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THE CLINICAL PHARMACIST'S ROLE IN POST-DISCHARGE FOLLOW-UP OF PATIENTS WITH CORONARY HEART DISEASE

A FOLLOW-UP PROGRAM

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"To salvage the acutely ischaemic myocardium without addressing the underlying causes of the disease is futile; we need to invest in prevention"

The EuroAction Study group, 2008 (1)

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ABSTRACT

Coronary heart disease (CHD) is the leading cause of death world-wide. Studies indicate that patients are treated inadequately, and efforts are consequently made world-wide to increase the appropriateness of care. Pharmaceutical care programs delivered by pharmacists are known to improve quality of care for both ambulatory and hospitalized patients with a variety of chronic and acute diseases, also CHD. Most of the programs are developed and carried out in the United States and United Kingdom, where 'Pharmaceutical Care Practice' was first established.

The overall aim of this PhD project was to develop a pharmacist-led follow-up program for patients with established CHD after hospital discharge. This thesis addresses the different steps made in order to do so. First, the thesis elucidates the development and validation of a medication assessment tool within secondary prevention of CHD (MAT-CHDSP). The tool can be used for identification of non-adherences with guideline recommendation, and hence identify improvement potentials. It may also function as a clinical tool during e.g. medication therapy reviews. Second, the thesis describes the use of the MAT-CHDSP in a retrospective study, that was performed in order to achieve baseline information on secondary prevention in patients discharged from the University hospital of North Norway. Third, the thesis presents the development of a clinical pharmacist-led follow-up program that was carried out as a randomized controlled trial to explore the effects of the program. Last, the thesis describes a qualitative study that was carried out in patients included in the follow-up program, in order to gain knowledge on how participants experienced the program.

The MAT-CHDSP was found applicable for use in this patient population, where good validity, feasibility and reliability results were achieved. The retrospective study revealed improvement potentials in secondary prevention of CHD, especially regarding follow-up on unachieved therapy goals and lifestyle counselling. This information was used to develop the one-year follow-up program, where RCT results showed an increase in documentation of lifestyle recommendations, however no significant impact on clinical outcomes in favour of the intervention group. The qualitative study did, however, indicate that the program was highly appreciated by the participants, that it influenced their knowledge of drugs and made them feel safe. The clinical pharmacist was acknowledged as a part of the interdisciplinary team, both for patient education, but also as a support for physicians in medication related problems and as an individual care taker.

In order to offer the follow-up program on a continuous basis to patients with CHD, several changes and more research in a larger patient population are warranted.

TABLE OF CONTENTS

LIST OF PAPERS

The present thesis is based on the following papers which will be referred to in the text by their Roman numerals[4].

I Garcia B, Utnes J, Naalsund L, Giverhaug T (2011) MAT-CHDSP, a novel medication assessment tool for evaluation of secondary prevention of coronary heart disease. *Pharmacoepidemiol Drug Saf*; 20(**3**):249-57

II Garcia BH, Smabrekke L, Trovik T, Giverhaug T. (2011) Guideline adherence and therapeutic target achievement in secondary prevention of coronary heart disease. Manuscript. Submitted to *Eur J Cardiovasc Prev Rehabil* on September 2011.

III Garcia BH, Giverhaug T, Utnes J, Smabrekke L. (2011) Influence of a pharmacist-led follow-up program on clinical outcomes and guideline adherence in patients with established coronary heart disease – a randomized controlled trial. Manuscript.

IV Garcia BH, Storli SL, Smabrekke L. (2011) Patient experience with a pharmacist-led follow-up program – a qualitative study in post-discharged patients with coronary heart disease. Manuscript.

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DEFINITIONS AND KEY CONCEPTS

Clinical pharmacy
Clinical pharmacy has been defined by the American College of Clinical Pharmacy as a "Health science specialty which embodies the application by pharmacists, of the scientific principles of pharmacology, toxicology, pharmacokinetics and therapeutics to care for the patient" (2).

Clinical Therapy Guideline (CPG)
A Clinical Therapy Guideline (CPG) is a "a systematically developed statement to assist decisions for practitioner and patient about appropriate health care for specific clinical circumstances"(3).

Coronary heart disease
Coronary heart disease (CHD) is defined as "a condition, and especially one caused by atherosclerosis, that reduces blood flow through the coronary arteries to the heart and typically results in chest pain or heart damage – also called coronary artery disease"(4). CHD represent the largest of six categories within coronary vascular diseases (CVD), and was in 2004 classified by WHO as the leading cause of mortality world-wide (5). CHD includes ST-elevated myocardial infarction (STEMI), non-ST-elevated MI (non-STEMI), stable angina pectoris (AP) and unstable AP (UAP). Major risk factors of CHD include smoking, high cholesterol, high BP, lack of physical activity and diabetes mellitus (DM), in addition to heredity, male gender and age.

Drug related problems
A drug related problem (DRP) has recently been defined by the Pharmaceutical Care Network Europe (PCNE) as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (6). Many definitions have existed throughout the years; however, all comprise a classification system of some kind. According to the new PCNE definition, a DRP can be divided into 4 primary domains for problems, 8 primary domains for causes and 5 primary domains for interventions. For a more thorough classification, see the PCNE's homepage (6). A Norwegian classification system has also been published (7).

Medication Assessment Tool (MAT)
A medication assessment tool (MAT) is a set of evidence-based review criteria to be used for assessing the level of adherence between CPG recommendations and clinical performance within a particular therapeutic field. Its structure takes justified non-adherence to CPG recommendations and missing information into account (definition not yet defined).

Medication profile
A medication profile is (as used in this thesis) a patient record specific to one single patient, including information on patient demographics, diagnoses and health problems, medications (both present and previous), doses, dosing frequency, allergies, dietary supplements, and other information relevant for the medication therapy review. Information is collected both from the electronic patient records at hospital and provided by the patient. The medication profile in used this thesis also includes a pharmaceutical care plan, including identified DRPs, possible solutions for the DRPs and the final outcome (when known). It may also be called a patient profile.

Medication Therapy Management
Medication therapy management (MTM) is a distinct service or group of services that optimize therapeutic outcomes for individual patients and may be defined as "the provision of pharmaceutical care services by a licensed pharmacist to optimize the therapeutic outcomes of the patients' medications" (8). MTM encompasses a broad range of professional activities and responsibilities within the licensed pharmacist's or other qualified health care provider's scope of practice, and normally includes five core elements: medication therapy review (MTR), personal medication record (PMR), medication-related action plan (MAP), intervention and/or referral, and documentation and follow-up (9). MTM was officially recognized by the US federal government in the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (10). In Norway, MTM by this definition is evolving.

Medication Therapy Review (also called Medication Review)
The medication therapy review (MTR) has by the American Pharmacist's Association been defined as a "systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them" (9), and by the PCNE as "an evaluation of patient‘s medicines with the aim of managing the risk and optimizing the outcome of medicine therapy by detecting, solving and preventing drug-related problems"(6). It is one of five core elements in MTM.

Pharmaceutical care
In 1990, pharmaceutical care was defines ad "The responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life"(11). The definition has changed and was in 2004 defined as "a patient-centered practice in which the practitioner assumes responsibility for a patient's drug-related needs and is held accountable for this commitment" (12). The professional orientation started in 1990 with the discussion of the philosophy by Hepler and Strand. In pharmaceutical care, the pharmacist works directly with a patient and other health care providers (8), with the purpose to provide safe and effective drug therapy, using a systematic strategy to identify, resolve and prevent DRPs in individual patients is used (11).

Pharmaceutical care practitioner
The pharmaceutical care practitioner is in line with the general practitioner which is "one who provides continuing comprehensive and coordinated care to a population undifferentiated by gender, drug treatment category, or organ system". However, the pharmaceutical care practitioner "assesses all of a patient's medications, medical conditions, and outcome parameters, not just those chosen by disease state, drug action , or quantity of medications consumed." Hence, the "pharmaceutical care practice is applicable in all patient care practice settings including ambulatory and long-term care, hospital and clinic settings"(12).

Performance indicator
A performance indicator is a "measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality, of care provided"(3).

Review criteria
Review criteria are "systematically developed statements that can be used to assess the appropriateness of specific health care decisions, services and outcomes"(13).

ABBREVIATIONS

AP	Angina Pectoris
ACEI	Angiotensin-Converting enzyme inhibitor
ARB	Angiotensin Receptor (II) Blocker
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CG	Control Group
CHD	Coronary Heart Disease
CHD_{SP}	Secondary Prevention of Coronary Heart Disease
CK-MB	Creatinine Kinase, the MB variant
CP	Clinical Pharmacist
CPG	Clinical Practice Guidelines
CVD	Cardiovascular Diseases
DBP	Diastolic Blood Pressure
DCF	Data Collection Form
DM	Diabetes Mellitus
DRP	Drug Related Problem
EF	Ejection Fraction
ESC	European Society of Cardiology
EuroAspire	European Action on Secondary Prevention through Intervention to Reduce Events
FIP	International Pharmaceutical Federation
FuP	Follow-up Program
GP	General Practitioner
HbA1c	Glycated Hemoglobin
IG	Intervention Group
ID	Insufficient data
IDq	Insufficient data to decide whether the qualifying statement is applicable
IDs	Insufficient data to decide upon the response of the standard
LDL	Low-density lipoprotein
LVSD	Left Ventricular Systolic Dysfunction (= heart failure)
MAI	Medication Appropriateness Index
MAP	Medication-related Action Plan
MAT	Medication Assessment Tool
$MAT\text{-}CHD_{SP}$	MAT for secondary prevention of CHD
MI	Myocardial Infarction
MTM	Medication Therapy Management
MTR	Medication Therapy Review
NICE	National Institute of Technology
Non-STEMI	Non-ST-elevated Myocardial Infarction
NT-proBNP	Biological inactive 76 amino acid N-terminal fragment co-secreted along with BNP
CRRC	Cardiovascular Risk Reduction Clinic
PCI	Percutaneous Coronary Intervention
PCNE	Pharmaceutical care network Europe
PIM	Potential Inappropriate Medication
PMR	Personal Medication Record
RCT	Randomized Controlled Trial
REK	Regional forskningsetisk komitè (Regional Committee for Medical Research Ethics)
SBP	Systolic Blood Pressure
SIGN	Scottish Intercollegiate Guideline Network
STATIN	Another name for 'HMG-CoA reductase inhibitor'
STEMI	ST-elevated Myocardial Infarction
UAP	Unstable Angina Pectoris
UK	United Kingdom
US/USA	United States of America
WHO	World Health Organization

1 INTRODUCTION

This thesis addresses a PhD project within clinical pharmacy. The following sections will give short introductions to the field of clinical pharmacy, approaches to endorse quality of drug therapy, challenges within coronary heart disease (CHD) management and existing follow-up programs (FuPs) within secondary prevention of CHD (CHD_{SP}), the latter specifically on the pharmacist's role.

1.1 CLINICAL PHARMACY

Pharmacists have traditionally been involved in compounding, production and dispensing of pharmaceutics. As the use of medications is increasing, both in numbers and complexity, new challenges in terms of inappropriate and unsafe medical therapy has emerged (11). This has also contributed to pharmacists being more involved in patient-centered pharmacotherapy. The specialty of clinical pharmacy has evolved from the United States (US), and since the international launch of the pharmaceutical care philosophy by Hepler and Strand in 1990 (11), underlining the pharmacists' responsibility to guide drug therapy to improve the quality of the patients' life, the role of the pharmacist in pharmaceutical care has been expanding world-wide. In 1997, the World Health Organization's (WHO) released the concept of the seven-star pharmacist, seeing the role of the pharmacist also as a care giver (14). The concept was taken up by the International Pharmaceutical Federation (FIP) in its policy statement on Good Pharmacy Education Practice in 2000. In the WHO handbook of 2006 'Developing pharmacy practice', it is stated: "It is in the additional role of managing drug therapy that pharmacists can now make a vital contribution to patient care" (15). With this, the international recognition of the pharmacist in drug therapy managing is confirmed.

In Norway, and most likely also in other countries, the terms clinical pharmacy and pharmaceutical care are used interchangeably; although, they rather should be looked upon as 'the health care specialty' and 'the practice', respectively, or as stated by the American College of Clinical Pharmacy: "The practice of clinical pharmacy embraces the philosophy of pharmaceutical care; it blends a caring orientation with specialized therapeutic knowledge, experience, and judgment for the purpose of ensuring optimal patient outcomes" (16). Despite the word 'pharmacist' not being mentioned in the definition of pharmaceutical care (see Definitions and Key Concepts), the clinical pharmacy specialty has evolved from many years of research and development within the profession of pharmacy. The pharmaceutical care

practitioner is a new patient care provider in the health care system, with no intention to be replacing the physician, the nurse or any other practitioner (12). Consequently, it is essential to be aware that pharmaceutical care involves more than the ability to make medication reviews, teach and counsel about medicines; it also involves a personal commitment and responsibility for the patients (17).

Linda Strand recently stated that "in 20 years of pharmaceutical care practice, we have not accomplished enough; there is limited recognition of payment for pharmaceutical services, there is limited demand for pharmaceutical care by patients and physicians, there is very little change in pharmacy education and there is too much talk and too little action" (17). This tends to be the situation not only in the US. Clinical pharmacist activities and the pharmacists' role as health care professionals were in 2004 formally accepted by the Norwegian government (18), and drug safety is also emphasized in the recently initiated patient safety campaign run by the Norwegian Ministry of Health (19). Nevertheless, clinical pharmacy services are not routinely being reimbursed and many providers of pharmaceutical care (i.e. mostly hospital pharmacies) strive to implement clinical pharmacy services in hospitals and communities.

1.2 APPROACHES TO ENSURE QUALITY OF DRUG THERAPY

Drug therapy is an important component of disease management, with the intention to prevent diseases, reduce morbidity and mortality, and to improve health-related quality of life. However, appropriate, safe and rational use of medications is a major challenge in modern health care, as the population of elderly is growing, the incidence of lifestyle-related diseases is increasing, preventive drug therapy is emphasized, new drugs are steadily marketed, and polymorbidity and polypharmacy is aggravated (15). In order to improve the quality of drug therapy, different approaches have been developed to measure quality. One common approach is the use of literature review and consensus panels to develop explicit drug lists or drug regimens that are either advocated as appropriate or branded as inappropriate (explicit refers to criterion based statements, defining the clinical setting and patient population to which they apply) (13). They can either refer to specific classes or groups of drugs, or prescribing for particular vulnerable patients (20). The most well-known list is the Beers criteria (Table 1.1), indicating inappropriate drugs in elderly patients (21;22). The Beers criteria have been adapted for use in many countries, and in Norway form a part of the NORGEP (Norwegian general practice) criteria (23). A second approach, which is closer to the classic medication therapy review (MTR), is the development of implicit indicators that take the assessment of

the entire drug profile of individual patients into account (implicit refers to a judgment-based process measure where an individual clinician assesses the appropriateness of a specific medication regime) (24). The Medication Appropriateness Index (MAI), is the most well-known (25). Implicit assessment is considered to better reflect the reality, as it allows for full and flexible assessment of individual drug therapy. However, it is time-consuming and considered less feasible for assessment of larger patient groups. Furthermore, implicit reviews require highly skilled users (24). Advantages and disadvantages have been shown for both approaches, and both have been shown valid and reliable (20).

Table 1.1 *Explicit lists and tools to measure quality of drug therapy*

Items	Therapeutic field	Care setting	Country
Drug lists or drug regimens			
ACOVE (26)	Geriatrics	Primary care	USA
Basger *et al.* (27)	Geriatrics	Primary care	AU
Beers (22)	Geriatrics	Primary care	USA
Huang *et al.* (28)	Miscellaneous	Primary care	CA
Martirosyan *et al.* (29)	Diabetes	Primary care	NL
McLeod *et al.* (30)	Geriatrics	Primary care	CA
NORGEP (23)	Geriatrics	Primary care	NO
Oborne *et al.* (31)	Neuroleptics	Primary care	USA
PDRM (32;33)	Elderly	Hospital care / Primary care	USA/ CA
Pont *et al.* (34)	Asthma	Primary care	NL
START (35)	Geriatrics	Hospital care	USA
STOP (36)	Geriatrics	Hospital care	USA
Tools including review criteria based on quality indicators			
MAT-CHF (37)	Congestive Heart Failure	Primary care	UK
MAT-CHD (38)	Coronary Heart Disease (CHD)	Primary care	UK
MAT-DM (39;40)	Diabetes Mellitus	Primary care	UK
MAT-CP (41)	Cancer pain	Hospital care	NO
MAT-CHD$_{SP}$ (42)	Secondary prevention of CHD	Hospital care / Primary care	NO
MAT-osteoporosis	Osteoporosis	NA	UK

ACOVE, Assessing Care of Vulnerable Elders; NORGEP, The Norwegian General Practice; PDRM, potentially drug-related mortality indicators; START, screening tool to alert doctors to the right treatment; STOP, Screening Tool of Older Person's Prescriptions; MAT, Medication assessment tool; CHF, congestive heart failure; CHD, Coronary Heart Disease; DM, Diabetes Mellitus; SP, Secondary prevention; NA, not applicable because it remains to be confirmed, probably primary care.

