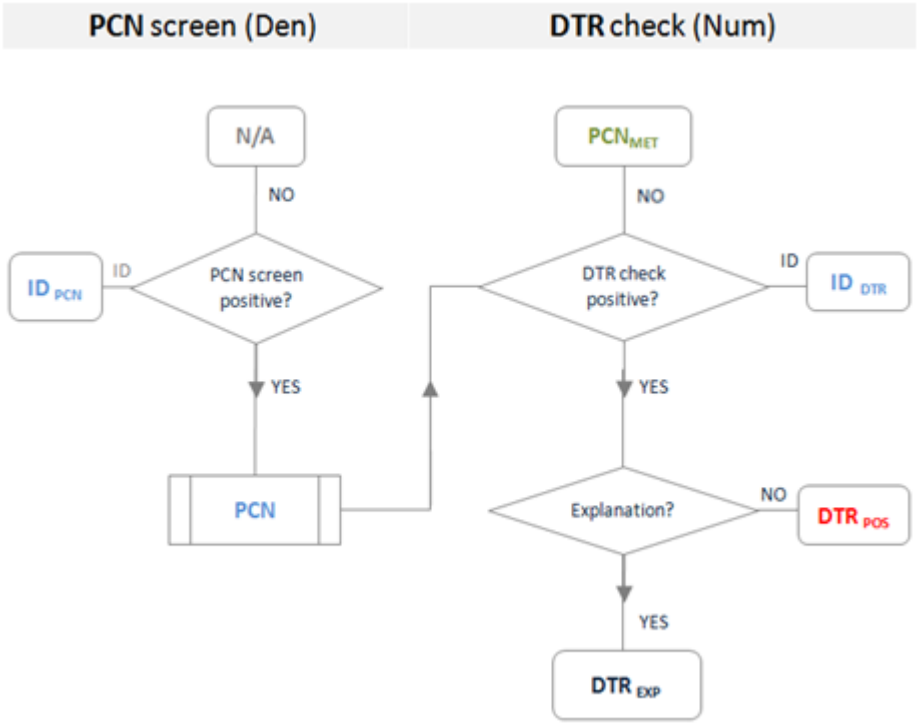
4.3.3 Measurement of guideline adherence

4.3.3.1 MAT$_{CVC}$ algorithm for the application of MAT$_{CVC}$ assessment criteria

The MAT$_{CVC}$ instrument and its development have been described in detail in chapter 3 of this thesis. For each of the 52 individual MAT$_{CVC}$ criterion, an algorithm was applied, which consisted of (1) screening for the presence or absence of a pharmaceutical care need (PCN) and (2) checking the presence or absence of a drug therapy risk (DTR) as shown in figure 4.2. The answer categories are explained in table 4.5.

In order to assign the DTR$_{EXP}$ category in cases where guideline recommended standards were not adhered to were adopted from chapter 3 of this thesis. Table 4.6 shows that the DTR$_{EXP}$ category was additionally assigned in cases where a prescriber's or a patient's choice to deviate from guideline standards was explicitly documented.

Figure 4.2: Algorithm for MAT$_{CVC}$ assessment.



N/A = not applicable; ID = insufficient data; PCI = Pharmaceutical care issue; DTR = drug therapy risk; Neg = negative; pos = positive; exp = explained

Table 4.5: Definitions and examples of answer categories used

Category	Description
N/A	The criterion is not relevant to the patient
ID PCN	The criterion is potentially relevant to the patient but this cannot be verified due to incomplete data
PCN	The criterion is relevant to the patient
ID DTR	Adherence to guideline recommendation cannot be verified
PCN MET	Guideline recommendation is adhered to
DTR POS	Guideline recommendation is NOT adhered to in the absence of pre-specified explanations
DTR EXP	Guideline recommended standard is NOT adhered to, but pre-specified explanations are present

Table 4.6: Scenarios yielding DTR EXP answers

DTR category	DTR EXP scenarios
E1: Target levels	a. Documented prescriber choice b. Documented patient choice c. Explicitly documented or recommended titration to effect/target
E2: Unmet indication/ **E3:** Suboptimal choice	a. Documented prescriber choice b. Documented patient choice c. Pre-specified clinical exemption d. Documented allergy/intolerance
E4: Target doses	a. Documented prescriber choice b. Documented patient choice c. Documented titration to effect/ target
S3: High risk choice	a. Documented prescriber choice b. Documented patient choice

4.3.3.2 Composite measures

Data for individual MAT$_{CVC}$ measures was aggregated using three sets of composite measures, namely 'action composites', 'prescribing composites' and 'MAT$_{CVC}$ as a whole'.

a) *'Action composites'* [iii] - Aggregation of individual measures, which pertain to the same drug therapy objective *and* target the same DTR category (see example in table 4.7). Each action composite points to a distinct DTR to be acted upon.

b) *'Prescribing composites' - Aggregation of 'action composites', which target the same DTR category (see example in table 4.7). Each prescribing composite, reflects a certain pattern of medication use.*

c) *'MAT$_{CVC}$ as a whole' – Aggregation of all 21 action composites as a global guideline adherence score (see explanation for table 4.7).*

Table 4.7: Example of the aggregation individual assessment criteria pertaining to the same drug therapy objective (e.g. control of dyslipidaemia) and drug therapy risk category (e.g. 'E2') into action composites. The corresponding quality indexes were calculated as the proportions of patients with at least one relevant PCN (indication for a statin), the denominator, who have not received treatment as recommended (DTR), the numerator.

1. Individual assessment criteria			
E2	1	Patient with CHD	*is not prescribed a statin*
E2	2	Patient with PVD	*is not prescribed a statin*
E2	3	Patient with a history of stroke or TIA	*is not prescribed a statin*
E2	4	Patient with DM	*is not prescribed a statin*
2. Corresponding action composite criterion			
E2	1 to 4	Patient with ≥1 indication for a statin	*is not prescribed a statin*
3. Corresponding Quality index for action composites			
E2	1 to 4	Denominator: No. of patients with ≥1 indication for a statin	Numerator: No. of denominator patients not prescribed a statin

Table 4.8: Example of the aggregation of action composites pertaining to the same drug therapy risk category ('E2') into prescribing composites. The quality indexes

[iii] Although not all measures represent composites (i.e. when only one relevant assessment criterion had been developed), the label 'composite' is used here for all measures in order to make explicit the higher level of measurement within the hierarchical structure of the **MAT**$_{CVC}$

for prescribing composites and for MAT$_{CVC}$ as a whole were calculated as the proportion of all identified PCNs, the denominator, that are unaddressed (DTRs), the numerator.

		Denominator	Numerator
1. Quality indexes for action composites			
E2	1	Denominator: No. of patients with ≥1 indication for thrombo-embolic prophylaxis	Numerator: No. of denominator patients not prescribed TE prophylaxis
E2	2	Denominator: No. of patients with ≥1 indication for a statin	Numerator: No. of denominator patients not prescribed a statin
E2	3	Denominator: No. of patients with ≥1 indication for for a RAS inhibitor	Numerator: No. of denominator patients not prescribed a RAS inhibitor
E2	4	Denominator: No. of patients with ≥1 indication for a beta-blocker or alternative rate limiting treatment	Numerator: No. of denominator patients not prescribed a beta-blocker or alternative rate limiting treatment
2. Quality index for corresponding prescribing composite			
E2	1 to 4	Denominator: No. of denominators triggered (PCNs identified)	Numerator: No. of numerators triggered (DTRs detected)

All prescribing composites and the action composites from which each was derived are shown in table 4.9.

Table 4.9: MAT$_{CVC}$ - 'Prescribing composite' measures (in bold)

DTO	DTR category and composite label	
1	ME	Monitoring of effectiveness parameters [iv]
2	E1	Inertia o Achievement of INR target o Achievement of cholesterol target o Achievement of HbA1c target o Achievement of Blood pressure target
3	E2	Under-prescribing o Unmet need for thrombo-embolic prophylaxis o Unmet need for a statin o Unmet need for a RAS inhibitor o Unmet need for a beta-blocker or alternative o Unmet need for short acting nitrate o Unmet need for digoxin
4	E3	Suboptimal drug choice o Choice/intensity of thrombo-embolic prophylaxis o Choice of first line oral antidiabetic o Choice/intensity of RAS inhibition
5	E4	Suboptimal drug dose o Suboptimal statin dose o Suboptimal dose of ACEI/ARB in CHF o Suboptimal dose of BB o Suboptimal dosing of regular nitrates
6	MS	Monitoring of safety parameters [v]
7	S1	Uncontrolled safety parameters o Excessive INR
8	S3	High risk drug choice o High risk choice of oral anticoagulants o High risk choice of drugs in CHD o High risk choice of drugs in CHF

DTO = Drug therapy objective; DTR = Drug therapy risk

[iv] Derived from E1 measures. An insufficient data response (ID_{DTR}) to E1 and S1 criteria was interpreted as a deficiency in monitoring for effectiveness.

[v] Derived from S1 measures. An insufficient data response (ID_{DTR}) to S1 criteria was interpreted as a deficiency in monitoring for safety.

4.3.3.4 Quality indexes

In order to quantify levels of non-adherence detected by MAT_{CVC}, five indexes were calculated at all levels of aggregation (MAT_{CVC} as a whole, prescribing composites, action composites) as shown in table 4.10.

Table 4.10: Definition of quality indexes

Index	Definition	Description
Data Gap Index (DGI) =	$\frac{ID_{DTR}}{PCN}$	Reflects the extent to which presence or absence of DTRs was unknown due to inconsistent monitoring
Adherence Index (AI) =	$\frac{PCN_{MET}}{PCN}$	Reflects the extent to which guideline recommendations were followed in eligible patients
Non-adherence Index (NAI) =	$\frac{DTR_{POS} + DTR_{EXE} + DTR_{MAN}}{PCN}$	Reflects the extent to which guideline recommendations were deviated from
Unexplained Non-adherence Index (UNAI) =	$\frac{DTR_{POS}}{PCN}$	Reflects the extent to which guideline recommendations were deviated from and where clinical exemptions or other context factors were NOT identified as per pre-defined rules
Explained Non-adherence Index (ENAI) =	$\frac{DTR_{EXP}}{PCN}$	Reflects the extent to which guideline recommendations were deviated from, but where clinical exemptions or other context factors were identified

DTR_{POS} = count of cases where drug therapy risk (DTR) is identified without a specific explanation; DTR_{EXE} = count of DTR cases, where clinical exemption is present; DTR_{MAN} = count of DTR cases with no clinical exemption but evidence of risk management

4.4 Identifying targets for quality improvement

4.4.1 Targeting medication use patterns using benchmarks

In order to identify currently achievable targets of non-adherence to MAT_{CVC} as a whole and for the 8 'prescribing' composite measures, achievable benchmarks were estimated from levels of achievement reported by large scale quality improvement programmes[vi], i.e. the 'Get with the Guidelines' programme[14,18-20], the 'Quality and Outcomes Framework'[21] and the Improve – HF programme[22]. Where not available, the benchmark was agreed within the research team, informed by the highest level of achievement among patient samples A, B and C1 as reflected by the Unexplained Non-adherence Index (i.e. the lowest UNAI score). Comparisons of observed index scores to benchmark scores tested the null-hypothesis that the observed levels of non-adherence were not higher than benchmark adherence using 1-sided z-tests with α=0.05.[23]

4.4.2 Targeting actions using funnel plots and Pareto charts

The results for the 21 action assessment criteria were displayed graphically using *funnel plots*, which exposed measures as priorities based on their UNAI scores. *Second*, Pareto charts were used to identify those action composite criteria, which accounted for high absolute numbers of non-adherences (DTR_{POS} events). The extent to which the two approaches agreed in identifying priorities was assessed by pooling the findings for all four patient samples and using Cohen's kappa.

[vi] 1. The 'Get with the Guidelines' programme, a scheme implemented by the American Heart Association in US hospitals, to support and facilitate improvement in the quality of care of patients with coronary heart disease, stroke and chronic heart failure. The programme includes interactive learning, best practice sharing, interactive workshops, post-meeting follow-up, and a web-based tool which enables routine performance feedback. Participation in this programme is voluntary.

2. The 'Quality and Outcomes Framework', a 'pay for performance' programme implemented in UK primary care, which provides financial rewards to general practices according to their achievements on a range of quality indicators including medication use. Participation is voluntary but practices generate a substantial amount of their income through the programme. Over 90% of general practices participate in the QOF.

3. The Improve – HF programme, a scheme implemented in US heart failure outpatient clinics providing performance data feedback and practice-specific performance improvement interventions.

4.4.3 Targeting patients based on the number of DTR$_{POS}$ events

In order to identify patients with the apparently greatest potential for quality improvement in relation to the 21 MAT$_{CVC}$ action criteria, the counts of DTR$_{POS}$ *events* per patient were considered. For each setting, a Pareto chart was designed, which allowed 'high priority' patients to be identified as those with the most substantial contribution to the total of unexplained non-adherence (DTR$_{POS}$) as detected by MAT$_{CVC}$ action composites. Those groups of patients with the highest number of unexplained non-adherences, who collectively accounted for at least 50% of all DTR$_{POS}$ events were identified as the 'highest priority' group.

4.5 Feasibility

4.5.1 Time required for data abstraction per patient

Research assistants documented the number of data abstraction sessions, their duration and the number of patients for whom data was abstracted. From this data, the time required per patient to populate the database with the minimum data set was estimated for each setting.

4.5.2 Estimation of sample size requirements

The number of patients (sample size) required to reliably identify under-performance in relation to an achievable benchmark depends on four[23,24] parameters as follows:

a) *Average number of PCNs identified per patient* - The average number of PCNs identified by MAT$_{CVC}$ as a whole and by each prescribing composite was estimated for each patient sample separately.

b) *Benchmark levels of unexplained non-adherence (UNAI score)* - The sample size estimates for MAT$_{CVC}$ as a whole and for prescribing composite measures were based on estimates of currently achievable benchmarks.

c) *'Tolerated' level of deviation from benchmark UNAI scores* - The 'tolerated' levels of deviation from benchmark UNAI scores were defined taking into

account the value of the benchmark UNAI score itself, i.e. lower levels of tolerance were assumed for lower UNAI scores.

d) *'Underlying hypothesis'* - Comparisons of observed index scores to benchmark scores tested the null-hypothesis that the observed levels of non-adherence were not higher than benchmark scores (1-sided comparison). [23]

The number of patients required for reliable comparisons of provider achievements to an UNAI benchmark in each setting was calculated as follows.[17]:

$$\text{Patient sample size} = \frac{Z^2 * (p) * (1-p)}{C^2 * \text{average PCN count/patient}}$$

Z = Z value (i.e. 1.64 for 1 tailed comparison with $\alpha = 0.05$); p = UNAI - Benchmark (e.g. 0.50); C = 'Tolerated deviation' from benchmark (e.g. 0.10 for an UNAI benchmark of 0.50); Average PCN count/patient = A sample specific estimate of PCN count per patient

4.6 Inter rater reliability

4.6.1 Design

Inter rater agreement of data capture of the minimum data set was tested between two data abstractors in each setting as follows:

A. Inpatient setting: The author of this thesis and a research assistant
B. Outpatient setting: Two research assistants
C. Primary Care: Community pharmacist and a research assistant

Research assistants were pre-registration pharmacists in all settings. Data abstractors independently populated the MAT_{CVC} data base with minimum data sets for a sample of enrolled patients. The main investigator subsequently applied the MAT algorithm to each abstracted data set separately. The MAT_{CVC} answer categories obtained for each data set in this way were tested for inter-rater agreement. The design of the evaluation of inter rater reliability is summarised in figure 4.3.

4.6.2 Patient sampling

Patient samples for testing of inter-rater reliability were identified using stratified random sampling. The strata were chosen in accordance with the targeted patient subgroups in each setting as detailed in table 4.11. In the inpatient and primary care settings, a total of 25 patients were randomly selected for each stratum. In the outpatient setting, all patients had heart failure and consequently only 2 strata were formed. For each of these strata, 40 patients were randomly selected using random numbers generator in MSEXCEL™.

Figure 4.3: Evaluation of inter rater agreement

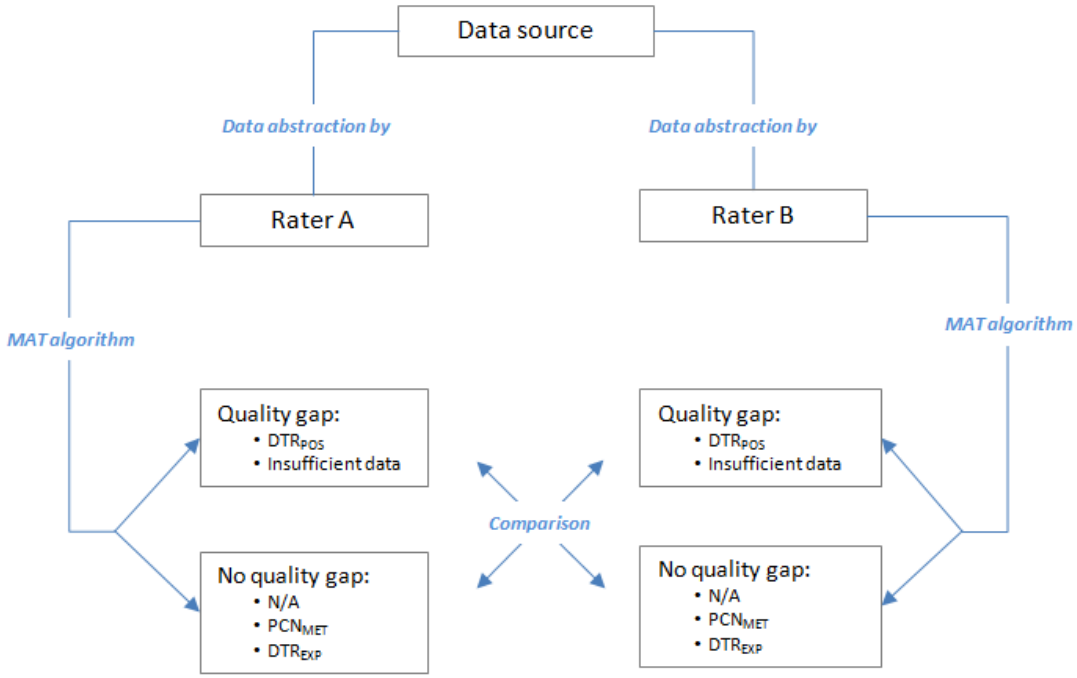


Table 4.11: Sampling frame for testing of inter rater agreement

Stratum	**Setting** A. Inpatient *(count of cases)*	B. Outpatient *(count of cases)*	C. Primary care *(count of cases)*
1. HTN or DM without established CVD, AF or CHF	-	-	25
2. Cardiovascular disease	25	40	25
3. Chronic heart failure	25	-*	25
4. Atrial fibrillation	25	40	25

* All patients had heart failure

4.6.3 Data analysis

The answer categories obtained for each independently abstracted data set were dichotomised into 'positive' (quality gap detected) and 'negative' (no quality gap detected) cases. For all three sets of composite measures (MAT$_{CVC}$ as a whole, prescribing/monitoring composites and action composites) tables were prepared as shown in table 4.12. Both overall agreement and chance-adjusted agreement were determined, the latter being quantified using kappa statistics (table 4.13). Kappa statistics were supplemented with the proportion of agreement on presence (ppos) and absence (pneg) of drug therapy risks (DTR $_{POS}$), respectively (table 4.14).

Table 4.12: Contingency table for the assessment of inter rater reliability of data capture as reflected by agreement on the presence/absence of drug therapy risks (DTR $_{POS}$)

		Rater A	
		DTR$_{POS}$	**DTR$_{NEG}$**
Rater B	**DTR$_{POS}$**	A	B
	DTR$_{NEG}$	C	D

A = Agreement that a quality gap is present
B /C = Disagreement about presence of a quality gap
D =Agreement that quality gap is absent

Table 4.13: Computation of Cohen's kappa [17]

Cohen's kappa (κ)	
$\kappa = \frac{\rho_0 - \rho_c}{1 - \rho_c}$	p_0: observed agreement p_c: agreement expected by chance

Table 4.14: Computation of ppos and pneg [17]

$$\text{pneg} = \frac{\sum (A)}{\sum (A,B,C)} \qquad \text{ppos} = \frac{\sum (D)}{\sum (B,C,D)}$$

A= Agreement that DTR is present (a 'DTR$_{POS}$'answer is identified in both data sets); B /C = Disagreement about the presence of a DTR D = Agreement that DTR is absent (assessments in both data sets yield an answer other than 'DTR$_{POS}$')

4.6.4 Interpretation

In order to characterise the level of inter rater reliability of data capture for the tested MAT$_{CVC}$ measures, the categorisation system shown in table 4.15 was used.[17] For MAT$_{CVC}$ measures with less than 'very high' chance-adjusted inter rater agreement, the observed proportions of agreement were explored.

Table 4.15: Categorisation of chance-adjusted agreement [17]

Strength of agreement	Value of Kappa	Value of po, ppos and pneg
Very high	> 0.80	> 0.95
High	0.61 to 0.80	0.91 to 0.95
Moderate	0.41 to 0.60	0.81 to 0.90
Low	≤ 0.40	≤ 0.80

4.7 Relevance of pre-specified explanations

The relevance of pre-specified explanations to the assessment of guideline adherence using MAT$_{CVC}$ in the recruited settings was explored by considering the *proportion of explanations over all non-adherences* (= explanation rate [ER]). The relative importance of pre-specified explanations was explored by using pre-specified categories as shown in table 4.16[vii]. As an example, an explanation rate of 0.50 implies that 50% of all detected non-adherences (DTR$_{POS}$ events) were explained by pre-specified rules.

Table 4.16: Categorisation of the relevance of pre-specified explanations to quality assessment for MAT$_{CVC}$ action composites

Relevance	Explanation rate
Low	<0.10
Moderate	0.10 to 0.24
High	0.25 to 0.49
Very high	≥ 0.50

[vii] These categories have not previously been used in the literature and have been defined by the author of this thesis.

4.8 Concurrent validity

4.8.1 Design

In order to test the concurrent validity of MAT$_{CVC}$ assessment, a sample of patients with drug therapy risks ('DTR $_{POS}$') detected by MAT$_{CVC}$ action composites were reviewed by resident clinicians. Clinicians' judgments on the appropriateness of deviations from guideline recommendations were considered the 'gold standard' against which non-adherences detected by MAT$_{CVC}$ were validated.

4.8.2 Patient sampling

A pragmatic approach was employed in that patients with the highest number of detected DTR $_{POS}$ cases were reviewed.

4.8.3 Validation process

For each patient case to be reviewed by clinicians, a two part questionnaire was prepared (illustrated in table 4.17). The first part summarised the detected non-adherences (DTR $_{POS}$) and corresponding guideline recommendations. Part 2 served the purpose of recording the reviewers' responses for each case of non-adherence (DTR $_{POS}$) to the following question:

> *On the basis of the available information:*
>
> Is a change of current drug treatment in accordance with the specified guideline recommendation desirable in this patient?'

Before clinicians embarked on case reviews, the main investigator (in the inpatient and outpatient settings) or a research assistant (in the primary care setting) explained the review process to clinicians using examples.

A. Inpatient setting

The reviews were conducted by the senior consultant, who was the head of the cardiology department in this hospital. Reviews were conducted on the basis of patient discharge letters and patient case summaries assembled from information stored in the MAT$_{CVC}$ data base (table 4.18).

B. Outpatient setting

The case reviews were conducted by an expert panel consisting of two clinical pharmacists. Both panel members had specialist interest and experience in providing pharmaceutical care to patients with cardiovascular conditions and both had academic affiliations. One of the panellists practiced as a member of the multidisciplinary team providing care to patients attending the enrolled heart failure outpatient clinic. Each panellist first conducted a review independently based on patient case summaries of the same format as in the hospital inpatient setting (table 4.18). Disagreements between panellists were identified and resolved by discussion at a subsequent meeting. At this meeting, patients' full medical notes were accessed where considered necessary by the panellists.

C. Primary Care setting

Reviews were conducted by each patient's GP on the basis of the full medical record for each patient.

Table 4.17: Validation questionnaire parts 1 and 2. Summary of detected unexplained non-adherences (DTR $_{POS}$) and corresponding guideline recommendations (part 1) and response form (part 2).

Part 1

MAT$_{CVC}$ No.	Guideline recommendation	Detected non-adherence
1	Anticoagulation is recommended for patients with 1 or more moderate risk factors: age ≥75 years, hypertension, HF, impaired LV function (LVEF <35%), DM (1-A recommendation)	Patient has CHF and DM ($CHADS_2$ score =2) and is not prescribed an oral anticoagulant
2	In patients with vascular disease, aim for current European prevention guidelines targets: <4.5 mmol/L (175 mg/dL) for total cholesterol and <2.5 mmol/L (96 mg/dL) for LDL cholesterol (good practice point)	Patient has CHD and is prescribed a stain but has not achieved the recommended lipid targets (based on latest levels within ≤12 months)

Part 2

	On the basis of information available to you: ***Would a medication change in accordance with the specified guideline recommendation be desirable in this patient?***			If NO, please choose one of the following:		
	Yes	**No**	**Uncertain**	*1. Not eligible*	*2. Managed*	*3. Patient choice*
1	☐	☐	☐	☐	☐	☐
2	☐	☐	☐	☐	☐	☐

'Not eligible': There is a permanent reason (other than patient choice) NOT to treat the patient according to the specified guideline recommendation

'Managed': The patient has a temporary reason (other than patient choice) NOT to be treated according to the specified guideline recommendation

'Patient choice': The patient denies treatment in accordance with the specified guideline recommendation or insists on high risk drug treatment

Table 4.18: Template for patient case summaries that formed the basis for reviews in the hospital in- and outpatient settings

Patient details									
Patient Study Code:			Sex		Weight				
Discharge/ Consultation Date:			Age						
Relevant medical history									
Diagnosis				Diagnosis					
(...)			*Year*	(...)					*Year*
Relevant drug history									
(...)									
Clinical measurements									
	Result 1		Result 2				Sinus	AF	unknown
BP		*Date*		*Date*	Heart rhythm	*Date*			
Heart rate		*Date*		*Date*		*Date*			
Signs and symptoms									
Oedema	*None*	*Ankle*	*Calf*	*Thigh*	*Waist*	*Unknown*			
Date	◻	◻	◻	◻	◻	◻			
Crepitations	*None*	*Basal*	*Few*	*Mild-chest*	*Widespread*	*Unknown*			
	◻	◻	◻	◻	◻	◻			
NYHA status	*NYHA I*		*NYHA II*	*NYHA III to IV*					
Date	◻		◻	◻					
LVSD	None	Mild	Moderate	Severe					
Date	◻	◻	◻	◻					
Medication									
Medication (Form, Dose, Route, frequency)				Start date	Stop date	Comments			
(...)									
Investigations									
	Date	*Date*	*Date*				*Date*	*Date*	*Date*
Na (135-145)mmol/l				Total Cholesterol (0-5.2)					
K (3.5-5.2) mmol/l				HDL Cholesterol (0.9-1.7)					
Urea (3.5-8.5) mmol/l				HbA1c					
Creat (60-120) µmol/l				INR					
eGFR (> 60)				Haemoglobin (11.5-16) g/dl					
GGT (0-45) IU/l				MCV (80-95) fl					
Alb (36-52) g/l				Plat(130-400)x10^9 /l					
Prot (62-82) g/l				WCC(3.6-11) x10^9 /l					
Triglycerides (0-2.4)				Neutrophils (2-7.5) x 10^9 /l					

4.8.4 Data analysis

Positive predictive value

A 'Yes' response to the question presented to clinicians (*'Is a medication change in accordance with guideline recommendations desirable?*) was interpreted as confirmation that MATCVC had detected a truly unexplained drug therapy risk. 'No' responses were interpreted as 'false positives' and 'uncertain' responses were excluded from the analysis. Positive predictive values (PPV), defined as the proportions of cases identified by MATCVC measures that were confirmed in individual assessments, for MATCVC as a whole, the 6 prescribing composites and 21 action measures were calculated as follows:

$$\text{PPV}^{17} = \frac{\text{Sum of true positive cases}}{\text{Sum of true positive cases} + \text{Sum of false positive cases}}$$

True positive = Adherence to guidelines is judged to be desirable
False positive = Adherence to guidelines is not judged to be desirable

5. Results

5.1 Settings

5.1.1 Hospital inpatient setting

The survey was conducted on all three peripheral (none-intensive care) cardiology wards of a teaching hospital in Hamburg, Germany. The team of practitioners comprised of one senior ('Chefarzt') and one junior cardiology consultant ('Oberarzt') and a variable number of medical registrars ('Assistenzaerzte'). A clinical pharmacist was present on these wards for approximately 1.5 hours per day.

5.1.2 Hospital outpatient setting

The survey was conducted in an outpatient heart failure clinic run by a multidisciplinary team of practitioners located at a teaching hospital in Glasgow, Scotland. The multidisciplinary team comprised of medical cardiologists, heart failure specialist nurses and a clinical pharmacist.

5.1.3 Primary Care setting

Community pharmacies and GP practices located in two communities in the North-East of Friesland, the Netherlands, were identified as eligible. Community A had approximately 28,000 and community B approximately 13,000 inhabitants. Community A was served by a total of 10 GP practices and 3 community pharmacies, while community B was served by four independently working GPs and one community pharmacy. Both community pharmacies, three GP partners practicing within the same health care centre in community A and two independently working GPs agreed to participate and were enrolled in the survey. A total of 12,844 patients were registered with the 5 participating GPs, amounting to approximately one third of the total population of both communities. The vast majority of these patients were also registered with the participating community pharmacies, although exact figures could not be obtained.

5.2 Patients

5.2.1 Hospital inpatient sample

5.2.1.1 Eligible patients

A total of 410 patients[viii] were consecutively admitted between 19/05/2008 and 30/06/2008. Of these patients, 250 had an admission diagnosis of at least one of the targeted conditions (CVD, CHF or AF). However, 46 (18%) of those patients meeting the inclusion criteria also met one of the exclusion criteria (table 4.19). Patient sample A therefore consisted of 204 patients, i.e. 82% of patients meeting the inclusion criteria and 50% of all patients admitted during the designated 6 week time period.

Table 4.19: Patient sample A. Reasons for excluding patients who met the inclusion criteria

Exclusion criterion	**Patients (n=250)** Count excluded
Palliative treatment	2 (1%)
Age <18 years	-
Relevant admission diagnosis excluded during hospital stay	12 (5%)
Patients referred to a different hospital (ward)	10 (4%)
Died during hospital stay	9 (4%)
Duration of hospital stay less than 24 hours	13 (5%)
Total	**46**

5.2.1.2 Reasons for admission

Among all patients enrolled in this survey (n = 204), the targeted conditions (CVD, CHF or AF) were the documented cause of hospital admission in two thirds (66%) of all cases. Acute coronary syndrome (ACS) was the most common reason (39%) for hospitalisation followed by acute heart failure (20%). Only a minority of patients

[viii] Each patient was only included once. Where a patient had been hospitalised more than once, only the most current episode of hospitalisation was considered.

(7%) were admitted for atrial fibrillation and none of the enrolled patients were admitted for stroke/TIA or PVD.

A total of 34% of patients were admitted for reasons other than the targeted conditions. These included in order of frequency: unspecific symptoms (general fatigue, dyspnoea, palpitations with or without syncope) in 15% of all admissions, elective coronary angiography (7%), arrhythmias other than AF (7%), electro-cardioversion (3%), hypertensive crisis (1%), endocarditis (<1%) or ICD-pacemaker implantation/monitoring (<1%).

5.2.1.3 Comparison of incidence rates in study and reference samples

Table 4.20 compares the cumulative incidence of admissions of patients with targeted conditions (CVD, CHF and AF) hospitalised within the six week enrolment period (19/05/2008 and 30/06/2008) with an estimate of the overall incidence of such admissions in this setting (based on the preceding 48 weeks). The overall proportion of patients who met at least one of the inclusion criteria and the proportions of patients with chronic heart failure and AF were similar. However, the incidence rate of patients with CVD was approximately 10% lower within the enrolment period than in the preceding 48 weeks.

Table 4.20: Comparison of the cumulative incidence of patients meeting the inclusion criteria observed in the inpatient sample (6 weeks) to a population estimate (48 weeks) for this inpatient setting

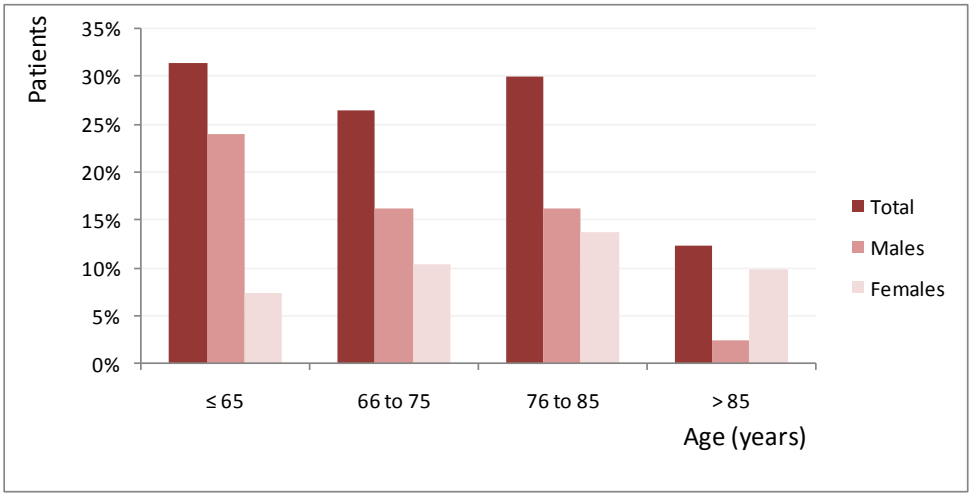
Inclusion criteria	**Incidence proportion (%)** Reference (n=2,979) 48 weeks		Sample (n=410) 6 weeks		Comparison
	Count	% (95% CI)	*Count*	% (95% CI)	*P*-value [X]
CVD	1636	54.2 (53.1, 56.7)	185	45.1 (16.8, 24.7)	< 0.001*
CHF	788	26.1 (24.9, 28.0)	106	25.9 (21.6, 30.1)	> 0.05
AF	832	27.6 (26.3, 29.5)	97	23.7 (19.6, 27.8)	> 0.05
≥1 of the above	1887	63.3 (61.6, 65.1)	250	61.0 (56.3, 65.7)	> 0.05

CVD = cardiovascular disease; CHF = chronic heart failure; AF = atrial fibrillation; X = X2 - test

5.2.1.4 Age and Gender

Of the 204 patients enrolled in this survey, the majority (59%) were male. The overall median (IQR) age was 73 (17). Figure 4.4 shows the frequency distribution of patients by age group and gender. Overall, men were significantly younger than women (median (IQR) age of 70(16) vs 78 (17); p<0.001)[ix] and table 4.21 shows that this age trend was consistent across all diagnostic subgroups, except in patients with lone AF.

Figure 4.4: Age distribution by gender in patient sample A (n=204)



5.2.1.5 Cardiovascular morbidity

Table 4.21 shows that almost 80% of all enrolled patients had a history of vascular disease (CVD), among which coronary heart disease (CHD) was the most common (75%). Hypertension was similarly prevalent (77%). Over half of all patients had a combination of two or more of the targeted conditions (CVD, CHF and AF). The most common disease combination in both genders was CVD/CHF, affecting almost 40% of patients overall. More than 10% of all patients had all three targeted conditions.

[ix] Mann-Whitney U test

Table 4.21: Prevalence and age of patients with relevant diagnoses in the total patient sample A (n=204), in males (n=120) and in females (n=84)

Diagnostic subgroup	Prevalence (%)				Age in years Median (IQR)			
	Total	M	F	M vs F *P*-value [X]	Total	M	F	M vs F *P*-value [U]
DM	28%	28%	30%	>0.05	71 (16)	70 (12)	77 (19)	>0.05
HTN	76%	73%	81%	>0.05	74 (17)	71 (15)	79 (17)	<0.001*
CVD	79%	86%	69%	0.003*	73 (16)	70 (16)	77 (16)	0.001*
CHD	75%	83%	63%	0.001*	72 (16)	70 (16)	76 (14)	0.004*
Stroke/TIA	12%	13%	10%	>0.05	80 (13)	73 (15)	86 (8)	0.001*
PVD	6%	6%	7%	>0.05	83 (16)	77 (19)	85 (18)	>0.05
CHF	47%	50%	43%	>0.05	75 (18)	70 (16)	81 (11)	<0.001*
AF	42%	34%	52%	<0.02*	78 (16)	73 (14)	82 (14)	0.002*
HTN/DM alone	-	-	-	-	-	-	-	-
CVD alone	30%	33%	26%	>0.05	68 (18)	68 (15)	71 (26)	>0.05
CHF alone	4%	3%	5%	>0.05	74 (25)	65 (35)	80 (22)	>0.05
AF alone	12%	9%	16%	>0.05	68 (16)	69 (34)	67 (20)	>0.05
CVD and CHF	25%	30%	17%	>0.05	71 (16)	67(18)	75 (14)	>0.05
CVD and AF	11%	8%	16%	>0.05	79 (13)	79 (11)	81 (14)	>0.05
CHF and AF	5%	2%	11%	0.01*	81 (15)	69 (-)	83 (9)	0.04*
CHF, CVD and AF	13%	15%	11%	>0.05	79 (12)	74 (14)	83 (19)	0.01*

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant

5.2.1.6 Comparison to reference populations

Patients with CVD

A recent survey has reported demographic information of 237,555 patients with coronary heart disease discharged from 472 US hospitals, which enrolled patients based on documented discharge diagnoses of acute myocardial infarction, unstable angina, chronic stable angina, and ischemic heart disease (*International Classification of Diseases*, 10th revision, diagnoses 410 to 414).[19] Patients with CVD included in study sample A were older and less frequently admitted for acute coronary syndrome than in the US survey. The prevalence of all relevant co-morbidities except DM was significantly higher in patient sample A.

