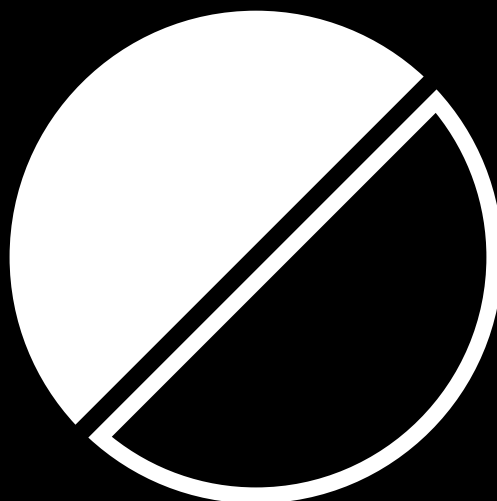


Thesis for doctoral degree (Ph.D.)

2019

EVERY COIN HAS TWO SIDES

The challenge of addressing inappropriate prescribing
in older patients in primary care



Katharina Schmidt-Mende



**Karolinska
Institutet**

From the Department of Neurobiology, Care Sciences and Society
Karolinska Institutet, Stockholm, Sweden

EVERY COIN HAS TWO SIDES

The challenge of addressing inappropriate prescribing in older patients in primary care

Katharina Schmidt-Mende



**Karolinska
Institutet**

Stockholm 2019

Cover illustration by Joel Sigurdsson

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet.

Printed by Arkitektkopia AB, 2019

© Katharina Schmidt-Mende, 2019

ISBN 978-91-7831-416-4

EVERY COIN HAS TWO SIDES

The challenge of addressing inappropriate prescribing in older patients in primary care

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Katharina Schmidt-Mende

Principal Supervisor:

**Medicine doktor
Jan Hasselström, PhD**
Karolinska Institute
Department of Neurobiology,
Care Sciences and Society
Division of Family Medicine
and Primary Care

Co-supervisor(s):

**Associate professor
Björn Wettermark**
Karolinska Institute
Department of Medicine, Solna
Centre for Pharmacoepidemiology

**Professor
Morten Andersen**
University of Copenhagen
Department of Drug Design
and Pharmacology
Faculty of Health and
Medical Sciences

Opponent:

**Professor
Bruce Guthrie**
University of Edinburgh
Usher Institute of Population
Health Sciences and Informatics

Examination Board:

**Associate professor
Hugo Lövheim**
University of Umeå
Department of Community
Medicine and Rehabilitation
Division of Geriatric Medicine

**Professor
Cecilia Stålsby-Lundborg**
Karolinska Institute
Department of Public
Health Sciences
Division of Global Health

**Professor
Anders Wimo**
Karolinska Institute
Department of Neurobiology,
Care Sciences and Society
Division of Neurogeriatrics

ABSTRACT

Background: Drug-related morbidity contributes to every tenth unplanned hospital admission in older patients. A way to address this problem is to identify and minimize potentially inappropriate prescribing (PIP). Two important types of PIP are the use of contraindicated or excessively dosed drugs in patients with renal impairment and drug-disease interactions, where a drug worsens a concomitant disease. It is largely unknown *how commonly* older patients (≥ 65) are exposed to these two types of PIP. Similarly, there is insufficient knowledge on *how* general practitioners (GPs) and nurses in primary care should *address* PIP in their older patients. One important step in *understanding* how to *address* PIP is to investigate GPs' and nurses' views on PIP and medication reviews.

Aim: 1) To increase knowledge on *how commonly* older patients in primary care are exposed to PIP in relation to renal function and drug-disease interactions; 2) To examine if an intervention on medication reviews combining several evidence-based educational strategies is a valuable measure *to address* PIP in primary care; and 3) *To understand* GPs' and nurses' views on PIP and medication reviews.

Material and methods: Two cross-sectional population-based studies (I+II) in patients aged ≥ 65 in primary care in Stockholm County were performed. Drug dispense was assessed during one year. PIP in relation to renal function was assessed in patients with chronic kidney disease stage 3 (n=30 372) or 4 (n=2161) according to CKD-EPI formula (I). Drug-disease interactions were analyzed among 336 295 patients. PIP was *addressed* in a cluster-randomized controlled trial including 69 primary care practices (III). The multifaceted educational intervention targeted GPs and nurses, with the aim to promote medication reviews in accordance with a new regulation, thus reduce PIP and unplanned healthcare use. Data (I-III) were derived from regional and national registers (diagnoses, drugs, healthcare use) and SCREAM database (creatinine). Qualitative data were collected after each educational session and explored with thematic analysis (IV).