A third approach is the development and use of performance indicators and review criteria (43). The performance indicators are usually developed from clinical practice guidelines (CPGs), and from research evidence or expert consensus in cases where CPGs do not exist. Performance indicators are usually defined within three areas; s*tructure indicators* are aspects of the health system, organization of care and available recourses, e.g. access to prescribing guidelines, *process indicators* cover the health care professionals' clinical performance, e.g. prescription of appropriate drugs, and *outcome indicators* relate to benefit or harm to the patients, e.g. achievement of blood pressure therapy goal and mortality (44). Outcomes of therapy are ideal indicators, however frequently long delayed and often affected by other factors. Processes, e.g. prescription of drugs, are easier to measure because they occur with little delay and vary in accordance with the care provider behavior. Processes are often more useful indicators than traditional outcomes, if they are proven by research to be reliable predictors of an eventual outcome (3).

Review criteria (also called 'quality criteria' or just criteria), are often erroneously used interchangeable with performance indicators. They are, however, developed from existing performance indicators or directly from CPGs, and used when assessing the level of adherence between actual practice and recommendations.Review criteria should be prioritized according to strength of research evidence and influence on outcome. They should be appropriate to the clinical situation they are used in, and be so clearly defined that it can be answered 'yes' or 'no' (3;43). Furthermore, the use of review criteria will require a standard to be set, i.e. a threshold for when adherence to the review criteria is considered appropriate, e.g. x % prescription of β-blockers in patients discharged after a myocardial infarction (MI). This may, however, not be feasible, as uniform standards across different settings may be difficult to define (3). Review criteria are most often used to assess aspects of care which can be verified retrospectively from patient records, and hence, measure whether something was done, and whether it was recorded (43). They can also be used to aid implementation of CPG recommendations by providing performance standards, and as such enable clinical audits. The latter have been promoted by many health care providers and policy makers (13). However, even if guidelines and recommendations based on evidence or well-established consensus usually have a universally applicable core, they must be adopted locally to remain valid (3).

1.3 THE MAT METHODOLOGY

The recently developed MAT (Medication Assessment Tool) methodology brings together the advantages of CPGs, performance indicators and review criteria. The description below is based on information in the PhD thesis by Håkonsen (2007), as MAT methodology issues are scarcely covered by published literature (45).

1.3.1 Appearance and application

A MAT comprises a set of review criteria within a specific field of therapy, e.g. heart failure. The MAT criteria define medical therapy in accordance with updated CPGs, and are constructed in such a manner that they facilitate assessing whether medication related care is in accordance with the defined CPG recommendations. The MAT criterion is made up by two components; a 'qualifying statement' and an 'audit standard'[5], examples are shown in Table 1.2. The qualifying statement decides whether the criterion is applicable in the specific patient. In cases where it is not, it is denoted 'not applicable' (NA). The standard decides whether performance is in accordance with the CPG recommendation.

Table 1.2 *Examples of medication assessment tool criteria*

Tool	Qualifying statement	Audit standard
Garcia *et al.* (41)	Patient with established CHD	… *is prescribed aspirin*
Hakonsen *et al.* (42)	Patient on long-term analgesics	… *has a record of formal assessment of pain intensity*
Ernst *et al.* (39)	Patient who is overweight an requires an oral hypoglycemic agent	… *is/has been prescribed metformin unless contraindicated or not tolerated*
Garcia *et al.* (41)	Patient with CHD and maintained on lipid-lowering therapy	… *has achieved target cholesterol levels of both Total cholesterol ≤ 4.5 mmol/L and LDL cholesterol ≤ 2.5 mmol/L*

CHD, Coronary Heart Disease; LDL = Low-density lipoprotein

If a criterion is applicable, it can be answered 'Yes' (Y) in cases of adherence, or 'No' (N) in cases of non-adherence. Because CPG recommendations are developed to assist in decision making, and hence may not be applicable in all cases, non-adherence to the MAT criteria may in some cases be the appropriate therapy. This is accounted for in the MAT methodology, as the response alternative 'justified No' (Nj) is present.

Justified reasons for non-adherence should be stated in the application guide, and three general reasons justifying for non-adherence have been suggested (42). First, an explicitly

[5] The *standard* in relation to the MAT criterion must not be confused with the standard in relation to review criteria, which indicate a threshold for appropriate performance.

documented contraindication, intolerance or allergy to the drug or therapy. Second, an explicitly documented choice by the patient's GP or hospital clinician to choose a different therapy than the one defined in the MAT criterion. Third, an explicitly documented patient choice to refrain to suggested therapy, e.g. a patient who denies taking β-blockers. In addition to the general justified reasons for non-adherence, specific justified reasons may exist, depending on the single criteria. For instance in the criterion concerning lipid-lowering therapy in Table 1.2: In cases of statin therapy, full effect will be expected 4-6 weeks after therapy start or dose adjustment, and hence, non-achieved therapy goals will be regarded justified before this point of time.

Prescription data only provide limited information on disease and patient factors important for judging the quality of prescribing (44). Hence, if data in addition is scarce, the validity of measurements is at stake. In the MAT methodology, this has been accounted for by recording cases of 'insufficient data' directly in the tool, elaborating result interpretation. When data is insufficient to decide whether the qualifying statement is applicable, the criterion is responded 'insufficient data to decide upon applicability' (IDq). When data is insufficient to answer the criterion standard, it is responded 'insufficient data to answer the standard' (IDs).

1.3.2 Adherence results and their application

Adherence to the MAT can be calculated on a single criterion or an overall basis. The overall MAT adherence indicates the general clinical performance within the specific therapeutic field concerned, however; only the single criterion adherence gives answers to specific performance and improvement potentials. Adherence is calculated as described in the 'Statistics' section 3.6 and is subject for further discussions in the methodology section.

Adherence result can be used to identify gaps between CPG recommendations and clinical performance, and hence, raise questions to whether prescribing is appropriate as well as to whether the existing CPG recommendations are appropriate. A feed-back of adherence results to health-care takers, should have an educational effect and, consequently, induce improvement (44). A new measurement can subsequently be made at a later stage, and the MAT can as such make a means for continuous quality assessment.

1.3.3 Available MATs and other instruments

Today, MATs within heart failure (MAT-CHF), CHD prevention (MAT-CHD), diabetes (MAT-DM), cancer pain management (MAT-CP) and CHDSP (MAT-CHDSP) have been published in the scientific literature (39-42;46). The research group in Scotland that invented

the MAT methodology (37), has continuously been working on developing MATs within different clinical areas. A PhD thesis concerning a MAT for cardiovascular diseases (MATCVC) has recently been submitted at the University of Strathclyde, Scotland (47). Another PhD student in Scotland is working on a MAT concerning osteoporosis, and a MAT concerning antibiotic therapy in community acquired pneumonia is under development and validation at the University of Tromsø (48).

1.4 CHD PREVENTION AND FOLLOW-UP PROGRAMS

The existing evidence for the benefits of medical therapy in CHD has facilitated the development of CPGs concerning disease management and prevention (49). Nevertheless, integration of CHDSP into daily practice has been shown inadequate for most patients (5;50;51). In Europe, this has for instance been shown by the EuroAspire (European Action on Secondary Prevention through Intervention to Reduce Events) I-III[6] surveys, initiated by the European Society of Cardiology (ESC), finally including twenty-two European countries (Norway not included) (1;50;52-55).

As a reaction to the results from the EuroAspire I and II surveys, showing inadequate CHDSP, the EuroAction model, the largest-ever Europe-wide preventive cardiology project, was developed by ESC in collaboration with European Heart Network (56). The aim of EuroAction is to raise standards of preventive cardiology in Europe by demonstrating that the recommended European and national lifestyle, risk factor and therapeutic goals in cardiovascular disease prevention are achievable and sustainable in everyday clinical practice. The model is carried out in eight European countries: Denmark, France, Italy, Poland, Spain, Sweden, the Netherlands and the United Kingdom, both in general practice and hospital care, involving a multidisciplinary team of nurses, dietitians, physicians and physiotherapists. Participants, both patients and partners, initially attend workshops and supervised exercise classes. Moreover, they receive close and frequent follow-up with focus on achievement of CHDSP related goals as e.g. smoking cessation, drug prescribing and therapy goal achievement. The first study published in 2008, showed that this family-based *nurse-led* cardiovascular-rehabilitation program successfully improved standards of preventive care in all eight countries (n=24 centers and 9026 patients) (57).

Pharmaceutical care programs developed and implemented by pharmacists have been found useful in improving the quality of care in both ambulatory care and hospitalized patients with

[6] EuroAspire I from 1995-1996, EuroAspire II from 1999-2000, EuroAspire III from 2006-2007

various diseases such as diabetes mellitus (DM) (58-60), hypertension (61-64) and dyslipidemia (65;66). Despite the known benefits of pharmacist involvement in relation to single risk factors for CHD, pharmacist-led FuP in CHDSP are relatively scarcely described in literature, see Table 3.1. The best described programs are developed in the US and the UK (67-69), where pharmacists have been recognized as health care practitioners since the 1990s (17). By comparison, pharmacists in Norway were not officially defined as health personnel until 2001 (70).

Taveira *et al.* describes the Cardiovascular Risk Reduction Clinic (CRRC) model, where the clinical pharmacist (CP) assesses medication adherence and laboratory parameters, develops treatment plans to control blood pressure (BP), lipids, and DM, discusses options for smoking cessation when applicable, creates individualized diet and exercise programs, and refers to a nutritionist and physical therapist on an as-needed basis. Follow-up sessions of 30 minutes each are scheduled every 6–8 weeks to monitor adherence and therapeutic effects, reinforce lifestyle modification, and adjust medications. Patients are discharged from the CRRC when CPG recommended therapy goals for systolic BP (SBP), HbA1c, total cholesterol and LDL cholesterol are met (67). Reilly *et al.* describes a primary care clinic for CHDSP in the UK, led by a practice nurse in collaboration with a pharmacist. Patients with established CHD are identified using the general practice computer system. They first receive a 15-20 minutes consultation with the CHD nurse who creates a medication profile document, takes BP and relevant blood samples. Later, the patients meet with the clinic pharmacist jointly with the CHD nurse for 30 minutes, where the clinical measurements, blood analysis, family and drug history and disease states registered in the patient profile are discussed. Recommendations for changes to medication are agreed with the patient and subsequently also by the family physician. Relevant lifestyle and health promotion advices are offered to the patient and referrals to a lifestyle modification clinic such as smoking cessation or weight loss are made according to patients' preferences indicated an interest. Patients are then followed-up after one year unless any further visits for statin dose titration or review are indicated. Geber *et al.* describes Pharmacist-Managed Pharmacotherapy Clinics in the US, receiving patients referred by Veterans Affairs Medical Center. The pharmacists in these clinics have prescribing privileges in accordance with predefined agreements. In the model, pharmacists are implementing and maximizing therapy with agents known to reduce the morbidity and mortality associated with cardiovascular disease (CVD).

Table 1.3 *Follow-up programs in secondary prevention of CHD*

Program	Leader	Focus	Care setting	Country	Outcome measures
Campbell (71)	Nurse	Promoting of medical and lifestyle aspects of secondary prevention. Regular follow-ups offered.	General practice	UK	Aspirin use, BP, lipids, physical activity, dietary fat, smoking status.
CHIP (72)	Trained volunteers	Lifestyle counseling, teaching, cooking, group discussions, exercise.	Primary care	USA	CVD risk factors and biometric measures relevant for CHD prevention
CRRC (67)	Pharmacist	Motivational interviewing, frequent medication titration	Primary care	USA	Achievement of CPG defined therapy goals
Debusk (73)	Nurse	Behavioural intervention (smoking, diet, exercise). At hospital, by phone, and ambulatory visits.	Hospital/ ambulatory	USA	Smoking status, LDL, HDL and total cholesterol, TG and functional capacity.
EuroAction (57)	Nurse + dietitian, physician, physiotherapist	Partner-supported, lifestyle, risk factors, drug treatment to target values	Primary/ Hospital	EU	Family-based life-style change, management of BP, lipids, blood glucose, medication prescription
Geber *et al* (68)	Pharmacist	Maximizing drug therapies known to reduce the morbidity and mortality associated with the disease	Primary care	USA	Prescription rate and therapy goal achievement
Hanssen *et al.*(74;75)	Nurse	Individual need information and support of patients' own coping efforts with respect to lifestyle changes and risk factor reduction.	Primary care (Phone)	NO	Health-related Quality of life (SF-36), smoking, exercise habits, return to work and rehabilitation due to chest pain.
PACET (76)	Physician extender	Post-ACS clinic	Ambulatory	USA	Therapeutic lifestyle changes, prescription rates achievement of LDL cholesterol therapy goal
PANACHE (77)	Not stated	Healthy weight intervention based on social cognition theory	Home-based	AU	Self-reported weight and BMI change, physical activity, sedentary time and nutrition habits, relative cost-effectiveness
ProActive Heart (78)	Special-trained health professionals	Appropriate modification of CHD risk factors, compliance with pharmacological therapy and management of psychosocial issues	Phone	USA	Quality of life, physical activity and cost-effectiveness
Reilly *et al.* (69)	Nurse, Pharmacist	Full health screen, appropriate disease modifying drug therapy, lifestyle and health promotion advice	General practice	UK	Smoking, prescription rate, LDL cholesterol
SPHERE (79;80)	GP (nurse-tailored)	Practices: training in prescribing and behavior change, administrative support, quarterly newsletter. Patients: Motivational interviewing, goal identification and target setting for lifestyle.	Primary care	UK	Achieved targets form BP and total cholesterol, hospital admissions, changes in physical and mental health status (SF-12)
SPRITE (81)	Nurses	Behavioral and education self-management intervention	Phone or Internet	USA	Reduction in SP related outcomes, adherence to guidelines on CHD prevention practice and improvement in health behavior

CHIP, Coronary Heart Improvement Project ; CRRC, cardiovascular risk reduction clinic; PACET, Parkland Acute Coronary Event Treatment Study; PANACHE; Physical Activity, Nutrition And Cardiac Health; SPHERE; Secondary Prevention of heart disease in general practice,; SPRITE, Secondary prevention risk interventions via telemedicine and tailored patient-education; BP, Blood pressure; CVD, Cardiovascular disease; LDL, low-density lipoprotein; HDL, High-density lipoprotein; TG, triglyceride; BMI, Body Mass Index; WC, waist circumference; LDL, Low-density lipoprotein;

Results from all programs clearly show that pharmacist-led follow-up can benefit patients by optimizing drug and lifestyle therapy, and that the risk of cardiovascular events is reduced. Reilly *et al.* even indicated that pharmacist input to a CHDSP clinic can have pharmacoeconomic benefits (69).

Based on the solid knowledge that involvement of CPs in patient care may contribute to improvement of medical therapy, both with regard to BP, cholesterol, blood glucose and medication adherence, the benefits of a CP-led FuP may also be present in Norway.

2 AIMS OF THE PHD PROJECT

The overall aims of this PhD project were to develop and carry out a post-discharge CP-led FuP in patients with CHD, and to explore its functionality and effect on patient related outcomes.

The specific objectives were the following:

- ✓ To develop and validate a MAT for the evaluation of adherence to CPG recommendations concerning CHD$_{SP}$ (hereupon denoted MAT-CHD$_{SP}$)

- ✓ To identify improvement potentials regarding adherence to CPG recommendations in patients with established CHD at discharge from the University Hospital of North Norway (UNN)

- ✓ To evaluate the effect of a CP-led FuP with regard to guideline adherence, clinical outcomes in relation to CHD$_{SP}$, and patient experience

3 MATERIALS AND METHODS

3.1 OVERVIEW

In accordance with aims and objectives described above, the PhD project can be arranged in four studies:

1. MAT-CHDSP development and validation (Paper I)
2. Retrospective study of CHDSP in patients with established CHD (Paper II)
3. Randomized controlled trial (RCT) to observe the effect of a CP-led FuP (Paper III)
4. Qualitative study of patient experience with the CP-led FuP (Paper IV)

An overview of the different studies and the relationship between them is presented in Figure 3.1.

3.2 SETTING

The PhD project was carried out at the Hospital Pharmacy of North Norway Trust, Tromsø, in collaboration with the Department of Pharmacy, Faculty of Health Sciences, University of Tromsø (UiT) and the University Hospital of North Norway (UNN). UNN serves as the local hospital for about 75 000 inhabitants in the city of Tromsø and surrounding areas, and is also the leading health care provider in the region of North Norway (82). Considering expertise within percutaneous coronary intervention (PCI) and coronary artery bypass graft operations (CABGs), UNN serves about 465 000 inhabitants and yearly performs about 1600 PCIs and 500 CABGs (83).

3.3 PARTICIPANTS

Content validation (Paper I)

A validation group was selected among cardiologists, geriatrics and junior doctors working at cardiology and geriatric departments, general practitioners (GPs) with special knowledge within cardiology and pharmacists with theoretical or practical expertise within CHD. In order to represent different therapy traditions, participants were recruited from geographically diverse parts of Norway. A total of 64 participants were in February/March 2008 asked by e-mail to participate in the validation of the MAT-CHDSP. Twelve participants completed all phases of the content validation procedure, and the final validation group comprised four physicians working at the cardiology department at UNN, one cardiologist working as a GP in

the southern part of Norway (Kristiansand), five pharmacists working in the south-eastern part of Norway and two pharmacists working in Tromsø (see Table 3.1). Three of the pharmacists were working in the clinic.