Patients with CHF

A large scale European survey (Euro Heart survey[25, 26]) was identified as a reference against which to compare patients with heart failure in patient sample A. Matching the inclusion criteria of this German inpatient survey, the Euro Heart survey[25, 26] enrolled patients, who had a documented clinical diagnosis of heart failure at hospital discharge. In contrast to the German inpatient survey reported here, however, the Euro Heart survey also included patients discharged from general medical wards (50%) and patients who died during hospitalisation (13.5%).

The average age of heart failure patients enrolled into both surveys was 71 years. Heart failure patients in study sample A had more severe heart failure with significantly higher proportions of patients being admitted for acute heart failure and those in NYHA status III/IV (table 4.21). The proportions of patients with diabetes, previous myocardial infarction and renal impairment were also significantly higher than in the Euro Heart survey.

Patients with AF

In the absence of studies that were exclusively conducted in hospital inpatient settings, the population of patients enrolled into the 'Euro Heart Survey on Atrial fibrillation'.[27, 28] was taken as the reference population. The survey included 5,333 patients (56% inpatients; 44% cardiology outpatient) with AF on ECG from 182 hospitals in 35 European countries.

Patients in study sample B were on average 9 years older (76 versus 67 years) than in the reference population. AF patients in the study sample A were significantly less often admitted for AF than in the Euro Heart survey. Similar proportions of patients with a $CHADS_2$ score ≥ 1 hint towards comparable stroke risks in study and reference populations.

Table 4.22: Summary of demographic differences between CHD, CHF and AF patients enrolled in the inpatient survey to reference populations[19]

Patient subgroup	**Reference population** Description	**Relevant differences** Study sample A vs reference population
CVD	237,225 US-inpatients with discharge diagnosis of CHD[19]	o Patients older (median age 72 vs mean age of 66) o Incidence of admission for ACS lower (57% versus 79%; p <0.001) o Prevalence of all relevant co-morbidities (CHF, AF, HTN) significantly higher (except DM)
CHF	11,304 EU-inpatients with discharge diagnosis of CHF[25, 26]	o Proportion of males higher (69% vs 53%; p=0.003) o Heart failure severity higher (78% vs 26% in NYHA II/IV; p <0.001) o Prevalence of DM, prior MI and renal impairment significantly higher
AF	5,333 EU in- and outpatients with ECG evidence of AF[27, 28]	o Patients older (median age 76 vs mean age of 67) o Prevalence of paroxysmal AF higher (41% vs 28%; p=0.01) o Prevalence of CHD and renal impairment significantly higher

5.2.2 Hospital outpatient sample

5.2.2.1 Eligible patients

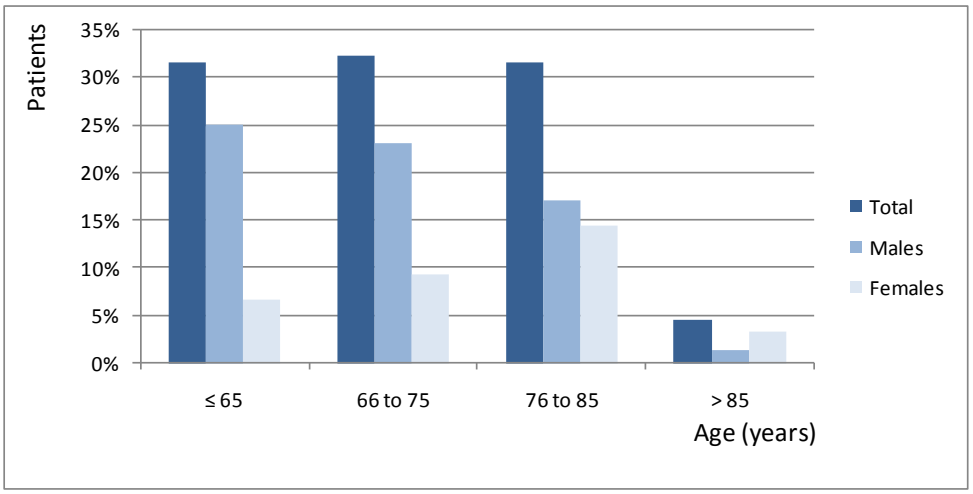
Within the time period 01/10 and 31/12/2007, clinic visits of 152 patients with a clinical diagnosis of heart failure were documented in the ATHENA™ system. None of these patients were treated for palliation only and therefore all patients were enrolled into this survey.

5.2.2.2 Age and Gender

Of the 152 patients recruited to this study, 101 (66%) were male. The overall median (IQR) age was 72 (16) and therefore similar to the cardiology inpatient sample with a median age of 73 (17). Figure 4.5 shows the frequency distribution of patients by age group and gender. As in the inpatient setting, men were significantly younger

than women (p=0.003)[x] with median (IQR) ages of 70 (15) and 76 (13) years, respectively.

Figure 4.5: Age distribution by gender in patient sample B (n=152)



5.2.2.3 Cardiovascular morbidity

Consistent with the inclusion criteria in this care setting, all patients had a diagnosis of heart failure. Table 4.23 shows that less than a third (29%) of all heart failure patients had heart failure alone. Over 60% of all patients had a history of vascular disease and over half of both males and females also had coronary heart disease. As in the inpatient sample, therefore, CHD was the most common co-morbidity of heart failure patients. Atrial fibrillation, hypertension and diabetes mellitus each were present in approximately one third of all enrolled patients. A quarter of all patients (25%) had all three targeted conditions, which was substantially higher than in the inpatient sample (10%).

[x] Mann-Whitney U test

Table 4.23: Outpatients. Prevalence and age of patients with relevant diagnoses in the total patient sample B (n=152), in males (n=101) and in females (n=51).

Diagnostic subgroup	**Prevalence** (%)			M vs F	**Age in years** Median (IQR)			M vs F
	Total	M	F	*P*-value[X]	Total	M	F	*P*-value [U]
DM	30%	35%	22%	NS	72 (13)	72 (13)	75 (14)	NS
HTN	33%	33%	33%	NS	72 (13)	72 (12)	77 (14)	NS
CVD	63%	66%	55%	NS	74 (13)	72 (12)	73 (12)	
CHD	58%	59%	55%	NS	74 (14)	73 (13)	77 (12)	0.010*
Stroke/TIA	14%	17%	8%	NS	74 (14)	74 (14)	72 (23)	NS
PVD	14%	14%	16%	NS	71 (8)	69 (9)	78 (10)	NS
CHF	100%	100%	100%	NS	72 (16)	70 (16)	76 (14)	0.003*
AF	34%	35%	31%	NS	74 (13)	73 (13)	80 (12)	0.013*
HTN/DM alone	-	-	-	NS	-	-	-	-
CVD alone	-	-	-	NS	-	-	-	-
CHF alone	29%	27%	33%	NS	64 (22)	59 (24)	69 (20)	NS
AF alone	-	-	-	NS	-	-	-	-
CVD and CHF	37%	39%	35%	NS	73 (12)	71(12)	76 (11)	NS
CVD and AF	-	-	-	NS	-	-	-	-
CHF and AF	9%	7%	12%	NS	76 (19)	74 (39)	78 (20)	NS
CHF, CVD and AF	25%	28%	20%	NS	74 (12)	72 (12)	81 (11)	0.004*

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NYHA = New York Heart Association; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant

5.2.2.4 Comparison to reference populations

Two large scale surveys were identified that included cardiology outpatients with chronic heart failure. The first was a US survey[29], which enrolled approximately 35,000 patients with chronic heart failure due to left ventricular systolic dysfunction (LVSD) from 167 US outpatient cardiology practices. A second survey was identified ('Euro Heart survey on atrial fibrillation[30]) as a reference against which the prevalence of AF subtypes and stroke risk in patients with concomitant heart failure and atrial fibrillation was compared (reference population 2). However, reference population 2 (in contrast to the study population) comprised of in- *and* outpatients. A summary of comparisons is shown in table 4.24.

Table 4.24: Summary of demographic differences between coronary heart disease (CHD), chronic heart failure (CHF) and atrial fibrillation (AF) patients enrolled in the outpatient survey (n=152) to reference populations[19]

Patient subgroups	**Reference population** Description	**Relevant differences** Study vs reference population
CHF	34,810 US cardiology outpatients with CHF due to LVSD	o Prevalence of HTN lower (33% vs 62%; p < 0.0001*) o Heart failure severity higher (23% vs 73% in NYHA III/IV; p < 0.0001*)
CHF and CHD	See above	o None identified
CHF and AF	1,816 EU in- and outpatients with CHF and ECG evidence of AF [27, 28]	o Prevalence of chronic AF higher (85% vs 63%; p = 0.01)

Age and gender of the study population and reference population 1 were similar and the prevalence of co-morbidities was comparable. However, patients enrolled into this survey had significantly more severe heart failure as reflected by a significantly lower prevalence of patients with NYHA I and II and, consequently, a significantly higher proportion of patients in NYHA III/IV. The estimated stroke risk ($CHADS_2$) was comparable.

5.2.3 Primary Care samples

5.2.3.1 Eligible patients

A total of 1,883 patients registered with one of the five participating GP practices were eligible on account of their medical history, but 7 (0.3%) patients were not registered with one of the community pharmacies. The remaining 1,876 patients constituted the patient sample and accounted for 14.6% of all patients registered with participating medical practices and 10.8% of all patients registered with the two community pharmacies, respectively.

5.2.3.2 Prevalence of targeted conditions

The prevalence of risk factors and manifest cardiovascular conditions varied substantially between GP practices as reflected by wide prevalence ranges (table 4.25). The prevalence of patients with hypertension, coronary heart disease and chronic heart failure appeared to be slightly below the ranges reported in the literature, while the prevalence of diabetes appeared to substantially exceed previously reported levels.

Table 4.25: Prevalence of targeted conditions in the primary care sample (n= 1,876)

Diagnosis	Prevalence in population of registered patients (n=12,844) (range between GP practices)	Reported prevalence [xi] in the general population
HTN	10 (7 to 14)%	11 to 13% (NL[31])
DM (type 1 and 2)	4.4 (2.3 to 5.4)%	1.9 to 2.4% (NL[31])
PVD (symptomatic)	0.5 (0.0 to 0.9)%	Not available
Stroke/TIA	1.3 (0.3 to 2.0)%	1.0 to 1.4% (NL[31])
CHD	1.8 (0.2 to 2.9)%	2.0 to 4.0% (EU[32])
History of MI	0.8 (0.5 to 1.9%)	1.3 to 1.8% (NL[31])
CHF with LVSD	0.3 (0.2 to 0.5)%	0.4 to 2.0% (NL[33])
AF	1.0 (0.2 to 1.8)%	0.4 to 1.0% (US[34])
≥1 of the above	15 (10 to 17)%	Not available

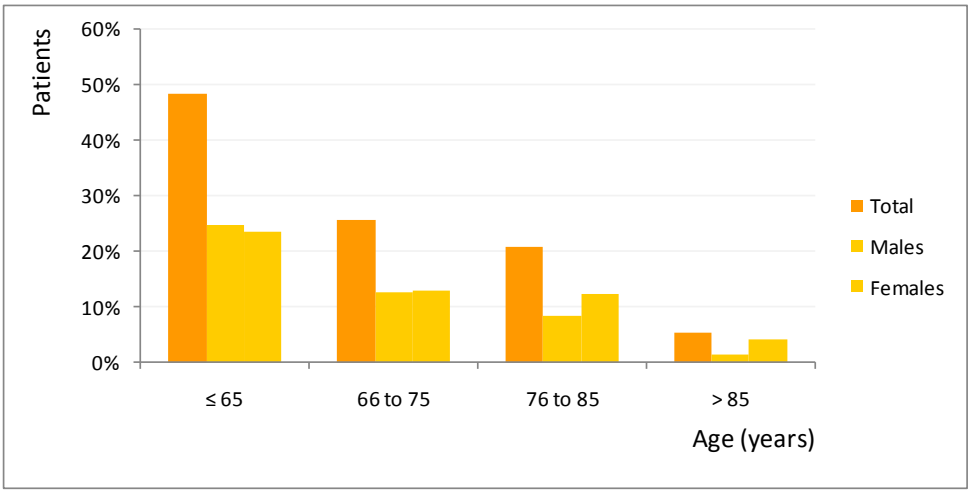
5.2.3.3 Age and Gender

The distribution of patients by age and gender is shown in figure 4.6. With a median (IQR) age of 66 (19), patients enrolled into this primary care survey were significantly younger than both the in- and outpatient samples ($p<0.001$ for both comparisons). A further difference to the hospital in- and outpatient patient samples was that the proportions of males (48%) and females (52%) were approximately equal in this setting, irrespective of whether patients had manifest CVD, CHF and

[xi] In order to assess whether the population of patients enrolled into this survey was consistent with the population served in primary care at large, comparisons were made to the general Dutch population where possible. Where demographic information for the Dutch population could not be located, comparisons were made (in order of preference) to overall European or US populations.

AF (46% males) or had cardiovascular risk factors alone (49% males). Similar to the in- and outpatient samples, however, men were statistically significantly younger than women (median (IQR) of 65 (15) vs 68 (13) years; p=0.002) although the absolute age difference was smaller.

Figure 4.6: Primary care patients. Age distribution in the total patient sample (n=1,876), in males (n=886) and in females (n=990)



5.2.3.4 Cardiovascular morbidity

Table 4.26 shows that approximately one third (29%) of all enrolled patients had a documented diagnosis of CVD, CHF or AF, while the remaining 71% had cardiovascular risk factors (DM or HTN) alone. Patients with manifest CVD, CHF or AF constituted 4.3% of the overall patient population registered with the participating GPs and community pharmacies. Hypertension was the most prevalent documented diagnosis among patients enrolled in this survey (70%) followed by diabetes (30%) and CVD (22%). Congestive heart failure was the least prevalent among the targeted conditions (2%). Overall, patients without manifest disease were significantly younger than patients with documented CVD, CHF or AF (median (IQR) 69(18) vs 65(19); p=0.002).

Table 4.26: Frequency distribution of cardiovascular risk factors and targeted conditions in the total patient sample (n=1,876), in males (n=886) and in females (n=990)

Diagnostic subgroup	**Prevalence**				**Age in years** Median (IQR)			
	Total	M	F	M vs F *P*-value[X]	Total	M	F	M vs F *P*-value[U]
DM	30%	30%	31%	NS	67 (20)	65 (21)	68 (20)	NS
HTN	70%	69%	71%	NS	66 (18)	65 (18)	68 (20)	NS
CVD	23%	24%	22%	NS	69 (17)	66 (17)	66 (17)	NS
CHD	12%	12%	12%	NS	66 (19)	70 (16)	70 (16)	NS
Stroke/TIA	9%	10%	8%	NS	65(16)	63 (18)	67 (18)	NS
PVD	3%	3%	3%	NS	66 (21)	64 (19)	73 (23)	NS
CHF	2%	2%	2%	NS	73 (21)	69 (21)	69 (21)	NS
AF	7%	7%	7%	NS	73 (21)	66 (21)	75 (18)	< 0.001*
				NS				
HTN/DM alone	71%	70%	72%	NS	65 (19)	65 (19)	66 (20)	NS
CVD alone	20%	22%	19%	NS	68 (18)	65 (17)	69 (19)	NS
CHF alone	1%	1%	1%	NS	70 (20)	67 (22)	73 (17)	NS
AF alone	5%	5%	5%	NS	70 (21)	67 (19)	76 (18)	0.002*
CVD and CHF	1%	1%	1%	NS	74 (21)	74 (13)	73 (22)	NS
CVD and AF	1%	1%	2%	NS	74 (16)	74 (27)	73 (42)	NS
CHF and AF	0.3%	0.3%	0.3%	NS	72 (30)	52 (22)	80 (0)	NS
CHF, CVD and AF	0.2%	0.1%	0.3%	NS	74 (6)	74 (-)	74 (12)	NS

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; M = male; F = female; X = X^2 - test; U = Mann-Whitney-U-test; * = statistically significant

5.2.3.5 Comparison to reference populations

Patients with CVD

No demographic data on the prevalence of co-morbidities among primary care patients with vascular disease in general or coronary heart disease in particular could be located.

Patients with CHF

The demographics of the subgroup of patients with CHF included into this primary care survey, was compared to the patient sample enrolled into a US survey of approximately 35,000 cardiology outpatients with chronic HF (see above).[29] Table 4.27 shows that the average age of both patient samples was similar. The proportion of heart failure patients with concomitant AF was also comparable while hypertension and coronary heart disease were significantly less common and DM significantly more common among patients enrolled into this primary care survey.

Patients with AF

In the absence of studies that were exclusively conducted in primary care settings, the population of patients enrolled into the 'Euro Heart Survey on Atrial Fibrillation' (see above[27,28]) was taken as a reference. The survey included 5,333 in- and outpatients (56% inpatients; 44% cardiology outpatient) with ECG evidence of AF from 182 hospitals in 35 European countries.

The average age of AF patients enrolled into this primary care survey and the proportion of males were higher than in the reference population. The prevalence of co-morbidities was consistently lower in the study population. Most strikingly, concomitant coronary heart disease was three times - and chronic heart failure more than four times more common in the reference population, respectively.

Table 4.27: Summary of demographic differences between CHF and AF patients enrolled in the primary care survey to reference populations

Patient subgroups	**Reference population** Description	**Relevant differences** Study vs reference population
Patients with CVD	No suitable reference population identified	-
Patients with CHF	34,810 US cardiology outpatients with CHF due to LVSD	o Prevalence of CHD lower (19% vs 64%; p < 0.001*) o Prevalence of HTN lower (42% vs 64%; p=0.01) o Prevalence of DM higher (63% vs 34%; p < 0.001*)
Patients with AF	5,333 EU in- and outpatients with ECG evidence of AF	o Average age higher (Median of 71 vs mean of 67) o Proportion of males higher (45% vs 33%; p=0.005*) o Prevalence of CHD lower (12% vs 32%; p=< 0.001*) o Prevalence of CHF higher (8% vs 37%; p=< 0.001*)

5.2.4 Comparison of inpatient, outpatient and primary care patient samples

The following section provides a comparative summary of the inpatient, outpatient and primary care samples enrolled into each survey as a reference for the remainder of this thesis. Table 4.28 summarises eligibility criteria and enrolled sample sizes.

Table 4.28: Summary of sample sizes and characteristics for settings A, B and C

Patient sample		Location	Sample size	Description of patient group
1.	Hospital inpatient	Germany	204 (50%[a])	All patients aged ≥18 with CVC (1 or more of CVD, CHF or AF) consecutively discharged from 3 cardiology wards to primary care within a time period of 6 weeks
2.	Hospital outpatient	Scotland	152 (100%[b])	All patients aged ≥18 with CHF attending a heart failure outpatient clinic within a time period of 12 weeks
3A.	Primary care	Netherlands	548 (4%[c])	All patients aged ≥18 registered with 1 of two community pharmacies and 1 of 5 GPs and CVC (1 or more of CVD, CHF or AF)
3B.	Primary care	Netherlands	1,328 (10%)	All patients aged ≥18 registered with 1 of two community pharmacies and 1 of 5 GPs without manifest CVC but CVC risk factors (HTN or DM)

a=proportion of all patients discharged from cardiology wards within a time period of 6 weeks, b= proportion of all patients attending the heart failure clinic within a time period of 12 weeks; c = proportion of all patients registered with 1 of two community pharmacies and 5 GPs

5.2.4.1 Age and gender

Table 4.29 summarises patient demographics in samples A, B, C1 and C2. The median (IQR) age of patients was highest (72 [12]) in the inpatient sample, followed by the outpatient [69 (12)] sample and primary care patients with CVC (69 [10]). The subgroup of primary care patients without established CVC was the youngest with a median (IQR) age of 65(9).

Table 4.29: Summary of patient demographics in settings A, B and C

	A. Inpatient	B. Outpatient	C. Primary Care	
			C1. With CVC	C2. Without CVC
Average age (years)	72 (12)	69 (12)	69 (10)	65 (9)
	%	%	%	%
Gender				
Male	58.8	66.4	49.3	46.4
Diagnoses				
DM	28.4	30.3	22.8	79.4
HTN	76.5	32.9	84.5	33.3
CVD	78.9	62.5	77.4	Not included
CHD	74.5	57.9	42.2	Not included
Stroke/TIA	11.8	13.8	30.1	Not included
PVD	6.4	11.8	11.3	Not included
CHF	47.1	100.0	7.8	Not included
AF	41.7	33.6	24.1	Not included
Diagnoses combinations				
HTN/DM (alone)	Not included	Not included	Not included	100.0
CVD (alone)	29.9	Not included	20.4	Not included
CHF (alone)	3.9	28.9	1.0	Not included
AF (alone)	11.8	Not included	5.3	Not included
CVD and CHF	24.5	37.5	0.8	Not included
CVD and AF	11.3	Not included	1.2	Not included
CHF and AF	5.4	8.6	0.3	Not included
CVD, CHF and AF	13.2	25.0 25.0	0.2	Not included

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; M = male; F = female; * = statistically significant

5.2.4.2 Cardiovascular morbidity

The composition of patient samples in terms of cardiovascular morbidity reflected the inclusion and exclusion criteria and has been described in detail above (table 4.29). However, a notable finding was that despite similar eligibility criteria (i.e. identical except for the exclusion of terminally ill patients in the inpatient but not in the outpatient setting) for patient samples A and C1, the proportion of patients with

CHF and AF was significantly ($p<0.001$) higher in patient sample A. Tables 4.30 to 4.32 compare the demographics of patient subgroups with CVD, CHF and AF in each setting.

Patients with vascular disease (CVD)

Table 4.30 compares the demographics of CVD patients in the three patient samples. The subgroup of patients with vascular disease (CVD) was significantly younger in the primary care sample C1 than in the hospital inpatient and outpatient samples. The proportion of patients with vascular disease was comparable in samples A and C1 but significantly lower in sample B. However, the proportion of patients with CHD was significantly lower in sample C1 than in sample A, while the prevalence of cerebrovascular disease ($p<0.001$) and peripheral vascular disease ($p = 0.04$) in patient sample C1 was significantly higher than in patient sample A. Cardiovascular co-morbidity was comparable between inpatient and outpatient settings (with the exception of CHF) and generally higher than in the primary care setting (with the exception of hypertension).

Table 4.30: Comparison of demographics of CVD patients in settings A, B and C1

	1.Inpatient	**2. Outpatient**	**3A. Primary Care**	***P* value**		
	N=161	N=95	N=424	A vs B	A vs C1	B vs C1
Average age (years)	73(16)	74(13)	69(17)	NS	NS	0.01*
Gender						
Male	64%	71%	49%	NS	< 0.001*	< 0.001*
Co-morbidity						
CHD	94%	93%	55%	NS	< 0.001*	< 0.001*
ACS	62%	52%	25%	NS	< 0.001*	< 0.001*
Stroke/TIA	15%	22%	39%	NS	< 0.001*	0.003*
PVD	8%	19%	15%	0.02*	0.03*	NS
CHF	48%	100%	5%	< 0.001*	< 0.001*	< 0.001*
AF	31%	40%	6%	NS	< 0.001*	< 0.001*
DM	29%	37%	24%	NS	NS	0.02*
HTN	80%	33%	48%	< 0.001*	< 0.001*	0.01*

* statistically significant

Patients with chronic heart failure (CHF)

Table 4.31 compares the demographics of CHF patients in the three patient samples. Age and gender were comparable across all three samples and heart failure patient samples A and B also had comparable severity of heart failure symptoms. Vascular co-morbidity was significantly higher in the inpatient than in the outpatient and primary care settings and significantly lower in the primary care than in the outpatient sample. Hypertension was significantly less common in the outpatient setting than in both inpatient and primary care settings.

Table 4.31: Comparison of demographics of CHF patients in settings A, B and C

	1.Inpatient	**2. Outpatient**	**3A. Primary Care**	***P* value**		
	N= 96	N= 152	N= 43	1 vs 2	1 vs 3A	2 vs 3A
Average age (years)	75(18)	72(16)	73(21)	NS	NS	NS
Gender						
Male	63%	66%	49%	NS	NS	NS
CHF severity						
NYHA I/II	21%	26%	Not available	NS	-	-
NYHA III/IV	78%	74%	Not available	NS	-	-
Co-morbidity						
CVD	80%	63%	44%	0.007*	<0.001*	<0.001*
CHD	73%	58%	19%	0.02*	<0.001*	<0.001*
ACS	54%	32%	9%	<0.001*	<0.001	<0.001*
Stroke/TIA	19%	14%	28%	NS	NS	NS
PVD	7%	12%	7%	NS	NS	NS
AF	40%	34%	23%	NS	NS	NS
DM	37%	30%	37%	NS	NS	NS
HTN	80%	33%	58%	<0.001*	0.01*	0.006*

* statistically significant

Patients with atrial fibrillation (AF)

Table 4.32 compares the demographics of AF patients in the three patient samples. Patients in the primary care sample were significantly older than in the inpatient and outpatient samples, while the median age in the latter was comparable. Vascular co-morbidity was significantly higher in the inpatient than in the

outpatient and primary care settings and significantly lower in the primary care than in the outpatient sample. The risk of thromboembolic stroke risk was highest in the outpatient sample as reflected by the highest proportions of patients with $CHADS_2$ scores of ≥2 and those ≥3. The median $CHADS_2$ score among primary care patients with AF was significantly lower than in both inpatient and outpatient samples.

Table 4.32: Comparison of demographics of AF patients in settings A, B and C

	1.Inpatient	**2. Outpatient**	**3A. Primary Care**	***P* value**		
	N=85	N=51	N=132	1 vs 2	1 vs 3A	2 vs 3A
Average age (years)	78(16)	74(13)	71(20)	NS	< 0.001*	0.05*
Gender						
Male	48%	69%	45%	0.03*	NS	0.006*
AF subtype						
Paroxysmal	41%	12%	Not available	0.001*	-	-
Chronic	59%	88%	Not available	0.001*	-	-
Stroke risk						
$CHADS_2$= 0	11%	0%	24%			
$CHADS_2$ =1	18%	16%	39%			
$CHADS_2$≥ 2	72%	84%	58%			
$CHADS_2$ ≥3	25%	49%	16%			
Median	2.0(1.0)	2 (0.5)	1(0.5)	NS	< 0.001*	< 0.001*
Co-morbidity						
DM	23%	28%	21%	NS	NS	NS
HTN	72%	45%	50%	0.003*	0.002*	NS
CVD	59%	75%	20%	NS	< 0.001*	< 0.001*
CHD	50%	71%	12%	0.03*	< 0.001*	< 0.001*
Stroke/TIA	14%	24%	7%	NS	NS	0.003*
PVD	7%	10%	2%	NS	NS	0.05*
CHF	45%	100%	8%	< 0.001*	< 0.001*	< 0.001*

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; M = male; F = female; X = X^2 - test; U = Mann-Whitney-U-test; * = statistically significant

5.3 MAT$_{CVC}$ assessment

5.3.1 Adaptation to local guidelines

Cholesterol targets

SIGN[35-39] differed from ESC[32] and NHG[40] guidelines in their definition of target for lipid lowering therapy. SIGN[39] makes reference to the 'Joint British Societies (JBS2)' guidelines[41], according to whom there are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events. Establishing cholesterol targets or statin doses for therapy is an extrapolation from the apparent benefits indicated by major trials of lipid lowering and a pragmatic approach in order to maintain appropriate margins for safety and taking into account economic implications. As previously described in chapter 3, SIGN states *'that the current NHS Scotland target for individuals at high cardiovascular risk is a TC level of < 5mmol/l and that reducing this target to 4.5 mmol/l (as recommended by ESC [32] and NHG [40] guidelines) would have major resource implications for NHS Scotland.' Pending further studies on mortality, safety and cost-effectiveness, the guideline development group therefore suggested that current NHS Scotland targets are maintained, as the minimum standard of care ('good practice point').*[39] It was therefore agreed within the research team that a target TC level of <5mmol/l be used for the cardiology outpatient setting.

Use of RAS inhibitors in patients with stable angina

As highlighted in chapter 3 of this thesis, the question of whether patients with stable angina but without left ventricular systolic dysfunction or history of myocardial infarction benefit from RAS inhibition is controversial. Four large RCTs have addressed this question, but the results are conflicting.[37] Two meta-analyses of these and other trials have found, however, that ACE inhibitors significantly reduced all cause and cardiovascular mortality.[42, 43] Based on these findings, the ESC guidelines recommend '*ACE-inhibitor therapy in all patients with angina and proven*

coronary disease to improve prognosis (I-B recommendation)' and SIGN states[37] that '*all patients with stable angina should be considered for treatment with angiotensin converting enzyme inhibitors* (grade A recommendation)'. In contrast, the NHG guidelines[40] recommend RAS inhibitors only in those patients with a history of myocardial infarction. However, the two relevant meta-analyses were published in 2006, i.e. after publication of the relevant NHG guideline on stable angina (2004). The MAT$_{CVC}$ was therefore not amended.

Use of beta blockers in patients with stable angina

The use of beta blockers in patients with CHD without prior myocardial infarction is similarly controversial as the use of RAS inhibitors in the same patient group. This is attributable to the fact that placebo controlled trials in these patient groups are considered unethical. All guidelines therefore rely on extrapolated evidence from meta-analysis that demonstrates potential to reduce mortality in patients with acute myocardial infarction or heart failure and SIGN cites an observational study, which suggests mortality benefit in patients with stable CHD without a history of MI (level 3 evidence) or LVSD.[37] SIGN and ESC guidelines recommend the use of beta blockers as first line agents for the relief of angina symptoms, whereas NHG guidance give preference to nitrates and recommend beta blockers only for patients with > 2 attacks per week or a history of MI. [44] Given that the launch of the NHG guidelines preceded publication of the above cited observational study that suggested a mortality benefit, the decision was made not to amend MAT$_{CVC}$ for use in the Dutch primary care setting. In summary, therefore, the only amendment to MAT$_{CVC}$ that was considered to be necessary in the light of differences between ESC, SIGN and NHG guidelines was the use of a cholesterol target of 5mmol/l in the Scottish heart failure outpatient clinic rather than the 4.5mmol/l threshold used in the cardiology inpatient and the Dutch primary care setting.

5.3.2 Exclusion of MAT$_{CVC}$ measures on feasibility grounds

Three action composite measures in the inpatient setting and six measures in the primary care setting had to be excluded a priori, since it was unfeasible to capture necessary patient information from the data sources used (table 4.33).

Table 4.33: Drug therapy objectives and individual MAT$_{CVC}$ measures that were considered to be unfeasible for implementation in each setting

	Setting Inpatient	Outpatient	Primary Care
Drug therapy objective 1: Thromboembolic prophylaxis			
M: Monitoring of INR	✓	✓	×
E1: Achievement of INR target	✓	✓	×
E3a: Suboptimal choice of antiplatelet treatment post ACS	✓	✓	×
Drug therapy objective 4: Blood pressure control			
M: Monitoring of blood pressure	×	✓	✓
E1: Achievement of blood pressure target	×	✓	✓
Drug therapy objective 7: Control of angina symptoms			
E2: Unmet need for short acting nitrate	×	✓	✓
E4: Suboptimal dosing of regular nitrates	✓	✓	×
Drug therapy objective 9: Haemorrhage			
M: Monitoring of INR	✓	✓	×
S1: Excessive INR	✓	✓	×

✓ = considered feasible to implement; X = considered unfeasible to implement and excluded from retrospective survey;

Inpatient setting

Achievement of blood pressure targets and under-prescribing of fast acting nitrates in patients with symptomatic coronary heart disease could not be implemented. Hospital discharge letters inconsistently provided information about patient's blood pressure and if so did not specify the point in time when it had been measured (drug therapy objective 4). Although the ESC guidelines recommended prophylactic prescription of fast acting nitrates in all patients with coronary heart disease, the resident clinicians felt that in patients who were asymptomatic during hospital stay,

ensuring sufficient stock of fast acting nitrates was outwith the scope of hospital treatment. Since it was not possible to reliably abstract information on the presence or absence of angina symptoms from discharge letters and a 'valid' indication for prophylactic prescription of acute angina relief could therefore not be identified, it was considered to be unfeasible to implement the MAT$_{CVC}$ measure for drug therapy objective 7 in this hospital inpatient setting.

Outpatient setting

All data items of the minimum data set (MDS) were principally available within the selected data sources (ATHENA data base including current and previous discharge letters; local electronic laboratory system). All MAT $_{CVC}$ measures were therefore considered feasible to be implemented in this cardiology outpatient setting.

Primary Care setting

It was not possible to obtain international normalised ratio (INR) data, since this information was held by a specialised anticoagulation service rather than the GP practices (drug therapy objective 1; achievement of INR targets (E1)). An additional limitation was that it was not possible to (a) obtain any information on whether or not patients with heart failure had a previous cardiac thrombus and (b) the date of previous acute coronary syndromes. The corresponding criteria that targeted (a) need or choice of thromboembolic prophylaxis in patients with heart failure and (b) choice of antiplatelet treatment in patients with prior ACS could therefore also not be implemented. Since the Pharmacom™ system did not contain information about the timing of doses, it was therefore also not feasible to assess whether nitrate dosing regimens were designed to avoid nitrate tolerance (drug therapy objective 7). Although information regarding presence or absence of angina symptoms in CHD patients was not available from either Medicom™ or Pharmacom™, the MAT$_{CVC}$ measure that targeted under-prescribing of fast acting nitrates was nevertheless implemented (in contrast to the hospital inpatient setting). The rationale was that

local primary care guidelines recommended prophylactic prescription of angina relief in all patients with CHD, i.e. irrespective of whether or not symptoms are reported.[40]

5.3.3 Assumptions

Angina symptoms

The presence of angina (relevant to verifying a need for acute acting nitrates in measure 7_E2 could not be ascertained in any of the three settings. However, it was assumed that all patients with coronary heart disease would be at risk of angina symptoms and would therefore benefit from prophylactic prescription of fast acting nitrates. While this criterion was excluded from the inpatient survey, in the context of long term (outpatient and primary care) the provision of fast acting nitrates was considered to be relevant, irrespective of documented evidence of angina symptoms.

Heart failure symptoms

The ESC guidelines recommend the use of digoxin in heart failure patients, who have heart failure symptoms despite optimal treatment with RAS inhibitors and beta blockers, but the severity of symptoms could not be elicited from routine documentation (measure 8_E2: Use of digoxin). In cases where patients were on optimal doses of RAS inhibitors and beta blockers, it was assumed that patients would be symptomatic if they had been prescribed a loop diuretic.

5.3.4 Survey findings

Figure 4.7 and table 4.34 provide an overview of the survey findings in each of the four surveyed patient samples for MAT$_{CVC}$ as a whole.