Results: I: Contraindicated medicines were used by 9% of patients with chronic kidney disease stage 3 compared to 38% with stage 4, and excessive dosing was present in 43% vs. 58%, respectively. II: Drug-disease interactions were found in 10.8 % of older adults, the most common was hypertension/NSAID. I+II: A limited number of potentially inappropriate medicines explained the majority of PIP, such as NSAIDs (I + II) and drugs acting on the renin-angiotensin-aldosterone system (I). III: Neither PIP nor unplanned healthcare decreased after a multifaceted educational intervention in primary care. IV: A possible explanation for this result is the complexity of prescribing in older patients, as expressed by GPs and nurses.

Conclusions: In patients with impaired renal function, excessive dosing was more common than the use of contraindicated medicines. Drug-disease interactions were less common than PIP in relation to renal function. Both types of PIP seem manageable as only a few medicines are implicated. Medication reviews that address PIP in its entirety are difficult to implement in primary care and may not improve prescribing in older patients. According to GPs and nurses, the complexity of PIP is a major challenge. Their efforts to improve prescribing are undermined by this complexity. In view of the potential harm of PIP in older patients, it is crucial to continue research on how it may be decreased.

LIST OF SCIENTIFIC PAPERS

- I Schmidt-Mende K, Wettermark B, Andersen M, Elsevier M, Carrero JJ, Shemeikka T, Hasselstrom J. Prevalence of renally inappropriate medicines in older people with renal impairment – a cross-sectional register based study in a large primary care population. *Basic Clin Pharmacol Toxicol*. 2019 Mar;124:256-65.
- II Schmidt-Mende K, Andersen M, Wettermark B, Hasselstrom J. Drug-disease interactions in older patients in primary care – observational register study (*manuscript*)
- III Schmidt-Mende K, Andersen M, Wettermark B, Hasselstrom J. Educational intervention on medication reviews aiming to reduce acute healthcare consumption in elderly patients with potentially inappropriate medicines-A pragmatic open-label cluster-randomized controlled trial in primary care. *Pharmacoepidemiol Drug Saf*. 2017;26:1347-56.
- IV Schmidt-Mende K, Hasselstrom J, Wettermark B, Andersen M, Bastholm-Rahmner P. General practitioners' and nurses' views on medication reviews and potentially inappropriate medicines in elderly patients – a qualitative study of reports by educating pharmacists. *Scand J Prim Health Care*. 2018;36:329-41.

These articles will be referred to in the text by their roman numerals I–IV. All published articles were reproduced with permission from the copyright holders. All three published articles (I, III, IV) have a supplementary file. These are not included in the thesis, but are available as online resources. Moreover, the manuscript (II) has a supplementary file. It is in parts included in the thesis.

LIST OF ABBREVIATIONS AND DEFINITIONS

ACE-inhibitor	Angiotensin-converting-enzyme inhibitor
ADR	Adverse drug reaction
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation; formula to calculate eGFR
DDSI	Drug-disease interaction: drug that “worsens a pre-existing condition” (quoted from (48))
EGFR	Estimated glomerular filtration rate
GP	General practitioner
Potentially inappropriate prescribing (PIP) in relation to renal function	This term includes medicines that are contraindicated as well as medicines that should be dose-adjusted in patients with impaired renal function
Janusmed	Janusmed Drugs and Renal function: computerized decision support tool for clinicians in Stockholm County that permits to identify PIP in relation to renal function
MR	Medication review
NSAIDs	Non-steroidal anti-inflammatory drugs
PIMs	Potentially inappropriate medicines
PIP	Potentially inappropriate prescribing
Practice	Primary care practice
RAAS	Renin-angiotension-aldosterone system
Renal PIP/PIMs	Potentially inappropriate prescribing/medicines in relation to renal function
SCREAM	Stockholm CREATinine Measurements (SCREAM) database
Swedish criteria	Swedish criteria of potentially inappropriate prescribing in older patients (1)