Table 3.1 *The number of experts participating in the content validation of the MAT-CHDSP*

	Hospital physicians	GPs	Pharmacists	Total
Invited to participate	44	3	17	64
Completing Delphi round 1	5	1	9	15
Completing Delphi round 2	4	1	7	12

Pilot study (Paper I)

Among patients who were electively[7] admitted to UNN for PCI, a total of 210 patients aged 18 to 80 years were recruited to the pilot study from August 1 to November 1, 2008. Finally, eighty-five (40 %) patients with PCI-confirmed established CHD were included in the study. Written informed consent were obtained, see attachment A for patient information/consent papers (in Norwegian).

Retrospective study (Paper II)

Patients that had undergone PCI with stent implantation during 2008 were eligible for inclusion. A list of all patients was supplied by the Department of Cardiology. The consecutive first 300 patients, i.e. all patients from January 1 to March 31, 2008, were selected for a clinical audit using the MAT-CHDSP. The number of selected patients was based on sample size calculation. Finally, a total of 247 patients were eligible for data analysis.

The FuP and RCT (Paper III)

Patients were recruited from the Department of Cardiology from February 1, 2009 to June 30, 2010. They were eligible for participation if they had established CHD, were aged 18 to 80 years, and were living in the three nearest communities of UNN, i.e. Tromsø, Balsfjord and Karlsøy. They were not eligible if they were already included in the NORStent trial (84), if they were unable to communicate or if they had terminal cancer. A total of 102 patients handed in consent papers, see Attachment B (in Norwegian), and 51 patients were randomized into both study groups. Five patients were lost to follow-up and finally, 94 patients were eligible for analysis.

[7] Elective patients arrive for planned hospital admissions. They have either a) been admitted to hospital on a previous occasion, where it has been decided to postpone the PCI or b) been referred to PCI by a hospital physician or their GP.

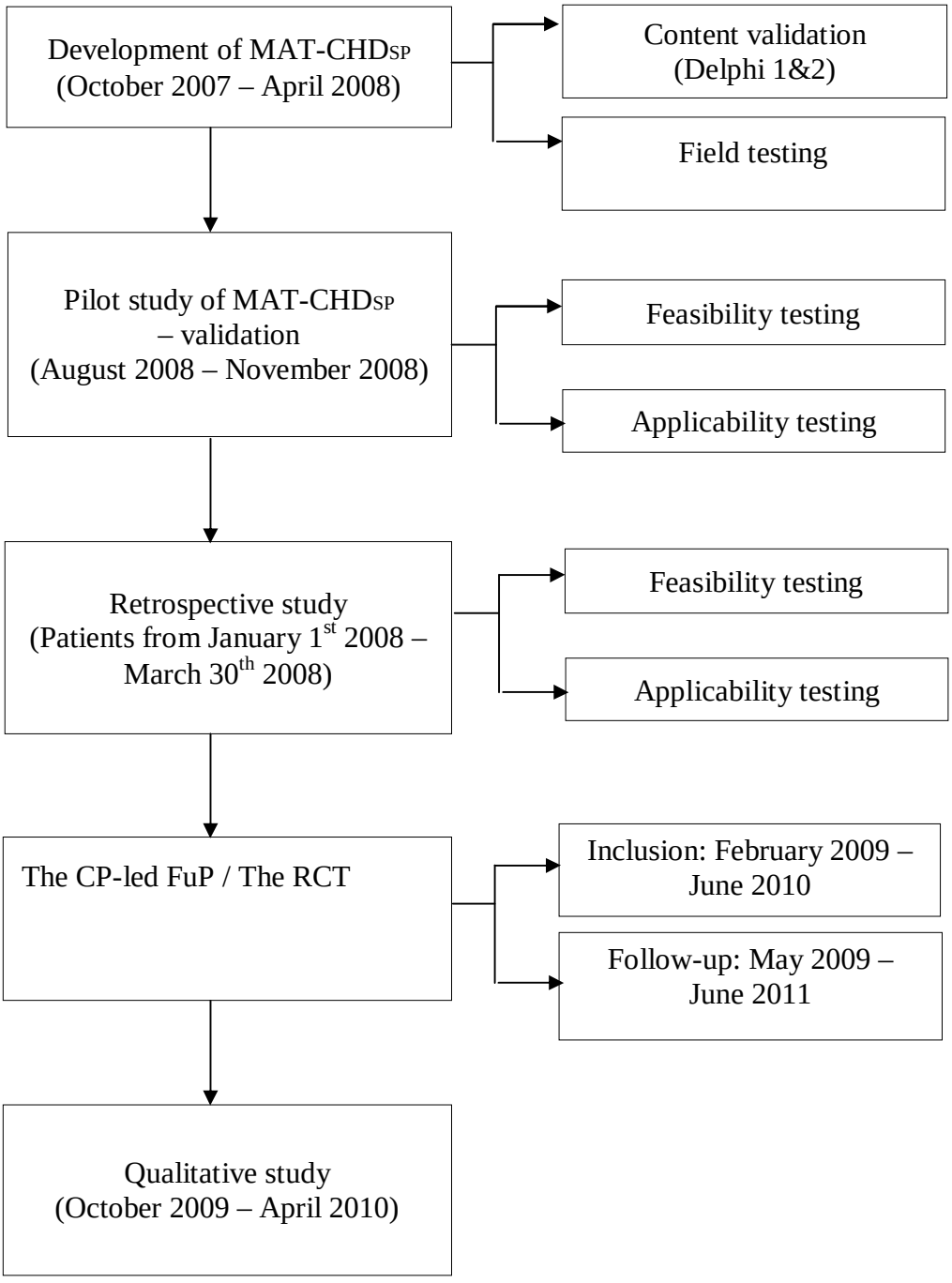

Figure 3.1 *Overview of the PhD project and the different studies*

The qualitative study (Paper IV)

Patients in the FuP/RCT described above were eligible for inclusion if they had met the CP at least twice and were living in the city of Tromsø. The CP recruited patients arriving for their second or third meeting with the CP during February/March 2010. A written consent was obtained from five patients; see Attachment C for patient information/consent papers (in Norwegian). One of the patients withdrew from the study due to acute illness.

3.4 DEVELOPMENT AND VALIDATION OF THE MAT-CHDSP (Paper I-III)

The MAT-CHDSP was developed in collaboration with a master student in pharmacy in 2007/2008 (85). To separate the different versions of the MAT, it was named the *initial*-MAT-CHDSP during development and content validation, *test*-MAT-CHDSP during field-testing and *draft*-MAT-CHDSP during pilot study (reproducibility and feasibility testing). The latter was performed in collaboration with another master student in pharmacy in 2008/2009 (86). The *final*-MAT-CHDSP was used during the retrospective study and the RCT. See Figure 3.2.

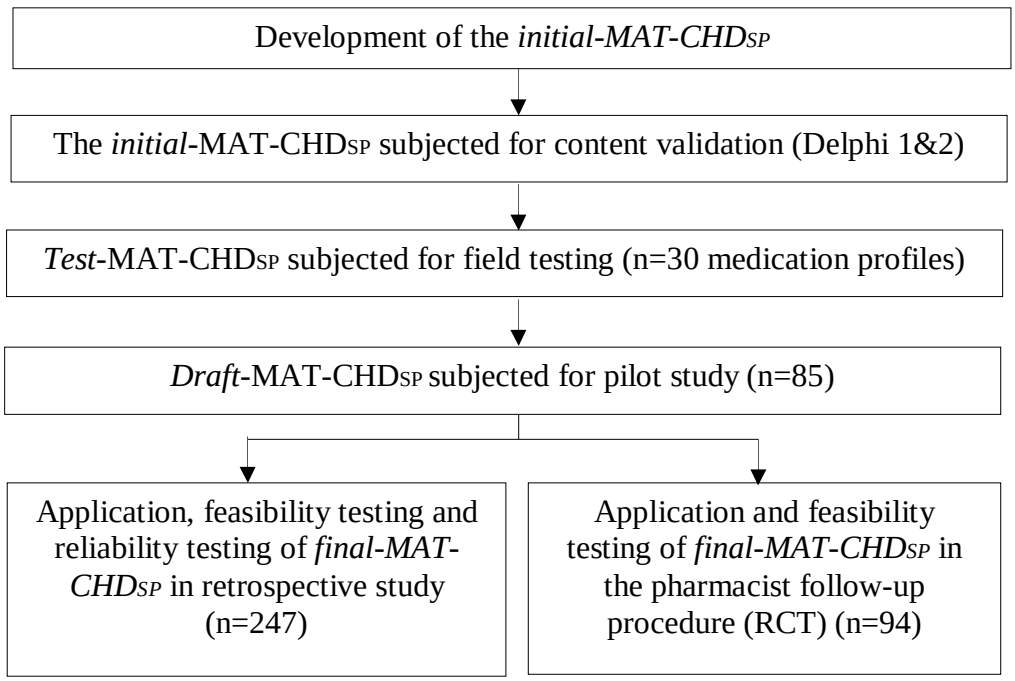

Figure 3.2 *Development, validation and application of the MAT-CHDSP throughout the PhD project.*

3.4.1 MAT-CHDSP criteria

The most recently published MAT-CHD by Kamyar *et al.* was used as a starting point (40). Some criteria were omitted or were merged with each other, others were updated or changed in order to improve comprehensibility and applicability, or to comply with the most recent ESC and national recommendations (Paper I).

From the initial-MAT-CHDSP to the test-MAT-CHDSP, wordings were simplified in accordance with validation group comments. From the test-MAT-CHDSP to the draft-MAT-CHDSP, length of therapy and contraindications/intolerances were placed in the application guide, defined into the justified reasons for non-adherences. From the draft-MAT-CHDSP to the final-MAT-CHDSP, the statin criterion, being inapplicable due to new national guidelines, was removed (Paper I and II). See Application Guide in Appendix E.

3.4.2 Content validation

Content validation was demonstrated through a two-round modified Delphi-technique (13;87) (Paper I). In both Delphi rounds, participants were asked to rate their level of agreement with each single criteria in the categories “agree”, “partly agree” and “not agree”, and were also encouraged to comment on single criteria. Consensus threshold was set to ≥ 75 %; i.e. a criterion remained if ≥ 75 % of the participants agreed upon it. Likewise, a criterion was removed if ≥ 75 % disagreed upon it. In other cases, criteria were reformulated in accordance with expert group comments. In Delphi 2, the validation group was presented with the revised criteria in addition to anonymously ratings from Delphi 1, and was asked to re-rate their agreement with the criteria, hence, having the opportunity to change their previous rating. After Delphi 2, criteria were amended in accordance with the consensus results and comments from the validation group.

3.4.3 Field testing

The test-MAT-CHDSP was subjected for field-testing using 35 anonymous medication profiles for patients with established CHD and left ventricular systolic dysfunction (LVSD). The aim of the field-testing was to obtain preliminary results regarding applicability and reliability of the MAT-CHDSP and to explore whether the medication profile in use included all relevant information for MAT-CHDSP application.

3.4.4 Feasibility testing

Applicability, both for single criteria and for the MAT-CHDSP overall, was explored in the three MAT studies (Paper I-III). Application time for the MAT-CHDSP was explored in the

pilot study, using the draft-MAT-CHDSP (Paper I) by measuring time for each single MAT-CHDSP application. In the retrospective study (Paper II), using the final-MAT-CHDSP, the total time for data collection and MAT-CHDSP application was measured in order to achieve a measure for MAT-CHDSP application in a clinical setting. Application time was not measured during the RCT (Paper III).

3.4.5 Reliability testing

Reliability of the MAT-CHDSP application was demonstrated by *inter*- and *intra*-observer agreement and expressed by Cohen's Kappa (κ) (88), see statistics section. Inter- and intra-observer agreements with the draft-MAT-CHDSP applications were explored in the pilot study (Paper I) and with the final-MAT-CHDSP applications in the retrospective study (Paper II). Only inter-observer agreement with the final-MAT-CHDSP applications was explored at study end in the RCT (Paper III). Three observers have been involved in reliability testing, BHG[8] in all three MAT-studies, EES[9] in the pilot study and the retrospective study, and JU[10] in the RCT. All observers had received training in MAT methodology. During intra-observer agreement testing, the same observer applied the MAT-CHDSP twice with three weeks in-between. A κ-value ≥ 0.75 was considered excellent agreement (88).

3.5 THE RCT (PAPER III)

A one-year lasting post-discharge CP-led FuP for patients with established CHD was developed and carried out as a non-blinded prospective RCT with an intervention group (IG) and a control group (CG). IG patients received CP-led follow-up as described in section 3.5.1, while the CG patients only met with the CP at study end for data collection.

3.5.1 The CP-led FuP (the intervention)

The FuP is described in detail in Appendix 1, but will be presented briefly here. The follow-up comprises three face-to-face meetings with the CP; the first at hospital discharge, the second three months after discharge and the third twelve months after discharge. The CP located patients before they left the hospital for the first meeting, and arranged the two last meetings by phone. Meetings (lasting 30-60 minutes) were held at the hospital pharmacy at UNN, and patients were asked to draw blood for analysis of total cholesterol, LDL cholesterol, blood glucose and HbA1c before they arrived for the meeting. The CP performed medication therapy reviews (MTR) based on information in electronic medication records

[8] Beate Hennie Garcia, candidate of this thesis
[9] Erik Eidem Skare, master student in pharmacy, UiT, 2008/2009
[10] June Utnes, PhD student in clinical pharmacy, UiT

before every patient meeting. During the meetings, the CP performed medication reconciliation and counseled about risk of CHD, appropriate use of medications and the importance of the medication and a heart-friendly lifestyle with smoking cessation, healthy diet and physical activity. Patients were encouraged to ask questions and to search for solutions themselves on how to lower their CHD risk based on the information they received. BP was also measured by the CP; see section 3.6 for further details. After the meeting, a new MRT, based on updated information, was made. Identified improvement potentials and DRPs were communicated to the patients' GP by letter, and also by phone when it was regarded especially important. A summary of the meeting, results from laboratory results including therapy goal, patient instructions, short patient-selective drug information and a correct medication list was mailed to the patients after the meetings. They also received a copy of the letter sent to their GP.

3.5.2 Data collection

At baseline, CHD relevant data was collected for both study groups in the electronic patient records. At three months, data was only collected for IG patients, when they arrived for follow-up. At study end at twelve months, data was collected for both study groups. The different data sources are presented in Figure 3.3. At UNN, electronic medication charts and electronic prescribing has not yet been implemented. Consequently, all medications and medication amendments during hospital stay are hand written in the paper-based medication chart. At discharge, the hand written medication information is manually transferred from the medication chart to the electronic discharge records.

Electronic patient records

At hospital admittance, an electronic *admission record* is always computed, comprising patient information considered relevant for the hospitalization. This document is seen as a reference document for health personnel involved in the treatment of the patient throughout the hospital stay. At discharge, an electronic *discharge letter* addressed to the referring physician (normally the GP) is routinely computed and submitted electronically. This document is a reference document for the particular hospital stay, and contains information considered crucial for the GP concerning the actual hospitalization, but also information considered relevant for potential future hospitalizations. At the Department of Cardiology at UNN, the patients also receive a *patient-friendly version* of the discharge document, including patient instructions.

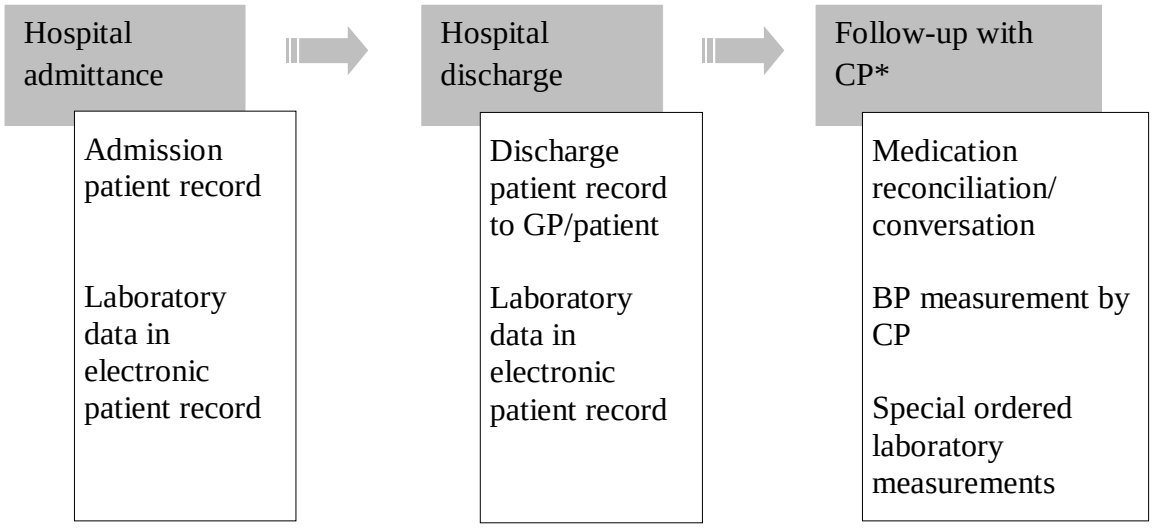

Figure 3.3*: Data sources during the RCT*
* At baseline, after 3 months and 12 months for the IG, after 12 months for the CG

BP measurement

The CP was trained by a nurse for the procedure and used a calibrated Dinamap® Procare 300 monitor, listed in the British Hypertension Society's list of validated BP monitors (89). An appropriate cuff size was chosen based on the circumference of the patients' upper arm. Three consecutive BPs were measured, separated by a ½ - 2 minutes, while the patient was sitting, had been resting for 15-30 minutes and had the arm outstretched and supported by a table so that the cuff was at heart level (90).