Figure 4.7: Graphical overview of findings for MAT$_{CVC}$ in the four patient samples. Sample A = inpatient (n=204); sample B = outpatient (n=152); Sample C1 = Primary care with CVC (n=548); sample C2 = Primary care without CVC (n = 1,328)

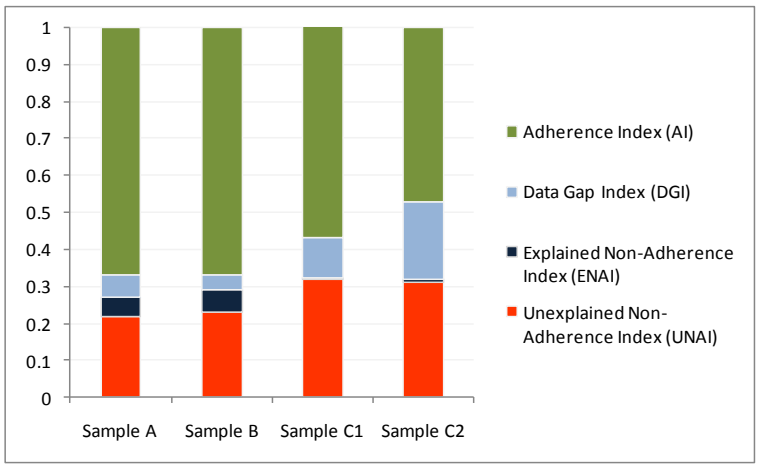


Table 4.34: Overview of findings for MAT$_{CVC}$ as a whole

Parameter	**Setting**			
	A. Inpatient (n=204)	**B. Outpatient** (n=152)	**C. Primary Care** 1. With CVC (n=548)	2. No CVC (n=1,328)
	Total count	Total count	Total count	Total count
PCN	1695	1512	3470	2462
PCN$_{MET}$	1135	1007	1941	1163
ID$_{DTR}$ total	102	65	388	506
DTR	458	440	1131	793
- DTR $_{EXE}$	20	67	19	18
- DTR $_{MAN}$	58	24	-	-
- DTR $_{POS}$	380	351	1112	775
Index	Score (95% CI)	Score (95% CI)	Score (95% CI)	Score (95% CI)
AI	0.67 (0.65, 0.69)	0.67 (0.64, 0.70)	0.57 (0.55, 0.58)	0.47 (0.45, 0.49)
DGI $_{DTR}$	0.06 (0.05, 0.07)	0.04 (0.03, 0.05)	0.11 (0.10, 0.12)	0.21(0.19, 0.23)
NAI [A]	0.27 (0.25, 0.29)	0.29 (0.26, 0.32)	0.33 (0.31, 0.34)	0.32 (0.30, 0.34)
ENAI [B]	0.05 (0.04, 0.06)	0.06 (0.05, 0.07)	0.005 (0.004, 0.006)	0.007 (0.004, 0.01)
UNAI	0.22 (0.20, 0.24)	0.23 (0.21, 0.25)	0.32 (0.30, 0.34)	0.31 (0.29, 0.33)

AI (PCN $_{MET}$/PCN) = adherence index; **DGI** (ID $_{DTR}$/PCN) = Data gap index; **NAI** (DTR/PCN) = Non-adherence Index; **ENAI** = Explained non adherence Index ([DTR $_{MAN}$ + DTR $_{EXE}$]/PCN); **UNAI** = Unexplained non-adherence Index (DTR$_{POS}$/PCN)

5.3.5 Prevalence

Overall prevalence in each sample

The prevalence of MAT$_{CVC}$ measures is defined as the percentage of patients in each sample, who had a pharmaceutical care need (PCN) identified by respective measures. Table 4.35 summarises the prevalence of the 21 action composites highlighting those with very high, high, medium, low and very low prevalence.

MAT$_{CVC}$ as a whole identified at least one pharmaceutical care need in all patients (100%) with a history of one of the targeted cardiovascular conditions (CVD, CHF and AF) and in 91.1% of patients with diabetes and/or hypertension only. The proportions of patients, to whom the MAT$_{CVC}$ action composites applied, were highly variable ranging from 0% to 100% of enrolled patients. In each setting, those composites that pertained to all patients with the most prevalent conditions were the most relevant in each setting. For example, in the inpatient setting, the majority of patients (75%) had coronary heart disease, so that action composites that targeted unmet need for thromboembolic prophylaxis, statins, RAS inhibitors and rate limiting therapy were highly prevalent. Three criteria were consistently of 'low' or 'very low' relevance to all samples, identifying pharmaceutical care needs in less than 5% of patients. These were 'E3 - choice of oral anticoagulants' in patients with AF and apparently low risk of stroke ($CHADS_2$ score = 0), 'E2 – Unmet need for digoxin' in heart failure patients and 'E4 –suboptimal dosing of nitrates'.

Table 4.35: Prevalence of action composite measures

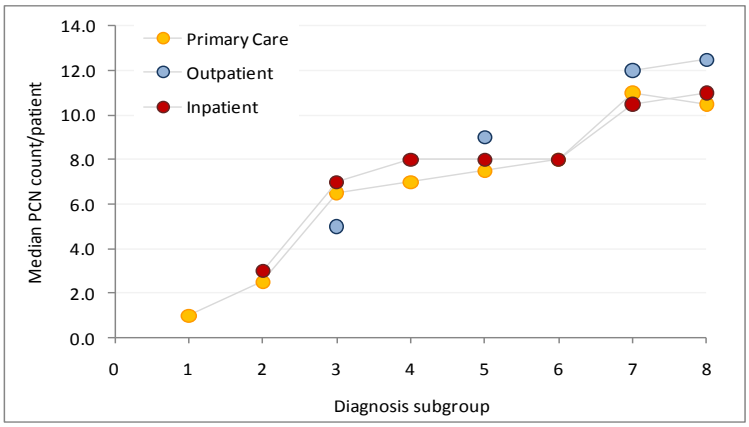
MAT$_{CVC}$ action composite		Patients in sample to whom measure is relevant (%)			
		A. Inpatient	B. Outpatients	C1. Primary Care	C2. Primary Care
E1	**Control of effectiveness parameters**				
	Achievement of INR target	18.6%	19.7%	Excluded	N/A
	Achievement of TC/LDL target	59.3%	46.1%	51.5%	N/A
	Achievement of HbA1c target	28.4%	24.3%	19.9%	27.6%
	Achievement of BP target	Excluded	31.6%	45.8%	70.5%
E2	**Unmet need for drug therapy**				
	TE prophylaxis	96.1%	71.1%	99.1%	N/A
	Statin	85.3%	69.7%	81.9%	33.3%
	ACEI or ARB	89.2%	100.0%	58.0%	33.3%
	Beta-blocker or alternative	99.0%	100.0%	68.1%	N/A
	Acute acting nitrate	Excluded	57.9%	42.2%	N/A
	Unmet need for digoxin	0.0%	2.0%	0.0%	N/A
E3	**Suboptimal choice/ intensity**				
	Thrombo-embolic prophylaxis	53.4%	35.5%	32.5%	N/A
	First line oral antidiabetic	10.8%	19.7%	15.3%	20.8%
	Intensity of RAS inhibition	1.0%	8.6%	0.0%	N/A
	Regular nitrates	2.9%	13.8%	Excluded	N/A
E4	**Suboptimal dosing**				
	Suboptimal dose of statin	59.3%	46.1%	51.5%	N/A
	Suboptimal dose of ACEI/ARB	44.1%	91.4%	6.2%	N/A
	Suboptimal dose of beta blocker	40.2%	79.6%	5.7%	N/A
S1	**Control of effectiveness parameters**	18.6%	19.7%	Excluded	Excluded
S3	**High risk drug choice**				
	Choice of oral anticoagulants	2.9%	0.0%	5.7%	N/A
	High risk choice of drugs in CHD	74.5%	57.9%	42.2%	N/A
	High risk choice of drugs in CHF	47.1%	100.0%	7.8%	N/A

Very high (> 80%) | High (51 to 80%) | Medium (21 to 50%) | Low (5 to 20%) | Very low (<5%)

Prevalence by patient subgroup

Figure 4.8 shows that there were substantial differences in the prevalence of MAT$_{CVC}$ measures between different patient subgroups. The median count of PCNs identified per patient generally increased with the number of targeted cardiovascular conditions, ranging from 1 in patients without established CVC to 12.5 among outpatients with all three targeted CVCs (CVD, CHF and AF).

Figure 4.8: Median PCN count/patient by diagnosis subgroup in each setting



1 = HTN/DM alone
2 = AF alone
3 = CHF alone
4 = CVD alone
5 = CHF + AF
6 = CVD + AF
7 = CVD + CHF
8 = CVD, CHF + AF

5.3.6 Non-adherence

Table 4.36 shows that the non-adherence index (NAI) ranged from 0.27 in the inpatient setting to 0.33 in the primary care subgroup of patients with CVC. The non-adherence indexes (NAI) of both primary care samples were significantly higher than in the inpatient and outpatient samples ($p< 0.001$ for all four comparisons).

Table 4.36: Prevalence of explanations as reflected by the Explained non-adherence index (ENAI)

	Inpatient		**Outpatient**		**Primary care**			
					Sample C1		Sample C2	
	DTR$_{EXP}$/PCN *(count)*	ENAI	DTR$_{EXP}$/PCN *(count)*	ENAI	DTR$_{EXP}$/PCN *(count)*	ENAI	DTR$_{EXP}$/PCN *(count)*	ENAI
MAT$_{CVC}$ total								
	78/1695	0.05	91/1512	0.06	9/3452	<0.01	18/2462	0.01
Prescribing composites								
E1	36/217	0.17	0/185	0.00	0/642	0.00	0/1302	0.00
E2	20/756	0.03	32/622	0.05	0/1914	0.00	0/844	0.00
E3	12/131	0.09	16/84	0.19	9/262	0.03	18/276	0.07
E4	10/299	0.03	43/351	0.12	0/347	0.00	N/A	

ENAI = Explained non-adherence index; DTR$_{EXP}$ = explained drug therapy risks, i.e. DTR$_{EXE}$ + DTR$_{MAN}$; E1= Achievement of targets; E2 = Unmet need; E3 = Effective drug choice; E4 = Effective dosing; S1 = Control of safety parameters; S3 = High risk drug choice

5.3.7 Explanations for non-adherence

Overall prevalence of explanations

The prevalence of explanations for detected non-adherences varied substantially between settings as reflected by the respective explained non-adherences indexes. Table 4.36 shows that for MAT$_{CVC}$ as a whole, the fraction of explained non-adherence (DTR$_{EXP}$) of all the times that MAT$_{CVC}$ measures applied (PCN events), was highest in the outpatient setting (0.06) followed by the inpatient setting (0.05). The overall ENAI was approximately 10 times lower in the primary care setting.

Explanations for non-adherence were exclusively found for effectiveness measures in all settings. Explanations for non-adherences relating to 'E1-Achievement of targets' were found in the inpatient setting only, and for composite measure *'E2 - Under-utilisation'* and '*E4 – suboptimal dosing'* in the inpatient and outpatient settings. For composite measure '*E3 – suboptimal choice'* explained non-adherences were identified in all settings.

Nature of explanations

Table 4.37 summarises the nature of explanations identified. The clinical exemption rules that were validated by the expert panel of four clinical pharmacists (chapter 3) were the main Outpatient setting) or the only type (primary care setting) of explanations for non-adherences identified in the outpatient and primary care settings, respectively, but in the inpatient setting, other explicitly documented explanations (prescriber choice, patient choice or recommendations to primary care clinicians in the inpatient and outpatient settings) were more prominent.

All clinical exemptions were attributable to six rules: recent haemorrhage (use/choice of thrombo-embolic prophylaxis), hepatitis/cirrhosis or elevated LFTs (use of statins), hyperkalaemia (RAS inhibitors), hypotension (use of RAS inhibitors, beta blockers), bradyarrhythmia (rate limiting therapy) and renal impairment (choice of metformin). 'Peptic ulceration', 'renal artery stenosis' or 'asthma' were not extracted in any of the three settings. In the primary care setting, all clinical exemptions pertained to the choice of metformin as the first line oral antidiabetic agent (renal impairment with eGFR < 50ml/min).

Table 4.37: Nature of identified explanations for non-adherence

Explanations	**Count of DTR_{EXP} events** (% of all explanations in each setting)			
	Inpatient	Outpatient	Primary care	
	Sample A	Sample B	Sample C1	Sample C2
Clinical explanations (validated rules)				
Haemorrhage	11	2	-	-
Hepatitis/cirrhosis/ LFTs elevated	-	6	-	-
Hyperkalaemia	-	5	-	-
Hypotension	-	27	-	-
Brady-arrhythmia	6	13	-	-
Renal impairment	3	14	9	18
Subtotal	20 (26%)	67 (74%)	9 (100%)	18 (100%)
Others				
Patient choice	2	6	-	-
Prescriber choice	7	4	-	-
Recommended	49	14	-	-
Subtotal	58 (74%)	24 (26%)	-	-
Total	**78 (100%)**	**91 (100%)**	**9 (100%)**	**18 (100%)**

5.3.8 Data gaps

All data gaps found for implemented measures referred to missing data in the detection of drug therapy risks ('ID $_{DTR}$ 'cases). Data gaps (ID$_{DTR}$) were exclusively found in those MAT$_{CVC}$ measures assessing the achievement or control of therapeutic targets (table 4.38).

Table 4.38: MAT$_{CVC}$ measures that were affected by data gaps

MAT$_{CVC}$ measures affected by missing data item		**ID$_{DTR}$/PCN** (DGI$_{DTR}$ for individual measure)							
		Inpatient (n=204)		Outpatient (n=152)		Primary care			
						With CVC (n=548)		No CVC (n=1,328)	
1_M/E1	INR	2/38	(0.05)	17/30	(0.57)	Excluded		Excluded	
2_E1	TC/LDL	76/121	(0.63)	21/70*	(0.30)	215/282*	(0.76)	N/A	
3_E1	HbA1c	22/58	(0.38)	10/37*	(0.27)	73/109*	(0.67)	245/366*	(0.67)
4_E1	Blood pressure	Excluded		-		100/251	(0.40)	261/936	(0.28)
9_M/S1	INR	2/38	(0.05)	17/30	(0.57)	Excluded		Excluded	

* within a time frame of 12 months prior to assessment

5.4 Targets for quality improvement

5.4.1 Targeting prescribing composites

In this first part of the analysis the medication use *patterns* (prescribing and monitoring composites) with the apparently largest scope for improvement in each setting are targeted by comparisons against benchmarks. In order to identify priorities for quality improvement, measured levels of adherence in each setting were subsequently compared to proposed benchmarks. The subgroup of patients without CVC in the primary care setting was not considered in this part of the analysis.

5.4.1.1 Estimation of benchmarks

Table 4.39 shows estimates of achievable benchmarks for MAT$_{CVC}$ as a whole, for monitoring and for prescribing composites. The proposed levels were informed by levels of guideline implementation found in quality improvement programmes in the United Kingdom (quality and outcomes framework – QOF) and the United States ('Get with the guidelines' and 'Improve HF'). Comparative data was not available for 'E1 - No comparable measure was available for MAT$_{CVC}$ as a whole. Similarly, no previously reported data on suboptimal dosing and safety monitoring could be located. In the case of achievement of therapeutic targets', data was only available for the primary care setting. Two different benchmarks were therefore used for settings A and B on the one hand and the primary care setting on the other. In the case of 'E4-Suboptimal dosing' no benchmark estimate was possible.

Table 4.39: Estimation of benchmark scores for MAT$_{CVC}$ as a whole and prescribing composite indexes based on literature sources and findings in surveys A, B and C1.

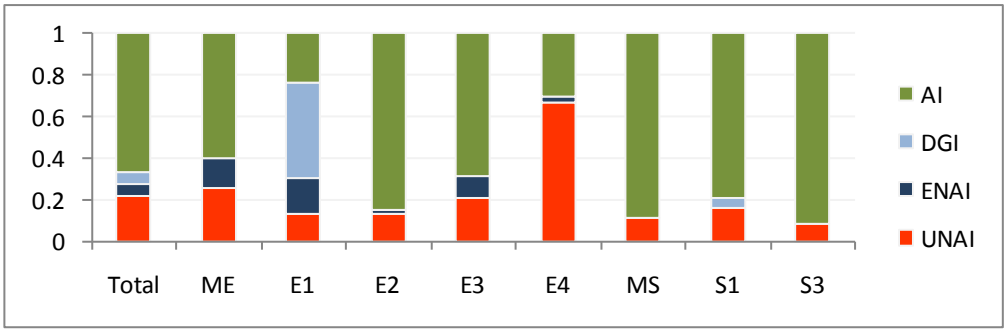
MAT CVC composite measure	Data Sources informing estimates UNAI score (95%CI)	Estimated benchmark
MAT CVC as a whole	Surveys A to C1: 0.22 (0.20, 0.24) to 0.32 (0.30, 0.34)	0.25
ME- Monitoring	QOF[21]: <0.10 for BP, HbA1c, cholesterol monitoring	0.10
E1-Achievement of targets	QOF[21] : TC < 5mmol/L = 0.25; HbA1c < 8% = 0.30; BP (<150/90 mmHg) = 0.12	A and B: 0.15 C1: 0.35
E2 - Under-prescribing	GWTG[19]: TE-prophylaxis = 0.06; statins = 0.09; RAS inhibitors post MI = 0.20; Beta blockers post MI = 0.06 IMPROVE HF[29]: Beta blockers in CHF = 0.08; RAS inhibitors in CHF = 0.15; QOF[21]: TE-prophylaxis = 0.08; RAS inhibitors = 0.08 post MI; 0.20 in DM plus proteinuria; Statins = n.a.; Beta-blockers in CHD = 0.20	0.15
E3 - Sub-optimal choice	IMPROVE HF[29]: TE prophylaxis in AF = 0.33; Aldosterone antagonist in CHF = 0.40	0.35
E4 - Sub-optimal dosing	Surveys A to C1: 0.44 (0.39, 0.49) to 0.67 (0.61, 0.72)	Not possible
MS – Monitoring	Surveys A to B: 0.05 (0.00, 0.10); 0.50 (0.39,0.74)	0.10
S1 - Control of safety parameters	Surveys A to B: 0.16 (0.04, 0.27); 0.07 (0.00, 0.16)	0.10
S3 - High-risk choice	Surveys A to C1: 0.08 (0.05, 0.12) to 0.16 (0.13, 0.19)	0.10

5.4.1.2 Comparison to benchmarks

A. Inpatient setting

Figure 4.9 and table 4.40 show that although the UNAI for MATCVC as a whole was found to be lower than the proposed benchmark, monitoring of effectiveness parameters (INR, TC/HDL, and HbA1c [xii]) was identified as a priority for quality improvement.

Figure 4.9 and table 4.40: A. Inpatient sample (n=204). Overview of quality indexes and comparison of unexplained non-adherence indexes (UNAI) for MATCVC total and prescribing composite measures to the corresponding benchmarks



Composite measure	Benchmark index	UNAI	95%CI	Comparison (1-sided; α=0.05) p-value
MATCVC	0.25	0.22	(0.20, 0.24)	NS
ME- Monitoring for effectiveness	0.10	0.47	(0.39, 0.53)	<0.001
E1- Achievement of targets	0.15	0.13	(0.09, 0.18)	NS
E2 - Under-prescribing	0.15	0.13	(0.10, 0.15)	NS
E3 - Sub-optimal choice	0.35	0.22	(0.15, 0.27)	NS
E4 - Sub-optimal dosing	nc	0.67	(0.61, 0.72)	nc
MS – Monitoring for safety	0.10	0.11	(0.09, 0.11)	NS
S1 - Control of safety parameters	0.10	0.16	(0.04, 0.27)	NS
S3 - High-risk choice	0.10	0.08	(0.05, 0.12)	NS

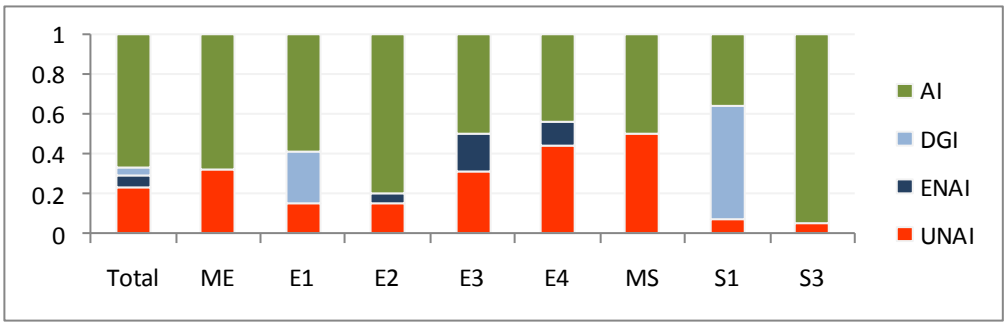
NAI = Non-adherence Index; ENAI = Explained Non-Adherence Index; UNAI = Unexplained non-Adherence Index; DGI = Data Gap Index

[xii] Blood pressure monitoring or achievement of targets was not assessed in this setting

B. Outpatient setting

Figure 4.10 and table 4.41 show that although the UNAI for MATCVC as a whole was found to be lower than the corresponding benchmark, four prescribing composites had significantly higher UNAIs. Monitoring of safety (INR) and effectiveness parameters (INR, BP, TC/HDL, and HbA1c[xiii]) and underutilisation were thus identified as potential targets for quality improvement.

Figure 4.10 and table 4.41: B. Outpatient sample (n=152). Overview of quality indexes and comparison of unexplained non-adherence indexes (UNAI) for MATCVC total and prescribing composite measures to the corresponding benchmarks



Composite measure	Benchmark index	UNAI	95%CI	Comparison (1-sided; α=0.05) p-value
MATCVC	0.25	0.23	(0.21,0.25)	NS
ME- Monitoring for effectiveness	0.10	0.35	(0.25,0.40)	<0.001
E1- Achievement of targets	0.15	0.15	(0.10, 0.20)	NS
E2 - Under-prescribing	0.15	0.20	(0.18, 0.22)	0.003
E3 - Sub-optimal choice	0.35	0.37	(0.21,0.43)	NS
E4 - Sub-optimal dosing	nc	0.44	(0.39, 0.49)	nc
MS – Monitoring for safety	0.10	0.50	(0.39,0.74)	<0.001
S1 - Control of safety parameters	0.10	0.07	(0.00, 0.16)	NS
S3 - High-risk choice	0.10	0.05	(0.00, 0.07)	NS

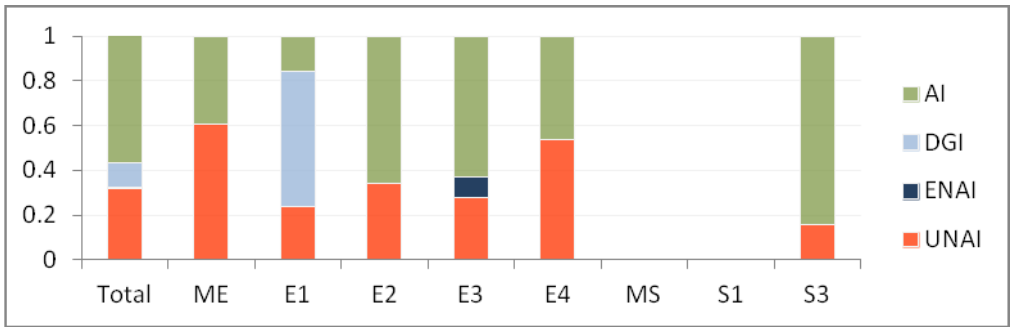
NAI = Non-adherence Index; ENAI = Explained Non-Adherence Index; UNAI = Unexplained non-Adherence Index; DGI = Data Gap Index

[xiii] Blood pressure monitoring or achievement of targets was not assessed in this setting

C. Primary Care setting

Figure 4.11 and table 4.42 show that the UNAIs for MATCVC as a whole and for four prescribing composites were significantly higher than the corresponding benchmark. Monitoring and achievement of effectiveness targets (INR, TC/HDL, BP and HbA1c), underutilisation (TE-prophylaxis, statins, RAS inhibitors and suboptimal choice of drug treatment (TE-prophylaxis, oral antidiabetic, RAS inhibitors) were thus identified as potential targets for quality improvement.

Figure 4.11 and table 4.42: C. Primary Care sample of patients with CVC (n=548). Overview of quality indexes and comparison of unexplained non-adherence indexes (UNAI) for MATCVC total and prescribing composite measures to the corresponding benchmarks



Composite measure	Benchmark index	UNAI	95%CI	Comparison p-value
MATCVC	0.25	0.32	(0.30, 0.34)	<0.001
ME- Monitoring for effectiveness	0.10	0.60	(0.57, 0.64)	<0.001
E1- Achievement of targets	0.35	0.24	(0.21, 0.27)	NS
E2 - Under-prescribing	0.15	0.34	(0.32, 0.36)	<0.001
E3 - Sub-optimal choice	0.35	0.28	(0.22, 0.33)	NS
E4 - Sub-optimal dosing	nc	0.54	(0.49, 0.59)	nc
MS – Monitoring for safety	0.10	Excluded		
S1 - Control of safety parameters	0.10	Excluded		
S3 - High-risk choice	0.10	0.16	(0.13, 0.19)	NS

NAI = Non-adherence Index; ENAI = Explained Non-Adherence Index; UNAI = Unexplained non-Adherence Index; DGI = Data Gap Index

5.4.2 Targeting action composites

5.4.2.1 Priorities in each setting

Figures 4.12, 4.14 and 4.16 (pp 229-232) show *funnel plots* of the 'Unexplained Non-adherence Index UNAIs (in %) for the 21 MAT$_{CVC}$ action composites found in the inpatient, outpatient and primary care samples. In each funnel plot, the UNAIs (%) (y-axis) are plotted against the PCN count (x-axis) for each measure. The means of all UNAIs are displayed as grey straight lines. The upper and lower limits of the 95% confidence interval around the mean and a given PCN count are shown as red and blue lines, respectively. Based on the position of each MAT$_{CVC}$ action composite in the funnel plot, measures are categorised into 'highest' priority (red marks), 'high' priority (yellow marks), 'medium priority' (light blue marks), and 'low priority' (dark blue marks). Action composites, where the PCN count (i.e. the denominator for the UNAI) is lower than 20, are shown as white marks. Figures 4.13, 4.15 and 4.17 (pp 229-232) show *Pareto charts* of unexplained non-adherence events (DTR$_{POS}$) identified for each surveyed patient sample. The x-axes show the MAT$_{CVC}$ criteria in ranked order of the percentage of the DTR$_{POS}$ total (data bars), that each measure accounted for (primary y-axis). On the secondary y-axis (line graph), the cumulative percentage of the DTR$_{POS}$ totals are plotted.

A. Inpatient sample

The funnel plot approach (figure 4.12) identified three action composites as 'highest priority' and two as 'high priority'. In comparison, the Pareto chart (figure 4.13) approach identified four criteria as highest priority (together accounting ~60% of all unexplained non-adherences) and two as 'high priority', together accounting for over 70% of all identified unexplained non-adherences. Three composites were identified by both approaches as 'highest' priority, all of which referred to 'E4-suboptimal dosing (statins in CVD, ACE inhibitor/ARBs and beta-blockers in CHF)'. However, only the Pareto chart approach identified 'E2 - Unmet need for statins' as highest priority and 'Unmet need for rate limiting therapy' as 'high' priority.

Reciprocally, achievement of INR targets was only identified as 'high' priority by the funnel plot approach with an UNAI of 0.39 but a smaller (4.4%) contribution to the DTR_{POS} total.

B. Outpatient sample

Both, the funnel plot approach (figure 4.14) and Pareto chart approach (figure 4.15) identified the same three action composites as highest priority: 'E4-suboptimal dosing of ACE inhibitor/ARBs', 'E4-suboptimal dosing of beta-blockers in CHF' and 'E2-unmet need for acute acting nitrates'.'E3- Suboptimal choice of TE-prophylaxis' was also identified by both approaches as 'high' priority. However, the Pareto chart approach additionally identified 'E2-Unmet need for a statin as 'high' priority. The 'highest priority' measures accounted for approximately 60% of all unexplained non-adherences. A further two action composites were identified by both approaches as 'high' priority, together contributing 13% to the DTR_{POS} total.

C1. Primary care setting –Patients with CVC

Funnel plot approach (figure 4.16). Two measures (5_E3 – 'Intensity of RAS inhibition', _E2 'need for digoxin') were excluded from the analysis because of PCN counts < 20. Four action composites were identified as 'very high' priority and three as 'high' priority. The Pareto chart approach (figure 4.17) also identified four action composite measures as 'highest priority', but four measures as 'high' priority. The highest priority measures accounted for 55% of the DTR_{POS} total and the high priority measures for an additional 31%. Only two of the six action composites that were identified as 'highest' priority by either approach overlapped. In addition, three of the measures identified as 'very high priority' were identified as 'medium' or 'low' priority by the respective other approach. 'Achievement of BP target' was identified as 'high' priority by both approaches.

C2. Primary care survey – patients without CVC

Funnel plot or Pareto charts were not designed for the subgroup of primary care patients without CVC, since only five action composites applied to these patients. The UNAI (%) for two measures referring lay above the 95% confidence interval of the mean and these action composites were therefore labelled 'very high' priority (table 4.43). The four highest ranking criteria each accounted for over 10% of all detected DTR_{POS} events and were therefore classified as 'very high' priority.

Figure 4.12: Inpatient sample A (n=204). Funnel plot of UNAIs (%) for action composites

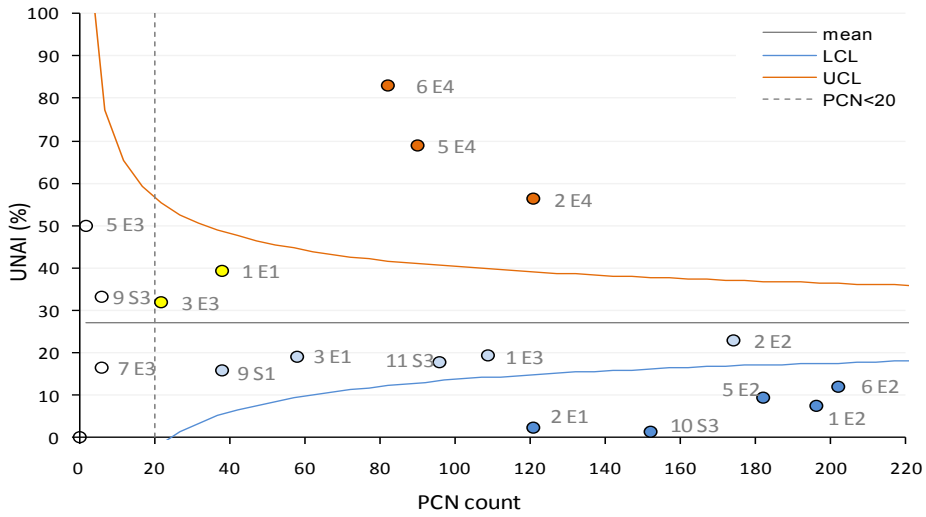
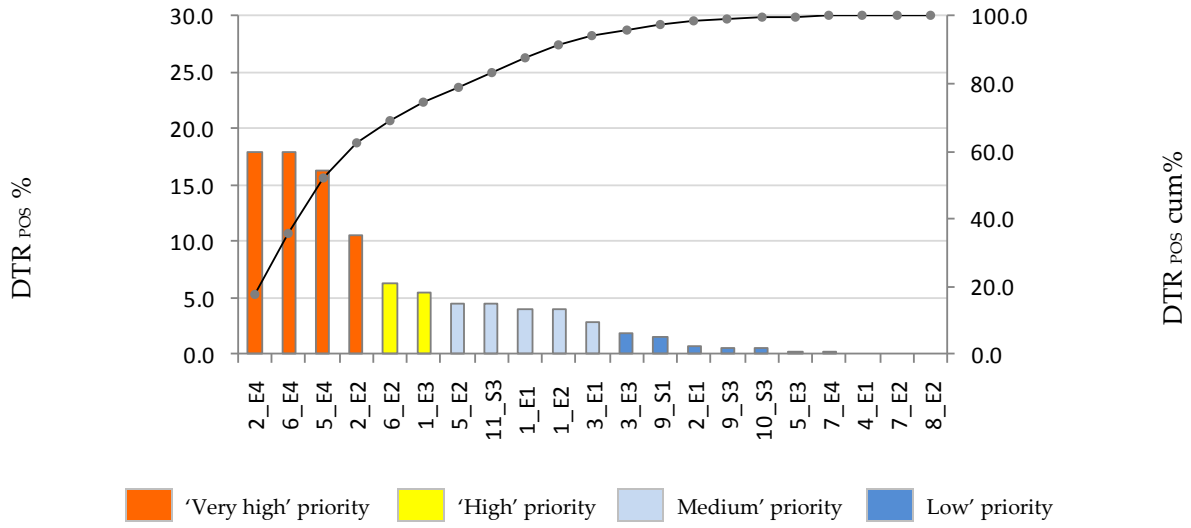


Figure 4.13: A. Inpatients (n=204). Pareto chart for action composites



PCN = Pharmaceutical Care Need; DTR$_{POS}$ = Unexplained non-adherence; UNAI = Unexplained Non-Adherence Index

Legend: **MAT**$_{CVC}$ action composites

1E1	Achievement of INR target
1E2	Unmet need for TE prophylaxis
1E3	Choice of thrombo-embolic prophylaxis
2E1	Achievement of TC/LDL target
2E2	Unmet need for a statin
2E4	Suboptimal dose of statin
3E1	Achievement of HbA1c target
3E3	Choice of first line oral antidiabetic
4E1	Achievement of BP target
5E2	Unmet need for ACEI or ARB
5E3	Suboptimal intensity of RAS inhibition
5E4	Suboptimal dose of ACEI/ARB
6E2	Unmet need for a beta-blocker or alternative
6E4	Suboptimal dose of BB
7E2	Unmet need for short acting nitrate
7E4	Suboptimal dosing of regular nitrates
8E2	Unmet need for digoxin
9S1	Excessive INR
9S3	Choice of oral anticoagulants
10S3	High risk choice of drugs in CHD
11S3	High risk choice of drugs in CHF

Figure 4.14: Outpatient sample B (n = 152). Funnel plot of UNAIs (%) for action composites

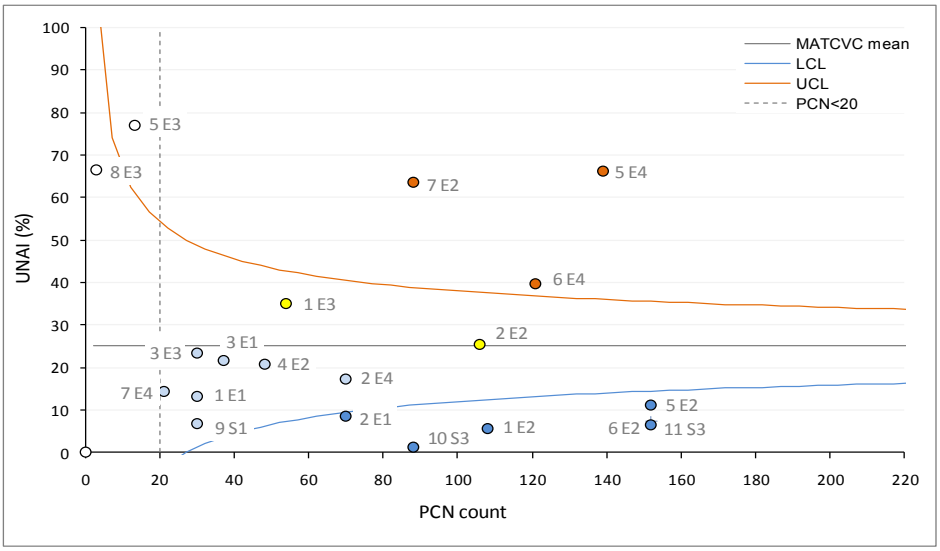
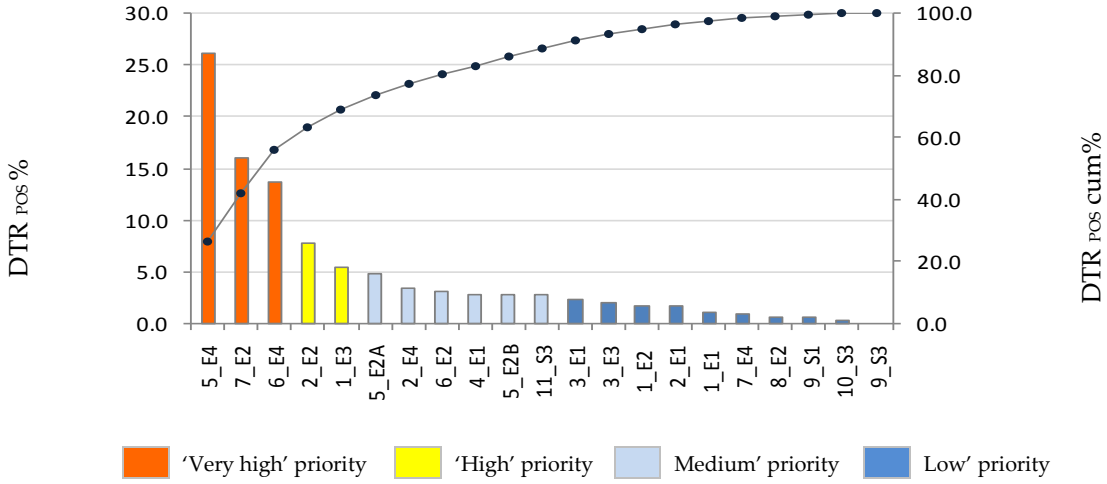