CONTENTS

1	PROLOGUE	1
2	BACKGROUND	2
2.1	The older patient	2
2.2	The complexity of medical care in older patients	3
2.3	Primary care and its key role in the care of older patients	4
2.4	What is potentially inappropriate prescribing, and why is it problematic?	4
2.4.1	The Swedish criteria of potentially inappropriate prescribing	7
2.4.2	Potentially inappropriate prescribing in relation to renal function	7
2.4.3	Drug-disease interactions	8
2.5	Prevalence of potentially inappropriate prescribing	8
2.5.1	Prevalence of potentially inappropriate prescribing in relation to renal function	9
2.5.2	Prevalence of drug-disease interactions	9
2.6	Who is at risk for adverse drug reactions?	9
2.7	How to address potentially inappropriate prescribing	10
2.7.1	Potentially inappropriate prescribing – general practitioners’ perspective	10
2.7.2	Interventions to improve potentially inappropriate prescribing	11
2.7.3	Where and how are interventions aiming to improve potentially inappropriate prescribing conducted?	14
2.7.4	Multifaceted educational interventions in primary care	14
2.8	Process evaluation of complex trials	18
3	AIM AND RESEARCH QUESTIONS	19
3.1	Overall aims	19
3.2	Contents of thesis	19
3.3	Research questions	20
4	RESEARCH METHODS AND MATERIAL	21
4.1	<i>How common</i> is potentially inappropriate prescribing?	21
4.1.1	Study design	21
4.1.2	Study population	21
4.1.3	Study I: Definition of potentially inappropriate prescribing in relation to renal function	22
4.1.4	Study II: Definition of drug-disease interactions	22
4.2	Data sources	23
4.2.1	Statistical considerations	24
4.3	<i>How to address</i> potentially inappropriate prescribing in clinical practice?	24
4.3.1	Study design and study population (III)	24
4.3.2	Data material	28
4.3.3	Definition of potentially inappropriate prescribing (III)	29

4.3.4	Outcomes	29
4.3.5	Statistical considerations	30
4.4	Ethical considerations	31
5	RESULTS	32
5.1	<i>How common</i> is potentially inappropriate prescribing?	32
5.1.1	Prevalence of potentially inappropriate prescribing in relation to renal function (I)	32
5.1.2	Prevalence of drug-disease interactions (II)	33
5.2	<i>How to address</i> potentially inappropriate prescribing?	35
5.2.1	Effects of multifaceted educational intervention (III)	35
5.2.2	GPs' and nurses' views on potentially inappropriate prescribing and medication reviews (IV)	37
6	DISCUSSION	40
6.1	Main findings	40
6.2	How do the main findings fit in?	40
6.2.1	Prevalence of potentially inappropriate prescribing	40
6.2.2	Physicians prescribe carefully, but there is room for improvement	42
6.2.3	Prescribing did not improve – why?	43
6.3	Strengths and limitations	44
6.3.2	Register data (I–III)	45
6.3.3	Renal function (I)	47
6.3.4	Diaries as a data source (IV)	47
6.3.5	Definition of potentially inappropriate prescribing (I-III)	48
6.4	How may the findings be useful for general practitioners and nurses?	49
6.5	Future perspectives	49
6.5.1	Understanding	49
6.5.2	How common?	50
6.5.3	How to address?	50
6.6	Every coin has two sides	50
6.7	Conclusions	51
7	EPILOGUE	52
8	ACKNOWLEDGEMENTS	53
9	REFERENCES	55

1 PROLOGUE

She walked slowly from the waiting room into my office. She was paler and more breathless than the last time I had met her two months ago. Sitting down heavily on the chair, she said: *“I feel so tired, doctor. My sleeping pills only work for two hours and then I wake up. Isn't there anything stronger? And I have to go to the toilet several times during the night. You know, my husband died in February and I feel alone, I am afraid to fall and lie on the floor the whole night. Who would notice?”*. I listened carefully, thinking by myself that – once again – the consultation time would not be sufficiently long to thoroughly evaluate her complaints... I knew that she suffered from heart failure and diabetes, urinary incontinence after having given birth to three children, was obese, had smoked but had been able to quit, had chronic back pain, and that her daughter had phoned me recently to express her concerns about her mother getting forgetful. According to the electronic patient journal she was treated with 11 drugs, among others zopiclone, enalapril, furosemide, metformin and paracetamol. I started to examine her, took a blood pressure and pulse, and deemed them to be normal. Were her ankles more swollen than the last time we had met? I suspected that her complaints were partly due to her heart failure, but wondered if she also was depressed? Did she really take all the medicines on her list? Could her complaints be due to side effects?