3.5.3 Outcome measures

The MAT-CHDSP was used to identify non-adherence to CPG recommendations, to measure prescription rate of secondary preventive medications, to measure achievement of therapy goals for BP and cholesterol, to identify appropriate amendments of therapy in order to achieve CPG defined therapy goals, and to identify documented lifestyle recommendations given to patients. Total cholesterol, LDL cholesterol, blood glucose and HbA1c values were compared in between the two study groups, and also within the same group.

3.6 PATIENT EXPERIENCE WITH THE FUP (PAPER IV)

In order to gain knowledge on how patients participating in the CP-led FuP experienced the follow-up, we performed a qualitative study with semi-structured interviews. A semi-structured interview-guide was developed, focusing on four main themes: i) Patients' knowledge about medicines, ii) feelings of safety and comfort with medicines, iii) the functionality of the FuP, and iv) the CP as a part of the interdisciplinary health care team. The interviews were performed by a master student in pharmacy during February/March 2010. They were audio-taped, and field notes were taken. Directly after the interviews were held, the interviews were transcribed verbatim (Paper IV).

'Qualitative content analysis', described by Graneheim and Lundman, was used for data analysis, and was performed as following: i) reading of all texts several times in order to obtain a sense of the whole; ii) identifying *units of analysis* in accordance with the main themes and bringing these into texts; iii) identifying *meaning units* and abstracting these into *condensed meaning units*; iv) labeling the condensed meaning units with a *code*; v) comparing the codes concerning similarities and differences and sorting them into *main-categories* and *sub-categories*, which constitute both the manifest and the latent content of the interviews, vi) summarizing the contents of the main categories to generalized descriptions and experiences reflecting the most important aspects of each theme in the interview guideline (91). An initial analysis was first performed by the master student (HM), focusing mainly on the manifest content of the interviews (92). A deeper analysis has subsequently been made by the candidate, also focusing on the latent content. Results from both analyses have been studied by the research team (SLS&LS), who agree upon the final interpretation.

3.7 STATISTICS

Management of data, statistical tests and significance level

Quantitative data was managed using Microsoft® Office Excel and Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.©. NCC-PASS© has been used for sample size calculations. Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as percentages with 95 % confidence intervals (CI). The student's *t*-test and the paired-sample *t*-test were used to compare continuous variables, while the Pearson *chi*-square test and Fisher's exact test were used to compare categorical variables. All statistical tests were considered significant when the 2-sided *P*-value was < 0.05.

Sample size calculation

Sample size calculations in the RCT were based on MAT-CHDSP adherence results from the pilot study where we had observed only 22 % adherence to the criteria concerning achievement of BP goal below 130/80 mmHg. To detect an increase in adherence from 20 % to 40 % in the IG (assuming no change in the CP), with a power of 80 % (alpha 0.02), a sample size of 101 patients in each group was required (assuming a 10 % loss to follow up).

MAT-adherence calculation

Adherence to the MAT-CHDSP criteria was calculated for each criterion and for the MAT overall by summing 'Y' responses and expressing them as percentage of the number of applicable cases as shown in the equation below (45).

$$\text{Adherence} = \frac{\sum_{i=1}^{n} Y(i)}{\sum_{i=1}^{n}[Y(i)+N(i)+Nj(i)+IDs(i)]} \text{ x } 100\ \%,$$

where (i) = the criterion number for which adherence is calculated. Note that inapplicable criteria and criteria applied IDq are excluded from the calculation. Adherence was defined as high when ≥ 75 %, intermediate when between 50 % and 75 % and low when ≤ 50 % (45).

Reliability testing

Reliability was tested by inter-and intra-observer agreement expressed by Cohen's kappa (κ), $\kappa = \frac{Po-Pc}{1-Pc}$, P_0 = exact agreement and P_0 = random agreement.

Appendix G gives a more detailed explanation on the κ-calculation. In accordance with Robson, we have interpreted agreement between the observers as excellent when $\kappa \geq 0.75$, good when $\kappa = [0.6 – 0.75]$, satisfactory when $\kappa = [0.4 – 0.6]$ and poor when $\kappa < 0.4$ (88).

3.9 ETHICS

All studies presented in this thesis have been conducted in accordance with world-wide recognized ethical conventions and manuals in addition to national legislation (93-99). The pilot study (Paper I), the RCT (Paper III) and the qualitative study (Paper IV) were presented to the local committee for Medical Research Ethics in North Norway (REK-Nord). The pilot study (Paper I) was also presented to The Norwegian Social Science Data Service (NSD), according to the legislation at that time being (100).[11] In the retrospective study (Paper II), patient consents were not collected because data was anonymously extracted from patient

[11] New from July 1, 2009, the regional ethics committees (REKs) in Norway now have the mandate to approve or disapprove studies within health research. Studies should no longer be presented to the NSD (101).

records without altering usual practice, and patient-identifiable information were never presented to the researchers. The study should consequently not be reported. The RCT and the qualitative study (Paper III&IV) were also registered at www.clinicaltrials.gov (study numbers NCT01115608 and NCT01131715). Written and informed consents were obtained from study participant in the pilot study (Paper II), the RCT (Paper III) and the qualitative study (Paper IV), see Attachment A, B and C (in Norwegian). Authors of the papers presented in this thesis have no conflicts of interest.

4 RESULTS

4.1 THE NEW MAT-CHDSP (PAPER I)

The new MAT-CHDSP comprises 21 review criteria, defining appropriate prescription and therapy goals within CHDSP, in accordance with CPG recommendations issued by ESC. It also comprises, which is new within MAT methodology, three follow-up criteria defining the appropriate action in cases of unachieved therapy goals at hospital admittance: to increase dose of drug, to change the drug or to add a new drug (nos 8, 11 and 16). These criteria were developed because it makes sense to change therapy when unachieved therapy goals are identified, and hence, we wanted to measure whether this actually happened. Finally, the MAT-CHDSP comprises five lifestyle criteria, defining appropriate documentation of weight, height, body mass index (BMI) or waist circumference in this patient group, in addition to advices concerning smoking cessation, weight reduction, diet and physical activity (nos 17-21) (Paper I).

4.2 MAT-CHDSP VALIDATION (PAPER I-III)

4.2.1 Content validity

Among the twelve participants in the validation group that completed both Delphi rounds, consensus was obtained for nineteen out of twenty-two criteria in the *initial*-MAT-CHDSP. We amended two of them in accordance with the validation group comments. For the third criterion, some of the participants argued that the threshold of an HbA1c value below 6.5 % was too strict. This is however the CPG recommendation, so we finally merged this criterion with the one defining a blood glucose value of ≤ 7.0 mmol/L as threshold for all patients with CHD (see Paper I, criterion no. 15). From now on, the MAT was named *test*-MAT-CHDSP.

4.2.2 Field testing

Preliminary applicability and reliability results for the test-MAT-CHDSP were promising with high applicability of the criteria and high level of agreement between the inter- and intra-observers (102). However, the medication profiles from patients with LSVD used during field testing were found not to include all relevant data for MAT-CHDSP application. Consequently, the existing medication profile was restructured to endorse collection of MAT-CHDSP specific data, see Appendix D. An application guide was also developed to facilitate MAT-CHDSP application and interpretation, see Appendix E. To further diminish ambiguity of the criteria and improve applicability, contraindications, intolerances and defined therapy

durations were moved from the criteria and into the application guide (Paper I). From now on, the MAT was named draft-MAT-CHDSP.

4.2.3 Face validity

The initial-MAT-CHDSP was assumed to possess 'face validity for the care givers' because the meaning of the criteria was understood and acknowledged by the validation group during Delphi rounds. During field testing with the test-MAT-CHDSP, in the pilot study with the draft-MAT-CHDSP, and in the retrospective study with the final-MAT-CHDSP, criteria were comprehensible for the different users (Paper I&II). This was also substantiated by the low application time of the MAT-CHDSP (se section 4.2.4 below.

4.2.4 Feasibility

The feasibility of a MAT concerns applicability of criteria, presence of data to apply the criteria, and resource utilization in criterion application. Overall applicability varied between 59 % and 66 % in the three MAT studies (Paper I-III), see Table 4.3. Applicability of single criteria varied between 0 % and 100 %. The presence of insufficient data (ID) was low in all three studies, both in order to decide upon applicability of the qualifying statements (IDq) and to answer the audit standards (IDs). Most of the IDs and IDq in all MAT studies were affecting criteria 18 and 19 because of missing information on body weight, height, BMI or waist circumference. The presence of IDq decreased from baseline to study end in the RCT, while the presence of IDs increased because follow-up data was not collected (Paper III). In the pilot study (Paper I), we showed a mean application time for the draft-MAT-CHDSP of 1.5 minutes (SD 0.3) for an experienced user BHG[12]. This was significantly lower than the mean application time of 6.1 minutes (SD 1.2) for the less experienced user EES[13], $P < 0.001$. For all users, application time decreased with an increased number of applied MATs (Paper I). In the retrospective study (Paper II), we found a mean time for both data extraction and final-MAT-CHDSP application of 10.9 minutes [95% CI; 10.6, 11.24]. In the RCT, the application time of the MAT-CHDSP was not measured.

4.2.5 Reliability

Cohen's kappa (κ) values for overall inter-observer agreements were 0.82 (95 % CI; 0.77 – 0.81), 0.93 (95 % CI; 0.91 – 0.94), and 0.91 (95 % CI; 0.89 – 0.94) for the pilot study, retrospective study and RCT, respectively (Paper I-III). κ-values for overall intra-observer agreements were 0.90 (95 % CI; 0.89 – 0.91) and 0.95 (95 % CI; 0.93 – 0.96) in the pilot

[12] Beate Hennie Garcia, first observer
[13] Erik Eidem Skare, second observer

study and the retrospective study, respectively (Paper I&II). Intra-observer agreement was not explored in the RCT.

4.3 MAT-CHDSP ADHERENCE STUDIES (PAPER I-III)

Only patients with established CHD were included in the three MAT-CHDSP studies. Mean age has varied between 63 and 65 years, and all study populations comprised about 70 % males. Overall adherence has ranged between 53 % and 78 %, lowest in the retrospective study, and highest at study end in the RCT, see Table 4.3. In the RCT, overall adherence increased from baseline to study end in both study groups, and the high increase observed in favor of IG patients, was mainly caused by an increase in documentation of lifestyle advices (Paper III).

Table 4.3 *Overall applicability, adherence and justified-non-adherence of the MAT-CHDSP in three MAT studies (Paper I-III)*

	Pilot study (n=1785 criteria)	Retrospective study (n=4446 criteria)	RCT (n=912 criteria in IG, n=874 criteria in CG)	
			Baseline	Study end
Applicability (%)	63	66	IG: 61, CG: 61	IG: 59, CG: 58
Adherence (%, 95 % CI)	65 (64 – 66)	58 (56 – 60)	IG: 53 (49 – 57) CG: 55 (50 – 59)	IG: 78 (74 – 82) CG: 61 (57 – 66)
Nj (%)	6	4	IG:4, CG: 5	IG: 6, CG: 4

RCT, randomized controlled trial; IG, intervention group; CG, control group; CI, confidence interval; Nj, justified non-adherence

4.3.1 Prescription of CPG recommended medications

Aspirin was prescribed in more than 90 % of the study patients throughout all MAT studies, whereas clopidogrel was prescribed in 100 % of eligible patients who had a stent implanted. In two patients in the retrospective study, justified reasons for non-adherence were identified (Paper II).

Statins were prescribed in more than 90 % of patients throughout the three MAT studies. The lowest prescription rate of 91 % [95 % CI; 87 – 94] was identified in the retrospective study (Paper II). Adherence was low in the CG patients at baseline of the RCT, but had increased at study end (Paper III).

B-blockers were prescribed in 62 % - 83 % of the eligible patients throughout all MAT studies. The lowest adherence was observed in IG patients at study end of the RCT, and was mainly due to justified discontinuation of the β-blockers (Paper III).

In patients with LVSD and an EF below 45 %, prescription rate of and ACEI or an ARB ranged from 71 % to 91 % throughout the MAT studies. Prescription rate of the same drugs in patients with diabetes and hypertension or nephropathy ranged from 50 % to 80 %. In IG patients in the RCT, an insignificant increase in prescription of ACEIs or ARBs from 60 % [95 % CI, 17 – 103] at baseline to 87.5 % [95 % CI, 65 – 110] at study end was observed, whereas no increase was observed for CG patients (Paper III).

4.3.2 Achievement of therapy goals

Cholesterol therapy goals (LDL cholesterol ≤ 2.5 mmol/L, and total cholesterol ≤ 4.5 mmol/L) were achieved in about 37 % of patients in both the pilot study (Paper I) and the retrospective study (Paper II). In the RCT, achievement of therapy goals increased in the CG from 38 % at baseline to 42 % at study end. In the IG, it did not change from 27 % at baseline (Paper III).

BP therapy goals (SBP ≤ 130 mmHg *and* DBP ≤ 80 mmHg) were achieved in 22 % of the patients in the pilot study (Paper I) and in 35 % in the retrospective study (Paper II). In the RCT, BP goal achievement increased from 35 % at baseline to 41 % at study end in both study groups (Paper III).

4.3.3 Follow-up criteria

At study end of the RCT, information whether therapy was amended by the patients' GP was missing for all follow-up criteria.

For patients whose cholesterol therapy goals were not achieved at hospital admission, therapy was amended before discharge in 73 %, 63 % and 59-60 % of the patients in the pilot study (Paper I), retrospective study (Paper II) and at baseline in the RCT (Paper III), respectively.

For patients whose BP therapy goals were not achieved at hospital admission, therapy was amended before discharge in 12 %, 39 % and 41-42 % of the patients in the pilot study (Paper I), retrospective study (Paper II) and at baseline in the RCT (Paper III), respectively.

For patients whose blood glucose value was above 7 mmol/L (fasting of non-fasting) at hospital admission, a new measurement of either blood glucose or HbA1c was documented in

25 %, 21 % and 44-53 % of the patients in the pilot study (Paper I), retrospective study (Paper II) and at baseline in the RCT (Paper III), respectively.

4.3.4 Documentation of lifestyle advices

Lifestyle advices concerning smoking cessation, diet and physical activity were documented given to 68 – 88 % of the pilot study patients (Paper I), 11 – 88 % of the retrospective study patients (Paper II), and in 0 – 57 % of the RCT patients at baseline (Paper III). Highest documentation rate was observed for smoking cessation advice in smokers, and lowest for weight reduction advice in overweight patients (BMI $\geq$ 30 kg/cm^2) and dietary advice (Paper I-III). Adherence to the lifestyle criteria increased to almost 100 % at study end in the RCT IG. This was not observed in the CG.

4.4 THE RCT (PAPER III)

The post-discharge CP-led one-year lasting FuP for patients with established CHD is described in details in Appendix 1 of Paper III. Out of the 102 patients recruited to the study (50 % of estimated sample size), eight patients (7.8 %) dropped out; three died, one was erroneously included and four withdrew from the study. Statistical analyses indicated no significant differences between the two study groups ($P < 0.05$ in all cases).

Applicability and adherence results have been given in section 4.3 above and more detailed in Paper III. Briefly, overall adherence to MAT-CHD$_{SP}$ criteria increased in both groups and were significantly higher in the intervention group at study end (78 %, 95% CI; 74, 82) compared to the control group (61 %, 95% CI; 57, 66), $P < 0.001$. This was mainly due to an increased documentation of lifestyle advices in intervention group patients. No significant changes in the clinical outcome measures were observed for intervention group patients, whereas a significant reduction in total cholesterol ($P = 0.001$) and LDL cholesterol ($P < 0.001$) was observed for control group patients. An increase in the prescription of ACEIs and ARBs in diabetes patients with hypertension was observed in the intervention group but not in the control group, however not statistical significant.

4.5 THE QUALITATIVE STUDY OF PATIENT EXPERIENCE (PAPER IV)

Analysis of the four interviews finally broke down patients' experience with the FuP into three main categories; 'Experiences of and opinions about the follow-up program', 'Knowledge of medications' and 'The CP's role in the interdisciplinary team'. The fourth theme mentioned in the interview guide, 'Safety and comfort with medications', was during

analysis process categorized under the theme ‘Experiences of and opinions about the follow-up program’. This was made because experiences of safety and comfort concerned how the program itself had made them feel safe and secure.

All four participants reported that the FuP had been a positive experience, and described the program with words like ‘great’, ‘a positive experience’ and ‘educative’. They told that they had felt ‘safeguarded’ and ‘fortunate’ to be participating. It seemed like the positive experience with the program, the CP’s knowledge about medications, and the predictable framework, had made them feel cared for. Altogether, this had also made them feel safe. They recommended the FuP to all users of medications.

Participants told that they had achieved insight into their medication use; concerning how to take medications, the importance of medication use in relation to their disease and about specific medication properties, e.g. effects, side effects and interactions. All of them were skeptical towards medications, but now seemed to realize the importance of them. They expressed a desire for being involved in their own medications, which resembled a level of concordance.