Figure 4.15: Outpatients (n = 152). Pareto chart for action composites



PCN = Pharmaceutical Care Need; DTR$_{POS}$ = Unexplained non-adherence; UNAI = Unexplained Non-Adherence Index

Legend: **MAT**$_{CVC}$ action composites

1E1	Achievement of INR target
1E2	Unmet need for TE prophylaxis
1E3	Choice of thrombo-embolic prophylaxis
2E1	Achievement of TC/LDL target
2E2	Unmet need for a statin
2E4	Suboptimal dose of statin
3E1	Achievement of HbA1c target
3E3	Choice of first line oral antidiabetic
4E1	Achievement of BP target
5E2	Unmet need for ACEI or ARB
5E3	Suboptimal intensity of RAS inhibition
5E4	Suboptimal dose of ACEI/ARB
6E2	Unmet need for a beta-blocker or alternative
6E4	Suboptimal dose of BB
7E2	Unmet need for short acting nitrate
7E4	Suboptimal dosing of regular nitrates
8E2	Unmet need for digoxin
9S1	Excessive INR
9S3	Choice of oral anticoagulants
10S3	High risk choice of drugs in CHD
11S3	High risk choice of drugs in CHF

Figure 4.16: Primary Care sample C1 (n = 548). Funnel plot of UNAIs (%) for MAT$_{CVC}$ action composites

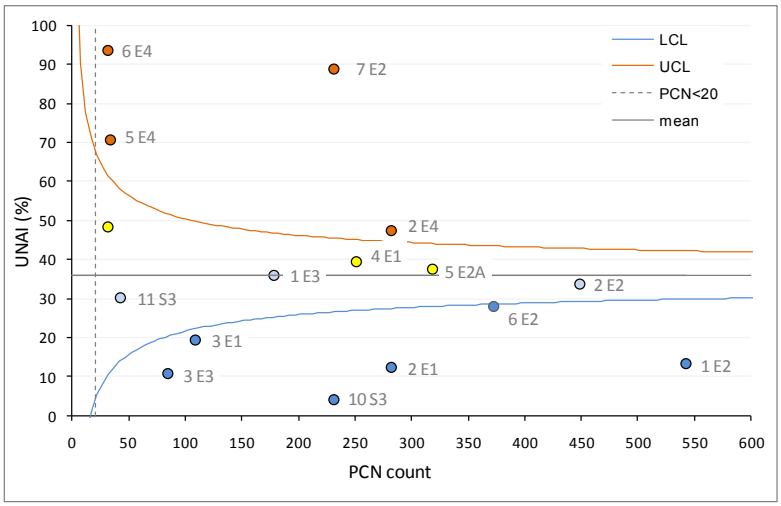
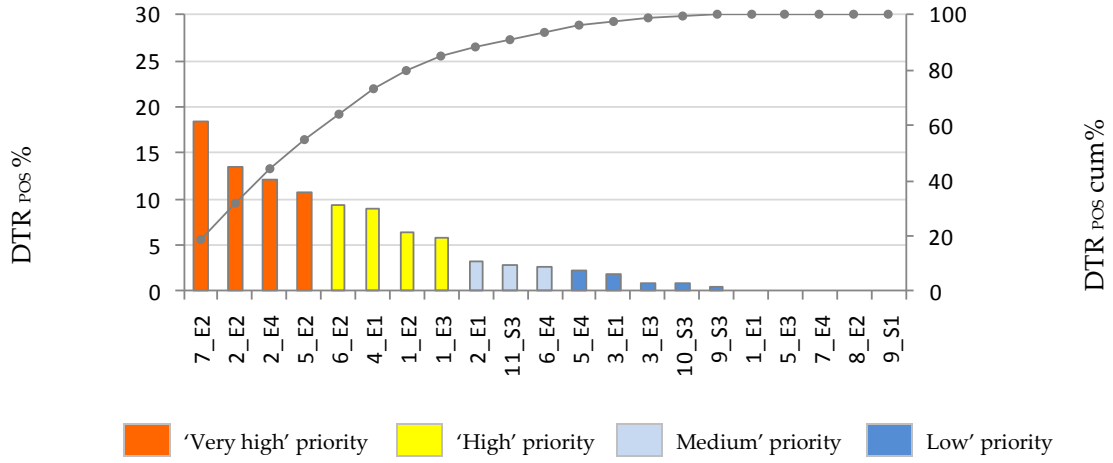


Figure 4.17: Primary Care sample C1 (n = 548). Pareto chart for action composites



PCN = Pharmaceutical Care Need; DTR$_{POS}$ = Unexplained non-adherence; UNAI = Unexplained Non-Adherence Index

Legend: **MAT**$_{CVC}$ action composites

1E1	Achievement of INR target	5E4	Suboptimal dose of ACEI/ARB
1E2	Unmet need for TE prophylaxis	6E2	Unmet need for a beta-blocker or alternative
1E3	Choice of thrombo-embolic prophylaxis	6E4	Suboptimal dose of BB
2E1	Achievement of TC/LDL target	7E2	Unmet need for short acting nitrate
2E2	Unmet need for a statin	7E4	Suboptimal dosing of regular nitrates
2E4	Suboptimal dose of statin	8E2	Unmet need for digoxin
3E1	Achievement of HbA1c target	9S1	Excessive INR
3E3	Choice of first line oral antidiabetic	9S3	Choice of oral anticoagulants
4E1	Achievement of BP target	10S3	High risk choice of drugs in CHD
5E2	Unmet need for ACEI or ARB	11S3	High risk choice of drugs in CHF
5E3	Suboptimal intensity of RAS inhibition		

Table 4.43: Primary Care sample C2 (n = 1,328). MAT$_{CVC}$ indexes for action composites

Funnel	Pareto	MAT$_{CVC}$ measures		DTR $_{POS}$/ PCN	UNAI	% of DTR $_{POS}$ total (n=775)
		4_E1	Achievement of BP target	224/442	0.51	28.9%
		2_E2	Unmet need for a statin	223/366	0.61	28.8%
		5_E2	Unmet need for RAS inhibitor	204/276	0.74	26.3%
		2_E4	Suboptimal dose of statin	80/936	0.09	10.3%
		3_E3	Suboptimal choice of oral antidiabetic	35/442	0.08	4.5%

'Very high' priority | 'High' priority | Medium' priority | Low' priority

PCN = Pharmaceutical Care Need; DTR$_{POS}$ = Unexplained non-adherence; UNAI = Unexplained Non-Adherence Index

Summary of identified priorities

Table 4.44 summarises the identified priorities for quality improvement in each setting and patient sample. The findings for MAT$_{CVC}$ *as a whole* show that approximately a quarter of all detected pharmaceutical care needs (PCNs) in the inpatient and outpatient settings, and a third of PCNs in each primary care sample, had apparently not been met in accordance with guideline standards, without identifiable explanations (unexplained non-adherence = DTR$_{POS}$).

In all patient samples, *monitoring* was identified to have substantial scope for improvement. Settings and patient sample differed, however, with respect to the relative priority assigned to different monitoring tasks. Monitoring of cholesterol targets was identified as 'very high' priority in the inpatient and primary care setting and 'high priority' in the outpatient setting.

The assessment of *recommended targets (E1)* for cardiovascular risk factors or INR was limited in all settings by deficiencies in monitoring. However, in the primary care sample without CVC, it accounted for almost 40% of all identified unexplained non-adherences (DTR$_{POS}$ events). Control of blood pressure in patients with and without CVC was identified as a 'high' and a 'very high' priority, respectively.

Underprescribing (E2) was identified as significantly higher than the proposed benchmarks in the outpatient and primary care settings, where it accounted for 36.3% and 58.6% of all detected unexplained non-adherences (DTR$_{POS}$ events). More

than half of these DTR_{POS} events in the outpatient setting and approximately a third in the primary care sample with CVC were attributable to the underuse of acute acting nitrates for angina prophylaxis. In addition, underuse of statins (2_E2) and RAS inhibitors (5_E2) was identified to be a 'very high' priority for quality improvement in patients with and without CVC. In the inpatient setting, the overall UNAI for under-prescribing was consistent with the proposed benchmark. However, the underuse of short acting nitrates was not assessed in this setting. In addition, underuse of statins was identified as a 'very high' priority, accounting for 10.5% of all identified DTR_{POS} events.

Suboptimal choice or intensity of treatment (E3). Lower than recommended intensity of thrombo-embolic prophylaxis was identified as a 'high' priority in all three settings, where it accounted for between 5 and 10% of the DTR_{POS} total. Although suboptimal choice of first line oral anti-diabetics in the inpatient setting only accounted for 1.8% of the DTR_{POS} total, the UNAI was relatively high (0.38) compared to the mean (0.22) and this aspect was therefore identified as a 'high' priority by the funnel plot approach.

Suboptimal dosing (E4). In the inpatient setting, suboptimal dosing accounted for over half of all detected non-adherences, to which apparent under-dosing of statins, beta blockers and RAS inhibitors contributed approximately equal parts, whereas inappropriate dosing of nitrates was a minor problem (0.3%). Underdosing of ACE inhibitors and beta blockers were also identified as 'very high' priorities in the outpatient setting on account of the respective UNAIs being higher than the UNAI mean in this setting. Underdosing of statins in patients with CVD was a much less widespread problem in the outpatient clinic than in the inpatient and primary care samples.

Only one of the *safety measures* was identified to be a 'high' priority in any of the three settings, which was higher than recommended choice/intensity of thrombo-embolic prophylaxis in patients with AF. This was attributable to the fact that all safety measures both had relatively low UNAIs and contributed only a minor proportion of unexplained non-adherences to the DTR_{POS} total.

Table 4.44: Summary of identified quality improvement priorities

MAT$_{CVC}$ measure		**A.** Inpatient (n=204)		**B.** Outpatient (n=152)		**C1.** Primary care (n=578)		**C2.** Primary care (n=1,328)	
		UNAI	Fraction of DTR$_{POS}$ total	UNAI	Fraction of DTR$_{POS}$ total	UNAI	Fraction of DTR$_{POS}$ total	UNAI	Fraction of DTR$_{POS}$ total
MAT$_{CVC}$ total		0.22	100%	0.23	100%	0.32	100%	0.31	100%
ME	**Monitoring**	0.47	100%	0.35	100%	0.60	100%	0.48	100%
	INR	0.05	2%	0.57	35%	Excluded		Excluded	
	TC/LDL cholesterol	0.63	76%	0.30	44%	0.76	55%	Excluded	
	HbA1c	0.38	22%	0.27	21%	0.67	19%	0.67	48%
	Blood pressure	Excluded		0.00		0.40	26%	0.28	52%
E1	**Achievement of targets**	0.13	8	0.15	7.9%	0.24	13.9%	0.24	39.2%
1_E1	INR	0.39	4%	0.13	1.1%	Excluded		N/A	
2_E1	TC/LDL cholesterol	0.02	1%	0.09	1.7%	0.12	3%	N/A	
3_E1	HbA1c	0.19	3%	0.22	2.3%	0.19	2%	0.22	10%
4_E1	Blood pressure	Excluded		0.21	2.8%	0.39	9%	0.24	29%
E2	**Under-prescribing**	0.15	25	0.20	36.3%	0.34	58.6%	0.48	55.1%
1_E2	TE-prophylaxis	0.08	4%	0.06	1.7%	0.13	7%		
2_E2	Statin	0.23	11%	0.25	7.7%	0.33	14%	0.50	29%
5_E2	ACEI or ARB	0.09	5%	0.11	4.8%	0.37	11%	0.46	26%
6_E2	Beta-blocker or alternative	0.12	6%	0.07	3.1%	0.28	9%	N/A	
7_E2	Acute acting nitrate	Excluded		0.64	18.4%	0.89	18%	N/A	
8_E2	Digoxin in CHF	0.00	-	0.67	0.6%	0.00	<1%	N/A	
E3	**Suboptimal choice/intensity**	0.10	7%	0.37	10%	0.28	7%	0.19	5%
1_E3	TE prophylaxis	0.19	6%	0.35	5.4%	0.35	6%	N/A	
3_E3	First line oral antidiabetic	0.32	2%	0.23	2.0%	0.10	<1%	0.19	5%
5_E3	RAS inhibition	0.50	<1%	0.77	2.8%	0.00	<1%	N/A	
E4	**Suboptimal dosing**	0.67	52.1%	0.44	9.1%	0.54	16.9%	N/A	
2_E4	Statins in CVD	0.56	18%	0.17	3%	0.47	12%	N/A	
5_E4	ACEI/ARB in CHF	0.69	16%	0.66	2%	0.68	2%	N/A	
6_E4	Beta blocker in CHF	0.83	18%	0.40	3%	0.94	3%	N/A	
7_E4	Regular nitrates	0.17	<1%	0.14	1%	0.00	<1%	N/A	
MS	**Monitoring**	0.05	2%	0.57	35%	Excluded		Excluded	
S1	**Excessive INR**	0.16	2%	0.07	0.6%	Excluded		N/A	
S3	**High risk drug choice**	0.25	6%	0.05	3.1%	0.16	4.1%	N/A	
9_S3	TE prophylaxis in AF	0.33	<1%	0	<1%	0.48	<1%	N/A	
10_S3	Drugs aggravating angina	0.01	<1%	0.01	<1%	0.04	<1%	N/A	
11_S3	Drugs aggravating CHF	0.18	5%	0.07	3%	0.30	3%	N/A	

Identified as 'very high' priority by ≥1 approach

Identified as 'high' priority by ≥1 approach, but not as 'very high' priority by any approach

5.4.2.2 Agreement of funnel plot and Pareto chart approaches

The extent to which the two approaches agreed in segregating between 'very high/high' priority measures on the one hand and 'medium/low' priority measures on the other, was assessed by pooling the findings for all four patient samples and using kappa statistics (table 4.45).

Table 4.45: Agreement between funnel plot and Pareto chart approaches in categorising action measures as 'very high/high' and 'medium/low' priority

		Pareto chart approach		
		Very high/ high	Medium/ low	**Total**
Funnel plot approach	Very high/ High	14	5	19
	Medium/ Low	9	35	44
	Total	23	40	63

$P_0 = 0.78$
Kappa = 0.50
ppos = 0.50
pneg 0.71

Overall, the Pareto chart approach identified slightly more 'very high/high' priorities for quality improvement than the funnel plot approach. Overall observed agreement was 78%, with higher agreement on identifying 'medium/low' priority measures (pneg = 71%) than on identifying 'very high/high' priority measures. Chance-adjusted agreement was 'moderate' (Kappa = 0.50).

5.4.3 Targeting patients

In order to identify *patients* with the greatest potential for quality improvement, the counts of DTR_{POS} events per patient detected by MAT_{CVC} as a whole were considered. For each setting, a Pareto chart displaying the frequency distribution of patients affected by different numbers of unexplained non-adherences (DTR_{POS}) was designed (figure 4.18). The x-axes show the DTR_{POS} counts/patient in descending order, with data columns (primary y-axes) representing the percentages of patients, who were affected by each respective number of DTR_{POS} events. The cumulative percentage of DTR_{POS} events (secondary y-axes) allowed determination of the

incremental percentage of DTR_{POS} events that could be addressed by reviewing each patient group, starting with those with the highest number of unexplained non-adherences.

A. Inpatients

Over 80% of patients with CVCs in the inpatient setting were affected by at least one unexplained non-adherence. The maximum number of identified DTR_{POS} events per patient was 5. The 32% of patients with three or more unexplained non-adherences were identified as the 'highest priority' group, accounting for 60% of all detected DTR_{POS} events.

B. Outpatients

Almost all heart failure outpatients (97%) were affected by at least one unexplained non-adherence. The maximum number of identified DTR_{POS} events per patient was 6. The 38% of patients with three or more unexplained non-adherences were identified as the 'highest priority' group, accounting for 60% of all detected DTR_{POS} events.

C1. Primary care patients with CVC

Over 80% of patients with manifest CVC were affected by at least one unexplained non-adherence. The maximum number of identified DTR_{POS} events per patient was 6. The 31% of patients with three or more unexplained non-adherences were identified as the 'highest priority' group, accounting for 55% of all detected DTR_{POS} events.

C2. Primary care patients without CVC

Less than 20% of patients with risk factors for (HTN or DM) but without manifest CVC were affected by at least one unexplained non-adherence. The maximum number of identified DTR_{POS} events per patient was 4. The 15% of patients with two

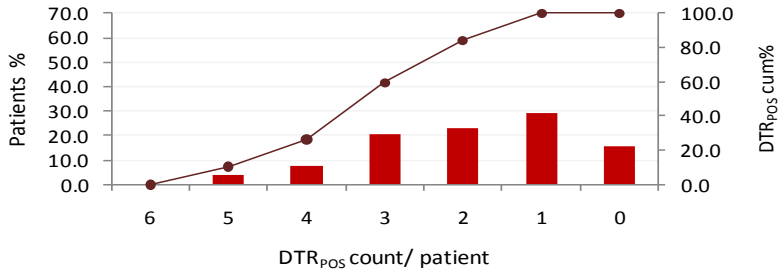
or more unexplained non-adherences were identified as the 'highest priority' group, accounting for 60% of all DTR_{POS} events detected in this sample.

Summary

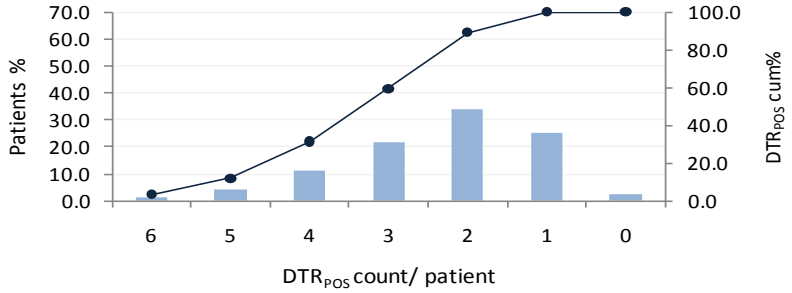
In all three samples that comprised of patients with manifest CVC, between 30% and 40% of patients accounted for between 50% and 60% of all non-adherences. In contrast, among primary care patients without CVC, non-adherences were concentrated in a smaller proportion of patients: 15% of patients with risk factors for CVC accounted for 60% of all non-adherences detected in this patient sample.

Figure 4.18: Pareto charts. Incremental contribution of patients affected by different numbers of unexplained non-adherences (DTR$_{POS}$ events) to the total of MAT$_{CVC}$ detected unexplained non-adherences (DTR$_{POS}$ total)

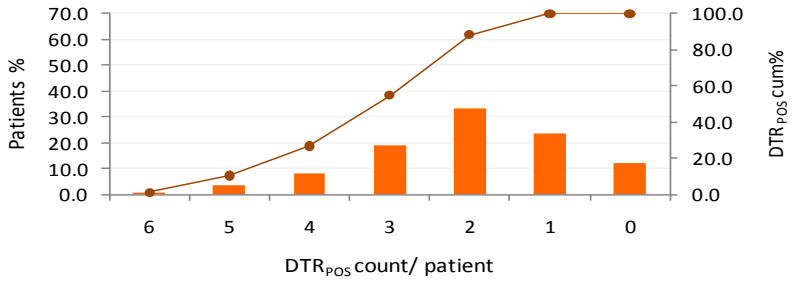
A. Inpatients: Patients with CVD, CHF or AF (n = 204)



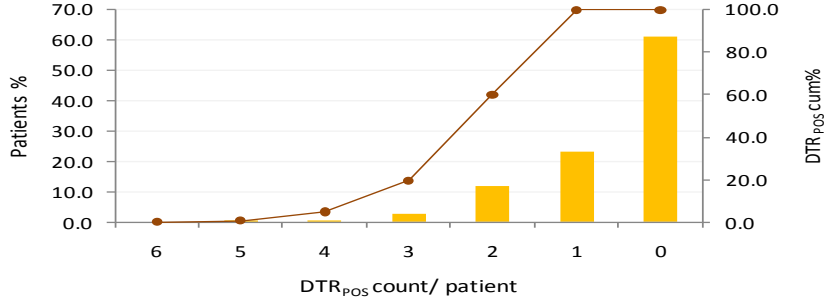
B. Outpatients: Patients with CHF (n = 152)



C1. Primary Care: Patients with CVD, CHF or AF (n = 548)



C2. Primary Care: Patients with HTN or DM without CVC (n = 1,328)



5.5 Feasibility

5.5.1 Time required for the abstraction of minimum data sets

A. Inpatient setting

It took the research assistant 15 sessions of (on average) two hours each in order to populate the MATcvc database with data extracted for 204 patients from patient discharge letters and the local electronic laboratory reporting system. The time required for information relevant to MATcvc to be extracted was therefore estimated at 10 min per patient.

B. Outpatient setting

The standardised data abstraction procedure required the research assistant to obtain information from multiple previous patient visits to the clinic in cases where relevant information, such as explanations for deviations from guideline recommendations, could not be identified from the most recent patient referral letters. This was frequently found to be the case and complicated the data abstraction procedure. It took the research assistant 11 sessions of (on average) four hours each to populate the MATcvc data base. The time required for the research assistant to populate the MATcvc data base was thus estimated at 15 to 20 min per patient.

C1. Primary care setting

Implementing the data base queries in each GP practices required approximately one hour per practice. The searches yielded case numbers of patients in electronic format, which facilitated data entry into the MATcvc data base. Locating the enrolled patients in the Pharmacom system and abstracting their relevant drug histories and biochemistry information took the research assistant 40 sessions of (on average) 4 hours duration. The estimated total time required to populate the MATcvc data base was thus estimated at 5 to 10 minutes per patient.

5.5.2 Definition of 90% confidence intervals

Table 4.46 shows proposals of 90% confidence intervals for MAT$_{CVC}$ as a whole and for prescribing composites indexes of unexplained non-adherence (UNAI). The proposed benchmarks for all indexes except for the monitoring indexes were based on the findings in the inpatient (n=204), outpatient (n=152) and primary care samples (n=548).

Table 4.46: Proposals for 90% confidence intervals for benchmark scores for MAT$_{CVC}$ as a whole and for prescribing composite indexes

MAT CVC composite measure	Proposed benchmark	Proposed 90% CI for benchmark
MAT CVC as a whole	0.25	± 0.075
ME- Monitoring for effectiveness	0.10	± 0.05
E1- Achievement of targets (Inpatient/Outpatient)	0.15	± 0.05
Achievement of targets (Primary Care)	0.35	± 0.10
E2 - Under-prescribing	0.15	± 0.05
E3 - Sub-optimal choice	0.35	± 0.10
E4 - Sub-optimal dosing	n.a.	
MS - Monitoring for safety	0.10	± 0.05
S1 - Control of safety parameters	0.10	± 0.05
S3 - High-risk choice	0.10	± 0.05

Since monitoring is perhaps less dependent on context factors than measures that pertain to underutilisation, medication choice, achievement of effectiveness and safety targets or target doses, respectively, the benchmark score was defined independent of the findings at UNAI = 0.10. The 90% confidence intervals were defined relative to the benchmarks proposed in order to account for the notion that higher targets (lower UNAI scores) may increase the demands on the reliability of measurements.

5.5.3 Estimated sample sizes under different sampling strategies

Table 4.47 shows estimates of sample sizes for MATCVC as a whole and for prescribing composite indexes based on the above proposed UNAI benchmarks and 90% CIs. The estimates shown are to be interpreted as the number of patients required for reliable estimation of UNAI scores under the assumptions that the same sampling strategies are employed and the case mix with respect to relevant cardiovascular conditions is similar as in the surveys reported here.

Table 4.47: Prescribing composites: Sample sizes required to achieve specified 90% confidence intervals on specified composite index benchmark scores based on sampling strategies used in the inpatient, outpatient and primary care surveys

Composite measure	**Index target** (90% CI)	**A. Inpatients (n=204)**		**B. Outpatient (n=152)**		**C1. Primary Care (n=548)**	
		Average PCN count/patient	Sample size	Average PCN count/patient	Sample size	Average PCN count/patient	Sample size
MATCVC	0.25(± 0.075)	8.8*	10	1.1*	8	7.0**	13
ME	0.10 (± 0.05)	1.1*	88	1.2*	81	1.2*	81
E1	0.15 (± 0.05)	1.1*	125	1.2*	115		
	0.35 (± 0.10)					1.2*	52
E2	0.15 (± 0.05)	3.7*	37	5.0**	28	3.0**	46
E3	0.35 (± 0.10)	0.7*	89	0.6*	103	0.5*	124
E4	nc		nc		nc		nc
MS	0.10 (± 0.05)	0.2*	485	0.2*	485	nc	nc
S1	0.10 (± 0.05)	0.2*	485	0.2*	485	nc	nc
S3	0.10 (± 0.05)	1.2*	81	1.6*	61	0.5*	194

<100 100 to 200 > 300; *= mean; ** = median ; Inpatient setting A: Sample of patients consecutively admitted to inpatient cardiology wards and diagnosed with CVD, CHF or AF; Outpatient setting B: Random sample of patients treated at an outpatient heart failure clinic; **C1** = Random sample of patients with CVD, CHF or AF registered with general practice in primary care; **C2** = Random sample of patients with DM or HTN but without CVD, CHF or AF registered with general practice in primary care; nc = not calculated

Based on these assumptions, the estimated sample sizes required for different composite measures were highly variable, ranging from less than 20 for MATCVC as a whole in all settings to almost 500 for the 'safety monitoring' and 'control of INR' measures. However, the latter of the aforementioned were not composite criteria in the strict sense, so that the maximum estimated sample size required for 'true' composite measures was under 300 (E3 - primary care setting). The estimated

required sample sizes were generally lower in the inpatient and outpatient settings than in the primary care setting, reflecting higher levels of cardiovascular co-morbidity and consequently, higher average counts of pharmaceutical care needs (index denominators) in the former. In the inpatient and outpatient settings, all six 'true' composite measures had estimated required sample sizes of less than 200 patients, while in the primary care setting, four composite measures fell below this threshold.

Based on estimates of the time required for the extraction of minimum data sets for MATCVC as a whole (10 to 20 minutes per patient), data capture for 100 patients by trained non-experts would take between 17 to 33 hours.

5.6 Inter rater reliability

5.6.1 Study samples

Stratified random sampling yielded 69 patient cases in the inpatient, 59 cases in the inpatient and 94 cases in the primary care setting. Although 25 patients were identified for each disease stratum in the inpatient (3 strata) and primary care settings (4 strata) and 40 patients in the outpatient setting (2 strata), the total numbers of patients do not add up to 75, 80 and 100, respectively, because the patients randomly selected from different strata overlapped in some cases.

5.6.2 Overall inter rater agreement for MATCVC

Comparison of the results of MATCVC assessments, that were obtained by applying MATCVC to the two independently abstracted data sets in each setting, yielded 'very high' levels of agreement with respect to both overall observed (p_o > 95%) and chance adjusted agreement (Cohen's kappa > 0.80). Chance adjusted agreement was very high in all three settings as reflected by overall Cohen's kappa values of 0.92 (outpatient setting) and 0.95 (inpatient and primary care setting), respectively.

5.6.3 Inter rater agreement for MAT$_{CVC}$ action composites

Table 4.48 shows observed and chance adjusted inter rater agreement for action composite measures. No DTR$_{POS}$ cases were identified for 6/19 implemented measures in the inpatient setting, for 3/21 implemented measures in the outpatient setting and for 4/18 implemented measures in the primary care setting. All action composites showed 'high' (Cohen's kappa 0.61 to 0.80) or 'very high' (Cohen's kappa < 0.80) levels of chance-adjusted agreement with the exception of one measure in the primary care setting (2_E1 - achievement of cholesterol targets), which showed moderate agreement (Cohen's kappa 0. 40 to 0.60). Inter rater agreement was 'high' (Cohen's kappa 0.61 to 0.80) for one measure (9_S1 – INR control) in the inpatient setting, one measure in the outpatient setting (2_E1 - achievement of cholesterol targets) and one measure (4_E1 - achievement of HbA1c targets) in the primary care setting. In all cases, where chance adjusted agreement was lower than 'very high', the percentage agreement on positive cases (ppos) was lower than for negative cases (pneg).

5.6.4 Inter rater agreement for MAT$_{CVC}$ prescribing composites

Among the prescribing composites, one measure could only be partially tested because DTR$_{POS}$ cases were identified from neither data set, so that only negative cases were available for comparison between raters (table 4.49). For all but one measure (S1 – Control of INR), very high' (Cohen's kappa > 0.80) levels of chance-adjusted agreement were found. For measure S1, only 2 DTR$_{POS}$ patient cases were detected from both data sets with one disagreement.

Table 4.48: Inter rater reliability: Action composites

MAT$_{CVC}$ measures												
	A. Inpatient (n = 69)				B. Outpatient (n = 59)				C. Primary Care (n = 94)			
	Po	ppos	pneg	Kappa	Po	ppos	pneg	Kappa	Po	ppos	pneg	Kappa
MAT$_{CVC}$ total												
	0.99	0.92	0.99	0.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Objective 1 - Thrombo-embolic prophylaxis												
1_E1	0.99	0.86	0.98	0.92	1.00	1.00	1.00	1.00	Excluded			
1_E2	0.99	0.83	0.98	0.90	1.00	1.00	1.00	1.00	0.99	0.86	0.99	0.92
1_E3	0.97	0.88	0.98	0.87	1.00	1.00	1.00	1.00	0.98	0.83	0.98	0.90
Objective 2 – Controlling dyslipidaemia												
2_E1	0.99	0.50	0.99	0.66	1.00	1.00	1.00	1.00	0.99	0.75	0.99	0.85
2_E2	1.00	1.00	1.00	1.00	0.95	0.79	0.94	0.85	1.00	1.00	1.00	1.00
2_E4	1.00	1.00	1.00	1.00	0.95	0.57	0.95	0.70	0.97	0.79	0.96	0.86
Objective 3 – Controlling diabetes												
3_E1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.99	0.88	0.99	0.93
3_E3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.99	0.88	0.99	0.93
Objective 4 – Controlling blood pressure												
4_E1	Excluded				1.00	1.00	1.00	1.00	0.94	0.78	0.92	0.83
Objective 5 – Controlling the RAS												
5_E2	0.99	0.86	0.98	0.92	0.97	0.78	0.96	0.86	1.00	1.00	1.00	1.00
5_E3	1.00	nc	1.00	nc	1.00	1.00	1.00	1.00	1.00	nc	1.00	nc
5_E4	0.97	0.90	0.96	0.93	0.97	0.67	0.96	0.78	1.00	nc	1.00	nc
Objective 6 – Controlling heart rate												
6_E2	0.99	0.88	0.98	0.93	0.95	0.86	0.93	0.89	1.00	1.00	1.00	1.00
6_E4	0.97	0.91	0.96	0.93	0.92	0.75	0.89	0.80	0.99	0.92	0.99	0.95
Objective 7 – Controlling angina symptoms												
7_E2	Excluded				1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
7_E4	1.00	nc	1.00	nc	1.00	nc	1.00	Nc	Excluded			
Objective 8 – Controlling fluid retention												
8_E2	1.00	nc	1.00	nc	0.98	1.00	1.00	0.74	1.00	nc	1.00	nc
Objective 9 – Controlling risk of haemorrhage												
9_S1	0.99	0.50	0.99	0.66	1.00	nc	1.00	Nc	Excluded			
9_S3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Objective 10 – Preventing drug induced angina												
10_S3	1.00	nc	1.00	nc	1.00	nc	1.00	Nc	1.00	nc	1.00	nc
Objective 11 – Preventing drug induced fluid retention												
11_S3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

nc = not calculable, because no patients were identified from either data set who had a DTR$_{POS}$ event for respective MAT$_{CVC}$ criteria. 5_E2 ACEI or ARB; 5_E3 Aldosterone ant. or ACEI+ARB comb.; 5_E4 Target dose ACEI/ARB; 6_E2 BB or alternative; 6_E4 Target dose BB; 7_E2 Short acting nitrate; 7_E4 Nitrate dosing; 8_E2 Use of digoxin; 9_S1 Excessive INR; 9_S3 Choice of TE prophylaxis; 10_S3 Drug choice in CHD; 11_S3 Drug choice in CHF;

Table 4.49: Inter rater reliability: MATCVC total and prescribing composites

MATCVC measures												
	A. Inpatient (n = 69)				B. Outpatient (n = 59)				C. Primary Care (n = 94)			
	Po	ppos	pneg	Kappa	Po	ppos	pneg	Kappa	Po	ppos	pneg	Kappa
Prescribing composites												
ME	0.99	0.93	0.99	0.96	0.99	0.63	0.92	0.93	0.88	0.63	0.85	0.69
E1	0.99	0.83	0.99	0.90	1.00	1.00	1.00	1.00	0.99	0.83	0.99	0.90
E2	0.99	0.91	0.99	0.95	0.97	0.84	0.97	0.90	1.00	0.98	1.00	0.99
E3	0.99	0.90	0.99	0.94	1.00	1.00	1.00	1.00	0.98	0.85	0.98	0.91
E4	0.99	0.94	0.98	0.96	0.96	0.70	0.95	0.80	0.99	0.85	0.98	0.91
MS	1.00	nc	1.00	nc	0.92	0.64	0.90	0.73	Excluded			
S1	0.99	0.50	0.99	0.66	1.00	nc	1.00	nc	Excluded			
S3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.91	1.00	0.95

nc = not calculable, because no patients were identified from either data set who had a DTRPOS event for respective MATCVC criteria. **E1** = Effectiveness parameters; **E2** = Under-prescribing, **E3** = Suboptimal choice; **E4** = Suboptimal dosing; **S1** = Safety parameters; **S3** = High risk choice

5.7 Relevance of pre-specified explanations

The overall prevalence of pre-specified explanations as a fraction of all identified pharmaceutical needs for MATCVC as a whole and prescribing composite measures has been reported above (subsection 4.5.2.2). It was shown that the prevalence was highest in the outpatient setting (0.06) followed by the inpatient setting (0.05) and was approximately 10 times lower in the primary care setting. Explanations for non-adherence (DTRs) were exclusively found for effectiveness measures in all settings. This section provides a more detailed account of the nature and relevance of explanations to quality measurement using MATCVC.

Table 4.50 summarises the rates of explained non-adherences (DTREXP) over all detected non-adherences (DTRs) found for MATCVC composite measures (ER = explanation rates). The explanation rates are reported for MATCVC as a whole and all prescribing composites, for which at least one explained non-adherence event was extracted in at least one setting. The colouring of cells identifies explanations to be

of low, moderate high or very high relevance to each measure as reflected by the respective explanation rates (see key for table 4.50).

Table 4.50: Summary of explanation rates (ER = DTR$_{EXP}$ / DTR)

MAT CVC measures	**A. Inpatient**		**B. Outpatient**		**C. Primary care**			
					C1. With CVC		C2. Without CVC	
	DTR count	ER	DTR count	ER	DTR count	ER	DTR count	ER
MAT CVC as a whole	458	0.17	442	0.21	1112	0.01	784	0.02
Prescribing/action composites								
E1-Achievement of targets	65	0.55	18	0.00	56	0.00	80	0.00
INR	17	0.12	4	0.00		0.00		0.00
TC/LDL	29	0.90	6	0.00	35	0.00		0.00
HbA1c	19	0.42	8	0.00	21	0.00	80	0.00
BP	Excluded		10	0.00	99	0.00	224	0.00
E2 - Under-prescribing	116	0.17	151	0.20	651	0.00	427	0.00
TE prophylaxis	22	0.32	6	0.00	72	0.00		0.00
Statin	47	0.15	34	0.15	151	0.00	223	0.00
ACEI or ARB	17	0.00	22	0.23	119	0.00	204	0.00
Beta-blocker (alternat.)	30	0.20	31	0.65	104	0.00		0.00
Acute nitrate	Excluded		56	0.00	205	0.00		0.00
Digoxin		0.00	2	0.00		0.00		0.00
E3 – Suboptimal choice	41	0.29	52	0.31	82	0.11	53	0.34
TE prophylaxis	30	0.30	21	0.10	64	0.00		0.00
Oral antidiabetic	10	0.30	21	0.67	18	0.50	53	0.34
RAS inhibition	1	0.00	10	0.00	0		0	
E4 - Sub-optimal dosing	209	0.05	198	0.23	187	0.00	0	0.00
Statin	68	0.00	13	0.08	134	0.00		0.00
ACEI/ARB	70	0.11	98	0.08	24	0.00		0.00
Beta-blocker	70	0.03	84	0.43	29	0.00		0.00
Nitrates	1	0.00	3	0.00		0.00		0.00

Low (<0.10) Moderate (0.10 to 0.24) High (0.25 to 0.49) Very high (≥ 0.50)

MAT$_{CVC}$ as a whole. Explanations that were identified by applying pre-specified rules were 'moderately' relevant in the inpatient and outpatient settings, explaining approximately 1 in 5 of all detected drug therapy risks in each setting, respectively. In contrast, in both primary care samples, the same set of rules explained only 1 and 2% of all detected non-adherences ('low' relevance).

Prescribing composites. When explanations were identified, they were of at least moderate relevance to most composite measures, with the exception of 'E4-suboptimal dosing' in the inpatient setting. The only prescribing composite, where explanations were found for more than half of all detected non-adherences was 'E1-Achievement of targets' in the inpatient setting.

Action composites. As for prescribing composites, explanations –when identified- were present in 10% or more of all detected non-adherences for the majority of measures, except for items pertaining to 'E4-suboptimal dosing'. Explanations were of 'very high' relevance to the 'achievement of cholesterol targets' in the inpatient setting, the 'underuse of beta blockers' in the heart failure outpatient clinic and 'suboptimal choice of metformin' as a first line oral antidiabetic in the primary care setting.

5.8 Concurrent validity

5.8.1 Comparison of validation and entire survey samples

Table 4.51 compares the demographics of patients, whose drug therapy was reviewed by resident clinicians, to the surveyed sample of each setting.

Inpatient sample

All 65 patients, for whom three or more unexplained drug therapy risks (DTR_{POS}) were identified, were reviewed by the cardiology consultant. In these patients, a total of 226 DTR_{POS} events had been detected. The average age of the validation sample was higher compared to the total sample of 204 patients enrolled into the inpatient survey. In addition, the proportion of patients with two or more of the targeted conditions (CVD, CHF and AF) was significantly (82% vs 54%) higher in the validation sample than in the total survey sample.

Table 4.51: Comparison of the demographics of the total survey sample and the sample selected for testing of concurrent validity in each setting

Demographics	A. Inpatient		B. Outpatient		C. Primary Care	
	Total n = 204, Sample n = 65 (32%)		Total n =152, Sample n = 58 (38%)		Total n=1,876, Sample n= 76 (4%)	
	Total	Sample	Total	Sample	Total	Sample
Age (years) median (IQR)	72(12)	79 (9)	72 (16)	75 (12)	66 (19)	73 (12)
Male	59%	59%	66%	63%	48%	54%
HTN/DM alone	N/A		N/A		71%	16%
CVD alone	30%	5%	N/A		20%	67%
CHF alone	4%	8%	29%	18%	1%	1%
AF alone	12%	-	N/A		5%	-
CVD and CHF	25%	41%	37%	38%	1%	8%
CVD and AF	11%	5%	-	-	1%	7%
CHF and AF	5%	16%	9%	8%	0.3%	-
CHF, CVD and AF	13%	25%	25%	35%	0.2%	1%

Outpatient sample

All 58 patients, for whom three or more unexplained drug therapy risks (DTR_{POS}) were identified, were reviewed by the panel of two clinical pharmacists. In these patients, a total of 209 DTR_{POS} events had been detected. On average, patients constituting the validation sample were 3 years older and a higher proportion of heart failure patients had relevant cardiovascular co-morbidities compared to the 152 patients enrolled into the outpatient survey.

Primary care sample

All 76 patients, for whom four or more unexplained drug therapy risks (DTR_{POS}) had been identified, were reviewed by each patient's general practitioner. In these patients, a total of 329 DTR_{POS} events had been detected. The average age of the validation sample was higher compared to the total sample of 1,876 patients enrolled into the primary care survey. As for the inpatient and outpatient samples,

the prevalence of cardiovascular co-morbidity was also higher in the validation sample compared to the surveyed population in total.

5.8.2 Validation

5.8.2.1 Uncertainty in the validation of DTR$_{POS}$ events

The resident clinicians, who conducted the reviews of DTR$_{POS}$ events, felt able to answer the validation question *('On the basis of the available information: Is a change of current drug treatment in accordance with the specified guideline recommendation desirable in this patient?'*) in the majority of cases in each setting based on the information available to them (table 4.51). In the inpatient setting the reviews were based exclusively on patient case summaries and patient discharge letters. In contrast, in the inpatient and outpatient settings, the whole medical record was available to reviewers. Nevertheless, the frequency with which 'uncertain' answers were recorded was lowest (4% of reviewed DTR$_{POS}$ events) in the inpatient setting while higher rates were found in outpatient (11%) and primary care settings (13%).

5.8.2.2 Positive predictive values

Table 4.52 shows the positive predictive values (PPVs) found in each setting for all MAT$_{CVC}$ measures. The PPV reflects the extent to which each measure succeeded in detecting truly unexplained non-adherence to guideline recommendations in each setting, as reflected by a 'Yes' answer to the question *'Is a change of current drug treatment in accordance with the specified guideline recommendation desirable in this patient?'.* A PPV of 1.00 reflects perfect success and a PPV of 0.00 implies complete failure.

The PPVs found for MAT$_{CVC}$ as a whole indicate that in the inpatient and outpatient settings, changes to current drug treatments were desirable in approximately 80% of reviewed DTR$_{POS}$ events. However, in the primary care setting, medication changes were considered to be indicated in less than 30% of allegedly unexplained non-adherences (DTR$_{POS}$ events). In the inpatient and outpatient settings but not in the

primary care setting, MAT_{CVC} as a whole was therefore found to be a valid instrument for the purposes of quality improvement (PPV > 0.50).

Table 4.53 shows that the overall findings for MAT_{CVC} as a whole were dominated by DTR_{POS} events relating to 'sub-optimal dosing' in the inpatient setting and 'under-prescribing' in the primary care setting, each accounting for approximately 60% of all reviewed DTR_{POS} events. In the outpatient setting, 'under-prescribing' and 'suboptimal dosing, together accounted for 82% of all reviewed DTR_{POS} events. For all prescribing composites, the positive predictive values were consistent with the PPV for the MAT_{CVC} as a whole. All prescribing composites in both inpatient and outpatient settings were found to have PPVs above 0.50, although the 95% confidence intervals for E3 (suboptimal choice), S1 (safety parameters) were wide, with lower limits below 0.50 (table 4.53).

Table 4.52: Positive predictive values for MAT$_{CVC}$ measures

MAT$_{CVC}$ measures	**1. Inpatient**				**2. Outpatient**				**3. Primary Care**			
	Tested	Uncertain	Yes	PPV	Tested	Uncertain	Yes	PPV	Tested	Uncertain	Yes	PPV
MAT$_{CVC}$ total	226	10	168	0.78	209	23	151	0.81	329	43	76	0.27
E1 Achievement of targets	21	3	18	1.00	23	6	9	0.53	61	7	26	0.48
INR	9	2	7	1.00	3	2	1	1.00	Excluded			
TC/LDL target	3	1	2	1.00	5	1	1	0.25	13	1	9	0.75
HbA1c target	9	0	9	1.00	7	2	1	0.20	16	1	9	0.60
BP target	Excluded				8	1	6	0.86	32	5	8	0.30
E2 Under-prescribing	42	0	34	0.81	74	8	59	0.89	198	27	37	0.22
TE prophylaxis	7	0	4	0.57	4	1	3	1.00	13	0	6	0.46
Statin	16	0	14	0.88	19	2	15	0.88	45	0	10	0.22
ACEI or ARB	8	0	7	0.88	11	0	10	0.91	49	0	6	0.12
BB or alternative	11	0	9	0.82	5	1	2	0.50	38	0	6	0.16
Acute acting nitrate	Excluded				35	4	29	0.94	53	27	9	0.35
Use of digoxin	0	-	-	-	0	0	0	-	0	-	-	-
E3 Suboptimal choice	13	3	6	0.60	29	5	16	0.67	16	0	0	0.00
TE prophylaxis	10	3	4	0.57	18	5	9	0.69	5	0	0	0.00
Oral antidiabetic	3	0	2	0.67	5	0	2	0.40	11	0	0	0.00
Intensity of RAS inhibition	0				6	0	5	0.83	0			
E4 Suboptimal dosing	129	0	100	0.78	74	3	62	0.87	41	4	9	0.24
Statin dose	38	0	36	0.95	7	1	6	1.00	29	3	8	0.31
ACEI or ARB	46	0	31	0.67	39	1	33	0.87	6	0	1	0.17
Beta Blocker	45	0	33	0.73	27	0	23	0.85	6	1	0	0.00
Nitrate dosing	0				1	1	0	1.00	Excluded			
S1 Safety parameters	2	0	2	1.00	1	0	1	1.00	Excluded			
S3 High risk drug choice	19	4	8	0.53	8	1	4	0.57	13	5	4	0.50
TE prophylaxis	2	2	0	1.00	0	-	-	-	5	0	2	0.40
Drugs aggravating angina	2	2	0	1.00	1	0	0	nc	5	5	0	nc
Drugs aggravating CHF	15	0	8	0.53	7	1	4	0.67	3	0	2	0.67

Table 4.53: Positive predictive values for prescribing composites

MAT$_{CVC}$ measures	**1. Inpatient**		**2. Outpatient**		**3. Primary Care**	
	Tested	PPV (95%CI)	Tested	PPV (95%CI)	Tested	PPV (95%CI)
MAT$_{CVC}$ total	226	0.78 (0.72,0.84)	209	0.81 (0.75, 0.87)	329	0.27 (0.22, 0.32)
E1	21	1.00 1.00	23	0.53 (0.29, 0.77)	61	0.48 (0.35, 0.61)
E2	42	0.81 (0.69, 0.93)	74	0.89 (0.81,0.97)	198	0.22 (0.16, 0.28)
E3	13	0.60 (0.30, 0.90)	29	0.67 (0.48, 0.86)	16	0.00 0.00
E4	129	0.78 (0.71, 0.85)	74	0.87 (0.79, 0.95)	41	0.24 (0.10,0.38)
S1	2	1.00 1.00	1	1.00 1.00		
S3	19	0.53 (0.28, 0.78)	8	0.57 (0.20, 0.94)	13	0.50 (0.15, 0.85)

E1 = Achievement of targets; E2 = Under-prescribing; E3 = Suboptimal choice; E4 = Suboptimal dosing; S1 = Safety parameters; S3 = High risk drug choice

The sample sizes for individual action composites were generally low, although for several measures, the numbers of cases reviewed were sufficiently large in all settings to highlight notable differences. For example, the PPV for '2E2 -Underuse of statins' was very high (0.88) in the inpatient and outpatient settings but much lower (0.22) in the primary care setting.

5.8.3 Stated reasons for non-adherence to guideline recommendations

In the inpatient and outpatient settings, the most commonly stated reason for apparent non-adherences to guideline recommendations was '*managed*' (71% of false positives identified in the inpatient sample and 83% in the outpatient sample), which meant that patients were clinically eligible in principle but that the current clinical state of the patient hindered the use of recommended treatments or the achievement of recommended targets (table 4.54). In contrast, in the primary care setting, over half (56%) of false positive cases were attributed to patients being permanently ineligible for guideline recommended treatments. This finding was most pronounced in the category 'Unmet need', where prescribers judged in 80/134 (60%) of detected instances that patients did not require or could not tolerate recommended treatments, respectively. 'Patient choice' accounted for a relatively minor proportion of false positive cases in all settings (0% in the inpatient, 3% in the outpatient setting and 5% in the primary care setting).

Table 4.54: Stated reasons for non-adherence in false positive cases

MAT$_{CVC}$ measures	**A.** Inpatient				**B.** Outpatient				**C.** Primary care			
	False positive	1. Not eligible	2. Managed	3. Pt choice	False positive	1. Not eligible	2. Managed	3. Pt choice	False positive	1. Not eligible	2. Managed	3. Pt choice
MAT$_{CVC}$ total	48 (100%)	14 (29%)	34 (71%)	0	35 (100%)	5 (14%)	29 (83%)	1 (3%)	210 (100%)	117 (56%)	83 (40%)	10 (5%)
E1 Achievement of targets	-	-	-	-	8	-	7	1	28	7	21	-
E2 Need for drug therapy	8	3	5	-	7	3	4	-	134	80	44	10
E3 Effective drug choice	4	1	3	-	8	2	6	-	16	8	8	-
E4 Effective dosing	29	3	26	-	9	-	9	-	28	21	7	-
S1 Safety parameters	-	-	-	-	-	-	-	-	Excluded			
S3 Safe drug choice	7	7	-	-	3	-	3	-	4	1	3	-

1. 'Not eligible': Patient is judged to be permanently ineligible for treatment according to guidelines
2. 'Managed': Patient is temporarily ineligible for guideline recommended treatment
3. 'Patient choice': Patient declines treatment or insists on high risk treatment

6. Discussion

6.1 Summary of findings

In order to explore the utility of a previously developed medication assessment tool for chronic cardiovascular conditions (MAT$_{CVC}$) within a model for continuous quality improvement of medication use, the instrument was field tested by conducting retrospective surveys in inpatient, outpatient and primary care settings. The surveys were conducted in specialist cardiology wards in a German hospital setting (setting A), a multidisciplinary heart failure outpatient clinic in Scotland (setting B) and a primary care setting in the Netherlands (setting C). In each setting, a representative sample of patients with relevant chronic cardiovascular conditions (CVC), comprising of cardiovascular disease, chronic heart failure or atrial fibrillation was identified and enrolled into respective surveys (patient samples A, B and C1). In the primary care setting, an additional sample of patients with cardiovascular risk factors (hypertension or diabetes) but without manifest CVC was studied (patient sample C2).

The MAT$_{CVC}$ was found to be implementable with minor amendments in order to account for differences between European and local guidelines and for variable access to relevant data, suggesting face and content validity of the instrument for use in a diverse range of settings. The estimated required time of data abstraction was in the range of 10 to 20 minutes per patient. Inter rater reliability for MAT$_{CVC}$ data capture was found to be high or very high in all settings. Pre-specified rules for contextualising MAT$_{CVC}$ assessment were identified to be of moderate relevance (in quantitative terms) to measured levels of guideline adherence in the inpatient and outpatient settings but of low relevance in the primary care setting. Concurrent validity was high in the inpatient and outpatient settings but low in the primary care setting.

A number of quality indexes were developed in order to facilitate reporting of explained and unexplained non-adherence and to make transparent limitations in

the underlying data sources. In order to illustrate the use of MAT$_{CVC}$ composite measures in a context of quality control, observed levels of achievements of inpatient, outpatient and primary care providers were compared to benchmarks. The feasibility of sample sizes required for reliable comparisons of MAT$_{CVC}$ composite scores to benchmarks were variable, but for the majority of prescribing and monitoring composite measures, sample sizes of less than 200 were estimated for all settings. In addition, two quantitative approaches (funnel plot and Pareto chart approaches) to identify specific quality improvement targets in an audit context were explored and compared, showing moderate agreement. By combining these approaches, priorities for quality improvement in guideline implementation in each setting were identified. The use of the MAT$_{CVC}$ as an instrument to target patients in each setting, who may benefit from a review of their medication was illustrated.

Global rates of guideline implementation in patients with manifest cardiovascular conditions (CVD, CHF or AF) as reflected by findings for MAT$_{CVC}$ as a whole, were found to be in the range of 67% to 72% in all three settings, but after adjustment for explained non-adherences rose to between 77 to 78% in the inpatient and outpatient settings.

6.2 MAT$_{CVC}$ measurement attributes

6.2.1 Reliability

Inter rater agreement of data capture of the MDS was tested between two data abstractors in each setting. The chance adjusted agreement for MAT$_{CVC}$ as a whole was 'very high' (Cohen's kappa 0.95 to 1.00) between pairs of pre-registration pharmacists, or pre-registration and fully trained pharmacists in all three settings.

Inter rater agreement for prescribing composites ranged from 'high' to 'very high' (Cohen's kappa 0.66 to 1.00) and for action composites from 'moderate' to 'very high' (Cohen's kappa 0.56 to 1.00). All prescribing composite measures and all except one action composite measure had at least 'high' chance adjusted inter rater agreement and for the vast majority 'very high' kappa values were found. Lower levels of agreement ('moderate' or 'high') were exclusively found for measures, which targeted the achievement of safety or effectiveness parameters, highlighting that accurately locating information on clinical or laboratory investigations may be more prone to random error than extracting medical diagnoses or current medication.

Strengths and limitations

The sampling strategy aimed to ensure that for each measure patients with unexplained non-adherences (DTR$_{POS}$ cases) would be selected, allowing inter rater agreement to be assessed on both positive and negative cases. However, for 6/19 (32%) action measures in the inpatient setting, 3/21 (14%) action measures in the outpatient setting and 4/18 (22%) action measures in the primary care setting, no DTR$_{POS}$ cases were included in respective samples. The distribution of positive and negative cases in samples subjected to inter rater reliability studies can be important to the interpretation of obtained kappa-values. If the prevalence of one category dominates within the sample, low kappa values may be obtained despite high levels of overall agreement, because the baseline probability of agreement by chance is higher in these cases (the kappa paradox[45,46]). Disagreement on a relatively small

number of cases within the less prevalent category therefore has a higher impact on kappa values. The fact that high kappa values were consistently obtained for MATcvc criteria despite low proportions of positive cases for a number of criteria can be seen as a further confirmation of the reliability of the measurement process.

The finding of high inter rater reliability is consistent with a previous investigation of the inter rater reliability of a medication assessment tool to assess guideline adherence of medication use in the management of heart failure (MAT-HF)[47], which has also found 'very high' (Cohen's Kappa 0.88) overall inter rater reliability for the 20 item instrument. In this study, the MAT-HF was applied by the developer of the tool and a 'second data collector' using the information collected from medical and nursing notes of 68 patients treated at a heart failure outpatient clinic.[47]

Previous research

Evidence that explicit criteria targeting high risk drug choice (S3) can be reliably applied by retrospective evaluation comes from application of a subset of the McLEOD's criteria (IPET) to 100 case note abstracts (Cohen's kappa = 1.0[48]) and from the STOPP criteria set (0.75 to 0.93 [49,50]) Similarly, Cohen's kappa values of 0.91 to 1.00 were found for the prescribing composite S3 in this MATcvc. START under-prescribing criteria have also yielded high levels of inter rater agreement when applied by pairs of community/academic pharmacists and physicians from different countries, yielding Cohen's kappa values ranging from 0.85 versus 0.87.[49,50] The MATcvc under-prescribing composite (E2) compared favourably, with Cohen's kappa values ranging from 0.90 to 1.00.

The pairs of assessors compared in the above cited studies have directly deployed respective instruments to medical case notes. In contrast, in the inter rater reliability studies presented here, data was first extracted by research assistants and subsequently analysed by the author of this thesis. Since the rather complex algorithm underlying the MATcvc assessment was identified as a potential source for error, the approach taken here was anticipated to make the assessment process

more reliable. Comparison of the findings shows, however, that both approaches may yield reliable results.

Conclusions on inter-rater reliability

The findings from the three inter rater reliability studies reported here (in addition to previous studies investigating similar approaches[47]) allow the conclusion that reliable MAT assessment by trained non-experts using routinely available clinical data sources is feasible.

6.2.2 Validity

6.2.2.1 Face and content validity - Need for local adaptation

In order to ensure the face and content validity of the MAT$_{CVC}$ instrument for use in different countries and care sectors, minimal adaptations of the instrument were required. Only one criterion in one setting required the adaptation of target cholesterol levels in order to account for current Scottish guidance.

The small differences between guidelines in different countries are a reflection of the fact that medication use in the management of chronic cardiovascular conditions is supported by a strong evidence base, which leaves little room for interpretation, which supports the MAT$_{CVC}$ as an instrument that is relevant to a wide range of clinical settings.

Although the scientific basis for the MAT$_{CVC}$ is strong, adaptation to local context will, however, often be required on feasibility grounds. For example, due to differences in the data sources available, not all MAT$_{CVC}$ items could be implemented in all settings (e.g. INR control in the primary care setting, prophylactic nitrate use in the inpatient setting). This factor needs to be taken into account when composite scores are used in order to compare achievements by different providers. In the surveys reported here, the exclusion of the action composite 'unmet need for acute acting nitrate' in the inpatient setting is likely to overestimate guideline adherence in comparison to the outpatient and primary care

settings. In the latter two settings, this measure contributed almost 20% to the total of all non-adherences. Exclusion of this item in the outpatient setting would lower the overall Unexplained Non-adherence Index (UNAI) from 0.23 to 0.20 and in the primary care sample with CVC from 0.32 to 0.28.

6.2.2.2 Contextual validity

In order to enhance the validity of MAT$_{CVC}$ without compromising feasibility and reliability, specific clinical exemption rules were designed to be deployed without clinical judgement. The explained non-adherence index (ENAI) was developed in order to make transparent the extent to which deviations from guideline recommendations may be 'clinically exempt' or 'managed'. Pre-specified clinical exemptions were extracted for all measures for which they had been designed in at least one setting. For MAT$_{CVC}$ as a whole these exemptions were categorised as being of 'moderate' relevance to the measurement of guideline adherence in the inpatient and outpatient settings, explaining approximately 20% of all detected non-adherences. However, in the primary care setting, explanation rates were lower (1-2%).

Strengths and limitations

An obvious limitation of the approach taken here is that reliance on routine documentation and pre-specified rules predisposes the findings to biases resulting from under-documentation of potentially relevant context factors. The findings suggest that this was particularly relevant in the primary care setting. However limited this approach may be, the fact that attempts have been made to take context factors into account, may lend credibility to the findings of MAT$_{CVC}$ assessment in an audit context.

Previous research

A Canadian group has taken a similar approach to the one described here in order to evaluate implementation rates for 17 'Proven interventions', of which all but two interventions overlapped with the 'E2 – Under-prescribing' criteria used here (1E2 - TE-prophylaxis, 2E2-statins, 5E2 - RAS inhibitors, 6E2 – rate limiting therapy).[52] In this survey of 150 inpatients discharged from general medical wards, pre-specified clinical exemption rules explained approximately half (48%) of all events, where 'proven interventions' were indicated but had not been implemented (non-adherence). In comparison, the pre-specified explanations used in the inpatient survey were approximately three times lower, explaining only approximately one fifth (17%) of the same non-adherence events. The likely explanation lies in the definition of exemptions rules, which overlapped in the case of beta blockers and statins, but were more lenient in the case of RAS inhibitors in the 'Proven Interventions' study (e.g. potassium >5.0 mmol/l vs 5.5 mmol/l and creatinine > 200µmol/l vs no exemption rule for renal impairment in 'Proven interventions' vs 'inpatient survey A', respectively). Consequently, 25% of all explanations in the Proven Interventions study but none (0%) in the inpatient survey reported here were found for underuse of RAS inhibitors. A further difference was that use of warfarin was defined as an explanation for non-use of aspirin in the 'Proven Interventions' study, whereas such cases were counted as 'adherence' under the MAT$_{CVC}$.

The surveys reported here confirm the feasibility of accounting for context factors, using pre-specified explicit rules. Comparison to the 'Proven Interventions approach'[52] suggests, however, that further validation work may be required in order to clarify the specific thresholds, at which guideline deviations are counted as 'explained' or justified. Further study is also required in order to define rules which allow the high risk choice of treatments that guidelines recommend should be

avoided in certain clinical situations (such as medication that may aggravate heart failure) to be contextualised.

6.2.2.3 Concurrent validity

In order to test the extent to which non-adherences detected by MAT$_{CVC}$ truly represented opportunities for quality improvement, a sample of cases in each setting was reviewed by resident clinicians. In each setting, those patients with the highest number of detected non-adherences were selected for review. The sampled patients were generally older and had more cardiovascular co-morbidities than in each sample overall. The positive predictive value for MAT$_{CVC}$ as a whole was > 0.80 in both inpatient and outpatient settings but substantially lower (0.27) in the primary care setting. In the inpatient and outpatient settings but not in the primary care setting, the concurrent validity was therefore considered to be sufficiently high for use in a quality improvement context.

Possible explanations for differences in findings between settings

A number of factors may explain the findings of lower concurrent validity in the primary setting versus the inpatient and outpatient settings. First, in the inpatient and outpatient settings, the reviewing clinicians were not directly involved in the care of patients. Similar to the MAT$_{CVC}$ assessment, the reviews were therefore reliant on routine documentation. In contrast, in the primary care setting, the reviews were conducted by each patient's general practitioner GP. It is possible that GPs had more information about each patient's clinical circumstances, which were unaccounted for by the MAT$_{CVC}$. Second, in the inpatient and outpatient setting, clinical exemptions were extracted approximately 10 times more frequently than in the primary care setting. This is likely to have increased the validity of the MAT$_{CVC}$ assessment, thereby increasing the likelihood that the detected non-adherences presented to clinicians were truly unexplained. Third, in the primary care setting, the main driver of the PPV obtained for MAT$_{CVC}$ as a whole pertained to the underuse of statins, RAS inhibitors and rate limiting therapy (37% of all reviewed

cases; PPV of 0.22 [statins], 0.12 [RAS inhibitors] and 0.16 [beta blockers]). The ubiquitous use of RAS inhibitors and beta blockers in patients with coronary heart disease without heart failure or prior acute coronary syndrome (ACS) is controversial[39,53] and this may provide a possible explanation for lower PPVs found for underuse of these drugs in the primary care setting, where substantially less CHD patients had co-morbid heart failure. However, the benefits of statin use for primary prevention in diabetes and for secondary prevention of vascular disease are uncontroversial. The fact that 78% of patients with identified unmet needs for statin treatment were considered not to require such treatment in the primary care setting (compared to 12% in both inpatient and outpatient settings), suggests differences in prescribing attitudes.

Strengths and limitations

The sampling strategy employed here (patients with the highest DTR_{POS} count were reviewed) in order to test the concurrent validity of the MAT_{CVC} instrument as a whole has limitations, since the patient population selected for review of clinicians was not representative of the patient population served in each setting. The patients selected for reviews were significantly older and had higher levels of co-morbidity. It is possible that both factors may influence the extent to which implementations of guideline recommendations are 'desirable'. It is currently unclear, however, whether and how these demographic differences may have influenced the findings. A number of studies suggest that higher levels of co-morbidity may favour the implementation of guidelines[25,30] while advanced age may reduce the propensity to receive guideline recommended treatments.[9,54,55]

Since it was not possible within the scope of this project to review all patients, the pragmatic approach taken here was taken in order to increase the overall number of DTR_{POS} cases reviewed and hence the accuracy of PPV estimates.

Previous research

Studies of concurrent validity for explicit medication assessment methods are relatively scarce in the literature. The concurrent validity between drugs-to-avoid criteria, such as the Beers set, and expert review of the same cases has been studied by Steinmann et al.[56], where 83/214 (39%) of instances of problematic prescribing identified by the Beers criteria, were considered problematic by expert review. Pont et al[57,58] have conducted a study, where the concurrent validity between automated applications of indicators to administrative data for underuse of inhaled corticosteroids in asthma were compared to individual patient assessments by patients' physicians. The corresponding PPVs ranged from 0.2 to 0.70[57,58]. None of the asthma indicators investigated was considered sufficiently valid to be used in performance assessment. However, one indicator met the pre-specified threshold for suitability in assessing prescribing behaviour (PPV = 0.70) Concurrent validity between the explicit STOPP/START criteria and expert application of the implicit Medication Appropriateness Index (MAI)/ Appropriateness of Underutilisation of Medicine (AUM) methods has been studied in a randomised controlled trial. Medication changes in accordance with STOPP/START criteria were associated with significantly lower mean MAI scores (lower scores indicating more appropriate prescribing) and increased use of START medications with significantly lower AUM scores, respectively.[59]

Although direct comparison between the findings for MAT$_{CVC}$ reported here and the latter reported study are not possible, the performance of MAT$_{CVC}$ in the inpatient and outpatient settings, but less so in the primary care setting, thus compares favourably to the Beers criteria and Pont's asthma indicators.

Conclusions on concurrent validity

The positive predictive value (and sensitivity) required for validity varies depending on the purpose for which a measure or a set of measures is to be used. If an instrument is to be used to screen for patients with potentially suboptimal

medication use (*patient targeting*), then it is desirable that the initial screening process identifies as many patients as possible who then undergo further review. Consequently, for this application sensitivity may be more important than the positive predictive value. If a measure is to be used to monitor changes in drug utilisation (*audit or quality control*), then it may be sufficient if only a selection of the patients of interest is identified. In this case, the PPV becomes relatively more important than the sensitivity.[57]

Although not formally tested, it is reasonable to assume that the sensitivity of MAT_{CVC} assessment in the detection of drug therapy risks is high. Potential threats to sensitivity are that (1) explanations are identified when they are absent, (2) drug treatments are identified to be prescribed when they are not or (3) therapeutic targets are considered to be achieved when they are not. With respect to (1), there is no risk that explained non-adherences are lost to patient follow-up in patient targeting applications, because the MAT_{CVC} algorithm distinguishes between *explained non-adherences* (DTR_{MAN} or DTR_{EXE}) and adherences (PCN_{MET}). In view of the finding of 'very high' inter rater reliability (Cohen's kappa > 0.80) of data capture, the second (2) and third (3) threat may also be considered theoretical.

In this study, the sample size estimate has been based on the assumption that a PPV of 0.50 would suffice for both patient targeting and quality control applications. Under the assumption of high sensitivity, the MAT_{CVC} as a whole can therefore be considered to be 'fit for purpose' in the inpatient and outpatient settings. This claim holds true, even if (consistent with previous authors[57]) a higher PPV of 0.70 is stipulated for applications in quality control, research or performance judgement.

6.2.3 Utility of MAT$_{CVC}$ in quality control, audit and patient targeting

Quality indexes

A number of indexes have been developed in order to account for and quantify the uncertainties associated with explicit quality assessment methods using routine data. The data gap index was developed in order to make transparent the extent to which limitations in routine clinical documentation hinder the assessment process. The 'explained non-adherence' index (ENAI) was designed to account for context factors that may impede the implementation of best practice standards in an attempt to increase the validity of findings. The calculation of these indexes was enabled by the use of the MAT$_{CVC}$ algorithm, which segregates assessed cases into six different answer categories.

All indexes have been defined to represent a fraction (numerator) of all instances, where respective measures were relevant (denominator), so that the sum of all indexes adds up to 1.00. The simple mathematical relationship of the indexes used facilitates graphical display and interpretation and compensates for the complexity of using multiple metrics. In addition, the reporting of the data gap index (DGI) alongside metrics that reflect levels of (non-)adherence allows shortcomings in documentation to be interpreted not only as limitations that potentially affect the validity of survey findings, but as quality problems in their own right.

An additional advantage of the quality indexes proposed here is that their relationship to each other allows changes in the quality of medication use to be easily traced. For example, improvements in the documentation of context factors that justify deviations from best practice standards would decrease the unexplained non-adherence index (UNAI) score by the same amount as it would increase the explained non-adherence (ENAI) score.

Composite measures

The potential advantages that composite measures have with respect to feasibility have been highlighted above. Composite measures may also have advantages with respect to communicability, because the number of individual measures is contained.

A number of authors[19,47,60,61] have previously used composite scores to reflect the quality of care provided for a particular disease or in order to assess the implementation of a specific guideline. In this thesis, composite scores have been defined at the level of drug therapy risk categories in order to reflect prescribing and monitoring processes. It is proposed that such measures may have advantages over disease level scores, because they may better allow the identification of the specific process stages within the medication system that may impede its performance. For example, relative underperformance in monitoring, achievement of targets for cardiovascular risk factor control or failure to achieve target doses of beta blockers or RAS inhibitors may indicate problems at the follow-up stage of the medication use process, whereas under-prescribing, suboptimal or high risk drug choice may indicate problems at the initiation stage. The distinction is relevant, since knowing the underlying cause is a pre-requisite to guide the choice of improvement strategies. Weaknesses at the initiation stage may point to knowledge gaps of practitioners, failures of decision support systems or adverse effects of policies, such as prescribing budgets. In contrast, problems at the monitoring stage may primarily point to problems in the organisation of care (care delivery design), including inadequate staffing. With reference to Donabedian's (S)tructure-(P)rocess-(O)utcome paradigm[62], composites that reflect medication use patterns may therefore allow linking process measurements to problems in the underlying *infrastructure*. In contrast, composites that aggregate measures at disease level may be better suited to predict patient *outcomes*. Since the focus in this thesis is on identifying strategies for quality improvement, the decision was made to explore the use of composites that may allow targeting medication use processes.

6.2.3.1 Targeting prescribing composites (Quality control)

Benchmarks for targeting medication use processes

In order to identify priorities for quality improvement at the level of prescribing and monitoring composites, benchmarks have been estimated, against which levels of unexplained non-adherence were compared. The benchmarks were derived from findings of large scale quality improvement programmes, where available. The rationale for this approach was to identify levels of guideline implementation that can be assumed to be achievable when targeted effort is applied. In a context of continuous quality improvement, such benchmarks may provide a more appropriate target than comparisons against provider averages, which may lead providers to falsely assume that implementation rates are acceptable, when considerable scope for improvement remains.

However, the benchmarks presented here require cautious interpretation. First, the literature has not reported composite scores of the same definition as used in the surveys here. In addition, for a number of composite measures (MAT$_{CVC}$ as a whole, safety monitoring, high risk drug choice and suboptimal dosing), it was not possible to locate publications that reported achievements against these or similar measures. A benchmark for suboptimal dosing was therefore not estimated. In the case of safety monitoring, it may be reasonable to assume that tests should be performed regularly in all patients, especially in the case of INR monitoring. Even in the absence of published data, it therefore appeared reasonable to define the benchmark at 0.10. In the absence of comparable information from other sources, the benchmark for MAT$_{CVC}$ as a whole were informed by the lowest level of non-adherence found in the surveys conducted here.

It is important to note that the proposed benchmarks refer to the '*Unexplained* Non-Adherence Index', which implies that the ideal level of achievement would be 0.00 for all measures (because all proposed benchmarks will be achievable either by improvements in guideline implementation or by explicitly documenting reasons

for deliberate deviations from recommended standards). However, the data sources used in the surveys reported here were not specifically designed for the purposes of quality assessment and UNAI of 0.00 may therefore be an unreasonable expectation at the current time. Comparing the observed levels of achievement against levels of guideline adherence achieved after the implementation of quality improvement programmes allowed encircling those prescribing patterns that may bear the largest scope for improvement in each setting. The proposed benchmarks may provide practitioners and managers with a rough guide of what is currently achievable.

Adequacy of sample size

In settings where routine quality assessment is hindered by limited accessibility of relevant data, periodic audit of medication use may be a means of exposing weaknesses in the performance of medication use systems. In this context, the use of composite measures has feasibility advantages, since the numbers of patients required to allow comparisons of findings to benchmarks are lower. The sample sizes required for reliable comparison against benchmarks were estimated for each setting separately in order to account for case mix variations and differing patient sampling strategies. Under the assumption that the same sampling strategies are employed as in the surveys reported here, the required sample size for MATcvc as a whole was below 20 in all settings. The sample sizes for all but two composite measures were below 200 in all settings. In the settings studied here, the time required for data to be abstracted for 100 patients was estimated to take between 2.5 to 5 days (primary care setting). Based on these estimates and the estimated time required for MATcvc data capture, the findings suggest that comprehensive quality assessment of medication use for multiple cardiovascular conditions may be feasible, but will require a commitment to quality improvement, especially where MATcvc assessment cannot be automated.

6.2.3.2 Targeting action composites (Audit)

Use of Pareto charts and funnel plots to identify improvement priorities

When large numbers of quality measures are used in order to characterise the quality of medication use in one setting, the most intuitive approach to identifying those measures that apparently bear the greatest potential for improvement would be to target those with the highest rates of unexplained non-adherence, as reflected by the UNAI index. However, since the numbers of patients to which different MAT$_{CVC}$ measures apply are highly variable, the UNAI index is more vulnerable to random variation for measures that are relevant to small numbers of patients only (large confidence intervals for measures with small denominators). One means of accounting for random variation are funnel plots, where those measures that are statistically significantly different from the mean UNAI of all measures are visually exposed.

The underlying assumption in this approach is that the desirable level of adherence is the same for all measures, where a greater departure from the same comparator (i.e. the mean in this case) would imply higher potential for improvement. The assumption holds true under the premise that guidelines should either be adhered to or, if deemed inappropriate, a reason for deviating from the guideline should be documented. As highlighted above, under this assumption, the ideal level for all measures would be an UNAI of 0.00. The funnel plot approach would thus identify those measures with the relatively greatest *rates* of departure from ideal in each setting

The funnel plot approach is, nevertheless, limited, in that measures with a relatively low UNAI (i.e. below the UNAI mean of all measures) but high *absolute numbers* of patients with unexplained non-adherences would be missed. The Pareto chart approach is supplementary in this respect, since it targets those measures with the greatest absolute numbers of patients affected by unexplained non-adherences, irrespective of the UNAI score.

The relevance of these considerations has been demonstrated by the comparison of the two approaches as means of segregating between 'high/very high' and 'medium/low' priorities for quality improvement in each setting. The chance adjusted agreement of the two approaches was only moderate (Cohen's Kappa = 0.50). After pooling the results for all four samples included in the surveys reported here, the Pareto chart identified 9 action composites that would have been missed by the funnel plot approach, while the Funnel plot approach identified 5 measures that would have been missed under the Pareto chart approach.