Regarding the CP’s role in the interdisciplinary team, this was assumed to increase drug safety, as the CP was regarded as having just as much knowledge about drugs as the physicians. The CP was consequently considered suitable for performing ‘quality checks’ of patients’ medication regimes, to inform patients about their medications and to assist physicians, both at the hospital and in general practice, in medication related questions.

Patient experiences were throughout all interviews expressed in relation with their experience with the rest of the health care system, i.e. shortage of time, drug information and follow-up with their GP and hospital physicians. This must be taken into account when interpreting results from the interviews. The fact that the FuP was led by one single CP must also be considered.

5 DISCUSSION

The aim of this PhD project was to develop a CP-led FuP for patients with established CHD after discharge from hospital. In our knowledge, such a program did not exist in Norway at the time when the PhD project was initialized. A medication assessment tool (MAT-CHDSP) was first developed in order to identify improvement potentials within CHDSP and for monitoring of potential effects of an intervention. We have shown that the MAT-CHDSP possesses content and face validity, and that it is reliable and feasible both as an audit tool and a clinical tool (Paper I-III). A CP-led FuP has been developed and carried out as an RCT with and IG and a CG. From the RCT we observed that the FuP led to an increase in documentation of lifestyle advices in favor of the IG; however, this did not have any effects on clinical outcomes (Paper III). A qualitative study on patient experiences with the FuP showed that participants were very positive to such a program, and also to the involvement of CPs in the interdisciplinary health care team (Paper IV). In this section, the different studies will be discussed, and the final section will be directed towards future perspectives and further investigations and development of the MAT-CHDSP and FuP.

5.1 THE MAT-CHDSP

5.1.1 Novel features of the MAT-CHDSP

As described in Paper I, both the follow-up and the lifestyle criteria are new features of the MAT methodology. Many studies have been exploring the appropriateness of prescribing and therapy goal achievement, e.g. the EuroAspire studies (53;54). In our knowledge, no studies have directly been measuring whether action is taken during hospital stay as a reaction to unachieved therapy goals at hospital admission. The follow-up criteria worked as intended in studies performed in hospitalized patients, because we were able to identify drug therapy before and after the hospitalization, in addition to instructions for the next care level, normally the GP. In the RCT (Paper III), however, the follow-up criteria did not work at study end because the response to the standard depended on future actions, i.e. whether the GP or hospital physician agreed with CP recommendations and effectuated an amendment to the medication regime. Application of the follow-up criteria at study end would request a pre-defined follow-up period, and a new meeting with (or phone call to) participants in order to confirm the outcome.

Concerning the lifestyle criteria, it could be argued that they have no place in a MAT, as a MAT by definition is a tool to assess medications. On the contrary, as smoking, obesity, diabetes and physical inactivity may have major impact on CHD disease; these factors should indeed be assessed along with prescription of appropriate drugs and therapy goal achievement. The EuroAspire group stated that "Coronary patients require comprehensive prevention and rehabilitation programs, not just revascularization and cardioprotective medication. Simply giving a prescription is clearly not sufficient and drug treatments need to be combined with professional lifestyle intervention"(50). Results from our RCT indicate that only documentation of lifestyle advices does not necessarily have an impact on therapeutic outcomes (Paper III). Our results are not supported by results from other lifestyle interventions studies, where significant impact on clinical outcomes have been observed at one-year follow-up (57). Also, we did identify significant improvements in cholesterol values in CG patients. The lifestyle criteria do have a place in the MAT-CHDSP, but we have to reconsider how they should be used and if they should remain as they are. Documenting lifestyle advices is clearly not enough; the patients need to adhere to them. Maybe the criteria have to be reformulated in order to also assess patient behavior.

5.1.2 Content validity

In order for review criteria to possess content validity, they should be evidence-based, and in accordance with updated recommendations and currently appraised CPGs. If they are developed from CPGs, they should accurately reflect the CPG recommendations, and explicitly state the clinical setting in which they apply. Meeting the criteria should be strongly associated with improvement of health (13;44). The MAT-CHDSP was developed from validated criteria and accepted CPGs (40;49). Hence, they were evidence-based and already considered relevant for CHDSP. Our validation group also agreed upon the validity of the criteria in respect of SP of CH, and we subsequently concluded that the MAT-CHDSP possessed content validity. However, several aspects of the validation procedure should be considered: *First*, only twelve persons were finally included in the validation group, which according to Robson is sufficient, but clearly not many (88). Increasing the number of participants was difficult, despite several reminders submitted. However, more effort could have been made to identify more candidates for e-mail invitation. We also realized that the complexity of the criteria subjected to Delphi 1 could have restrained people from participating; hence, simplifying criteria before the content validation phase may have increased the number of respondents. *Second*, most of the validation group represented North-

Norway and Southwest-Norway, and hence therapy traditions here. Mid-Norway and West-Norway was not represented, and only one participant from the South-Norway was present. However, in accordance with the Norwegian Medicines Agency in 2007, the ESC guidelines concerning CHDSP should be applied all over Norway (personal communication with Steinar Madsen, Medical Director). *Third*, the Delphi technique did not enable thorough discussions which could have been achieved by e.g. a focus group approach. However, as MAT-CHDSP criteria were developed from an already validated tool and based on valid CPG recommendations, we selected the less time consuming and recourse demanding procedure, which we also assumed would facilitate participation. *Fourth*, as all participants of the validation group were familiar with our research group, they may have been reluctant to disagree with our original criteria. Because several comments and disagreement arguments were received during the Delphi processes, we believe this was not the case.

Altogether, our validation group comprised sufficient number of participants in accordance with literature, and was represented by both practitioners and academics, as recommended when developing review criteria (13;88). Even if CPGs differ slightly in regard to ACEI prescription and recommended therapy goals for lipid values, recent literature matches our choice of review criteria within CHDSP (103). Hence, we believe in the content validity of the MAT-CHDSP. The final version of the MAT-CHDSP does not differ significantly from the initial-MAT-CHDSP that was subjected to content validation. The changes have included simplification of wordings, and rearrangement of elements from the criteria into the application guide, in order to decrease ambiguity. One outdated criterion has also been deleted.

5.1.3 Feasibility

Feasibility of review criteria relates to their applicability, the availability of data to apply the criteria and resource utilization. To prove this, they need to be tested on clinical data (13;104). Only the *draft*-MAT-CHDSP and the *final*- MAT-CHDSP have been submitted for feasibility testing, only distinguished by the outdated simvastatin criterion that was removed in the final version.

Applicability

Applicability of MAT criteria should be reported in all MAT studies, in order to identify the proportion of the patient population the criteria could be applied in. This will indicate the generalizability of the results. Applicability of the MAT-CHDSP criteria has in our MAT-studies oscillated around 60 % [range 0-100 %] (Paper I-III). Some criteria with low

applicability (nos 2 and 3) have been kept throughout all three studies because they describe important aspects of care that are relevant to patients (13). Others, with higher applicability (nos 12 and 13) have been recommended for replacement into other MATs, because they were not always relevant in our patient population (Paper I) (13). We have also omitted criterion 14 in the retrospective study and the RCT because information to answer the standard has been non-existing in patient records (Paper II&III).

An applicability threshold for deciding upon a criterion's further use has not yet been set in literature, even if a cut-off threshold of 1 % have been tried (43). Excluding criteria based on low applicability may not be appropriate, as seldom occurring, but clinically important, aspects thus may be disregarded. As MAT developers, it is important to make sure that the criteria achieve as high applicability as possible. This can be done by allocating the appropriate criteria to the appropriate MATs, which then can be selected for use in the appropriate patient population. E.g. if the heart failure criterion in the MAT-CHDSP (no 12) was placed in a heart failure MAT, it is very likely that applicability would have been higher. At the time being, however, MATs for several clinical conditions remains to be developed.

Availability of data

If not reporting ID in prescription studies, incorrectly judged inappropriate prescribing may occur (20). In MAT methodology, this has been accounted for by the MAT rating system, which allows for ID documentation. A high level of ID may nevertheless still influence the results. In such situations, an improvement in the data collection procedure or clinical documentation is requested. When using a MAT as a clinical tool, the presence of ID would trigger data collection before finalizing medication assessment.

The low ID observed in our MAT studies was likely due to the special designed medication profile used for data collection (Appendix D) and the nine criteria that are applicable in *all* patients with established CHD. We experienced, however, a systematic lack of information concerning body weight, body height, BMI and waist circumference, which often seems to be missing in electronic patient records at the Department of Cardiology, UNN. It might be that the hospital physicians do not consider this information crucial for therapy purpose; however, the lack of it precludes an assessment of the health-care takers lifestyle advices.

From personal judgment, weight and height are more commonly present in hand-written medical charts compared to the electronic patient records. This may be caused by the available boxes for this information in the hand-written medication chart. In order to make

this information available also electronically, documentation procedures may need to change. This may also be important for clinical purposes, e.g. renal function calculation. Perhaps it will be introduced with the imminent electronic prescribing.

Application time

Our studies are the first MAT studies to present application time measures. It is important for the feasibility of MAT application, and depend on three aspects; i) data collection time, ii) familiarity with the tool and iii) the number of criteria and how fast they can be applied (45). In the pilot study (Paper I), we reported a mean application time of the MAT-CHDSP of 1.5 minutes for an experienced user. This was measured by applying the *draft* version of the MAT-CHDSP. In the retrospective study (Paper II), we reported a total mean time of 11 minutes for data collection in medication profile and MAT-CHDSP application, using the *final* version of the MAT-CHDSP (where one criterion had been deleted from the previous version). In all three MAT studies, we used a short audit period (current hospital admission), predefined patient records to search for data, and a medication profile to direct data collection. This facilitated data collection procedure and kept data collection time short (Paper I-III). A decrease in application time with the number of applications was observed, which indicates the influence of instructions and training (Paper I).

The threshold for acceptable application time may differ according to how the tool is used; for audit purposes or as a clinical tool, but also in between the different types of MATs. Our goal is, however, to keep this at a minimum. Automating review criteria application in electronic patient records will decrease application as much as possible, and has been described in a recent thesis on MAT development from the University of Strathclyde, Scotland (105). At the time being, such an approach will not be feasible at UNN, where electronic prescribing and electronic medication charts has yet to be implemented. However, when electronic prescribing is introduced, the electronic databases should be structured so that data relevant for quality assessment is made available and accessible. In this manner, MAT criteria, or similar tools, can run automatically in all relevant patients, submitting an electronic alarm to health care takers at identification of non-adherences.

Distinguishing between different levels of care

The two first MAT-CHDSP studies were performed in hospitalized patients (Paper I&II). In the RCT, patients were in hospital care at baseline and in general practice at study end (Paper III). We were able to apply the MAT-CHDSP in all studies, and were also able to identify an increase in adherence from baseline to study end in the RCT. This indicates that the MAT-

CHDSP may be applicable in different levels of care and is sensitive to change. This will, however, need further investigation, as we used different patient populations in all three studies.

5.1.4 Reliability

In the three MAT-CHDSP studies (Paper I – III), reliability has been measured using Cohen's kappa (κ) to express inter- and intra-observer agreement in MAT-CHDSP application. Cohen's kappa is generally thought to be a more robust measure than percent agreement, since κ also takes the random agreement between the observers into account. If the observers are in complete agreement, κ = 1. If there is no agreement among the observers other than what would be expected by chance, κ = 0 (88). Overall κ-values have been above 0.8 in all studies, which is interpreted as excellent agreement (88). A recognized problem with Cohen's Kappa is that, even if percent agreement is high, κ may be low in cases where the expected random agreement is high. In cases where we experienced this, we had to evaluate the κ-value against percent agreement. For some of the single criteria, we did however experience 'true' low κ-values. During field testing of the *test*-MAT-CHDSP, this was due to misunderstandings of the MAT criteria; during pilot study of the *draft*-MAT-CHDSP, this was due to misinterpretation of justified reasons for non-adherence in the application guide. Both criteria and application guide have subsequently been amended in order to improve comprehensibility and decrease ambiguity. This demonstrates the fact that, even if MAT criteria by nature are explicit, determination of applicability, adherence and justified non-adherence may depend on the user's interpretation (45).

5.1.4 Face validity

Face validity is related to relevance, credibility and acceptability, which can have two dimensions: (i) *Face validity to care givers* concern whether the tool is acceptable to the likely prospective users of the tool and reflects what the assessment tool appears to measure and whether it 'looks valid'. This can be assessed using different consensus methods, like e.g. Delphi (44). After our Delphi study, we concluded that the MAT-CHDSP criteria had 'face validity to care givers', as they were accepted by the validation group and found relevant to SP to CHD. We also believe that the 'face validity to care givers' was increased by simplifying wordings in accordance with the validation group's comments, as this decreased ambiguity (13). (ii) *face validity to patients* or *predicative validity* concern whether the tool is positively correlated with treatment outcome, which in our situation concern appropriate prescribing, achievement of therapy goals, improvement in lifestyle and in the end a reduction

in morbidity and mortality (24). As the MAT-CHDSP criteria are derived from the current evidence-base and accepted CPGs (49), it is assumed that adherence to the MAT-CHDSP criteria is positively correlated with CHDSP and that the tool criteria hence have predicative validity. However, we observed an increase in adherence to the MAT-CHDSP criteria in IG patients in the RCT, which was not correlated with improvement in outcome measures. Hence, our lifestyle criteria do not seem to have predicative validity, and should be reconsidered. We may though need to follow these patients for some additional time, as these outcome measures may be delayed in time, in contrast to for instance outcomes in pain management (45).

5.2 THE CLINICAL TOOL

The MAT-CHDSP was developed as an audit tool with the features of a clinical tool, meaning that the criteria are "valid indicators for appropriate prescribing that can be used in the context of the individual patient" (20). The short and comprehensible MAT-CHDSP promotes the clinical efficacy, while the one-page outfit makes it appear clear, simple and manageable. The low application time and the high level of agreement between observers also indicate its feasibility as a clinical tool, as it was used during the FuP, when the CP used it for identify improvement potentials with regard to the CHDSP (Paper III). The low level of ID during our three MAT-studies also indicates a high level of *operational validity* of the MAT-CHDSP, meaning that data is available for application (Paper I-III) (106).

For health care takers who are familiar with CHDSP, review criteria presented in the MAT-CHDSP may seem simple, straight-forward and almost redundant. However, in a busy clinical daily life, the risk of bypassing even simple recommendations increases with an increased number of patients. Results from our MAT-CHDSP studies, showing low adherence to criteria concerning achievement of therapy goals and documentation of lifestyle advices, indicate that health care takers may need reminders on what to consider before discharging patients from hospital. Also, as explicit clinical tools for medication assessments and MTR are scarcely described in literature, these tasks become highly dependent on individual skills, and may therefore result in relatively large inter-individual differences in identification of DRPs and other therapeutic issues. The MAT methodology may serve as a means to aid and structure MTR and medication assessment, and consequently reduce inter-individual differences. Whether the MAT-CHDSP will work as a clinical tool with other CPs and other health care personnel will need to be explored.

5.3 LONGITUDINAL PERSPECTIVE OF CHDSP

Utilization of the MAT-CHDSP in three MAT-studies, including totally 426 patients, has allowed for a longitudinal perspective of CHDSP in the period 2008 to 2011 (Paper I-III). Even if patients have been included by different selection methods, patient populations are quite similar with regard to gender, age and co-morbidities. In this section, different aspects of CHDSP will be discussed based on the three studies.

Overall adherence

Even if the overall adherence results have been relatively low in all MAT-CHDSP studies, adherence to the prescription criteria have remained high (Paper I-III). This shows that SP status cannot be evaluated based on overall adherence results only. In order to achieve a true picture, the overall adherence needs to be considered along with adherence to the single criteria.

Prescribing of appropriate medications

Adherence to the criteria concerning prescribing of aspirin, β-blockers, statins and ACEIs/ARBs in eligible heart failure patients has been relatively high in all three studies. In Paper II, we described an increase in prescribing of these medications compared to 2004 observations (107). This correspond to e.g. observations in the EuroAspire surveys (54;108-110). In the period from 2008 to 2011, adherence to the prescribing criteria has remained more or less stable. In Paper III, we concluded that the CP-led FuP failed to influence prescription rates, perhaps except from prescription of ACEI/ARBs in eligible patients with diabetes mellitus (DM). A reason for this may be that the basic level of appropriate prescription was already high. Frequency of statin prescription does, however, seem slightly higher in our studies compared to other (54).

Achievement of therapy goals

In Paper II, we describe that BP and cholesterol goal achievement has increased since the 2004-study (107), which correspond to observations in the EuroAspire surveys (54;108-110). No increase in therapy goal achievement from 2008 to 2011 can be been observed by comparing results from the three MAT-CHDSP studies (Paper I –III). The strict BP thresholds defined in the MAT-CHDSP (i.e. 130/80 mmHg) may partly explain the low achievement of BP therapy goals shown in our studies. However, as described in Paper II, achievement of BP therapy goal increased only slightly by increasing the threshold to 140/90 mmHg.

Our observations indicate that a high level of appropriate prescribing does not necessarily lead to adequate achievement of therapy goals, which also correspond with observations in the EuroAspire surveys (54;108-110). With our follow-up criteria, we have also revealed an improvement potential concerning hospital procedures, as a considerable proportion of patients were discharged without appropriate amendments in drug therapy in order to achieve therapy goals, or a new blood glucose measurement (or Hba1c) to investigate an undiagnosed diabetes mellitus (DM).