An important limitation of both approaches is, however, that both are merely quantitative, implying the risk that crucially important measures with both low UNAI scores *and* low numbers of non-adherences would be missed by both approaches. The high-risk use of medication that may aggravate heart failure, such as non-steroidal anti-inflammatory drugs or verapamil, is an example. The above proposed measures on their own therefore do not suffice as a means of prioritisation and need to be supplemented by clinical judgement in relation to their relative impact on patient outcomes. Nevertheless, if the clinical relevance of a number of measures is considered to be similar, the combination of the above proposed quantitative strategies of highlighting the apparently largest shortcomings in guideline implementation may prove useful.

6.2.3.3 Patient targeting

In all three samples that comprised of patients with manifest CVC, between 30% and 40% of patients accounted for between 50% and 60% of all non-adherences. In contrast, among primary care patients without CVC, non-adherences were concentrated in a smaller proportion of patients: 15% of patients with risk factors for CVC accounted for 60% of all non-adherences detected in this patient sample.

The approach taken here, illustrates the potential use of the MAT_{CVC} as an instrument to encircle subgroups of patients who may benefit from a review of their medication. It is important to note, however, that, especially in samples of patients

with manifest cardiovascular conditions, solely concentrating on those with the highest numbers of drug therapy risks would still miss a substantial proportion of apparently unaddressed drug therapy risks. In addition, the same limitations regarding the purely quantitative nature of this approach apply as highlighted above.

6.3 Status quo of guideline implementation

Unadjusted levels of non-adherence to guideline recommendations as reflected by the non-adherence indexes (NAI) for MAT_{CVC} as a whole were comparable in inpatient (0.27) and outpatient settings (0.29) but significantly higher ($p<0.001$) in the primary care samples (0.33 and 0.32). These differences were further pronounced after adjustment for pre-specified scenarios of explained non-adherence, which were also significantly more commonly identified in inpatient and outpatient settings than in the primary care setting. As a result of such adjustments, the *unexplained* non-adherence index (UNAI) found in the inpatient setting was 0.22, in the outpatient setting 0.23, while it was only marginally different from the NAI in both primary care samples (0.32 and 0.31). Comparison to benchmarks identified '*ME – monitoring'* of cardiovascular risk factors and *'E2 - under-prescribing'* as the medication use processes with the greatest potential for quality improvement. In addition, in the inpatient and outpatient settings, *'E4 – Underdosing'* accounted for more than 50% of all identified unexplained non-adherences.

6.3.1 Comparison to large scale surveys

Monitoring and achievement of targets

While hospitalisations provide an opportunity to assess risk factor control and to initiate or intensify treatment under professional supervision, patient monitoring and achievement of targets is primarily the responsibility of long term care providers. In the Dutch primary care setting, 33% of patients treated for hypertension, 67% of patients treated for diabetes and 76% treated with statins did not have a documented blood pressure, HbA1c and cholesterol level in the previous 48 weeks. In comparison, under the UK quality and outcomes framework (QOF)[xiv], monitoring gaps for the same risk factors were 10% or lower within the same time frame. These findings suggest considerable scope for improvement.

The observed deficiencies in monitoring meant that 'E1-Achievement of targets' could only be assessed in a proportion of patients in each setting, implying that the results should be interpreted cautiously. In the primary care setting, 39% of treated patients with and 51% of those without manifest CVC had not achieved recommended blood pressure, cholesterol or HbA1c targets. Comparative data (again) comes from the QOF, where approximately 25% of patients with CVD or diabetes had not achieved recommended cholesterol targets (total cholesterol < 5mmol/l), approximately 30% had not achieved HbA1c targets (< 8%) and 12% had not achieved blood pressure targets (<150/90 mmHg). The results are not directly comparable, because in the surveys reported here, care was assessed against optimal targets rather than the audit standards used in the QOF. Nevertheless, the achievements in the Dutch primary care setting for cholesterol and HbA1c control compared favourably to the QOF data, with unexplained non-adherence rates of < 25%. However, in view of the fact the assessment of cardiovascular risk factor

[xiv] All QOF data reported here represent 'unadjusted' levels of achievement, since the QOF accepts a larger range of exceptions than used in the surveys reported here and exception rates are substantially higher.

control was constrained by data gaps for all risk factors as described above, it is likely that the reported levels overestimate achievements in the primary care population enrolled into this survey. Patients who are monitored more consistently are also likely to be treated more intensively than those where regular monitoring did not take place.

Under-prescribing

'E2-Underprescribing (E2)' was identified as a priority for quality improvement in the outpatient and primary care settings. While in the outpatient setting, underuse of short-acting nitrates was mainly responsible for apparent under-achievements against the proposed benchmark (UNAI = 0.15), in the primary care setting, apparent underutilisation of thrombo-embolic prophylaxis, statins, RAS inhibitors and rate limiting therapy were additionally identified. Although, under-prescribing of the aforementioned treatments was much less common in the inpatient and outpatient settings, apparent underuse of statins was a prominent problem in all surveyed patient samples.

The underuse of evidence based drug therapies for cardiovascular conditions has been studied in numerous surveys, over the last decade. Surveys have mainly been conducted in inpatient and outpatient settings and have focussed on the implementation of thromboembolic prophylaxis, statins, RAS inhibitors and beta blockers from the perspective of one condition, namely coronary heart disease, chronic heart failure or atrial fibrillation. A recent survey (2009), which enrolled 237,555 patients with coronary heart disease discharged from 472 US hospitals and closely matched the patient inclusion criteria for the inpatient survey reported here, found relatively low rates of under-prescribing of thrombo-embolic prophylaxis (6%), statins (9%), RAS inhibitors (20%) and beta blockers (6%) at the point of hospital discharge.[19] While similarly low or lower rates of under-prescribing of thromboembolic prophylaxis (8%), RAS inhibitors (9%) and rate limiting therapy (12%) were found in the inpatient survey reported here, comparison to the US

survey confirms that substantial scope remains in this setting in relation to statin use (23% of CVD patients undertreated).[19]

In the primary care setting, comparison to the QOF appears to confirm scope for improvement mainly for the underuse of RAS inhibitors in patients with CVD, diabetes and heart failure, which was 37% (in patients with CHD or CHF) and 46% (in patients with diabetes only) versus 8% and 20% in the QOF[21], respectively. Rates of underuse of thromboembolic prophylaxis in patients with CVD or AF (13% in the primary care survey versus 8% in the QOF[21]) and of beta blockers (28% versus 20 to 40% in different patient subgroups in the QOF[21]) were similar.

The use of RAS inhibitors and beta blockers in patients enrolled into the outpatient heart failure clinic survey were consistent with the findings of a similar survey conducted in the US, where RAS inhibitors were apparently under-used in 15% (11% in the survey reported here) and beta blockers in 5% (7% in the survey reported here) of heart failure patients.[29]

Suboptimal choice and treatment intensity

The composite UNAI score for 'E3 -suboptimal choice or intensity of drug treatments' was found to be significantly higher than proposed benchmarks in outpatient and primary care settings, where lower than recommended intensity of thromboembolic prophylaxis was identified as the most prominent quality problem, affecting 35% of eligible patients (CHD or AF) in both settings. The findings were, however, consistent with levels reported in larger scale inpatient and outpatient surveys (33% [29] to 40% [28]).

Suboptimal dosing

Comparative data for under-dosing of statins in CVD could not be located in the literature. Similarly, only one survey was found which reported the achievement of target doses of RAS inhibitors and beta blockers in CHF (Euro heart survey on heart failure 2002).[25] However, this survey did not report the proportion of patients, who

had achieved recommended targets but rather the percentage of the recommended target dose that patients were prescribed on average (approximately 50% for RAS inhibitors and 'far below target doses' for beta blockers). Comparisons are therefore not possible and the extent to which improvements against the respective MAT_{CVC} criteria are achievable remains unclear.

The approach of appropriate dosing of RAS inhibitor and beta blockers taken here may have advantages, when used to identify patients, who may benefit from dose intensification but may be limited in an audit or quality control context, where the percentage of target doses achieved on average may be more meaningful.

High-risk prescribing

High risk use of medication was overall rare, accounting for 5% or less of all detected unexplained non-adherences in all three settings. Nevertheless, in the primary care setting, 48% of patients with AF with apparently low risk of stroke received oral anticoagulants and 30% of heart failure patients received treatments that are known to aggravate heart failure. Comparative data could not be located in the literature.

The $CHADS_2$ score is only one among other stroke risk stratification schemes for patients with AF and has recently been refined to include previously not considered vascular risk factors (myocardial infarction, peripheral vascular disease) and female gender (CHA_2DS_2-VASc).[63] According to this score, all female patients would be appropriately treated with oral anticoagulants and it is therefore likely that the UNAI scores observed for this MAT_{CVC} measure may underestimate the appropriateness of thrombo-embolic prophylaxis provided.

6.3.2 Strengths and limitations

Accuracy of data sources

A previously acknowledged limitation of the surveys reported here is the reliance on routinely available data which meant that not all measures could be implemented in all settings. In addition, since non-adherences were only labelled as 'explained' when pre-specified rules applied, the prevalence of explained non-adherence reported here is an underestimation of the true prevalence, especially in the primary care setting, as demonstrated in the concurrent validity studies discussed above.

In the inpatient and outpatient setting, diagnostic and medication related information was extracted from patient discharge or referral letters, which can be assumed to be of acceptable accuracy. In the Dutch primary care setting, the prevalence of all targeted conditions was comparable to the reported prevalence in the general Dutch, European or US populations, although the prevalence of heart failure and coronary heart disease was slightly lower and the prevalence of diabetes higher than reported prevalence ranges. Not all general practices included in the primary care survey solely used the electronic record (MEDICOM™), from which diagnostic information was abstracted and it is therefore possible that not all patients with relevant diagnoses or risk factors could be identified.

6.3.3 Conclusions for guideline implementation

Although not a declared aim of the surveys reported here, it is important to acknowledge that inferences about levels of guideline adherence in populations of hospital inpatients, heart failure outpatients or primary care patients at large, are not possible due to the small sample size. This limitation is further supported by the findings that the inpatient and outpatient populations enrolled into the surveys reported here had significantly higher levels of cardiovascular co-morbidity, were

older and in the outpatient sample, had higher severity of heart failure than in identified reference populations.

While it is therefore clear that the survey findings are not generalisable to patient populations beyond those served in each respective setting, the patient samples can be assumed to reflect the status quo of guideline implementation *within* each setting at the time the surveys were conducted. In the primary care setting, all patients with relevant cardiovascular conditions (cardiovascular disease, chronic heart failure or atrial fibrillation) or risk factors (diabetes or hypertension) were enrolled. In the inpatient setting, the incidence rate and distribution of relevant cardiovascular conditions was found to be representative of the general patient population served in this setting. Nevertheless, the extent to which the Scottish outpatient sample was representative of the heart failure population served in this setting could not be confirmed.

The survey findings show considerable scope for quality improvement in the implementation of guidelines in the pharmacological management of patients with risk factors for or manifest chronic cardiovascular conditions. Deficiencies in global rates or specific aspects of monitoring and achievement of targets for cardiovascular risk factor control, underuse of recommended treatments, suboptimal choice and dosing referring to patients with all targeted risk factors and conditions were identified in all settings. These findings have two main implications: First, the findings support the argument for systematic multifaceted approaches to address shortcomings at the initiation, monitoring and follow-up stages of the medication use process and suggest that such approaches will be required across all health care sectors. Second, quality assessment approaches, which solely focus on one disease or drug therapy risk category, are likely to miss a large proportion of deficits in the provision of pharmaceutical care. The MAT$_{CVC}$ is an example of how multiple diseases and medication use processes can be organised into an instrument, which is capable of exposing medication use processes in need of improvement (at system level) and drug therapy risks to be addressed (at patient level). It is hoped that it

will serve as a starting point for the integration of explicit quality assessment instruments, which can collectively provide a comprehensive picture of the quality of medication use across the continuum of pharmaceutical care.

7. Chapter summary and conclusions

The work presented here has tested a large set of explicit assessment criteria for the pharmacological management of multiple cardiovascular conditions for measurement attributes that have been identified to be desirable for applications of quality assessment instruments in a quality control, audit and patient targeting context. Table 4.55 summarises the findings.

The study has highlighted a number of opportunities to the use of the instrument in clinical practice. As highlighted above, the feasibility of reliable quality measurement using MAT_{CVC} via data abstraction from routine clinical data sources, which is facilitated by explicit operational rules, has been demonstrated in a diverse range of practice settings. Data, which is required for the deployment of MAT_{CVC} has also been shown to be generally available. Missing data was exclusively found for measures, where lack of data represents a quality deficit in its own right. The time required for data abstraction was manageable in the context of this research programme, but whether or not 10 to 20 min per patient is sustainable in routine practice will depend on the motivation and resources available to different providers. The latter, will depend on the perceived need for quality improvement in each setting and any incentives to change practice.

Table 4.55: Summary of desirable attributes tested for MAT$_{CVC}$

Attribute	Parameters
Reliability (precision)	
Reliability of measurement	**Independent of subjective judgement:** ✓ All assessments based on explicit operational rules **Accurate and consistent data available:** ✓ All identified data gaps constitute quality deficits in their own right **Inter-rater reliability** ✓ Very high for MAT$_{CVC}$ as a whole (Cohen's kappa > 0.8)
Reliability of discrimination	**Adequacy of sample size** ✓ Required sample size < 50 patients MAT$_{CVC}$ as a whole (Setting A, B, C1); 'E2 – Under-prescribing' (Setting A, B, C1) (✓) Required sample size 50 to 100 patients - 'E1 – Achievement of targets (Setting C1) - 'E3 – Suboptimal dosing' (Setting A) - 'S3 – High risk choice (Setting A,B)
Validity (accuracy)	
Face validity	**Stakeholders can see that improvement on measure is better care** ✓ For measures applied in large scale QI schemes (Majority of ME, E1, E2) ? Not assessed for remaining measures (E3,E4, MS, S1, S3)
Content validity	**Evidence based** ✓ All measures derived from evidence based guidelines **Relevance to patient outcomes** ✓ All measures based on evidence or expert consensus
Criterion validity	**Concurrent validity** ✓ Inpatient: PPV = 0.78; ✓ Outpatient = 0.81; × Primary care = 0.27 **Contextual validity** ✓ Explicit exemption rules × Comprehensive accounting for context factors not possible **Predictive validity** ? Not tested
Utility	
Feasible	**Ease of data access** (✓) Time required for data capture: 10 to 20 min/patient
Interpretable	**Interpretation of core underlying system performance** ✓ Each measure addresses distinct drug therapy risk category ✓ Composite measures for medication use processes
Communicable	**Appeal to target audiences** ? Not tested
Actionable	**Point to actionable tasks for improvement** ✓ Action composite measures designed to target specific actions
Remediable	**Improvement is achievable by those assessed** ? Not tested

✓ Attribute met; (✓) = Attribute partially met; × = Attribute not met; ? = Not tested

Measures, which target the same drug therapy risk category within each drug therapy objective, have been aggregated into 'action' composites and these measures have been used rules, automated data retrieval and deployment of the instrument using electronic information systems is possible in principle and will enhance the efficiency of the approach. The multiple ways in which individual items within the MAT_{CVC} are organised has allowed the definition of aggregate measures and the computation of composite quality indexes. Composite indexes at the level of drug therapy risk categories may provide quality managers with useful insights into the performance of the medication use system by exposing process stages in need for improvement, as discussed in detail above. For the 'E2- Under-prescribing composite', the sample size required for reliable comparison to the proposed benchmark was below 50, implying that 1 to 2 days (8 to 16h) of data abstraction by technical staff would suffice in order to assess with 95% accuracy, whether this process is consistent with expectations (UNAI ≤ 0.05 higher than the proposed UNAI benchmark of 0.85).

In view of the facts that (1) the use of thrombo-embolic prophylaxis, statins, RAS inhibitors and rate limiting therapy is supported by strong evidence, (2) the proposed benchmark has been demonstrated to be achievable in a number of quality improvement programmes and (3) that the concurrent validity was high in the inpatient and outpatient settings, this composite may have the greatest potential for routine implementation in quality control applications. Whether or not '7E2 - Use of acute acting nitrates' should or should not be included in this composite would, however, require consensus among stakeholders as to whether this aspect falls within their responsibilities. In the primary care setting, where the PPV was lower, it may be necessary to exclude patient groups (patients without prior myocardial infarction or heart failure), where current evidence is more controversial, in order to make measurements more robust.

In order to identify specific priorities for quality improvements in an audit context and to target patients for a review of their medication, composite measures were

designed. In *audit* applications, the main advantage is that the numbers of measures to be fed back to practitioners could be contained without loss of specificity with respect to the likely tasks that would be required to address any detected quality deficits. It is therefore likely that composites support the communicability and interpretability of quality information generated by the $MAT_{CVC,}$ although this claim requires empirical confirmation. In *patient targeting* applications, the main advantage of composites were that double counting of identical drug therapy risks (i.e. 'identical with respect to the action required to address each drug therapy risk) were avoided. Action composites may inform the follow up of patients with drug therapy risks (DTR) in a more meaningful way than if each DTR was counted separately (e.g. one DTR for underuse of thrombo-embolic prophylaxis for atrial fibrillation and one DTR for underuse of the same treatment in coronary heart disease).

A limitation of all composite measures is, however, that they aggregate aspects of care, which may have variable impact on patient outcomes. This implies that aspects of care that are rare but of crucial importance add less weight to the overall score than relatively less important aspects that are common. This raises questions of weighting, which is inherently difficult for a number of reasons. One way of assigning weights could be based on the strength of the supporting evidence base, but the fact that an aspect of care has demonstrated superiority over placebo in multiple randomised trials does not necessarily imply large benefits in clinical practice. Interventions that are supported by weaker evidence may have relatively larger impact on patient symptom control, such as the use of digoxin or diuretics in heart failure. An alternative approach to assigning weights may therefore be based on the expected size of the benefit, but this is difficult to quantify since direct comparisons of different treatments are rare and inferences from absolute risk reductions (ARR) observed in different trials are limited by the fact that patient populations and therefore baseline risks vary.

These limitations are perhaps less relevant in quality control applications (for prescribing composites) than they are in audit or patient targeting (for action composites). The key difference is that quality control aims at identifying system weaknesses, i.e. correctable shortcomings in care delivery design, and may therefore be less concerned with patient outcomes. In contrast, when certain aspects of medication use (audit) or patients (patient targeting) are prioritised for quality improvement, the likely relative impact of different measures on outcome is crucial. The MAT_{CVC} attempts to contain this risk by aggregating only those measures into action composites that pertain to the same drug therapy objective and drug therapy risk category, which would allow practitioners to select those, which are considered to be of highest relevance before quantitative approaches, such as funnel plots and/or Pareto charts are applied in order to identify quality improvement priorities. In addition, the hierarchical organisation under drug therapy outcomes (effectiveness versus safety) and drug therapy aims (prognosis improvement versus symptom control) may additionally guide prioritisation.

Identifying priorities for quality improvement at both provider and individual patient levels is further complicated by the fact that the accuracy (positive predictive value) with which truly unexplained non-adherences can be detected differs between measures. Although the sample size for PPV testing of individual action composites was low, the fact that PPVs ranged from 0.53 to 1.00 in the inpatient setting, from 0.20 to 1.00 in the outpatient setting and from 0.00 to 0.75 in the primary care setting, supports this statement. This implies that even if relative clinical relevance *and* the number of detected drug therapy risks are taken into account, uncertainty remains as to whether improvements in medication use are actually achievable. This uncertainty can only be resolved by improvements in the documentation of context factors that identify deviations from standards of best practice as deliberate decisions rather than unintended omissions. At the moment, it is therefore safest to assume that all patients with one or more detected drug therapy risks require follow-up.

The MAT_{CVC} includes 52 individual criteria and 21 action composites and it addresses only a small number of diseases and medication use aspects, among which medication safety features only marginally. If the aim is comprehensive coverage of the spectrum of medication use, than the numbers of measures that would be of potential importance to patients are likely to go into the hundreds. It is unreasonable to expect prescribers to explicitly document an explanation for deviating from best practice standards in each case, because it would presuppose that prescribers are aware of such deviations. However, the increasing implementation of electronic clinical information systems will offer new opportunities in this respect. If standards are integrated into clinical decision support systems, which alert practitioners to the violation of best practice rules *and* demand that an explanation is recorded in each case, more accurate and meaningful quality measurement becomes possible. This notion will be further explored in chapter 5.

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Appendix 3: Minimum data set for complete MAT$_{CVC}$ assessment

Patient details

Aged > 75 Gender

Medical History (Diagnosis- presence/absence [additional information])

Circulatory system

CHD
ACS (date)
CHF
(NYHA status)
AF
Stroke/TIA
PVD (symptoms)
AV Block
Hypertension
Hypotension
(symptoms, date)
Bradycardia
(HR, date)

Renal

Renal impairment
Renal artery stenosis

Respiratory

Asthma

Gastro-intestinal

Diabetes mellitus
Liver cirrhosis
Hepatitis
GI ulcer (date)

Blood

Haemorrhage (date)

Other

Retinopathy

Investigations (below/above threshold and date measured)

Blood pressure, eGFR, HbA1c, TC/LDL, liver enzymes, INR, K [≤ 1 week ago]

Drug history (prescribed/not prescribed [additional information])

Antithrombotic
Vit-K antagonist*
Aspirin*
Clopidogrel*
Dipyridamole*

Antianginal
Oral nitrate (drug, dose, timing)
Molsidomine
GTN Spray*

Antidiabetic
Any oral
Metformin*
Insulin

Antiarrhythmics
Class I
Class III (drug)

Lipid lowering
Statin*
(drug, dose)
Ezetimib
Fibrate

Cardiovascular
ACE-I
(drug, dose)*
ARB (drug, dose)*
BB (drug, dose)*
DHP -CCB
Diltiazem
Verapamil
Alpha blocker
Alpha- 2- agonist
(Di)hydralazin
Minoxidil

Digitalis*
Diuretic (drug, dose)
Eplerenone*/
Spironolactone*

Other
NSAID,
TCA,
Oral steroid,
Beta- 2- agonist
(oral /inhaled)

For drugs indicated with * above: Prior intolerance or allergy, contraindication

CHD = coronary heart disease; ACS = acute coronary syndrome; CHF = chronic heart failure; AF = atrial fibrillation; TIA = transient ischaemic attack; PVD = peripheral vascular disease; AV = atrio-ventricular; HR = heart rate; GI = gastro-intestinal; Vit = vitamin; eGFR = estimated glomerular filtration rate; TC = total cholesterol; INR = international normalised ratio; K = potassium; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BB = beta blocker; DHP = dihydropyridine; CCB = calcium channel blocker; NSAID = non-steroidal anti-inflammatory drug; TCA = tricyclic antidepressant

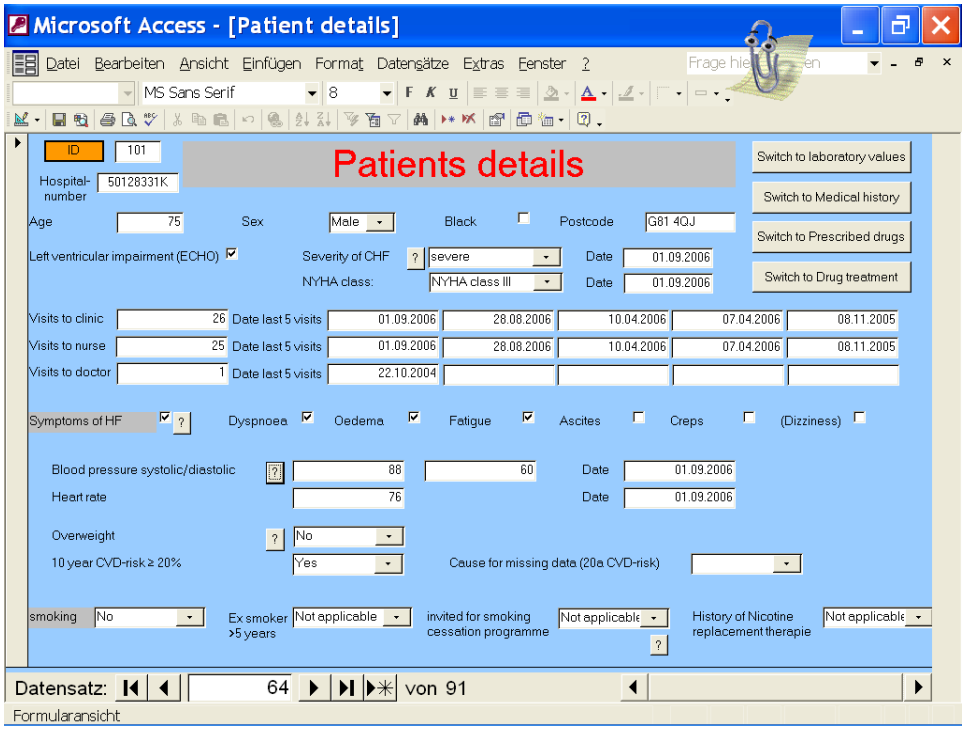
Appendix 4: Definitions, specifications and operational rules for MATcvc data capture

Data item	Definition or specification
1. Medical history	
DM	Documented diagnosis of diabetes mellitus type 1 or 2
Hypertension (complications)	Documented diagnosis of hypertension (with ≥1 of the following: documented renal impairment or eGFR<60ml/min; diabetes mellitus, established CVD)
CVD	(1) Coronary Heart Disease (CHD), (2) TIA/ stroke (3) Peripheral vascular disease (PAD)
CHD	Stable angina, (History of) Acute Coronary Syndrome (ACS), (History of) Coronary Artery Bypass Graft (CABG), Stent
Stroke/ TIA	Syn. Thrombotic stroke, cerebrovascular accident (CVA), cerebrovascular disease, transient ischaemic attack (TIA)
PVD	Syn. Peripheral arterial disease, Intermittent claudication
CHF	A documented diagnosis of heart failure and/or left ventricular systolic dysfunction (LVSD)
AF	A documented diagnosis of atrial fibrillation including all subtypes
AF subtype	1. Paroxysmal = syn. Intermittent 2. Chronic = syn. persistent/permanent (duration>7d with/without electrical/pharmacological cardioversion)
CHADS 2 score	Add up the following points (pt): **C**ardiac failure (1pt); Hypertension (1pt), **A**ge ≥75 years (1pt); **D**iabetes mellitus (1pt); **S**troke (2pts)
Persistently elevated LFTs	AST and/or ALT are elevated ≥3 times the upper limit of the reference range: Setting A. : ≥1 occasion during hospital stay; Setting B/C: ≥1 occasion within the last 48 weeks
Active peptic ulceration	Documented diagnosis of either peptic ulcer or gastrointestinal bleeding and use of gastro-protection (PPI, H2 antagonist or misoprostol) Setting A. : During or within 48 weeks prior to admission Setting B/C: Within the last 48 weeks
Renal impairment	Documented chronic renal failure, dialysis for renal failure, eGFR < 30, documented proteinuria
NYHA status	Assumptions when NYHA status is not explicitly documented - NYHA III/IV if: Patient was admitted for heart failure (setting A); use of a loop diuretic at a dose equivalent to furosemide ≥40mg (all settings A to C)-
Microalbuminuria/ Proteinuria	≥30 mg/L

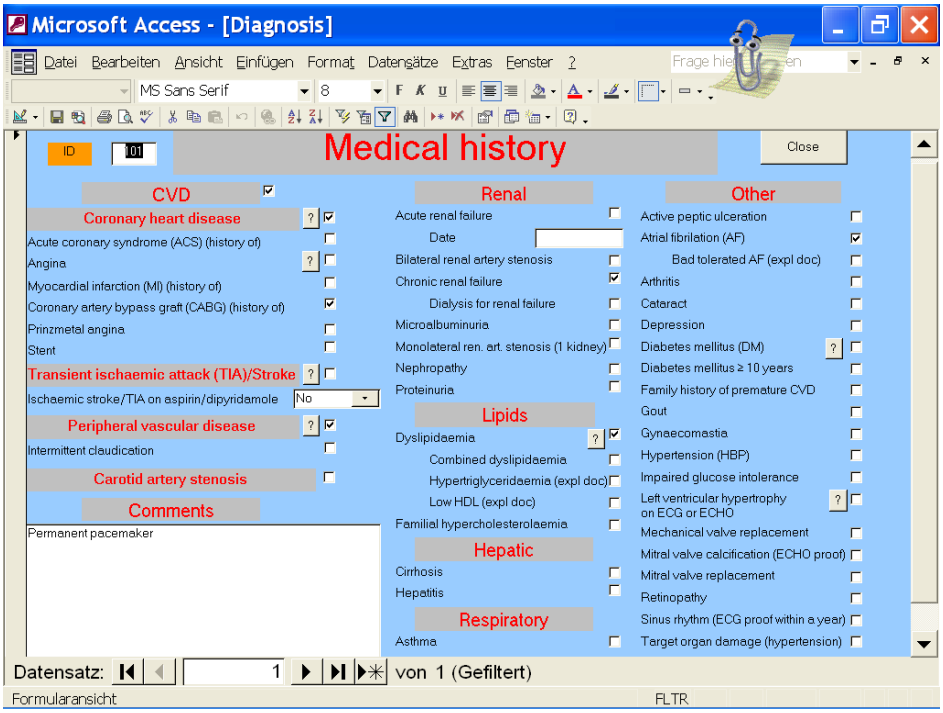
Data item	Definition or specification
2. Drug history	
Antihypertensive therapy	Documented diagnosis of hypertension and prescribed at least one of the following drugs: BB, ACEI, ARB, CCB, thiazide, alpha blocker, clonidine, moxonidine, hydralazine/ dihydralazine.
Antihyperglycaemic therapy	Oral antidiabetic or insulin
ACEI target dose	Captopril: 75mg/d, enalapril 20mg/d, lisinopril 20mg/d, ramipril 10 mg/d, trandolapril 4mg/d
ARB target dose	Candesartan: 32mg, valsartan: 320mg, eprosartan: 800mg, losartan: 100mg, irbesartan: 300mg, telmisartan: 80mg
BB target dose	Bisoprolol: 10mg/d, metoprololsuccinat: 200mg/d, carvedilol: 50mg/d, nebivolol 10mg/d
Equivalent doses to 40mg Simvastatin	Rosuvastatin 10mg/d, atorvastatin 20mg/d, pravastatin 80mg/d, fluvastatin 80mg/d
Dose regimen to avoid nitrate tolerance	Preparation / Strength / Maximum dose frequency *ISDN/ISMN (regular)* / *≤ 20mg* / *Three times daily* *ISDN/ISMN (regular)* / *21-40mg* / *Two times daily with max. of 8h between doses* *ISDN/ISMN (SR)* / *≤ 20mg* / *Three times daily* *ISDN/ISMN (SR)* / *21-40mg* / *Two times daily with max. of 6h between doses* *ISDN/ISMN (SR)* / *> 40mg* / *Once daily*
3. Investigations	
Blood pressure	Inpatient setting: Not available Outpatient: Latest recorded ≤ 48 weeks ago prior to latest consultation Primary care: Latest recorded ≤ 48 weeks ago
Total cholesterol	Inpatient setting: Latest recorded before discharge Outpatient: Latest recorded ≤ 48 weeks ago prior to latest consultation Primary care: Latest recorded ≤ 48 weeks ago
INR	Inpatient setting: Latest recorded before discharge Outpatient: Latest recorded ≤ 24 weeks ago prior to latest consultation

Appendix 5: MS-ACCESS™ data base for MAT$_{CVC}$

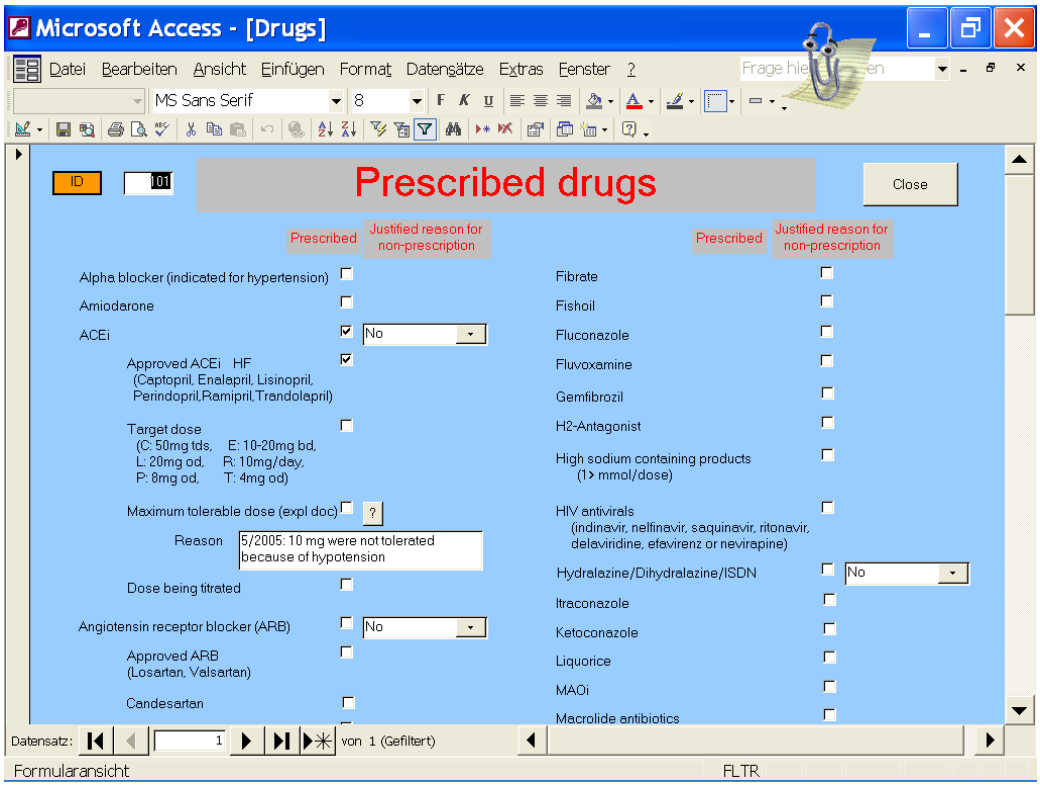
Main data collection form – Patient details