With the CP-led FuP, we aimed to increase achievement of therapy goals for BP and cholesterol in IG patients. The RCT results do, however, indicate that the FuP had no influence in favor of the IG (Paper III). This does not correspond with results from other studies showing that pharmacist involvement has a positive influence on achievement of therapy goals for BP and cholesterol (61-66). In Paper III, we discuss that our results may have been influenced by selection bias, a small number of patients included, that CP recommendations were not always effectuated by the GP, and that outcomes from the last follow-up meeting was not collected.

Lifestyle interventions

Despite a high risk patient population with obesity, smoking and diabetes, we have throughout our three MAT-studies observed an inadequate frequency of lifestyle advices (Paper I-III). Although we are aware that utilization of patient records to retrospectively assess patient care aspects may introduce information bias due to lack of recording, literature indicate that information in medical records relate to care actually given, and that there is an association between the quality of record keeping and the outcome of care (43). The importance of lifestyle interventions as part of CHDSP is specifically pinpointed in the CPG on 'Cardiovascular disease prevention in clinical practice' issued by ESC in 2007 (49). Also, a recent Cochrane review (n=47 studies) reports a significant reduction in total and cardiovascular mortality in addition to hospital admissions in patients participating in exercise-based cardiac rehabilitation (111). Although among hospital physicians perhaps considered to be a GP task, and maybe also more practically long-term managed by the GP, *nothing* is stated in the CPG indicating that lifestyle recommendations is a GP task only.

We are aware that some of our patients have benefited from participation in a program called "The Heart School", which is a part of follow-up from UNN, offered to all patients that have experienced a heart attack. It comprises two days of teaching (cardiologist and pharmacist),

physical exercise (physiotherapist), heart-friendly food/diet counseling (dietitian) and cooking and finally a physical examination by a cardiologist. We are also aware that some patients are having a long-term stay, e.g. four weeks, at the rehabilitation center "Nord-Norges Kurbad", where physical activity, physical therapy and nutrition is focused upon. These patients do most likely receive appropriate lifestyle-counseling. However, the systematic and long-term lifestyle counseling program, embracing all patients with established CHD discharged from the Department of Cardiology, is missing. Most likely not because of lack of knowledge or intentions, but because of scarce resources allocated to this purpose.

5.4 THE CP-LED FuP AND THE PHARMACEUTICAL CARE PRACTICE

Results from our MAT-studies (Paper I-III) and other clinical studies, indicate the inadequacy in CHDSP (50;54). Even if prescription rates in the recent years may have increased towards appropriateness, achievement of therapy goals remains insufficient (50). On a European level, the ESC has tried to narrow the gap between CPG recommendations and clinical performance by developing the EuroAction model, which have significantly influenced several outcomes both in general practice and in hospital care; reduced consumption of saturated fat, increased consumption of fruits, vegetables and oily fish, increased physical activity, reduced BMI, increased achievement of BP below 140/90 mmHg and increased prescription of statins and ACEIs (56).

Compared to the EuroAction and other models, we have in Paper III discussed how the FuP can be improved. Briefly, a close and committed collaboration with prescribers (hospital physicians and GPs) and CP prescribing opportunity are suggested, appropriate medication amendments should be made at hospital before discharge, partners could be involved, focus upon smoking cessation and adherence with medication regimes should be increased, the CP should have the possibility of referring patients to dietitians and physiotherapist when appropriate, follow-up meetings could be more frequent and patient demands concerning lifestyle modifications could be enforced.

As experienced by the CP and also suggested by results from the qualitative study (Paper IV), several aspects of the CP-led FuP were appreciated and should be retained. *First*, it should be a pharmacist in charge of the FuP because drug explanations had been more extensive and comprehensible compared to what participants had received by their GP or other health personnel. In addition, the CP was trusted as an expert in medications from whom a 'second opinion' on the medication regime was appreciated and approved. This had made participants

feel safe and taken care of. *Second*, follow-up meetings should not be allocated too far away from where participants lived. And *third*, the written summary after follow-up and the compiled medication list should be retained. A further development of this could be to make wallet-format medication cards, which the patient should be instructed to carry. Experience from Mid-Norway indicate that these cards are frequently used by patients and also brought in when at hospital admissions (personal communication with Master in Pharmacy Kristine Lundereng, Levanger Hospital Pharmacy). Such cards have also been appreciated in other setting, both by patients and physicians (112).

In the qualitative study it was suggested that the FuP should be part of the already established 'Heart School' (Paper IV). Another, and more comprehensive idea, is to establish a 'follow-up clinic', where CPs, dietitians and physiotherapists (maybe also behavioral-psychiatrists) form a clinical team supported by a cardiologist, and where physicians can refer their patients with established or high risk of CHD. Such a clinic will facilitate multidisciplinary discussions and clearly allocate the responsibility of CHDSP. Such ambulatory clinics have been shown successful, e.g. in heart failure patients (113).

Some of our suggestions on how to improve our FuP and hence patients care, are clearly resource demanding. For instance, additional health care personnel time, more aggressive medical regimen and laboratory measures are additional costs to patient care, so are patients' travelling expenses. Studies indicate that pharmacist provided direct patient care may offset additional cost by e.g. avoiding DRPs, reducing medication errors and hospitalizations, optimizing drug therapy and increasing quality of life (8;69;114;115). However, large studies to investigate the cost-effectiveness of CP services and their health economic impact are missing (115;116). Before recommending the CP-led FuP for implementation in standard patient care as suggested above, further studies of its cost-effectiveness are warranted.

Regarding CPs involvement in pharmaceutical care practice, the positive impact of CPs in prevention of CHDSP has been shown (67-69). Even if we failed to identify any impact OR OIR FuP with regard to clinical outcomes (Paper III), CPs should continue to be involved in patient care, in order to improve quality of medical therapy and inform about correct use of medications. However, for clinical pharmacy to become fully implemented in the health care system, pharmacists need to be acknowledged as fully and vital members of the multidisciplinary health-care team. This is however a two-edged plot, as full recognition also require that pharmacists "adopts the essential attitudes required by health professionals

working in this area: visibility, responsibility, accessibility in a practice aimed at the general population, commitment to confidentiality and patient orientation" (15). Hence, pharmacists will need to show their competence within drug therapy managing and patient care. In addition, both vision and a voice are necessary to be fully integrated into the health care team.

5.6 METHODOLOGICAL CONSIDERATIONS

5.6.1 The Medication Assessment Tool

The MAT methodology supports a structured, evidence-based and reliable medication assessment, whether the tool is used in clinical audits or in practice. The main advantage above other tools is its explicit character that simultaneously allows for registration and consideration of applicability, justified non-adherence (Nj) and lack of data (ID). Methodology issues to be considered in order to provide appropriate presentation and interpretation of MAT results will be discussed below.

Calculation of adherence

The adherence calculation used throughout the three MAT-CHDSP-studies (Paper I-III), i.e. 'Y' responses presented as a percentage of the sum of 'Y', 'N', 'Nj' and 'IDs' responses, creates a 'worst-case' scenario that needs to be seen in context with the presence of 'IDs' and 'Nj'; the higher the 'IDs' and 'Nj', the lower the adherence, and vice versa. For instance in IG patients in the RCT, we observed an erroneous decrease in adherence from baseline to study end in relation to aspirin prescription because of an increase in 'Nj' responses (Paper III). Adherence was actually as high as it could be, but due to the number of 'Nj', it seemed lower. A solution for this dilemma has been suggested; namely summing the 'Y' responses over the total number of 'Y' and 'N' responses, i.e. the denominator declines. This approach creates a 'best case' scenario, however; also requires a separate reporting of 'Nj' and 'IDs'. It has been suggested, that adherence may be calculated the original way when the presence of 'IDs' and 'Nj' is low, and the alternative way when 'Nj' is high, as this will better approximate the 'true' adherence (45). In our case, this approach would have presented 100 % adherence.

An alternative approach could be to present *non*-adherence, i.e. 'N' responses presented as percentage of the sum of 'Y', 'N', 'Nj' and 'IDs' responses. This approach may however underestimate 'true' *non*-adherence, especially when 'IDs' and 'Nj' is high, and it will also require a separate reporting of 'Nj' and 'IDs'. Nevertheless, this may be closer to a clinical approach: "How bad are we and how can we improve?" This aspect of MAT adherence calculation needs further clarification.

The medication profile and the application guide

During field testing, we realized that the design of the medication profile was critical to collection of MAT-CHDSP-relevant data and to facilitate MAT-CHDSP application. The medication profile was amended, and the new medication profile has been used throughout all three MAT studies (Paper I-III), both as a data collection form and as a clinical tool for the CP during follow-up (Paper III). If medication profiles from other CPs should form basis for MAT-CHDSP application, they may not include sufficient information. However, as CHDSP is relevant in many patient populations, e.g. diabetes and chronic obstructive lung disease, amendment of medication profiles may be beneficial in order to apply the MAT-CHDSP.

Because the MAT-CHDSP criteria were simplified by placing description of intolerances, contraindications and justified reasons for non-adherence in the application guide (Paper I), this guide is a mandatory supplement to the MAT-CHDSP. The application guide also reduces ambiguity of the criteria. However, it is important that the application guide, as well as the MAT-CHDSP, is updated as CPG recommendations change, outdates or new ones are added.

When is adherence good enough?

Adherence results has arbitrarily been defined as 'acceptable/high' if adherence is ≥ 75 %, 'intermediate' if adherence is between 50 and 75 % and 'low' if adherence is below 50 % (41;45), which have also been used in the present thesis (Paper II). These thresholds need to be discussed and set in relation to the clinical area and local settings. As mentioned in the 'Introduction' section, setting a standard may not even be feasible. Nevertheless, when comparing a 'high' level of prescription with a 'low' level of achievement of therapy goals in clinical studies, it seems like an acceptable threshold may be somewhere around 70-80 % (50). The cut-off for acceptable adherence still remains unclear and needs further debate.

5.6.3 Internal validity

The internal validity of our MAT-CHDSP studies (Paper I-III) is threatened by selection bias, information bias and observation bias that may have been systematically introduced. *Selection bias* may have been introduced in our pilot study (Paper I) and RCT (Paper III) due to that participation was voluntarily, and in the retrospective study (Paper II) because we only analyzed patients undergoing PCI with stent implantation during January, February and March. Adherence results did not, however, vary significantly between the three studies, which argue for the similarity between the three patient groups. Our patient populations comprised about 70 % male, which is higher than expected in according to the prevalence of CHD (5). A similar proportion of male was, however, observed in the retrospective study

(Paper II), where patients were identified consecutively from a list (Paper II). This may indicate that men are over-represented among this patient population at UNN. This overrepresentation of men in our patient populations may however have influenced our adherence results. From the EuroAspire surveys, it has been indicated that female patients achieve therapy goals for cholesterol and BP in a lower extent than male patients (108). A higher proportion of females in our study populations could thus have resulted in even lower achievement of therapy goals than we have observed. In the RCT, we tried to reduce selection bias by using a randomization procedure that stratified on gender (Paper III). However, here we managed to include only half of the estimated patient population, which may have contributed to the non-significant differences between our study groups. However, as we observed an improvement in both study groups, in addition to the higher achievement of BP therapy goals at baseline (starting point for our sample size calculation), we would have needed an even larger patient population than originally estimated in order to observe significant differences.

Information bias may have been introduced in data collection from patient records (Paper I-III), from patients (Paper III), and during laboratory measurement (Paper III). We tried to reduce this by introducing the medication profile for data extraction and by standardizing medication reconciliation process, BP measurements, blood sampling as well as analyzing procedures. Concerning data quality, we observed a low frequency of insufficient data (ID), except for body mass measures. Our data extraction procedure will however need further validation, in order to verify that different observers extract the same data.

Observer bias of MAT application will depend on user skills and data interpretation. In Paper I, we observed that application time decreased with the number of applications, hence indicating an increase in application skills. It may be assumed that this also influences MAT application; however, we observed high inter-observer agreement between different users in all MAT-studies (Paper I-III). The application guide, developed to diminish ambiguity in MAT application, has likely contributed to this. All users of the MAT-CHDSP in our studies were pharmacists, and further studies are needed to explore the reliability of application between different health care professions, e.g. nurses and physicians. If the same results are obtained in several groups of users, a general use of the MAT-CHDSP can be recommended.

Another threat to the internal validity, are the Hawthorn effects that were discussed in relation to our RCT (Paper III) (117). This effect can neither can measure nor adjust for. Blinding, which was not possible in our case, could have reduced this effect.

The internal validity of our qualitative study, or 'credibility' and 'dependability' when it comes to qualitative research, has been discussed in Paper IV. Clearly, a selection of four patients have introduced selection bias, however, both male and female were equally represented. In qualitative research, the interviewer and the analyzer will inevitable influence results. It is, however, necessary that these processed are explained in detail, for the reader to judge upon the validity of findings.

5.6.4 External validity

Threats to the external validity of our MAT-CHDSP results include whether (i) the CPG recommendations in the MAT-CHDSP is applicable in other countries and settings, (ii) our patient populations represent the general population with CHD, (iii) the MAT-CHDSP can be used in other hospitals or care settings, e.g. primary care, and (iv) attention to study objective have made clinical practice to change.

(i) The CPGs used as basis for the MAT-CHDSP are widely accepted and used throughout Europe (Paper I). They do not differ much from the American CPGs, but slightly from the SIGN guidelines in according to ACEI prescription and lipid therapy goals. The Norwegian simvastatin-criterion that now is outdated (Paper I) and removed, clearly proves that application in other settings will require at least content validation, e.g. a new criterion concerning ACEI/ARB use to all patients in CHDSP may need to be added.

(ii) Our study patients were selected from only one Norwegian hospital and department (Paper I-III), the proportion of males in our studies were high and only patients living in certain communities were included in the RCT (Paper III). Nevertheless, the overall interpretations of adherence results seems to correlate with results from populations in other studies (54;108). We do however need to validate the MAT-CHDSP for use in other hospitals and countries, maybe also in other patient populations.

(iii) The MAT-CHDSP was mostly tested in hospital care (Paper I-III), which can be different from e.g. community care and nursing homes, where patients are not individually treated by specialists in cardiology and SP. At the RCT study end (Paper III), however, most of the patients were no longer in hospital care, but in community care. Except from that follow-up

criteria were not applicable at study end (because of insufficient information concerning effectuation of CP recommendations), the MAT-CHDSP criteria were applicable also at study end. Further validation in general practice and nursing homes is however desirable, also in order to verify that necessary information can be collected.

(iv) We observed only minor changes in MAT-CHDSP adherence throughout 2008-2011, and it does not seem that the health-care takers' actions have been influenced by our studies. Neither did we observe any influence of the CP-led FuP on clinical outcomes. This would actually have been desirable, as feed-back on non-adherences ideally should improve practice. We now have a job to do in order to inform health care takers in our hospital about our results.

Considering the external validity of our qualitative study, the term 'transferability' is used within qualitative research and has been discussed in Paper IV. Our new knowledge concerning experiences with a CP-led FuP, relates to a FuP involving only one CP. Hence, patient experiences with the FuP may not be transferable to other FuPs. Also, the study only included patients with established CHD. However, because CHD is highly prevalent in the general population, as well as in other patient populations (e.g. in patients with diabetes, renal failure and chronic obstructive pulmonary disease), we believe our findings may be applicable also in other patient groups. However, this remains to be explored. It is said, that "the most useful indicator of credibility of the findings is when the practitioners themselves and the readers of the theory view the study findings and regard them as meaningful and applicable in terms of their experience"(118). We need to present our results for the health personnel at stake and investigate this further.

6 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

A novel tool has been developed to assess medications, follow-up measures and lifestyle advices in relation to CHDSP; the MAT-CHDSP. The tool has been shown to possess face validity and content validity as well as being feasible and reliable as an audit tool and as a clinical tool. Both prospective and retrospective use of the MAT-CHDSP has revealed high prescription of recommended drugs in CHDSP, but also inadequate achievement of therapy goals for total cholesterol, LDL cholesterol and BP. In addition, insufficient follow-up during hospitalization in order to achieved therapy goals has been identified, as well as low documentation of lifestyle advices.

A one-year lasting CP-led FuP in patients with established CHD has been developed and carried out as an RCT, focusing on therapy goal achievement and lifestyle recommendations. From RCT results, we observed an increase in adherence to guideline recommendations in both study groups. A higher increase was observed in IG patients; however, this was mainly caused by an increase in documentation of lifestyle advices, which did not seem to influence clinical outcomes. This may have had several causes, including CP performance, patient performance, FuP structure and contents, and methodological weaknesses with the RCT. The qualitative study in FuP participants did however show that patient satisfaction with the FuP was very high, that participants recommended the FuP to all users of medications and that the CP was recognized as part of the interdisciplinary health care team, both as a medication counselor for physicians and patients, but also as an independent health care taker. Several improvements of the FuP have been suggested for further use. However, before implementing it in standard patient care, further measures are warranted, also with regard to costs.