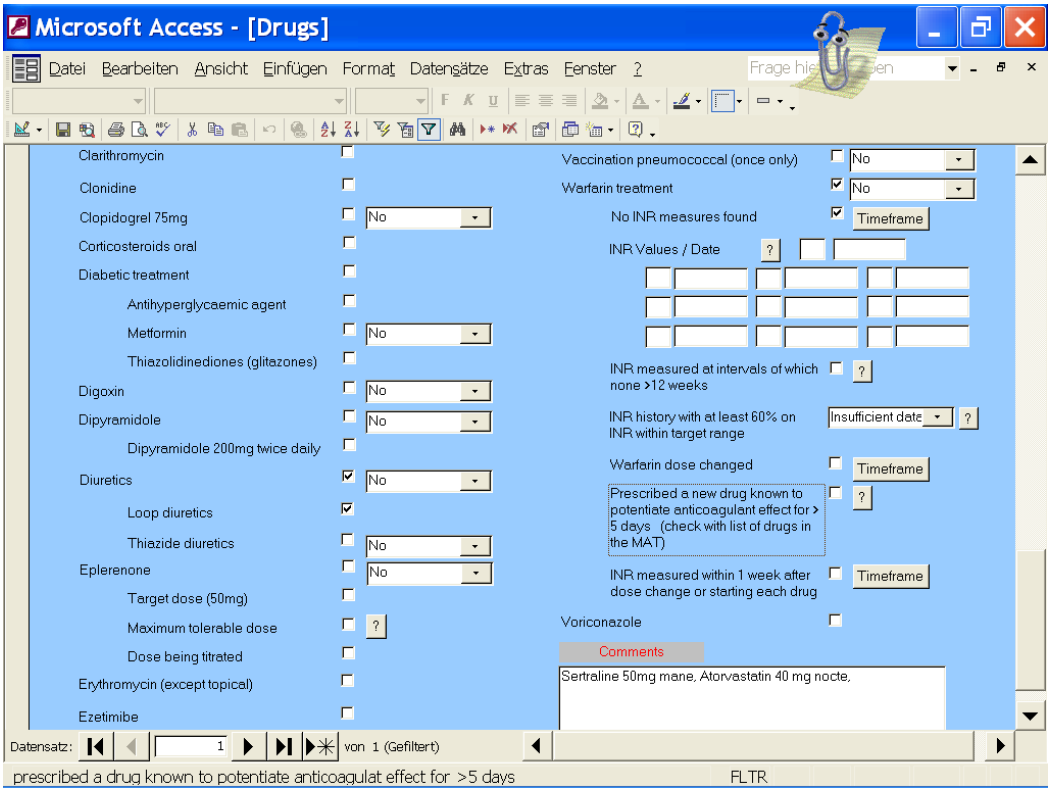


Data collection form 2 – Medical history

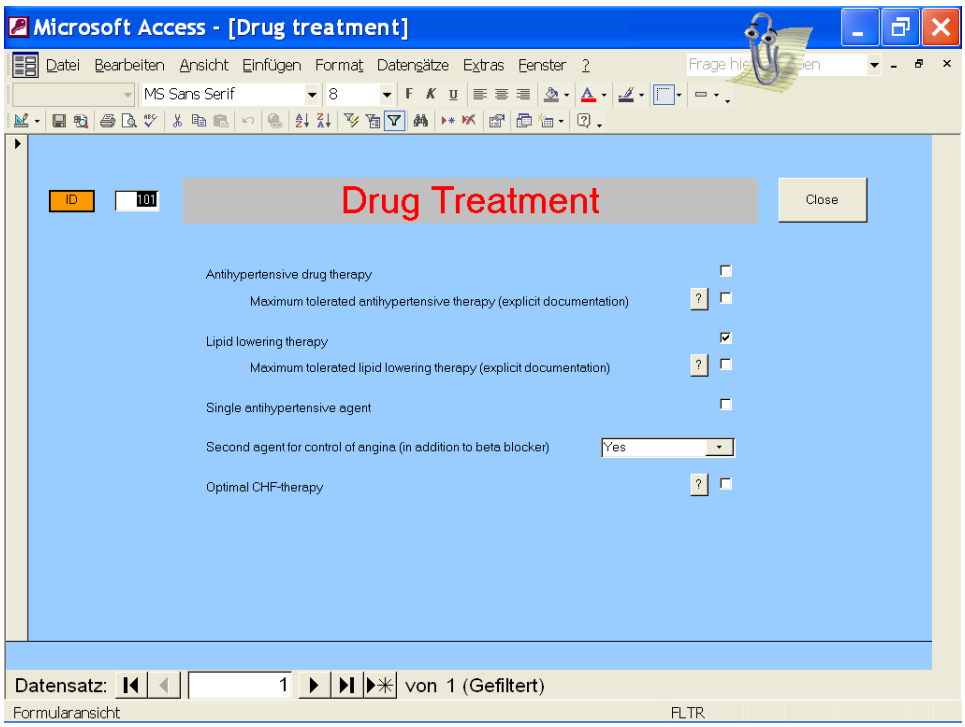


Data collection form 3 – Drugs

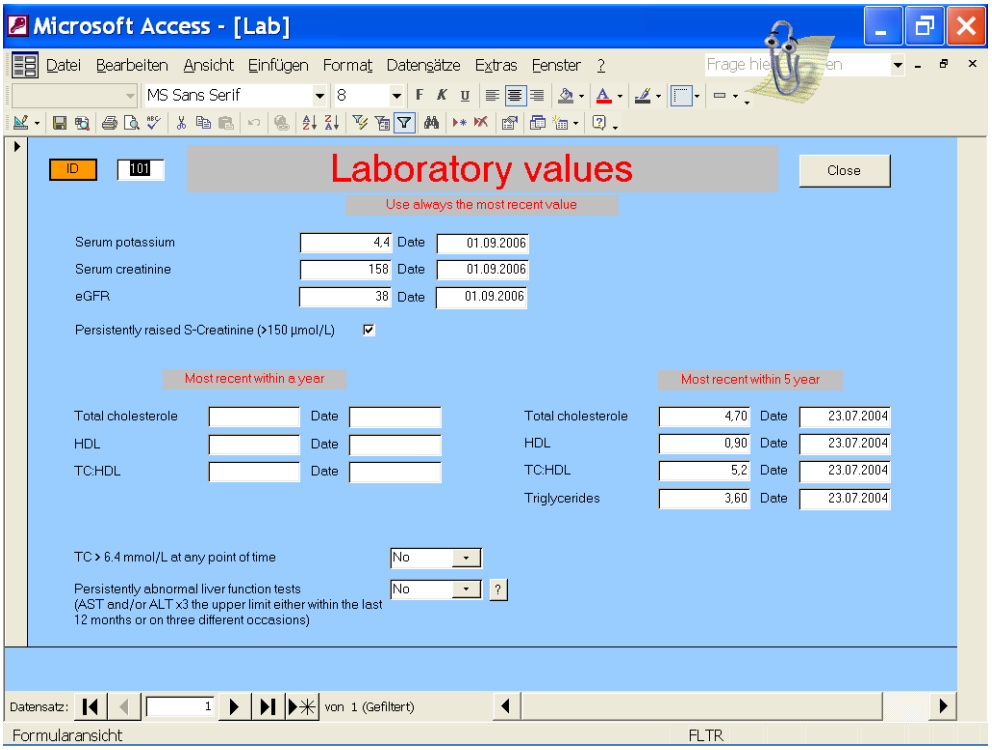




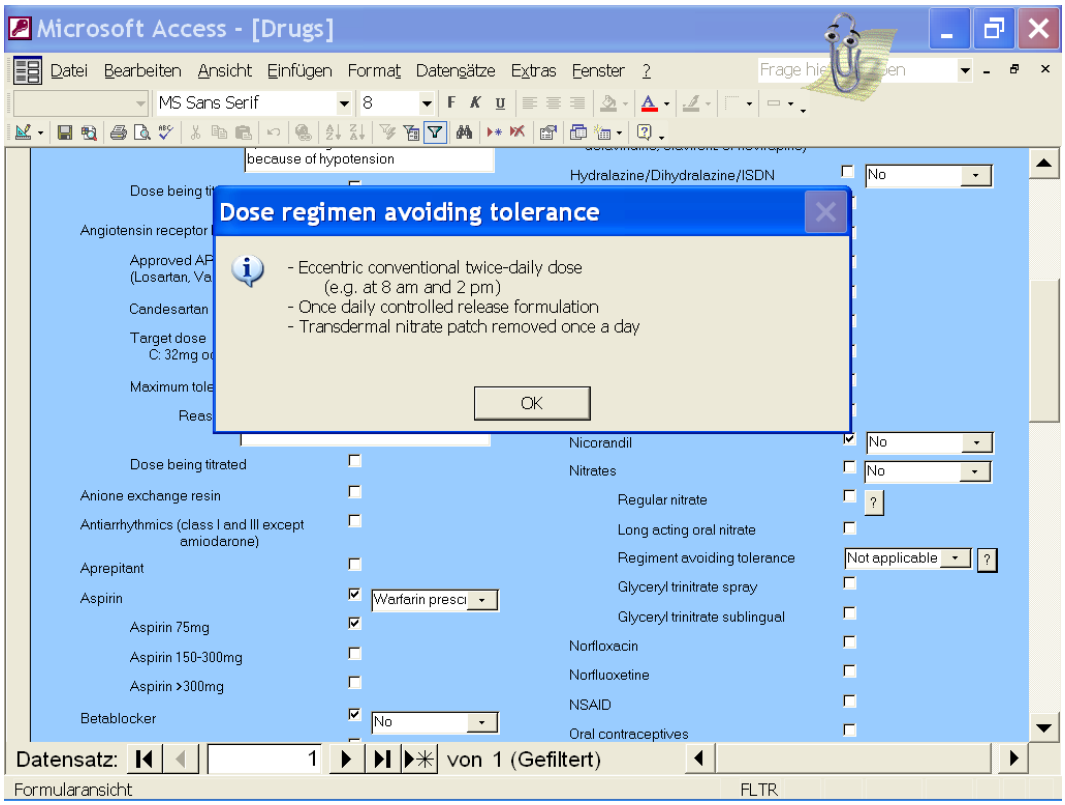
Data collection form 4 – Drug treatment



Data collection form 5 – Laboratory values



Data collection instructions and specification



Appendix 6: ICD 10-Codes used in the inpatient setting

Diagnoses codes	Description in German (*English translation*)
I20.0	Instabile Angina pectoris *(Instable angina pectoris)*
I20.8	Sonstige Formen der Angina pectoris *(Other forms of angina pectoris)*
I21.0	Akuter transmuraler Myokardinfarkt der Vorderwand *(Acute transmural anterior myocardial infarction)*
I21.1	Akuter transmuraler Myokardinfarkt der Hinterwand *(Acute transmural posterior myocardial infarction)*
I21.2	Akuter transmuraler Myokardinfarkt an sonstigen Lokalisationen *(Acute transmural myocardial infarction of other location)*
I21.4	Akuter subendokardialer Myokardinfarkt *(Acute subendocardial myocardial infarction of other location)*
I21.9	Akuter Myokardinfarkt, nicht näher bezeichnet *(Acute myocardial infarction, not otherwise specified)*
I23.6	Thrombose des Vorhofes, des Herzohres oder der Kammer als akute Komplikation nach akutem Myokardinfarkt *(Thrombus of the atrium, auricle or ventricle as acute complication after myocardial infarction)*
I25.11	Atherosklerotische Herzkrankheit: Ein-Gefäßerkrankung *(Atherosclerotic heart disease: one vessel disease)*
I25.12	Atherosklerotische Herzkrankheit: Zwei-Gefäßerkrankung *(Atherosclerotic heart disease: two vessel disease)*
I25.13	Atherosklerotische Herzkrankheit: Drei-Gefäßerkrankung *(Atherosclerotic heart disease: three vessel disease)*
I25.14	Atherosklerotische Herzkrankheit: Stenose des linken Hauptstammes *(Atherosclerotic heart disease: stenosis of the left coronary artery)*
I25.15	Atherosklerotische Herzkrankheit: Mit stenosierten Bypass-Gefäßen *(Atherosclerotic heart disease: stenosis of bypass vessels)*
I25.16	Atherosklerotische Herzkrankheit: Mit stenosierten Stents *(Atherosclerotic heart disease: stenosis of coronary stents)*
I25.19	Atherosklerotische Herzkrankheit: Nicht näher bezeichnet *(Atherosclerotic heart disease: not otherwise specified)*
I25.21	Alter Myokardinfarkt: 4 Monate bis unter 1 Jahr zurückliegend *(Old myocardial infarction: 4 months to 1 year ago)*
I25.22	Alter Myokardinfarkt: 1 Jahr und länger zurückliegend *(Old myocardial infarction: more than 1 year ago)*
I25.29	Alter Myokardinfarkt: Nicht näher bezeichnet *(Old myocardial infarction: not otherwise specified)*
I48.10	Vorhofflimmern: Paroxysmal *(Atrial fibrillation: paroxysmal)*
I48.11	Vorhofflimmern: Chronisch *(Atrial fibrillation: paroxysmal)*
I48.19	Vorhofflimmern: Nicht näher bezeichnet *(Atrial fibrillation: not otherwise specified)*
I50.00	Primäre Rechtsherzinsuffizienz *(Primary right ventricular heart failure)*
I50.01	Sekundäre Rechtsherzinsuffizienz *(Secondary right ventricular heart failure)*
I50.11	Linksherzinsuffizienz: Ohne Beschwerden, NYHA-Stadium I *(Left ventricular heart failure: without symptoms, NYHA status I)*
I50.12	Linksherzinsuffizienz: Mit Beschwerden bei stärkerer Belastung, NYHA-Stadium II *(Left ventricular heart failure: ordinary exercise causes symptoms, NYHA status II)*
I50.13	Linksherzinsuffizienz: Mit Beschwerden bei leichterer Belastung, NYHA-Stadium III *(Left ventricular heart failure: less than ordinary exercise causes symptoms, NYHA status III)*
I50.14	Linksherzinsuffizienz: Mit Beschwerden in Ruhe, NYHA-Stadium IV *(Left ventricular heart failure: symptoms at rest , NYHA status IV)*
I50.9	Herzinsuffizienz, nicht näher bezeichnet *(Heart failure, not otherwise specified)*

Appendix 7: Comparison of patient samples to reference populations

Hospital inpatients

Comparison of demographics of CHD patients enrolled in the inpatient survey to the population enrolled in a larger survey of CHD patients with similar inclusion criteria[19]

	Reference population[19] Total (n=237,225)	**Study population** Total (n=152)	**Comparison** *P* – value [X]
Average age (years)	66 [a]	72 [b]	
Male	63%	63%	
Co-morbidity			
HTN	69%	79%	< 0.003*
DM	34%	28%	NS
Current/prior MI	87%	66%	< 0.001*
Stroke/TIA	Not reported	11%	
PVD	Not reported	7.2%	
COPD	Not reported	18%	
CHF	14%	46%	< 0.001*
AF	10%	28%	< 0.001*
Renal impairment	10%	26%	< 0.001*

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant; a=mean; b=median

Comparison of demographics of CHF patients enrolled in this inpatient survey to the population enrolled in a pan-European survey of CHF patients with similar inclusion criteria[25, 26]

	Reference population Total (n=11,304)	**Study population** Total (n = 96)	*P* value [X]
Average age (years)	71[a]	71[b]	NS
Male	53%	69%	0.014
Reason for admission			
CHF	32%	43%	0.029*
ACS	9%	29%	< 0.001*
AF	Not reported	3%	-
Arrhythmias (total)	7%	8%	NS
Other cardiology	27%	17%	0.038*
Non-cardiology	25%	-	<0.001*
Co-morbidity			
HTN	53%	80%	< 0.001
DM	27%	37%	0.038*
CVD		80%	NS
CHD	68%	73%	NS
Stroke/TIA	19%	19%	NS
PVD	Not reported	7%	-
AF	42%	40%	NS
COPD	32%	23%	NS
Prior MI	38%	54%	< 0.002*
Renal impairment	17%	35%	< 0.001*
CHF severity			
NYHAI	36%	1%	< 0.001*
NYHA II	37%	21%	< 0.002*
NYHA III/IV	26%	78%	< 0.001*

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NYHA = New York Heart Association; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant

Comparison of demographics of AF patients enrolled in this inpatient survey to the population enrolled in a pan-European survey of in- and outpatients with ECG confirmed AF[27, 28]

	Reference population[27, 28]			**Study population**	
	Total (n=5,333)	Inpatient (n=2,987)	Outpatient (n=1,813)	Total (n = 85)	*P* value [X]
Average age (years)	67[a]			76[a]	0.025*
Male	33%			24%	NS
AF subtype					
First detected	18%	21%	12%	11%[Δ]	0.034*
Paroxysmal	28%	28%	29%	41%[Δ]	0.012*
Chronic	51%	49%	55%	56%[Δ]	NS
Reason for admission/consultation					
AF	39%			17%	< 0.0001*
CHF	Not reported			27%	NS
ACS	3%			18%	< 0.0001*
Other (cardiology)				39%	NS
Co-morbidity					
HTN	62%			72%	NS
DM	18%			14%	NS
CVD	Not reported				NS
CHD	32%			47%	0.005*
Stroke/TIA	10%			11%	NS
PVD	7%			7%	NS
CHF	37%			45%	NS
Respiratory	13%			12%	NS
Prior ACS	15%			22%	NS
Renal impairment	6%			29%	< 0.0001*
Prior haemorrhage	2%			2%	NS
Stroke risk					
$CHADS_2 = 0$	16%			11%	NS
$CHADS_2 \geq 1$	84%			89%	NS
$CHADS_2 = 1$	Not reported			15%	-
$CHADS_2 = 2$	Not reported			31%	-
$CHADS_2 = 3$	Not reported			30%	-

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; $CHADS_2$ = Score for strike risk assessment in AF; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; Δ= comparison to inpatient subpopulation; * = statistically significant

Hospital outpatients

Comparison of demographics of CHF outpatients enrolled in this survey to the populations enrolled into a larger US survey of CHF outpatients[29] and a European survey[30] including in- and outpatients.

	Reference population 1 (n = 34,810)	Study population (n =152)	*P* value [X]
Average age[29]			
(years)	70	72	NS
Male	71%	66%	NS
Co-morbidity [29]			
HTN	62%	33%	< 0.0001*
DM	34%	30%	NS
CVD	-	63%	-
CHD	65%	58%	NS
Stroke/TIA	-	28%	-
PVD	12%	12%	NS
Atrial fibrillation	31%	34%	NS
Prior MI	40%	32%	NS
Renal impairment	Not reported	32%	
CHF severity [29]			
NYHAI	35%	2%	< 0.0001*
NYHA II	37%	25%	0.003*
NYHA III/IV	23%	73%	< 0.0001*
	Reference population 2 (n=1,816)	Study subpopulation with AF (n=34)	*P* value [X]
AF subtype[30]			
First detected	14%	0%	nc
Paroxysmal	20%	15%	NS
Chronic	63%	85%	0.01*
Stroke risk in AF patients[30]			
$CHADS_2 = 1$	15%	12%	NS
$CHADS_2 = 2$	30%	35%	NS
$CHADS_2 \geq 3$	55%	53%	NS

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; $CHADS_2$ = Score for strike risk assessment in AF; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant

Primary care patients

Comparison of demographics of CHD patients enrolled in this inpatient survey to the population enrolled in a larger survey of CHD patients with similar inclusion criteria[19]

	US inpatient survey population[19] Total (n=237,225)	**Study population** Total (n=152)
Average age (years)	66 [a]	66 [a]
Male	63%	47%
Co-morbidity		
HTN	69%	49%
DM	34%	27%
Prior MI	87%	46%
Stroke/TIA	Not reported	6%
PVD	Not reported	7%
CHF	14%	4%
AF	10%	7%
Renal impairment	10%	5%

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant; a=mean

Comparison of demographics of CHF outpatients enrolled in this primary care survey to the population enrolled into a larger US survey of CHF outpatients[29]

	Reference population (n = 34,810)	Study population (n = 43)	*P* value [X]
Average age[29]			
(years)	70[a]	72[a]	NS
Male	71%	66%	NS
Co-morbidity [29]			
HTN	62%	42%	0.01*
DM	34%	63%	< 0.001*
CVD	Not reported	44%	
CHD	65%	19%	< 0.001*
Stroke/TIA	Not reported	28%	
PVD	12%	7%	NS
Atrial fibrillation	31%	23%	NS
Prior MI	40%	9%	< 0.001*
Renal impairment	Not reported	7%	
CHF severity [29]			
NYHAI	35%	Not available	
NYHA II	37%	Not available	
NYHA III/IV	23%	Not available	

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; * = statistically significant; a=median

Comparison of demographics of AF patients enrolled in this primary care survey to the population enrolled in a pan-European survey of in- and outpatients with ECG confirmed AF [27, 28]

	Reference population[25, 26]			**Study population**	
	Total (n=5,333)	Inpatient (n=2,987)	Outpatient (n=1,813)	Total (n = 132)	*P* value [X]
Average age	67 [a]			71 (20) [b]	NS
Male	33%			45%	0.005*
AF subtype					
First detected	18%	21%	12%	Not available	
Paroxysmal	28%	28%	29%	Not available	
Chronic	51%	49%	55%	Not available	
Co-morbidity					
HTN	62%	50%	18%	21%	0.007*
DM	Not reported			20%	nc
CVD	32%			12%	< 0.001*
CHD	10%			7%	NS
Stroke/TIA	7%			2%	0.03*
PVD	37%			8%	< 0.001*
CHF	15%			5%	0.003*
Prior ACS	6%			7%	NS
Renal impairment	2%			1%	NS
Prior haemorrhage					
Stroke risk					
$CHADS_2 = 0$	16%			24%	0.02*
$CHADS_2 \geq 1$	84%			76%	0.02*
$CHADS_2 = 1$	Not reported			39%	
$CHADS_2 = 2$	Not reported			21%	
$CHADS_2 \geq 3$	Not reported			16%	

DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; CHD = coronary heart disease; TIA = transient ischaemic attack; PVD = peripheral vascular disease; CHF = chronic heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; $CHADS_2$ = Score for strike risk assessment in AF; M = male; F = female; X = X2 - test; U = Mann-Whitney-U-test; Δ= comparison to inpatient subpopulation; * = statistically significant

Appendix 8: Results of retrospective surveys

A. Inpatient Cardiology setting

Recommend. strength	DTR Type	**PCN screener**/ *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Outcome – Effectiveness (Prognosis improvement)						
Objective 1 – Controlling risk of thrombo-embolism						
I-A	E1	**1. AF and on an a vitamin K antagonist /** *has achieved the target INR*	38	17	15	2
I-A	E2	**2. AF and $CHADS_2$ score = 0 and aged ≥60/** *not on TE prophylaxis*	9	3	1	-
I-A	E2	**3. AF and $CHADS_2$ score = 1/** *not on TE prophylaxis*	15	3	3	-
I-A	E2	**4. AF and $CHADS_2$ score = 2/** *not on TE prophylaxis*	31	5	3	-
I-A	E2	**5. AF and $CHADS_2$ score ≥ 3/** *not on TE prophylaxis*	30	7	4	-
I-A	E2	**6. Coronary heart disease/** *not on TE prophylaxis*	152	6	6	-
n.a.	E2	**7. Peripheral vascular disease/** *not on TE prophylaxis*	13	-	-	-
n.a.	E2	**8. Prior stroke or TIA/** *not on TE prophylaxis*	24	3	1	-
I-C	E2	**9. CHF and prior TE or intracardial thrombus/** *not on TE prophylaxis*	6	1	1	-
I-A	E3	**10. History of stroke/TIA or ACS ≤ 12 months ago and on TE prophylaxis/** *not on dual antiplatelet or oral anticoagulant*	70	8	7	-
I-A	E3	**11. AF and $CHADS_2$ = 2 and on TE prophylaxis/** *not on oral anticoagulant*	26	13	6	-
I-A	E3	**12. AF and $CHADS_2$ ≥ 3 and on TE prophylaxis/** *not on oral anticoagulant*	23	9	6	-
I-C	E3	**13. CHF with prior TE or intracardial thrombus and on TE prophylaxis/** *not on oral anticoagulant*	5	1	1	-
Objective 2 – Controlling dyslipidaemia						
☑	E1	**1. CVD without prior vascular events but on a statin/** has *TC > 175 mg/dl*	38	7	2	25
I-A	E1	**2. CVD with prior vascular events and on statin/** *LDL > 100 mg/dl*	83	22	1	51
I-A	E2	**3. Coronary heart disease (CHD)/** *not on a statin*	152	34	27	-
n.a.	E2	**4. Peripheral vascular disease (PVD)/** *not on a statin*	13	2	2	-
n.a.	E2	**5. History of stroke or TIA/** *not on a statin*	24	11	10	-
n.a.	E2	**6. Diabetes mellitus/** *not on a statin*	58	18	14	-
☑	E3	**7. CVD and prescribed a statin/** *not on simvastatin 40 mg**	121	68	68	-

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR$_{POS}$	ID$_{DTR}$
Objective 3 – Controlling diabetes						
I-B	E1	**1. DM, who is prescribed anti-hyperglycaemic therapy/** *has not achieved HbA1c < 6.5%*	58	19	11	22
IIa-B	E3	**2. DM, who is overweight and is prescribed an oral antidiabetic agent/** *not on metformin*	22	10	7	-
Objective 4 – Controlling blood pressure						
I-A	E1	**1. HTN and complications (CVD, DM or CKD) who is treated for hypertension/** *has not achieved SBP of ≤ 130mmHg AND DBP ≤80mmHg*	Excluded			
I-A	E1	**2. Uncomplicated HTN (no CVD, DM, or CKD), who is treated for hypertension/** *has ot achieved an SBP of ≤ 140 AND DBP ≤ 85mmHg*	Excluded			
Objective 5 – Controlling the Renin Angiotensin System (RAS)						
I-A	E2	**1. Coronary heart disease/** *not on an ACEI or ARB*	152	14	14	-
I-A	E2	**2. Chronic heart failure/** *not on an ACEI or ARB or H-ISDN*	96	6	6	-
n.a.	E2	**3. Diabetes mellitus/** *not on an ACEI or ARB*	37	1	1	-
I-A	E2	**4. CHF and prior MI or in NYHA III-IV and on a BB, ACEI/ARB and a diuretic/** *not on an aldosterone antagonist or an ACEI plus ARB*	2	1	1	-
☑	E4	**5. CHF and on an ACEI or ARB/** *not on target dose or a documented max. tolerable dose*	90	70	62	-
Objective 6 – Controlling the heart rate						
I-A	E2	**1. Chronic heart failure/** *is not on a beta blocker (BB)*	96	14	11	-
☑	E2	**2. Coronary heart disease without prior ACS**/** *is not on a BB or rate limiting CCB*	52	10	9	-
I-A	E2	**3. Coronary heart disease with prior ACS */** *is is not on a BB or rate limiting CCB*	52	10	10	-
I-B	E2	**4. Atrial fibrillation/** *is not on a BB, a rate limiting CCB or amiodarone*	100	17	12	-
IIa-B	E2	**5. Paroxysmal AF and on digitalis/** *is not on a BB, a rate limiting CCB or amiodarone*	35	-	-	-
☑	E4	**6. CHF or LVSD and on a beta blocker/** *is not on recommended target dose*	82	70	68	-
Outcome – Effectiveness (Symptom control)						
Objective 7 – Controlling angina symptoms						
I-B	E2	**1. Stable angina/** *is not on a short acting nitrate*			Excluded	
IIa-C	E3	**2. CHD and on a regular nitrate/** *is on a dosing regimen, which provokes nitrate tolerance*	6	1	1	-

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Outcome – Effectiveness (Symptom control continued)						
Objective 8 – Controlling fluid retention						
I-B	E3	**1. CHF and on optimal treatment with ACEI, ARB, aldosterone antagonist and diuretic** *is not prescribed digoxin*	-	-	-	-
Outcome – Safety						
Objective 9 – Controlling risk of haemorrhage						
☑	S1	**1. AF and on OAC/** *has latest recorded INR >3.0*	38	6	6	2
III-C	S3	**2. AF and $CHADS_2$= 0/** *is on an oral anticoagulant*	6	2	2	-
Objective 10 – Preventing drug induced angina symptoms						
☑	S3	**1. Coronary heart disease** / *is prescribed dipyridamol***e**	152	-	-	-
☑	S3	**2. Patient with CHD/** *is on dihydropyridine CCB without use of a BB*	62	-	-	-
Objective 11 – Preventing drug induced fluid retention						
IC	S3	**1. Chronic heart failure /** *is prescribed antiarrhytmic class 1 (IC)*	96	3	3	-
IIb-B	S3	**2. Chronic heart failure /** *is prescribed a glitazone*	96	-	-	-
☑	S3	**3. Chronic heart failure /** *is prescribed a PDE 5 inhibitor*	96	-	-	-
☑	S3	**4. Chronic heart failure /** *is prescribed an NSAID*	96	1	1	-
☑	S3	**5. Chronic heart failure /** *is prescribed a tricyclic antidepressant*	96	3	3	-
☑	S3	**6. Chronic heart failure /** *is prescribed an oral steroid*	96	8	8	-
☑	S3	**7. Chronic heart failure /** *is prescribed lithium*	96	-	-	-
☑	S3	**8. Chronic heart failure /** *is prescribed minoxidil*	96	1	1	-
☑	S3	**9. Chronic heart failure /** *is prescribed diltiazem or verapamil*	96	1	1	-
☑	S3	**10. Chronic heart failure /** *is prescribed a short-acting DHP-CCB*	96	-	-	-

B. Outpatient heart failure clinic

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Outcome – Effectiveness (Prognosis improvement)						
Objective 1 – Controlling risk of thrombo-embolism						
I-A	E1	**1. AF and on an a vitamin K antagonist /** *has achieved the target INR*	23	4	4	17
I-A	E2	**2. AF and $CHADS_2$ score = 0 and aged ≥60/** *not on TE prophylaxis*	-	-	-	-
I-A	E2	**3. AF and $CHADS_2$ score = 1/** *not on TE prophylaxis*	8	-	-	-
I-A	E2	**4. AF and $CHADS_2$ score = 2/** *not on TE prophylaxis*	18	-	-	-
I-A	E2	**5. AF and $CHADS_2$ score ≥ 3/** *not on TE prophylaxis*	25	-	-	-
I-A	E2	**6. Coronary heart disease/** *not on TE prophylaxis*	88	6	6	-
n.a.	E2	**7. Peripheral vascular disease/** *not on TE prophylaxis*	18	-	-	-
n.a.	E2	**8. Prior stroke or TIA/** *not on TE prophylaxis*	21	1	1	-
I-C	E2	**9. CHF and prior TE or intracardial thrombus/** *not on TE prophylaxis*	2	-	-	-
I-A	E3	**10. History of stroke/TIA or ACS ≤ 12 months ago and on TE prophylaxis/** *not on dual antiplatelet or oral anticoagulant*	11	-	-	-
I-A	E3	**11. AF and $CHADS_2$ = 2 and on TE prophylaxis/** *not on oral anticoagulant*	18	10	10	-
I-A	E3	**12. AF and $CHADS_2$ ≥ 3 and on TE prophylaxis/** *not on oral anticoagulant*	25	10	8	-
I-C	E3	**13. CHF with prior TE or intracardial thrombus and on TE prophylaxis/** *not on oral anticoagulant*	2	1	1	-
Objective 2 – Controlling dyslipidaemia						
☑	E1	**1. CVD without prior vascular events but on a statin/** has *TC > 175 mg/dl*	25	1	-	8
I-A	E1	**2. CVD with prior vascular events and on statin/** *LDL > 100 mg/dl*	54	5	-	13
I-A	E2	**3. Coronary heart disease (CHD)/** *not on a statin*	88	13	11	-
n.a.	E2	**4. Peripheral vascular disease (PVD)/** *not on a statin*	18	3	-	-
n.a.	E2	**5. History of stroke or TIA/** *not on a statin*	21	14	13	-
n.a.	E2	**6. Diabetes mellitus/** *not on a statin*	46	9	6	-
☑	E3	**7. CVD and prescribed a statin/** *not on simvastatin 40 mg**	70	13	12	-

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Objective 3 – Controlling diabetes						
I-B	E1	**1. DM, who is prescribed anti-hyperglycaemic therapy/** *has not achieved HbA1c < 6.5%*	37	8	8	10
IIa-B	E3	**2. DM, who is overweight and is prescribed an oral antidiabetic agent/** *not on metformin*	30	21	14	-
Objective 4 – Controlling blood pressure						
I-A	E1	**1. HTN and complications (CVD, DM or CKD) who is treated for hypertension/** *has not achieved SBP of ≤ 130mmHg AND DBP ≤80mmHg*	32	8	8	8
I-A	E1	**2. Uncomplicated HTN (no CVD, DM, or CKD), who is treated for hypertension/** *has ot achieved an SBP of ≤ 140 AND DBP ≤ 85mmHg*	16	2	2	2
Objective 5 – Controlling the Renin Angiotensin System (RAS)						
I-A	E2	**1. Coronary heart disease/** *not on an ACEI or ARB*	88	8	3	-
I-A	E2	**2. Chronic heart failure/** *not on an ACEI or ARB or H-ISDN*	152	13	-	-
n.a.	E2	**3. Diabetes mellitus/** *not on an ACEI or ARB*	46	5	3	-
I-A	E2	**4. CHF and prior MI or in NYHA III-IV and on a BB, ACEI/ARB and a diuretic/** *not on an aldosterone antagonist or an ACEI plus ARB*	13	10	-	-
☑	E4	**5. CHF and on an ACEI or ARB/** *not on target dose or a documented max. tolerable dose*	139	98	6	-
Objective 6 – Controlling the heart rate						
I-A	E2	**1. Chronic heart failure/** *is not on a beta blocker (BB)*	152	31	15	-
☑	E2	**2. Coronary heart disease without prior ACS**/** *is not on a BB or rate limiting CCB*	45	9	1	-
I-A	E2	**3. Coronary heart disease with prior ACS** */ *is is not on a BB or rate limiting CCB*	2	-	-	-
I-B	E2	**4. Atrial fibrillation/** *is not on a BB, a rate limiting CCB or amiodarone*	121	84	48	-
IIa-B	E2	**5. Paroxysmal AF and on digitalis/** *is not on a BB, a rate limiting CCB or amiodarone*	39	10	5	-
☑	E4	**6. CHF or LVSD and on a beta blocker/** *is not on recommended target dose*	49	7	-	-
Outcome – Effectiveness (Symptom control)						
Objective 7 – Controlling angina symptoms						
I-B	E2	**1. Stable angina/** *is not on a short acting nitrate*	88	56	-	-
IIa-C	E3	**2. CHD and on a regular nitrate/** *is on a dosing regimen, which provokes nitrate tolerance*	21	3	-	-

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Outcome – Effectiveness (Symptom control continued)						
Objective 8 – Controlling fluid retention						
I-B	E3	**1. CHF and on optimal treatment with ACEI, ARB, aldosterone antagonist and diuretic** *is not prescribed digoxin*	3	2	-	-
Outcome – Safety						
Objective 9 – Controlling risk of haemorrhage						
☑	S1	**1. AF and on OAC/** *has latest recorded INR >3.0*	30	2	-	17
III-C	S3	**2. AF and $CHADS_2$= 0/** *is on an oral anticoagulant*	-	-	-	-
Objective 10 – Preventing drug induced angina symptoms						
☑	S3	**1. Coronary heart disease** / *is prescribed dipyridamol***e**	88	1	-	-
☑	S3	**2. Patient with CHD/** *is on dihydropyridine CCB without use of a BB*	-	-	-	-
Objective 11 – Preventing drug induced fluid retention						
IC	S3	**1. Chronic heart failure /** *is prescribed antiarrhytmic class 1 (IC)*	152	-	-	-
IIb-B	S3	**2. Chronic heart failure /** *is prescribed a glitazone*	152	-	-	-
☑	S3	**3. Chronic heart failure /** *is prescribed a PDE 5 inhibitor*	152	1	-	-
☑	S3	**4. Chronic heart failure /** *is prescribed an NSAID*	152	-	-	-
☑	S3	**5. Chronic heart failure /** *is prescribed a tricyclic antidepressant*	152	2	-	-
☑	S3	**6. Chronic heart failure /** *is prescribed an oral steroid*	152	2	-	-
☑	S3	**7. Chronic heart failure /** *is prescribed lithium*	152	5	-	-
☑	S3	**8. Chronic heart failure /** *is prescribed minoxidil*	152	-	-	-
☑	S3	**9. Chronic heart failure /** *is prescribed diltiazem or verapamil*	152	-	-	-
☑	S3	**10. Chronic heart failure /** *is prescribed a short-acting DHP-CCB*	152	-	-	-

C. Primary Care setting

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR$_{POS}$	ID$_{DTR}$
Outcome – Effectiveness (Prognosis improvement)						
Objective 1 – Controlling risk of thrombo-embolism						
I-A	E1	**1. AF and on an a vitamin K antagonist /** *has achieved the target INR*	Excluded			
I-A	E2	**2. AF and CHADS$_2$ score = 0 and aged ≥60/** *not on TE prophylaxis*	31	10	10	-
I-A	E2	**3. AF and CHADS$_2$ score = 1/** *not on TE prophylaxis*	51	9	9	-
I-A	E2	**4. AF and CHADS$_2$ score = 2/** *not on TE prophylaxis*	28	5	5	-
I-A	E2	**5. AF and CHADS$_2$ score ≥ 3/** *not on TE prophylaxis*	22	1	1	-
I-A	E2	**6. Coronary heart disease/** *not on TE prophylaxis*	231	15	15	-
n.a.	E2	**7. Peripheral vascular disease/** *not on TE prophylaxis*	62	10	10	-
n.a.	E2	**8. Prior stroke or TIA/** *not on TE prophylaxis*	165	23	23	-
I-C	E2	**9. CHF and prior TE or intracardial thrombus/** *not on TE prophylaxis*	-	-	-	-
I-A	E3	**10. History of stroke/TIA or ACS ≤ 12 months ago and on TE prophylaxis/** *not on dual antiplatelet or oral anticoagulant*	142	62	62	-
I-A	E3	**11. AF and CHADS$_2$ = 2 and on TE prophylaxis/** *not on oral anticoagulant*	142	62	62	-
I-A	E3	**12. AF and CHADS$_2$ ≥ 3 and on TE prophylaxis/** *not on oral anticoagulant*	23	1	1	-
I-C	E3	**13. CHF with prior TE or intracardial thrombus and on TE prophylaxis/** *not on oral anticoagulant*	21	2	2	-
Objective 2 – Controlling dyslipidaemia						
☑	E1	**1. CVD without prior vascular events but on a statin/** has *TC > 175 mg/dl*	108	7	7	76
I-A	E1	**2. CVD with prior vascular events and on statin/** *LDL > 100 mg/dl*	174	28	28	139
I-A	E2	**3. Coronary heart disease (CHD)/** *not on a statin*	231	52	52	-
n.a.	E2	**4. Peripheral vascular disease (PVD)/** *not on a statin*	62	19	19	-
n.a.	E2	**5. History of stroke or TIA/** *not on a statin*	165	75	75	-
n.a.	E2	**6. Diabetes mellitus/** *not on a statin*	567	251	251	-
☑	E3	**7. CVD and prescribed a statin/** *not on simvastatin 40 mg**	282	134	134	-