For furhter use of the MAT-CHDSP and the FuP described in this thesis, the following validation measures and research tasks have been identified:

MAT-CHDSP

- ✓ Consider re-defining the lifestyle criteria to also assess patient behavior
- ✓ Validation of data collection procedure
- ✓ Validation of MAT-CHDSP application in other patient populations, in other health care settings, and by other health care professionals
- ✓ Continuously update of the MAT-CHDSP and application guide (including content validation) in accordance with new CPG recommendations

- ✓ Feed-back to health care personnel concerning the identified improvement potentials

The FuP

- ✓ Improve structure and content in order to increase impact on clinical outcomes
- ✓ Explore long-term outcomes in the RCT study population
- ✓ Explore its use in other patient populations
- ✓ Explore transferability of qualitative results with clinicians and GPs

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APPENDIX A

Patient information and consent papers (Norwegian)

Pilot study – Paper I

UNIVERSITETSSYKEHUSET NORD-NORGE
DAVVI-NORGGA UNIVERSITEHTABUOHCCEVIESSU

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT OM FOREBYGGENDE BEHANDLING VED HJERTESYKDOM

Til pasienter som gjennomgår angiografi/PCI ved Hjertemedisinsk avdeling, UNN

Institutt for farmasi ved Universitetet i Tromsø driver forskning innen kvalitetssikring av legemiddelbruk. I samarbeid med Sykehusapoteket og UNN gjennomfører vi nå en undersøkelse om legemidler som brukes for å forebygge hjerteinfarkt. Dette er først og fremst legemidler som senker blodtrykket og kolesterolet samt blodfortynnende legemidler. Vi vet fra andre undersøkelser at en del pasienter ikke får full virkning av slike legemidler. Vi ønsker nå å se hvor mange pasienter gjelder, om det gjelder en spesiell gruppe pasienter, og om det er noe som kan gjøres slik at flere får et best mulig behandlingsresultat.

Pasienter som gjennomgår angiografi (undersøkelse av blodårene i hjertet) med blokking i perioden 1. august til 1. november 2008 vil bli spurt om å delta i studien. Deltagelse innebærer at opplysninger som er notert i sykehusjournalen blir brukt til å besvare forhåndsbestemt kriterier i et skjema (se side 2 for journalopplysninger som vil bli anvendt). Skjemaet fylles ut av en doktorgradsstudent i farmasi. Det vil ikke bli gjort endringer i pasientenes legemiddelbehandling som følge av dette. Videre kontakt med sykehuset vil heller ikke bli påvirket. De utfylte kriterieskjemaer registreres avidentifisert, dvs. med kode i stedet for navn. Resultatene av undersøkelsen vil bli brukt i en masteroppgave ved Institutt for farmasi, i en doktorgradsavhandling ved Sykehusapotek Nord/Institutt for farmasi, og vil bli offentliggjort i et medisinsk tidsskrift. Deltagere kan når som helst trekke samtykket tilbake uten begrunnelse ved å ta kontakt med prosjektleder Trude Giverhaug (se telefonnummer og e-postadresse nederst på arket). Et ønske om ikke å delta eller en eventuell tilbaketrekning av samtykke, vil ikke ha konsekvenser for den videre behandling på sykehuset.

Regional komité for medisinsk og helsefaglig forskningsetikk Nord-Norge har godkjent undersøkelsen. Undersøkelsen er også behandlet av Personvernombudet for forskning ved Norsk Samfunnsvitenskapelige Datatjeneste AS. Alle som er involvert i prosjektet har taushetsplikt. Så lenge studien pågår har deltakeren rett til fullt innsyn om hvilke opplysninger som er innhentet om seg selv. Datamaterialet vil bli anonymisert ved prosjektslutt, som beregnes å være 31. desember 2008.

Dersom du ønsker å delta i studien, undertegnes det ene eksemplaret av samtykkeskjemaet og avleveres ved utskrivning til sykepleier eller lege. Eventuelt kan det sendes per post til prosjektleder Trude Giverhaug (se nederst på arket). Det andre eksemplar kan beholdes.

Samtykkeerklæring

Jeg har lest informasjonen om prosjektet og fått muntlig informasjon og samtykker i å delta.

……..……
Dato Sted Navn (helst også med BLOKKBOKSTAVER))

Fødselsdato: …….

UNIVERSITETET I TROMSØ
Institutt for farmasi
9037 Tromsø, Telefon 77 64 40 00, Telefax 77 64 61 51
Førsteamanuensis Trude Giverhaug, direkte innvalg 77 64 61 64,
e-mail: trudeg@farmasi.uit.no

UNN HF
Hjertemedisinsk avdeling
Postboks 84, 9038 Tromsø
Tlf: 77626000

Journalopplysninger som vil bli anvendt:

- Fødselsår
- Kjønn
- Høyde og vekt, eventuelt BMI eller hofte-midje-mål og eventuell historie rundt vektreduksjon
- Røykestatus og eventuell historie rundt røykestopp
- Diagnose(r) som gjelder hjertesykdom
- Blodtrykksverdier og blodtrykkssenkende legemidler
- Kolesterolverdier og kolesterolsenkende legemidler
- Legemidler mot blodpropp, eller blodfortynnende legemidler
- Eventuelle årsaker til at blodtrykksenkende, kolesterolsenkende eller blodfortynnende legemidler ikke er forskrevet
- Eventuell sukkersyke (diabetes) og legemidler mot dette.
- Blodsukkerverdier
- Laboratorieverdier som viser nyrefunksjon

UNIVERSITETET I TROMSØ
Institutt for farmasi
9037 Tromsø, Telefon 77 64 40 00, Telefax 77 64 61 51
Førsteamanuensis Trude Giverhaug, direkte innvalg 77 64 61 64,
e-mail: trudeg@farmasi.uit.no

UNN HF
Hjertemedisinsk avdeling
Postboks 84, 9038 Tromsø
Tlf: 77626000

APPENDIX B

Patient information and consent papers (Norwegian)

Randomized controlled trial – Paper III

Forespørsel om deltakelse i forskningsprosjektet

"Utvikling av klinisk farmasøytisk tjeneste - kvalitetssikring av sekundærprofylaktisk legemiddelbehandling hos pasienter med etablert hjertesykdom"

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie for å ***utvikle en klinisk farmasøytisk tjeneste*** som omhandler legemiddelinformasjon samt oppfølging i forhold til legemidler, legemiddelbruk og oppnåelse av kliniske målsetninger. På apoteket er det vanskelig å holde oversikt over alle legemidler hver enkelt bruker, hvilket gjør det svært vanskelig å kvalitetssikre bruken av alle dine legemidler. På ***Sykehusapotek Nord*** ønsker vi å utvikle strukturerte rutiner for optimal rådgivning og oppfølging i forhold til de legemidlene du bruker. I den anledning starter vi nå et prosjekt som involverer legemiddelbrukere med etablert hjertesykdom, hvor vi ønsker å utvikle en ny tjeneste som skal ivareta den enkelte legemiddelbruker i større grad. Pasienter som ønsker å delta, blir delt i to like store grupper ved loddtrekning, studiegruppe og kontrollgruppe. *Alle som blir loddtrukket til studiegruppen* ***tilbys ett års oppfølging*** hvor 1) legemidlene de bruker vil gjennomgås og kvalitetssikres, 2) de vil motta informasjon om de legemidlene de bruker og 3) de vil selv kunne stille spørsmål. Ved bruk av et nyutviklet verktøy vil vi kunne identifisere problemområder samt måle om vår oppfølging medfører endringer og eventuelt forbedringer for deg og for resten av studiegruppen. Studien er godkjent av REK Nord (Regional komité for medisinsk og helsefaglig forskningsetikk, Nord-Norge).

Hva innebærer studien?

Studien innebærer **IKKE** endring av den oppfølging du får på sykehuset eller hos fastlegen.
Studien innebærer at deltakerne ved loddtrekning fordeles til to grupper; studiegruppe og kontrollgruppe. ***Studiegruppen*** vil i tillegg til standard oppfølging på sykehuset bli fulgt opp av sykehusfarmasøyt i et helt år med tre møtepunkter (se under for nærmere beskrivelse). ***Kontrollgruppen*** vil ikke bli fulgt opp av farmasøyt, men kun motta standard oppfølging på sykehuset og hos fastlege. Dog vil kontrollgruppen bli kontaktet etter ett år per telefon eller brev for innsamling av opplysninger om helsetilstand og behandling som så skal benyttes i forskningsøyemed. Det spesifiseres at opplysninger vedrørende kontrollgruppen ikke behandles før etter ett år. Hvis eventuelle problemer skulle avdekkes på dette tidspunkt, vil den det gjelder samt fastlege orienteres. Din fastlege vil orienteres om at du deltar i studien.

Hva innebærer farmasøytisk oppfølging?

Tre møter med følgende møterekke:
Møte nr 1: direkte etter sykehusinnleggelse/ved utskrivning fra sykehuset
Møte nr 2: etter 3 måneder
Møte nr 3: etter 1 år
Farmasøytens forberedelser før hvert møte:

- Registrering av informasjon om helsetilstand og behandling som er registrert i pasientjournal.
- Gjennomgang av innsamlet informasjon samt legemiddelliste.
- Eventuell samtale med lege ved eventuell avdekking av problemer relatert til dine legemidler

Hva skjer under møtene:

- Du vil kunne stille spørsmål angående legemidler og ellers annet du lurer på
- Du vil få informasjon om de legemidlene du bruker
- Evt. manglende opplysninger vil bli innhentet fra deg for at det skal kunne gjøres en fullstendig vurdering av ditt legemiddelregime.

Hvis du *ikke* har time på UNN ved oppfølging etter 3 mnd og 1 år, vil du bli kontaktet av farmasøyt for nærmere avtale av møtetidspunkt. I så tilfelle vil du også motta en blodprøverekvisisjon som du skal ta med deg til fastlege/UNN for blodprøvetakning. Dette er nødvendig for å få innhentet informasjon angående kolesterol- og blodsukkerverdier.

Hvilke opplysninger innhentes og registreres om deg?

- Personalia (navn, fødselsdato, kontaktopplysninger)
- Høyde og vekt og eventuell historie rundt vektreduksjon
- Røykestatus og eventuell historie rundt røykestopp
- Sykdomshistorie inkludert diagnoser
- Legemidler og legemiddelhistorie
- Laboratorieverdier (for eksempel blodsukker, kolesterol, verdier som viser nyrefunksjon)
- Eventuelle årsaker til at legemidler ikke er forskrevet
- Eventuelle endringer i legemiddelregime eller sykdomsstatus
- Eventuelle allergier, intoleranser eller kontraindikasjoner for legemidler.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hva som er registrert om deg og kan korrigere eventuelle feil. Kun prosjektleder og prosjektmedarbeidere har tilgang til registrerte data. Alle data blir oppbevart innelåst på Sykehusapoteket Nord Tromsø og vil bli anonymisert ved prosjektslutt (innen 31. desember 2012). Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Mulige fordeler og ulemper

Deltakelse i studien vil ***ikke*** påvirke videre kontakt med sykehuset eller fastlegen. Derimot vil du oppleve tettere oppfølging fra Sykehusapoteket med legemiddelinformasjon og større mulighet for avdekking av problemer relatert til dine legemidler. I tilfelle slik avdekking, vil den forskrivende lege/din fastlege kontaktes. Skriftlig informasjon vil i så fall også sendes til relevante parter. Ved at du deltar bidrar du til at nye og strukturerte tjenester utvikles slik at forholdene legges bedre til rette for avdekking av problemer relatert til legemidler hos den enkelte legemiddelbruker. Deltakerne vil ha rett til informasjon om utfallet/resultatene av studien.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen nedenfor. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du ønsker å trekke deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Ved spørsmål, kontakt prosjektadministrator og sykehusfarmasøyt *Beate Hennie Garcia* (se nederst på arket).

Økonomi og Sykehusapoteket Nords rolle

Studien er finansiert gjennom forskningsmidler fra Sykehusapotek Nord HF i form av en doktorgradsstilling. Ingen økonomiske ytelser blir gitt og ingen interessekonflikter er identifisert.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Beate Hennie Garcia, Sykehusfarmasøyt og doktorgradsstudent
Sykehusapoteket Nord Tromsø, Tlf dir.: 776 26754 Mobil: 90 80 23 61
E-post: beate@unn.no

APPENDIX C

Patient information and consent papers (Norwegian)

Qualitative study – Paper IV

Forespørsel om deltakelse i forskningsprosjektet

"Farmasøytisk oppfølging av pasienter med hjertesykdom - en kvalitativ studie av pasientenes erfaringer"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie som utgjør mitt masterprosjekt i klinisk farmasi. Du er allerede med i en studie hvor du får oppfølging fra klinisk farmasøyt med fokus på legemidler og legemiddelbruk. I denne studien får du oppfølging i ett helt år etter at du ble utskrevet fra hjertemedisinsk avdeling ved Universitetssykehuset Nord-Norge (UNN). Mitt masterprosjekt har sitt utspring i denne studien, og jeg ønsker å vite mer om hvilken **erfaring** og **opplevelse du** har av denne oppfølgingen.

For å belyse dette ønsker jeg å utføre dybdeintervjuer med 4-5 av dere som allerede mottar oppfølgingen fra farmasøyt. Dette vil være åpne samtaler hvor jeg ikke legger så mange føringer, men hvor du får fortelle fritt om dine erfaringer og opplevelse av oppfølgingen.

Hva skjer i studien?
Hvis du samtykker til å delta vil du bli kontaktet av meg for nærmere avtale om tid og sted for intervjuet. Jeg kan komme hjem til deg, men intervjuet kan også foregå på UNN eller på Universitetet hvis du ønsker. Det er beregnet at intervjuet vil vare i 1- 1½ time. Intervjuet vil i sin helhet bli tatt opp på bånd slik at jeg i etterkant kan analysere hva som er blitt sagt. Hvis du under intervjuet skulle ha behov for å ha en liten pause eller skulle ha lyst til å slette noe av det du har sagt, er dette fullt mulig.
OBS! Farmasøyten du mottar oppfølging fra vil ikke få innsyn i hvem som har takket ja til å delta i dette prosjektet.

Hvis du har lyst til å delta, skriver du ditt navn med blokkbokstaver, fyller ut med ditt telefonnummer og underskriver på siste side av dette dokumentet. Arket legger du så i den vedlagte frankerte konvolutten og postlegger denne. Den andre kopien av dette skrivet beholder du selv.
VIKTIG: Av praktiske hensyn må du gjøre dette **innen 14 dager** etter at du har fått denne forespørselen. Hvis ditt samtykke kommer senere enn dette, kan du dessverre risikere å ikke få være med likevel da kun de første 4-5 som melder seg får muligheten.

Mulige fordeler og ulemper
Dette prosjektet vil ikke ha noen direkte fordeler for deg. Men ved å fortelle oss om dine opplevelser og erfaringer vil prosjektet kunne bidra til å utvikle tilbudet om oppfølging av legemiddelbruk.

Prosjektet innebærer heller ingen direkte ulemper for deg. Men om vi i løpet av intervjuet kommer inn på tema som du syntes er vanskelig å snakke om, vil jeg ta hensyn til det.

Hva skjer med informasjonen om deg?
Alle samtaler som er tatt opp på bånd vil bli skrevet ned i tekst uten at det knyttes navn til denne teksten. Når prosjektet er avsluttet vil alle båndopptak bli slettet og den nedskrevne teksten vil bli avidentifisert. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen nederst på siden. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker behandlingen din. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte prosjektleder, se informasjon nederst på siden.

Rett til innsyn og sletting av opplysninger om deg og sletting av informasjon
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Informasjon om utfallet av studien
Som deltaker i studien har du rett til å få informasjon om utfallet av studien når den er ferdig.

Med vennlig hilsen

Herem Mahmoud
Masterstudent i farmasi ved Universitetet i Tromsø

Samtykke til deltakelse i studien

Jeg bekrefter at jeg har fått informasjon om studien og er villig til å delta

---
(Din signatur, sted og dato)

(Ditt navn med blokkbokstaver)

Ditt telefonnummer

APPENDIX D

Patient profile / data collection form

APPENDIX D

Admission date:	**MEDICATION PROFILE / Data Collection Form**	Department:

Name	Date of birth	Height: Weight: BMI =	Date of monitoring	2)
			1)	3)

Reason for admission / symptoms	Familiar disposition: Yes / No / ?	Counsel given	Allergies
	Smoking: Yes, … per week/day /No / Ex / ?	Yes / No / ?	
	Alcohol: Much / Normal / Little / No / ?	Yes / No / ?	
	Phys. activity: Much / Normal / Little / No / ?	Yes / No / ?	
	Ethic origin: black / non-black / ?		

Diagnoses and procedures	Present situation	Previous drug history
Diagnoses at discharge		
Previous diagnoses		
Medical procedures during hospitalisation	No info ❑ EF evaluated ……./…… Normal ❑ by …… : ……%	

Drugs at discharge	Drugs at admission
Comments	Comments
BP ...../……..mmHg HR……., irreg ./ reg.	BP ...../……..mmHg HR……., irreg ./ reg.

Date →							Date →						
Hb							Total chol.						
Leukocyt							HDL chol.						
Tromboc							TG						
SR							AST						
INR							ALT						
Na^+							TropT						
K^+							CK						
Ca^{2+}							CK-MB						
Mg^{2+}							ProBNP						
Urea							Thyroxin						
Creatinin							TSH						
Uric acid							D-Dimer						
Albumin													
CRP													
Glucose													
HbA1c													
LDL chol.													

APPENDIX D

CL(creatinin) = $\frac{\text{(140 – age) x weight (kg)}}{\text{0.8 x creatinin concentration (mmol/L)}}$ **x 0.85 (female) =**

DRUG CONCENTRATION MEASUREMENTS

Date/time → Drug							

Pharmaceutical Care plan

Date	DRP	Evaluation/follow-up	Result

APPENDIX E

Application guide for MAT-CHD$_{SP}$

APPLICATION GUIDE FOR MAT-CHDSP

1. GENERAL INSTRUCTIONS

The medication assessment tool (MAT) for secondary prevention of Coronary Heart Diseases (MAT-CHDSP) comprises 24 criteria derived from guidelines for secondary prevention of CHD issued by the European Society of Cardiology (ESC). The criteria are given in the form of two statements where a qualifying statement (*q*) is followed by an audit standard (*s*). Each criterion is evaluated and responded to, based on information recorded in the Data Collection Form (DCF) which is an extraction of relevant data from the patients' medical records. The appropriate responses to the criteria are selected among four main response categories; applicability (NA), adherence (YES), non-adherence (NO) and insufficient data (ID).

Criterion applicability

When applying the MAT-CHDSP criteria to patient data, the qualifying statement (qualifier) of each criterion needs to be addressed first. The qualifier determines whether the criterion applies to the patient and indicates if the standard can be tested. If the circumstance specified by the qualifier is not present for the patient in question, the criterion is answered by ticking NA (not applicable).

Adherence or non-adherence to guideline standards

If the criterion is applicable, the standard following the qualifier can be tested. The standard is a statement of the guideline recommendation and requires a 'YES' or 'NO' response on the basis of evidence that the standard is being met. If a deviation (no-response) from the guideline standard is justified by a cause documented in the patients' medical records, this is indicated by adding a 'j' (justified) next to the appropriate box (also indicated as 'NOj'). Further information on conditions considered as justified reasons for non-adherence is given in chapter 3 below.

Missing information

If sufficient information is missing for the appropriate response to the qualifier or the standard, this is recorded as insufficient data (ID) affecting either the application of the qualifier (IDq) or the standard (IDs). If information is missing on both the qualifier and the standard, the appropriate response is always 'IDq'. Missing information is recorded by ticking the 'ID'-box and indicating which of the statements (*q* or *s*) that is affected. A '*q*' is written next to the box when data regarding applicability is missing. Similarly, an '*s*' is denoted when data regarding the standard is missing.

2. ABBREVIATIONS

Abbreviation	Full text	Comments
DCF	Data Collection Form	Patient profile with information extracted from patients' medical records
IDq	Insufficient information related to the qualifier	Missing information affecting the application of the MAT-CP criterion
Ids	Insufficient information related to the standard	Missing information affecting the response to the MAT-CP criterion standard
NA	Not applicable	The MAT-CP criterion qualifier is not applicable to the patient
Nj	No justified	A justified cause of non-adherence to the criterion standard
q	Qualifier	A statement to determine whether the MAT-CP criterion applies to the patient and indicates that the standard can be tested
s	Standard	A statement of the guideline recommendation for a specific qualifier
NSTEMI	Non-ST-elevated myocardial infarction	
STEMI	ST-elevated myocardial infaction	
MI	Myocardial infarction	
ACS	Acute coronary syndrome	
UAP	Unstable angina pectoris	
ACEI	Angiotensin-converting-enzyme inhibitor	
ARB	Angiotensin-II-receptor blocker	
CHD	Coronary heart disease	
HbA1c	Glycated hemoglobin	
LDL	Low-density lipoprotein	
SBP	Systolic blood pressure	
DBP	Diastolic blood pressure	
BMI	Body mass index (kg/m^2)	
EF	Ejection fraction	

3. INSTRUCTIONS SPECIFIC FOR EACH CRITERIA

ANTIPLATELET THERAPY (CRITERIA 1-4)

1 Patient with CHD — *is prescribed aspirin daily* ❑ *75 mg* ❑ *160 mg*

The criterion will always be applicable in patients with CHD and **NA/'IDq'** will not be relevant **'YES'** if patients is prescribed aspirin, independent of the dose. Tick the correct daily dose.

'NO' if patient is not prescribed aspirin.

'NOj' applicable but **'NO'** due to

- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if information concerning prescription overall is missing.

2 Patient with CHD and not prescribed aspirin due to contraindications/intolerances — *is prescribed clopidogrel 75 mg daily*

'NA' if patient is prescribed aspirin, i.e. **'YES'** in no 1

'IDq' if 'no' in no 1+ clopidogrel is not prescribed + CI/I to aspirin is unknown.

'YES' if applicable and clopidogrel is prescribed.

'NO' if applicable but clopidogrel is not prescribed

'NOj' if applicable but **'NO'** due to

- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing.

3 Patient with CHD and with a diagnose of acute coronary syndrome and not stented — *is prescribed clopidogrel 75 mg daily in addition to aspirin for 9 -12 months*

'NA' if the patient does not have a diagnose of ACS (Stemi, Nstemi and UAP) or has been stented

'IDq' if diagnosis are unknown

'YES' if applicable and prescribed clopidogrel

'NO' if applicable but not prescribed clopidogrel

'NOj' if applicable and **'NO'** due to

- Diagnose of ACS ≥ 9 months ago
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

4 Patient with CHD and a stent inserted — *is prescribed clopidogrel 75 mg daily in addition to aspirin for 6-12 months*

'NA' if the patient has not undergone PCI with stent implantation

'IDq' if stent implantation is unknown

'YES' if applicable and clopidogrel is prescribed for 6-12 months

'NO' if applicable but clopidogrel is not prescribed for 6-12 months

'NOj' if applicable and **'NO'** due to

- Stent inserted ≥ 6-12 months ago
- Another time interval for therapy has been documented
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

LIPID-LOWERING THERAPY (CRITERIA 5-8)

5	Pasient med CHD	*is prescribed a statin*

The criterion will always be applicable in patients with CHD and **'NA'/'IDq'** will not be relevant
'YES' if patient is prescribed a statin
'NO' if patient is not prescribed a statin
'NOj' if patient is not prescribed a statin due to
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

6	Patient with CHD and prescribed a statin	*is prescribed simvastatin*

Outdated

7	Patient with CHD and maintained on lipid-lowering therapy	*has achieved target cholesterol levels of total cholesterol ≤ 4.5 and LDL[a] cholesterol ≤ 2.5 mmol/l*

'NA' if patient is not prescribed any lipid-lowering therapy
'IDq' if information regarding prescription is missing
'YES' if applicable and both target values have been achieved
'NO' if applicable and both target values have not been achieved, also if one of the targets have been achieved but not the other
'NOj' if applicable and **'NO'** due to that
- duration of therapy is < 6 weeks
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but cholesterol values are missing

8	Patient with CHD and maintained on lipid-lowering therapy with one or both cholesterol values above therapy target: ❑ Total cholesterol > 4.5 mmol/l ❑ LDL[a] cholesterol > 2.5 mmol/l	*has had the lipid-lowering therapy amended* ❑ *dose increase* ❑ *change of drug* ❑ *added drug*

'NA' if either 1) patient is not prescribed lipid-lowering therapy or 2) both therapy targets have been achieved or 3) a justified reason for non-achievement of therapy goal is documented, i.e. **'NA'**, **'YES'** or **'NOj'** in no 6 above.
'IDq' if cholesterol values are missing
'YES' if applicable and amendments have been done
'NO' if applicable and amendments have not been done
'NOj' if applicable and **'NO'** due to
- duration of therapy (on new dose) is < 6 weeks
- maximum tolerated dose has been achieved so that additional lowering is not possible
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

ANTIHYPERTENSIVE AND CARDIOPROTECTIVE THERAPY (CRITERIA 9-14)

9 Patient with CHD — *is prescribed a β-blocker*

The criterion will always be applicable in patients with CHD and **'NA'/'IDq'** will not be relevant
'YES' if a β-blocker is prescribed
'NO' if a β-blocker is not prescribed
'NOj' if **'NO'** due to
- if patient has not experienced an MI (Non-STEMI or STEMI)
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if information regarding prescription is missing

10 Patient with CHD — has documented systolic blood pressure ≤ 130 and diastolic blood pressure ≤ 80 mmHg

The criterion will always be applicable in patients with CHD and **'NA'/'IDq'** will not be relevant
'YES' if both blood pressure target values are achieved
'NO' if both blood pressure target values are not achieved
'NOj' if **'NO'** but
- duration of therapy on new dose is < 4 weeks
- maximum tolerated dose has been achieved so that additional lowering is not possible
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but blood pressure values are missing/not accessible

11 Patient with CHD and with
❑ systolic blood pressure > 130 and/or
❑ diastolic blood pressure > 80 mmHg
— has had the antihypertensive regime amended:
❑ dose increased ❑ drug changed ❑ drug added

'NA' if either 1) both blood pressure targets have been achieved or 2) a justified reason for non-achievement is given, i.e. **'YES'** or **'NOj'** in no 9 above.
'IDq' if blood pressure values are missing/not accessible
'YES' if applicable and amendments have been done, tick the correct box.
'NO' if applicable and amendments have not been done
'NOj' if applicable and **'NO'** due to
- duration of therapy on new dose is < 4 weeks
- maximum tolerated dose has been achieved so that additional lowering is not possible
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

12	Patient with CHD and left ventricular systolic dysfunction (ejection fraction < 45%)	is prescribed an ❑ ACE[b]-inhibitor or an ❑ angiotensin receptor blocker

'NA' if patient is not diagnosed with heart failure (LSVD) with EF < 45 % or if information regarding EF or heart failure (LSVD) is missing in patient information profile
'IDq' if diagnoses concerning heart failure or EF value is unknown
'YES' if applicable and ACE-inhibitor or ARB is prescribed
'NO' if applicable and ACE-inhibitor or ARB is not prescribed
'NOj' if applicable and **'NO'** due to
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

13	Patient with CHD and diabetes mellitus with hypertension or nephropathy	is prescribed an ❑ ACE[b]-inhibitor or an ❑ angiotensin receptor blocker

'NA' if patient is not diagnosed with diabetes mellitus with either hypertension or nephropathy
'IDq' if diagnoses are missing
'YES' if applicable and ACE-inhibitor or ARB is prescribed
'NO' if applicable and ACE-inhibitor or ARB is not prescribed
'NOj' if applicable and **'NO'** due to
- GP advised
- an explicitly documented contraindication or intolerance (CI/I)
- documented allergy
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

14	Patient with CHD prescribed an angiotensin receptor blocker and not and ACE-inhibitor	has a documented contraindications/intolerances to the ACE[b]-inhibitor

'NA' if ARB is not prescribed, or if both ARB and ACEI is prescribed
'IDq' if information concerning medications are missing
'YES' if applicable and a documented contraindication / intolerance to ACEI is identified (e.g. side effects , allergy, contraindication of intolerance)
'NO' if applicable and a documented contraindication/intolerance to ACEI is *not* identified
'NOj' if applicable and **'NO'** due to
- GP advised
- documented prescriber choice
- documented patient choice

'IDs' if applicable but information regarding prescription is missing

GLYCEMIC CONTROL AND MODIFIABLE RISK FACTORS (CRITERIA 15-21)

15	Patient with CHD	has documented target values of ❑ Blood glucose ≤ 7.0 mmol/L or ❑ Hb_{A1c}[c] < 6.5 %

The criterion will always be applicable in patients with CHD in order to identify diabetes, and **'NA'/'IDq'** will not be relevant
'YES' if one or both values are documented below target
'NO' if one or both values are documented above target
'NOj' there will be no justified reasons, see criterion 20 below
'IDs' if blood glucose or HbA1c values are missing or not accessible

16	Patient with CHD and documented target values of ❑ Blood glucose > 7.0 mmol/L or ❑ Hb_{A1c}[c] > 6.5 %	has a documented new measurement of ❑ blood glucose or ❑ Hb_{A1c}[c]

'NA' if one or both values are below target value, i.e. **'YES'** in no 13 above
'IDq' if blood glucose of HbA1c values are missing or not accessible, i.e. **'IDs'** in no 13 above
'YES' if applicable and a new blood glucose measurement has been made
'NO' if applicable and no new blood glucose measurement has been made
'NOj' if applicable but
- HbA1c has been measured and found to be below target value
- HbA1c has been measure ≤ 3 months ago and found below target value

'IDs' if applicable, will become a **'NO'** if information regarding a new measurement is lacking

17	Patient with CHD who is a known smoker	has a record of receiving smoking cessation advice

'NA' if patient is a non-smoker
'IDq' if smoking status is unknown
'YES' if applicable and smoking cessation-advice has been given
'NO' if applicable and smoking cessation-advice has not been given
'NOj'/ IDs' – there's no justified reasons for non-adherence and **'IDs'** becomes a **'NO'**

18	Patient with CHD	has documented information concerning ❑ body weight ❑ height ❑BMI[d] or ❑ waist circumference

The criterion will always be applicable in patients with CHD and **'NA'/'IDq'** will not be relevant
'YES' if information regarding bodymass is documented. Tick the correct box.
'NO' if information regarding bodymass is missing
'NOj'/ IDs' – there's no justified reasons for non-adherence and **'IDs'** becomes a **'NO'**

19	Patient with CHD who is overweight (BMI[d] $\geq$ 30 kg/m^2)	has a record of receiving weight reduction advice

'NA' if patient is not overweight (BMI > 30)
'IDq' if information regarding bodymass and height/bmi is missing, i.e. **'NO'** in no 16
'YES' if applicable and weight reduction advice is documented
'NO' if applicable and no information concerning weight reduction advice is documented
'NOj'/ IDs' – there's no justified reasons for non-adherence and **'IDs'** becomes a **'NO'**

20	Patient with CHD	has a record of receiving dietary advice

The criterion will always be applicable in patients with CHD and **'NA'/'IDq'** will not be relevant
'YES' if dietary advice is documented
'NO' if dietary advice is not documented
'NOj'/ IDs' – there's no justified reasons for non-adherence and **'IDs'** becomes a **'NO'**

21	Patient with CHD	has a record of receiving exercise advice

The criterion will always be applicable in patients with CHD and **'NA'/'IDq'** will not be relevant
'YES' if exercise advice is documented
'NO' if exercise advice is not documented
'NOj'/ IDs' – there's no justified reasons for non-adherence and **'IDs'** becomes a **'NO'**

APPENDIX F

Cohen’s kappa (κ) calculation – an overview

AGREEMENT MATRIX FOR TWO MAT-CHDSP APPLICATORS

		Observer 2						
		Yes	**No**	**Nj**	**IDs**	**IDq**	**NA**	**Total**
Observer 1	**Yes**	A_{11}	A_{12}	A_{13}	A_{14}	A_{15}	A_{16}	R_1
	No	A_{21}	A_{22}	A_{23}	A_{24}	A_{25}	A_{26}	R_2
	Nj	A_{31}	A_{32}	A_{33}	A_{34}	A_{35}	A_{36}	R_3
	IDs	A_{41}	A_{42}	A_{43}	A_{44}	A_{45}	A_{46}	R_4
	IDq	A_{51}	A_{52}	A_{53}	A_{54}	A_{55}	A_{56}	R_5
	NA	A_{61}	A_{62}	A_{63}	A_{64}	A_{65}	A_{66}	R_6
	Total	C_1	C_2	C_3	C_4	C_5	C_6	**N**

Nj = justified non-adherence, IDs = insufficient data to answer the standard, IDq = insufficient data to know whether the criterion is applicable, NA = not applicable. 'A' represents the number of applications in the different categories, 'R' the rank sum and 'C' the colon sum. N is the total rank or colon sum.

Based on the application matrix, Cohen's kappa (κ) is calculated as:

$$\kappa = \frac{Po - Pc}{1 - Pc}$$

,where exact agreement, $Po = \frac{1}{n}\sum_{i=1}^{6} a(i)(i)$ and random agreement, $Pc = \frac{1}{n}\sum_{i=1}^{6} r(i)c(i)$

[$r_{(i)} = \sum_{j=1}^{6} a(i)(j)$ and $c_{(j)} = \sum_{i=1}^{6} a(i)(j)$]

INTERPRETATION OF κ-VALUES (1)

Excellent when	κ ≥ 0.75
Good when	κ = [0.6 – 0.75]
Satisfactory when	κ = [0.4 – 0.6]
Poor when	κ < 0.4

(1) Robson C. Real world research. A resource for social scientists and practitioner-researchers. 2nd ed. Malden: Blackwell Publishing; 2002.

APPENDIX G

The semi-structured interview guide

INTERVIEW GUIDE

Before the interview, the following information will be given:

- ☐ Me and my master student project
- ☐ The background of the project
- ☐ Time aspect of the interview
- ☐ Information about pauses and drinking
- ☐ Tape recording information
- ☐ Deletion of data if wanted
- ☐ Anonymity, confidentiality of the data
- ☐ Notes taken under the interview, to remember important things
- ☐ There are some fields that I would like to dig into, however, it is important that you speak freely, I'm interested in your experiences
- ☐ It's YOUR experience that is in my interest

Opening question:

"Can you tell me about the follow-up you receive from the pharmacist?"

Themes to explore during the interview:

Patients' knowledge about medications

Feeling of safety and comfort with medications

The CP's role in the interdisciplinary team

The functionality of the follow-up program

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