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Objective 3 – Controlling diabetes						
I-B	E1	**1. DM, who is prescribed anti-hyperglycaemic therapy/** *has not achieved HbA1c < 6.5%*	475	101	101	318
IIa-B	E3	**2. DM, who is overweight and is prescribed an oral antidiabetic agent/** *not on metformin*	360	71	44	-
Objective 4 – Controlling blood pressure						
I-A	E1	**1. HTN and complications (CVD, DM or CKD) who is treated for hypertension/** *has not achieved SBP of ≤ 130mmHg AND DBP ≤80mmHg*	416	170	170	100
I-A	E1	**2. Uncomplicated HTN (no CVD, DM, or CKD), who is treated for hypertension/** *has ot achieved an SBP of ≤ 140 AND DBP ≤ 85mmHg*	771	153	153	261
Objective 5 – Controlling the Renin Angiotensin System (RAS)						
I-A	E2	**1. Coronary heart disease/** *not on an ACEI or ARB*	231	94	94	-
I-A	E2	**2. Chronic heart failure/** *not on an ACEI or ARB or H-ISDN*	43	9	9	-
n.a.	E2	**3. Diabetes mellitus/** *not on an ACEI or ARB*	567	240	240	-
I-A	E2	**4. CHF and prior MI or in NYHA III-IV and on a BB, ACEI/ARB and a diuretic/** *not on an aldosterone antagonist or an ACEI plus ARB*	-	-	-	-
☑	E4	**5. CHF and on an ACEI or ARB/** *not on target dose or a documented max. tolerable dose*	34	24	24	-
Objective 6 – Controlling the heart rate						
I-A	E2	**1. Chronic heart failure/** *is not on a beta blocker (BB)*	43	12	12	-
☑	E2	**2. Coronary heart disease without prior ACS**/** *is not on a BB or rate limiting CCB*	125	34	34	-
I-A	E2	**3. Coronary heart disease with prior ACS** */ is is not on a BB or rate limiting CCB*	106	24	24	-
I-B	E2	**4. Atrial fibrillation/** *is not on a BB, a rate limiting CCB or amiodarone*	132	70	70	-
IIa-B	E2	**5. Paroxysmal AF and on digitalis/** *is not on a BB, a rate limiting CCB or amiodarone*	-	-	-	-
☑	E4	**6. CHF or LVSD and on a beta blocker/** *is not on recommended target dose*	31	29	29	-
Outcome – Effectiveness (Symptom control)						
Objective 7 – Controlling angina symptoms						
I-B	E2	**1. Stable angina/** *is not on a short acting nitrate*	231	205	205	-
IIa-C	E3	**2. CHD and on a regular nitrate/** *is on a dosing regimen, which provokes nitrate tolerance*	Excluded			

Recommend. strength	DTR Type	**PCN screener/** *DTR checker*	PCN	DTR	DTR_{POS}	ID_{DTR}
Outcome – Effectiveness (Symptom control continued)						
Objective 8 – Controlling fluid retention						
I-B	E3	**1. CHF and on optimal treatment with ACEI, ARB, aldosterone antagonist and diuretic** *is not prescribed digoxin*	-	-	-	-
Outcome – Safety						
Objective 9 – Controlling risk of haemorrhage						
☑	S1	**1. AF and on OAC/** *has latest recorded INR >3.0*	Excluded			
III-C	S3	**2. AF and $CHADS_2$= 0/** *is on an oral anticoagulant*	31	15	15	-
Objective 10 – Preventing drug induced angina symptoms						
☑	S3	**1. Coronary heart disease** / *is prescribed dipyridamol***e**	231	9	9	-
☑	S3	**2. Patient with CHD/** *is on dihydropyridine CCB without use of a BB*	-	-	-	-
Objective 11 – Preventing drug induced fluid retention						
IC	S3	**1. Chronic heart failure /** *is prescribed antiarrhytmic class 1 (IC)*	43	0	0	-
IIb-B	S3	**2. Chronic heart failure /** *is prescribed a glitazone*	43	0	0	-
☑	S3	**3. Chronic heart failure /** *is prescribed a PDE 5 inhibitor*	43	0	0	-
☑	S3	**4. Chronic heart failure /** *is prescribed an NSAID*	43	4	4	-
☑	S3	**5. Chronic heart failure /** *is prescribed a tricyclic antidepressant*	43	2	2	-
☑	S3	**6. Chronic heart failure /** *is prescribed an oral steroid*	43	4	4	-
☑	S3	**7. Chronic heart failure /** *is prescribed lithium*	43	0	0	-
☑	S3	**8. Chronic heart failure /** *is prescribed minoxidil*	43	0	0	-
☑	S3	**9. Chronic heart failure /** *is prescribed diltiazem or verapamil*	43	4	4	-
☑	S3	**10. Chronic heart failure /** *is prescribed a short-acting DHP-CCB*	43	1	1	-

Appendix 9: Inter rater reliability – Detailed findings

Inter rater reliability for MAT$_{CVC}$ measures. Counts of agreements on positive cases (A), negative cases (D) and disagreement (B and C)

	A. Inpatient (n=69)				B. Outpatient (n=59)				C. Primary Care (n=94)			
	A	B	C	D	A	B	C	D	A	B	C	D
MATcvc total	122	7	6	1390	129	10	10	993	167	9	9	1607
Prescribing measures												
E1 Achievement of targets	10	1	1	195	14	0	0	222	31	5	3	243
E2 Need for drug therapy	32	3	1	571	75	5	5	290	87	1	0	488
E3 Effective drug choice	9	1	1	127	13	0	0	105	17	2	2	167
E4 Effective dosing	63	2	2	140	23	5	5	144	22	1	3	256
S1 Control of safety param.	1	0	1	67	0	0	0	59	Excluded			
S3 Safe of drug choice	7	0	0	290	4	0	0	173	10	0	1	453
Action measures												
1_E1 INR target	6	0	1	62	2	0	0	57	Excluded			
1_E2 TE prophylaxis	5	1	0	63	4	0	0	55	6	1	0	87
1_E3 TE prophylaxis	7	0	1	60	9	0	0	50	10	1	1	82
2_E1 TC/LDL target	1	1	0	67	2	0	0	57	3	0	1	90
2_E2 Use of a statin	14	0	0	55	11	1	2	45	29	0	0	65
2_E4 Suboptimal statin dose	23	0	0	46	4	2	1	52	11	0	3	80
3_E1 HbA1c target	3	0	0	66	2	0	0	57	7	1	0	86
3_E3 Oral antidiabetic	2	0	0	67	4	0	0	55	7	0	1	86
4_E1 BP target	Excluded				8	0	0	51	21	4	2	67
5_E2a Use of ACEI or ARB	6	1	0	62	7	1	1	49	18	0	0	76
5_E2b Aldosterone ant. or ACEI+ARB combination	0	0	0	69	31	0	0	28	0	0	0	94
5_E4 Target dose ACEI /ARB	19	1	1	48	4	1	1	53	0	0	0	94
6_E2 BB or alternative	7	0	1	61	19	3	0	37	12	0	0	82
6_E4 Suboptimal dose of BB	21	1	1	46	15	2	3	39	11	1	0	82
7_E2 Short acting nitrate	Excluded				2	0	0	57	22	0	0	72
7_E4 Nitrate dosing	0	0	0	69	0	0	0	59	Excluded			
8_E2 Use of digoxin	0	0	0	69	1	0	0	57	0	0	0	94
9_S1 Excessive INR	1	0	1	67	0	0	0	59	Excluded			
9_S3 TE prophylaxis	1	0	0	68	1	0	0	58	2	0	0	92
10_S3 Drug choice in CHD	0	0	0	69	0	0	0	59	0	0	1	93
11_S3 drug choice in CHF	6	0	0	63	3	0	0	56	8	0	0	86

Chapter 5

Overall summary and conclusions

1. Overall summary

Regulatory systems are in place to ensure the safety and efficacy of new drug products entering the market based on pre-marketing experience with these drugs, but a system which manages safe and effective medication use in clinical practice is currently missing. This is in spite of overwhelming evidence that preventable drug related morbidity (PDRM) is sufficiently prevalent and severe to constitute a threat to public health and that the drug products most frequently implicated in preventable harm have been on the market for decades. In addition, the management of chronic disease will present the greatest challenge to health care systems internationally in the 21st century. Although much research into PDRM has focussed on medication safety, optimising the use of drug treatments that can effectively prevent and manage long term conditions are paramount to decrease its societal burden.

The aims of this thesis were four-fold (chapter 1 to 4): (1) to advance the conceptual understanding of the causes of preventable drug-related morbidity (PDRM), (2) to identify components of a model for continuous quality improvement of medication use systems, (3) to develop an instrument to measure the quality of medication use for multiple conditions and (4) to test the instrument for its utility within the proposed quality improvement model.

The following sections 1.1 to 1.4 summarise the previous chapters in turn, highlighting what was known from the literature before, summary of research undertaken and how each chapter has contributed to the existing literature.

1.1 Understanding the quality gap in medication use systems

What was known before?

Terms to describe and quantify the extent to which drug products cause patient harm have been used in pre-and post-marketing clinical trials and post-marketing

surveillance for over 40 years (pharmacoepidemiology and pharmacovigilance). More recently, these and related terms have been developed further and used in research to describe and quantify the extent to which the suboptimal use of drugs in clinical practice translates into preventable drug related morbidity, i.e. harm and unrealised health benefit, and to measure the impact of interventions targeted at practitioners (Quality Improvement) and patients (Pharmaceutical Care). This has led to a situation, where multiple terms with variable definitions co-exist, creating ambiguity in their use by researchers and practitioners alike. This observation applies in particular to the term 'Drug Therapy Problems (DTPs)', a cornerstone of the philosophy and practice of pharmaceutical care.

Summary of research undertaken

The first part of this thesis has therefore critically reviewed key concepts used in the literature in order to gain a better understanding of where medication use systems fail and how they can be improved. As the output of this review, three new concepts have been introduced in an effort to address identified limitations of existing concepts: First, the concept of drug therapy failure (DTF) was proposed in order to capture the undesirable consequences of sub-optimally effective medication use and to separate such consequences from direct drug-related harm (adverse drug events). Second, the concept of drug therapy risk (DTR) was introduced in order to more clearly separate negative drug related outcomes from situations that put patients at risk of such outcomes. Third, the concept of pharmaceutical care need (PCN) was introduced in order to address an identified lack of a concept that captures patient circumstances (risk factors), which pre-dispose to risk. The relationships between existing and newly introduced concepts were characterised. The three newly proposed terms formed the basis for a revised theoretical model of the aetiology of PDRM and the foundation for a three step approach to its prevention: *screening* for pharmaceutical care needs, *checking* for drug therapy risks and *acting* to address detected drug therapy risks.

What this work adds

Unambiguous definitions and consistent use of concepts to describe drug related morbidity and its causes are pre-requisites to consolidate findings from different bodies of research. Where assessment of research outcomes relies on clinicians' documentation of the care they provide (often the case in Pharmaceutical care interventions), any definitions used must also be readily understood and reliably applied by practitioners to yield interpretable results. The terms pharmaceutical care need, drug therapy risks and the extension of undesirable outcomes to include the consequences of sub-optimally effective medication use have the potential to describe PDRM less ambiguously and more comprehensively. The screen-check-act approach developed in this chapter accommodates the newly proposed concepts within a framework for practice that aims at systematically preventing PDRM.

1.2 Components of a model for continuous quality improvement of medication use systems

Building on the theoretical model of the aetiology of PDRM developed in chapter 1, this chapter sought to identify effective strategies for its prevention.

What was known before?

Systematic reviews[1,2] into the causes of preventable drug related hospital admissions demonstrate that current deficits in the quality of medication use mainly reside in patients with long term conditions. In UK primary care, the root causes of such hospital admissions have largely been attributed to the interplay of shortcomings in pharmaco-therapeutic knowledge and deficiencies in the information infrastructure, which have hindered the implementation of effective defence mechanisms against PDRM, such as closer collaboration between prescribers and pharmacists, to take effect.[3] The chronic care model[4] (CCM- an integrated multifaceted approach to the delivery of care for patients with long term

conditions) had previously been developed in order to facilitate systematic and integrated approaches to improve the quality of care for patients with chronic conditions, but had not been previously operationalised to address the problem of PDRM.

Summary of research undertaken

A structured literature review of the impacts of interventions advocated by the CCM (audit and feedback, clinical decision support, and collaborative models of care) on the quality of medication use processes and outcomes was therefore conducted in order to substantiate the working hypothesis that the CCM may be successfully applied to address current deficiencies in medication use systems. This literature review supports each strategy as a means to improve medication use processes in principle. However, there is little evidence to support audit and feedback[5] and clinical decision support[6] interventions as a means to improve therapeutic and patient outcomes. Studies of collaborative services involving pharmacists[7-13] have shown mixed results. A more detailed discussion of studies investigating pharmacist delivered services identified limitations in patient inclusion criteria, questionable quality of intervention delivery and inconsistent pharmacist-prescriber collaboration as factors that may hinder more consistent positive effects. It was argued that a multi-faceted strategy is likely to be required for improvements in drug therapy outcomes to be achieved.

What this work adds

The literature review informed the proposal of components of a model for continuous quality improvement of medication use systems, which enables quality management by means of medication use assessment against standards of best practice and was based on the screen-check-act approach developed in chapter 1. Within this model, quality assessment serves three functions: (1) to provide decision support through the standardised detection of drug therapy risks, (2) to organise

patient follow-up by a multidisciplinary team of providers and (3) to enable quality control (audit) of medication use systems at provider level.

1.3 Development of an instrument to assess the quality of medication use for multiple conditions (MATCVC)

Chapter 2 has highlighted that instruments to routinely assess the quality of medication use may play a central role in the design of medication use systems that are capable of preventing PDRM. This chapter aimed to develop and demonstrate the use of a framework for the design of medication assessment tools that have the potential to function as decision support, patient targeting and audit tools.

What was known before?

Previously developed instruments have focused on the assessment of medication safety[14-16] or single diseases[17-21] and those that do address multiple conditions[22-26] cover a limited spectrum of relevant medication use aspects. In addition, none of the multi-disease instruments[22-26] provided a framework that allowed a large number of medication assessment criteria to be presented in a structured way to facilitate feedback of information to potential users in a quality improvement context. Furthermore, at the time this research was conducted, viable approaches of accounting for patient context factors that may impede adherence of medication use to standards of best practice were not available.

Summary of research undertaken

The increasing burden of chronic cardiovascular conditions (CVC), the strong evidence supporting medication use in its prevention and management, evidence of deficits in the implementation of evidence based guidelines and a high prevalence of cardiovascular co-morbidity made CVCs an obvious target for the development of a medication assessment tool that targets the management of multiple related diseases (MATCVC). The design of the MATCVC instrument drew on the development

of a generic framework for explicit quality assessment of medication use that was informed by existing categorisation systems for drug therapy problems. Guideline recommendations suitable for translation into explicit assessment criteria were systematically identified from evidence based practice guidelines using specific inclusion and exclusion criteria. Using the developed generic framework as a template, the identified recommendations were subsequently translated into explicit assessment criteria, each of which representing a standardised drug therapy check for an identified pharmaceutical care need. Individual criteria in the resulting MAT$_{CVC}$ instrument were organised at five hierarchical levels reflecting the drug therapy outcomes, aims, objectives, drug therapy risks and pharmaceutical care needs targeted. For a subset of MAT$_{CVC}$ criteria, explicit clinical exemption rules were validated by a panel of four clinical pharmacists.

What this work adds

The work presented here provides a previously missing generic template for the development of instruments to assess the quality of medication use for patients with multiple conditions. The resulting instrument offers an efficient way of systematically identifying clinically important drug therapy risks in individual patients that is aligned with established practice frameworks of pharmaceutical care delivery (the pharmacotherapy workup). The criteria within the tool are characterised at multiple levels, thereby offering opportunities to aggregate individual criteria at each level in order to facilitate and customise performance feedback to the needs of health care providers and managers. The developed clinical exemption rules allow individual clinical circumstances that may impede adherence of medication use to evidence based practice standards to be identified without the need for expert judgement.

1.4 Field testing of a medication assessment tool for chronic cardiovascular conditions (MATCVC)

This chapter sought to field test and demonstrate the use of the MATCVC instrument developed in chapter 3 in patient targeting and quality control applications.

What was known before?

Instruments to measure the quality of medication use require, as a minimum, field testing for reliability and validity before they are implemented in practice. Further desirable attributes pertaining to the use of such instruments in a quality improvement context have previously been described.

Summary of research undertaken

In order to test the MATCVC for desirable methodological attributes and to gain experience in the application of MATCVC within the model for continuous quality improvement of medication use proposed in chapter 2, the instrument was used to conduct retrospective surveys of guideline implementation in four samples of patients from inpatient, outpatient and primary care practice settings in Germany, Scotland and the Netherlands. A standard operating procedure was developed in order to operationalise MATCVC assessment within the context of each respective setting. The multiple ways in which MATCVC criteria are characterised were exploited to aggregate individual MATCVC items into composite measures for use in quality control, audit and patient targeting applications. Four quality indexes were developed and applied to summarise the findings of MATCVC assessment with respect to the prevalence of (1) data gaps in clinical documentation, (2) adherence, (3) explained and (4) unexplained non-adherence to guideline recommendations. A number of quantitative strategies of using MATCVC findings to identify targets for quality improvement at provider and patient levels were identified and modelled using survey data. Gaps in guideline implementation were identified in all settings, revealing shortcomings in the initiation, monitoring and timely adjustment of medication use.

What this work adds

MATcvc assessment was identified as a reliable albeit potentially resource intensive method of assessing the status quo of guideline implementation for multiple conditions in a variety of practice settings. The extent to which MATcvc quality assessment concurs with assessments by local clinicians was identified to be variable and dependent (among other factors) on the accuracy of documentation of context factors that explain deviations from guideline recommended standards. The limited extent to which such context factors can be extracted from routine clinical documentation are identified as key factors that currently limit the utility of explicit quality assessment methods for applications in quality improvement.

1.5 General conclusions from chapters 1 to 4

A number of policy reports published at the beginning of this millennium have raised the profile of PDRM.[27,28] However, efforts to systematically address the PDRM problem remain patchy internationally. Systematic improvements in medication use are currently hindered by a lack of a common understanding of the causes of PDRM, deficiencies in the health care infrastructure, limited transparency in the quality of medication use provided and insufficiently defined models of care that allow a better integration of pharmaceutical care services provided by different stakeholders. Drawing on the findings in this thesis, the following section further expands on how collaborative approaches to continuous quality improvement of medication use systems may be operationalised and implemented.

2. Continuous quality improvement of medication use systems in the 21st century

Medication use systems are complex, comprising of multiple inter-related steps that are provided by stakeholders from different professional backgrounds and are embedded within an health care environment that is influenced by policy makers and health care funders. Adding to the complexity is the fact that practitioners outside of hospitals usually operate from disjointed settings.

Medication use systems must fulfil three essential functions, i.e. (1) care plan design, (2) professional monitoring and (3) drug administration (see chapter 1). The plethora of drug products available on the market, accumulating knowledge from clinical trials that can be conflicting and the unique characteristics of individual patients create uncertainty and complexity in all three of these functions, reflected in the definition of 'quality in medication use' (chapter 1): 'An optimal balance of scientific knowledge, patient preference and patient need in the planning, implementation and monitoring of medication use'.

Qualitative research[3] has demonstrated that the failure of current medication use systems to recognise and manage these complexities and uncertainties are the root causes of PDRM (see chapter 2). Consequently, quality improvement approaches for medication use systems should focus on methods to reduce complexity.[29] Clinical information systems that facilitate evidence based decision making and improve communication between all health care participants has a lot to offer in this respect (see chapter 2).

2.1 The Plan-Do-Study-Act-model for continuous quality improvement

The Plan-Do-Study-Act (PDCA) cycle has first been described by Deming as a cycle for organisational 'learning and improvement'.[30] It is based on the notion that industrial processes should be analyzed and measured to identify sources of

variations that cause process outcomes to deviate from the requirements of consumers. In this model, evaluations of processes are placed in a continuous feedback loop so that organisations can identify and change the parts of the process that need improvements:

Plan - An area for improvement is identified. A Pareto chart or funnel plot can be utilised in this step to identify the most prominent quality problems. A multidisciplinary team is formed to identify an improvement intervention.

Do - The improvement intervention is tested on a small scale, e.g. a sample of patients

Check/study **-** Next, the small-scale intervention is checked to see if it works by comparing the new state of the system against the old one using statistical methods

Act **–** If successful, the small scale study is implemented on a larger scale and its sustained impact is measured periodically thereafter. If unsuccessful, the cycle begins again at the *'Plan'* stage.

2.2 Operationalising MATCVC assessment within the PDCA cycle

Chapter 3 has developed an evidence based instrument to assess the quality of medication use and chapter 4 has explored systems of reporting on the quality of medication use for applications in a quality improvement context. Different approaches have been modelled on how the instrument may guide the selection of priorities for quality improvement in the '*Plan'* step of the PDCA cycle. The following section proposes ways of utilising MATCVC (and similar instruments based on the same principles) in the 'Do'/'Act' and 'Check' steps of the cycle (see figure 5.1 overleaf).

'Do'/ 'Act' – Providing and documenting pharmaceutical care activity

The provision of pharmaceutical care has been described as a process of checking for pharmaceutical care needs, checking for drug therapy risks and acting on identified drug therapy risks (chapter 1) and the MATCVC has been designed (chapter 3) in order to assist practitioners in the 'screen' and 'check' stages (decision

support). Applying the MAT at the individual patient level exposes drug therapy risks as inconsistencies in the implementation of evidence based standards (MATCVC answer category DTRPOS) or corresponding monitoring activities (MATCVC answer category IDDTR).

Figure 5.1: Application of MATCVC in continuous quality improvement (PDCA cycle)

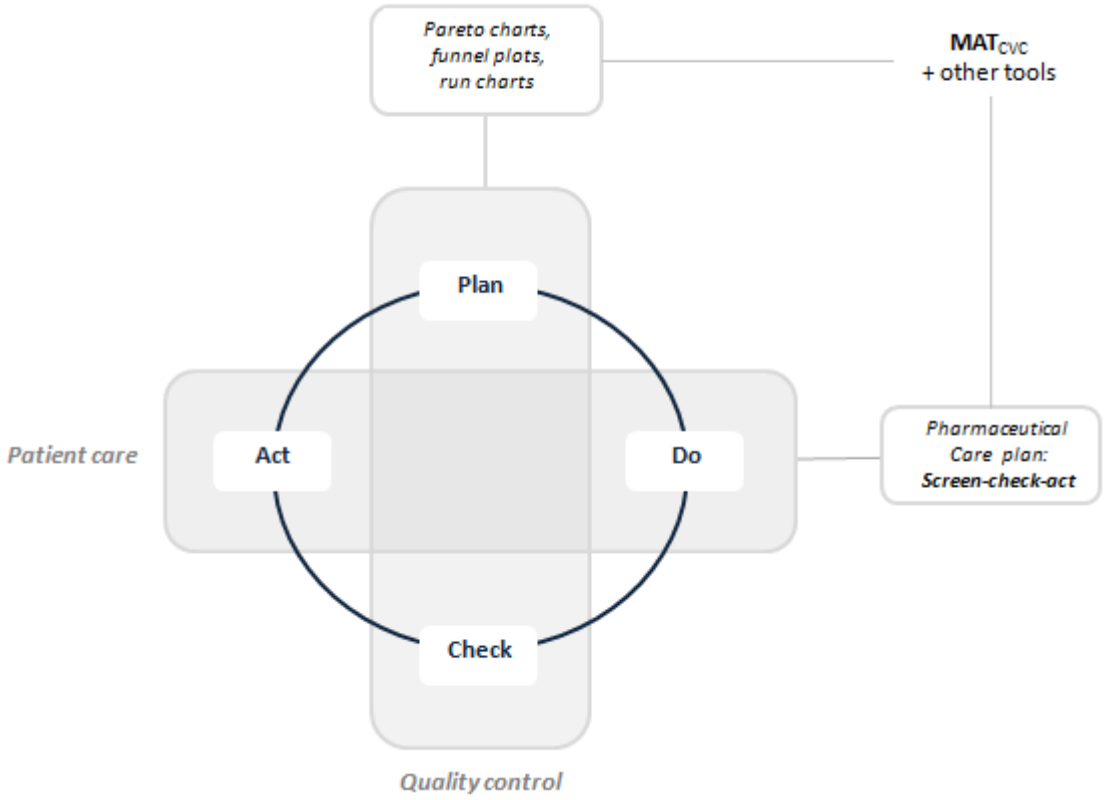


Table 5.1 (see page 334) illustrates how drug therapy risks detected by the application of the MATCVC at the individual patient level may be integrated into a pharmaceutical care plan based on the screen-check-act approach. The example highlights that non-adherence to therapeutic standards, such as those that can be detected by explicit medication assessment tools, will often not provide a comprehensive picture of all the factors that may put an individual patient at risk of PDRM. At the individual patient level, MATCVC assessment must therefore be

integrated into a more holistic approach to the detection of drug therapy risks. Nevertheless, the MAT$_{CVC}$ will ensure that relevant standards are always considered in the decision making process. Where the detection of drug therapy risks relating to therapeutic standards becomes a routine (ideally automated) task, this may yield resources for practitioners to engage in clinical decisions that must be made in areas, which are not supported by a strong evidence base.

Table 5.1: Illustration of a pharmaceutical care plan based on the screen-check-act

Screen →	Check →	Act →		
PCN	DTR$_{POS}$	PCN$_{MET}$	DTR$_{EXP}$	
			Not relevant in this patient	*Managed*
CLINICAL				
Effectiveness				
Adherence to standards				
History of MI	E2: Not on TE prophylaxis	□	□	□
AF with $CHADS_2$ =3	E2: Not on warfarin	□	□	□
On beta blocker for CHF	E4: Not on BB target dose	□	□	□
Other identified patient complaints				
...				
Safety				
Adherence to standards				
CHF	S3: Verapamil prescribed	□	□	□
On warfarin	S1: INR > 4	□	□	□
On warfarin	S3: NSAID prescribed	□	□	□
Other identified patient complaints				
...				
COST-EFFECTIVENESS				
On statin	C: On non-formulary statin	□	□	□
...				
PATIENT EDUCTION/SELF-MANAGEMENT SUPPORT				
Commenced on opioid	Counselling due	□	□	□
CONTINUITY OF CARE				
Discharged from hospital	Record update due	□	□	□
....				

The care plan example also accounts for the fact that although deviations from guideline standards represent risks to patient outcomes, complying with these standards may sometimes put patients at even greater risk (e.g. because of a permanent or temporary contraindication or intolerance) or it may simply be unnecessary (e.g. because of limited life expectancy). In order to account for these situations, clinical exemption rules have been validated (chapter 3) and operationalised through the answer category DTR_{EXP} (chapter 4).

Chapter 4 has, however, also demonstrated that pre-defined exemption rules identified from routine documentation cannot comprehensively account for all clinical circumstances that may hinder the implementation of guidelines. In cases where the MAT_{CVC} fails to identify such context factors (DTR_{POS}), the care plan (table 5.1) allows clinicians to identify deviations from such standards as deliberate clinical decisions (DTR_{EXE}). Such explained non-adherences may be further segregated into those, where patient clinical or non-clinical context factors permanently ('Not relevant') or temporarily ('managed') hinder the implementation of guideline recommended treatments, since the latter –in contrast to the former- would require periodic review.

'Check' - Monitoring change in the quality of medication use

Changes in the quality of medication use over time are reflected quantitatively by changes in the MAT_{CVC} quality indexes. Table 5.2 shows that quality improvement is reflected by:

- A decrease in the Data Gap Index (DGI) as a consequence of conducting and documenting overdue monitoring tests
- A decrease in the Unexplained Non-Adherence Index (UNAI) as a consequence of either recording an explanation for the non-adherence (DTR_{POS} → DTR_{EXE}) or by implementing medication use changes in line with guideline recommendations (DTR_{POS} → PCN_{MET})
- An increase in the Adherence Index (AI) as a consequence of implementing medication use changes in line with guideline recommendations (DTR_{POS} → PCN_{MET})

The effectiveness of quality improvement interventions conducted under 'Do' could therefore be assessed by performing a before and after comparison of DGI and UNAI scores. Another approach would be to perform a time series analysis of the number of patients with unexplained non-adherences (DTR_{POS}). For each of these approaches, potential users may consider, whether and at which level individual MAT_{CVC} measures may be aggregated in order to minimise sample size requirements (see chapter 4).

Table 5.2: DTR prompts, corresponding actions and their reflection in MAT_{CVC} quality indexes

	Patient care		**Quality control**
MAT category	DTR	Action	Quality Indexes
ID_{PCN}	Patient record incomplete	Update record	No change
ID_{DTR}	Monitoring overdue	Schedule follow-up visit/ investigation	Data Gap (DGI) ↓
DTR_{POS}	Treatment regimen deviates from best practice standards	a. Exemption identified → Reclassify as DTR_{EXP}	Unexplained non-adherence (UNAI) ↓ Explained non-adherence (ENAI) ↑
		b. Exemption excluded → Change treatment	Unexplained non-adherence (UNAI) ↓ Adherence (AI) ↑
DTR_{EXP}	Treatment regimen deviates from best practice standards, but context factors hinder its implementation	a. Exemption is permanent	No change
		b. Exemption is temporary → Schedule review	No change

2.3 Collaboration in continuous quality improvement

Quality assessment integrated into a system of continuous quality improvement has the potential to facilitate collaboration between different providers in a variety of ways. First, it requires clinicians to agree on a set of quality standards, thereby

establishing common goals to be accomplished. Second, once standards and goals are established, a multidisciplinary team may be formed in order to collect data for quality measurement. For example, chapter 4 has highlighted how data from community pharmacy and general practice records was linked in order to enable MATcvc assessment. Third, quality improvement initiatives may draw on all health care professionals, who have the necessary expertise in order to contribute to medication use optimisation, thereby reducing the workload for individual clinicians and making improvements more sustainable.

The ubiquitous use of electronic medical records in UK primary care and the existing information technology infrastructure available in the National Health Service (NHS) provide ideal opportunities to implement collaborative models for continuous quality improvement of medication use. Furthermore, there is a strong commitment to advance the role of the community pharmacist in the prevention and management of patients with long term conditions that is perhaps best reflected in the document 'Establishing Effective Therapeutic Partnerships'[31], published by the Scottish government in 2009. The report provides a basis for the implementation of the Chronic Medication Service (CMS) element of the Community Pharmacy Contract in NHS Scotland. It describes how patient care may be improved through the establishment of therapeutic partnerships between patients, general medical practitioners and community pharmacists. '*It introduces a more systematic way of working and formalises the role of community pharmacists in the management of individual patients with long term conditions in order to assist in improving the patient's understanding of their medicines and optimising the clinical benefits from their therapy.*'[32]

The specifications of the pharmacist's role in the CMS outlined in the document parallel the ideas reflected in the screen-check-act approach (chapter 1). The document has also established the need to underpin the CMS by a 'governance system' that ensures continuous quality improvement (including regularly measuring and evaluating practice) facilitated by information technolgy (eCMS). Chapter 4 has demonstrated, how the MATcvc or other sets of explicit medication

assessment criteria can contribute to the further definition of the service, namely by supporting patient targeting ('pharmaceutical care planning'), providing decision support (individual patient care) and quality control ('clinical governance'). Implementing such instruments may also help to define shared and distinct responsibilities, where pharmacists may be commissioned, for example, to ensure adequate cardiovascular risk factor control or to review and manage patients with high-risk prescribing, an area that has always been a focus of the pharmacy profession and is currently not represented in the quality and outcomes framework (QOF).[33] Such focussed approaches may have advantages over more generic medication review services (reviewed in chapter 2) in initiating new working partnerships, because it allows the multidisciplinary team to practice new models of care in a defined, largely protocol-driven clinical area. Once viable processes have been established, the longer term aim must, however, be to provide holistic pharmaceutical care, in which the spectrum of patients' pharmaceutical care needs and drug therapy risks are continuously and systematically identified and addressed.

3. Conclusions and further research

This thesis has made an attempt to describe the scope of PDRM and its precursors and to advance the understanding of its aetiology, which has provided a theoretical foundation for the proposal of a model of continuous quality improvement of medication use and the development and testing of instruments to operationalise the model in practice. Chronic cardiovascular conditions have been used as an example to explore the use of medication assessment tools for multiple conditions in a quality improvement context, but the design of the instrument and the methods of applying it in practice are generalisable to other disease areas and medication use aspects.

Since the completion of this thesis, further work has been undertaken to extend the range of medication use measures covered by the MATCVC and other previously

published instruments within the 'Data-driven quality improvement programme in primary care (DQIP)' research programme (accepted for publication in BMC Clinical pharmacology 17/01/2012). A total of 176 medication assessment criteria that are intended for implementation in electronic medical records routinely available in UK primary care were validated by a panel of 10 general medical practitioners and pharmacists.

The DQIP set of 176 medication assessment criteria are focussed on long term conditions commonly encountered in primary care and on the drugs most frequently implicated in PDRM hospital admissions or severe PDRM events. The majority of these criteria target medication use that has been validated as representing care that is either 'necessary to do' or 'necessary to avoid' and were considered to be priorities for quality improvement in a larger DELPHI panel of 40 primary care clinicians.

The large number of criteria reflects the large scale and spectrum drug therapy risks that need to be managed in order to address only the most pertinent problems in current medication use systems. A study applying 9 of the developed criteria to patients registered with 315 general practices[34] has estimated that approximately 60 patients in an average sized practice (list size of 5,500 registered patients) are affected by high-risk prescribing targeted by at least one these measures annually. In the Dutch primary care setting (chapter 4), the 52 MAT$_{CVC}$ criteria detected at least one drug therapy risk in 15% of patients registered with participating GP practices, equating to 808 patients per average sized practice (list size of 5,500 registered patients). It is reasonable to assume, that applying all medication assessment criteria included in the DQIP set is likely to identify numbers of patients at risk that are no longer manageable by existing general practice teams. Furthermore, both the MAT$_{CVC}$ and DQIP criteria sets only target the prescribing and monitoring stages of the medication use process, but do not address risks relating to patient compliance or self-management, which are estimated to account for a third of preventable drug-related hospital admissions.[1]

There is still a paucity of interventions to effectively reduce preventable drug related morbidity, especially outside the United States (chapter 2), but given the public health relevance of PDRM, such interventions are urgently needed. Applying the principles of continuous quality improvement, the DQIP research programme is currently testing a complex intervention to reduce high-risk prescribing of non-steroidal anti-inflammatory drugs and antiplatelets in a cluster randomised controlled trial in Scottish primary care. The core of the intervention is an informatics tool, which identifies patients who are affected by this high-risk prescribing and prompts GPs to review them and take corrective action where necessary. The intervention is currently limited to general medical practices and focuses on a narrowly defined therapeutic area. However, if shown to be effective and cost-effective, the approach may be extended to include other health care professionals and additional pharmaco-therapeutic areas. It is time for health care systems internationally to make the development, testing and implementation of collaborative approaches to systematically address the problem of preventable drug related morbidity a priority.

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Glossary

Act	An activity to address a drug therapy risk
Action composite	A composite measure which aggregates individual assessment criteria at the level of drug therapy risk categories within the same drug therapy objective
Adverse drug event (ADE)	Any injury due to medication
Adverse drug reaction (ADR)	A noxious, unintended and undesired effect of a drug, which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy
Appropriateness in medication use	An optimal balance of scientific knowledge, patient preference and patient need in the planning, implementation and monitoring of medication use within the constraints of society
Assessment criterion	A measurement item, representing a best practice standard against which medication use is assessed
Cardiovascular condition (CVC)	Comprises of cardiovascular disease, chronic heart failure and atrial fibrillation
Cardiovascular disease	A cardiovascular condition that is attributable to atherosclerosis
Check	An activity to confirm, exclude or prevent a drug therapy risk
Composite measure	A metric which aggregates two or more assessment criteria
Data gap	The lack of data to verify adherence to a best practice standard
Data gap index (DGI)	The rate of times where adherence to a best practice standard cannot be verified due to missing data over the number of times that the standard is relevant
Drug therapy failure (DTF)	A negative change in health status due to a medical condition that is modifiable by drug therapy
Drug therapy risk (DTR)	A pre-cursor to ADEs or DTFs, which requires professional action in order to prevent an ADE or DTF
DTR positive (DTRPOS)	An unaddressed drug therapy risk or unexplained non-adherence to a best practice standard
DTR explained (DTREXP)	A scenario, where a drug therapy risk has been identified and the patient is either clinically exempt or the drug therapy risk is managed
Explained non-adherence index (ENAI)	The rate of explained non-adherence to a best practice standard over the number of times that the standard is relevant
Non-adherence Index (NAI)	The rate of non-adherence to a best practice standard over the number of times that the standard is relevant