2 BACKGROUND

2.1 The older patient

Older people are a growing population group. In 2050, every fourth person is expected to be 65 or older (2). Drug treatment is one reason to why more and more people reach old age. The benefits of drugs in older patients are numerous. Drugs reduce symptoms, such as for example antidepressants (3). Drugs treat risk factors, such as antihypertensives (4). Drugs prevent complications of diseases, such as warfarin reducing the risk of stroke in patients with atrial fibrillation. Drugs may delay death, such as antibiotics, or increase survival rates, such as ACE-inhibitors in patients with heart failure (5). Moreover, drugs may improve poor quality of life, such as opioids reducing pain.

Parallel with age, the number of diseases increase. Multimorbidity, defined as the presence of two or more diseases at the same time, is more common than suffering from a single disease (6). Problematically, prescribing guidelines generally focus on single diseases (7, 8). Drug treatment according to guidelines in a 72 year old male obese patient with heart failure after myocardial infarction, diabetes and benign prostate hyperplasia would add up to at least 9 medicines administered as several doses at different time points during the day (such as: acetyl salicylic acid, statin, enalapril, furosemide, betablocker, metformin, glimepiride, alfuzosin, finasterid), which illustrates that polypharmacy is the rule rather than the exception in older age (7). In western countries, every third older adult is treated with five or more substances on a regular basis (9, 10).

The more drugs a person uses, the higher the risk for adverse drug reactions and consequently drug-related morbidity. Older patients are particularly prone to experiencing adverse drug reactions. This is due to age-related pharmacokinetic and pharmacodynamic changes. Pharmacokinetics relate to the absorption, distribution and elimination of a substance, whereas pharmacodynamics refer to the physiologic effects of a drug (11). An example of pharmacokinetic changes in older age is the decrease of renal plasma flow and glomerular filtration rate which favors the accumulation of renally cleared drugs such as ACE-inhibitors. Examples for pharmacodynamic changes are the higher sensitivity for benzodiazepines in older compared to younger patients favoring side effects such as dizziness and sedation; and the impairment of blood pressure regulation due to increased vessel stiffness making falls more likely.

2.2 The complexity of medical care in older patients

Drug-related morbidity contributes to every tenth unplanned hospital admission in older patients (12, 13). The verb “contributes” instead of “causes” accounts for the uncertainty of a causal relationship between the exposure to a (potentially inappropriate, thus harmful) drug and an (undesired) adverse drug reaction (14). The clinician who evaluates an older patient will only rarely be sure if a symptom or abnormal laboratory test is caused by a drug or the underlying disease. An example is hyponatremia in patients with heart failure and diuretics. It is crucial to be aware of this complexity. Figure 1 illustrates the relationship between morbidity, drug use, PIP and unplanned healthcare in older patients.

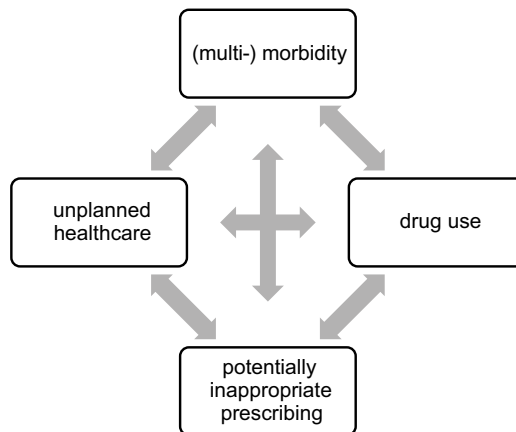


Figure 1. Relationship between (multi-) morbidity, drug use, potentially inappropriate prescribing and unplanned healthcare in older patients.

(Multi-) morbidity leads to drug use. The more drugs are used, the higher the risk for PIP which in its turn may cause new symptoms and entail the prescription of more drugs (15) (16), cause unplanned healthcare or further morbidity. Multimorbidity itself is also associated with unplanned healthcare, and vice versa may inpatient healthcare cause illness (such as falls (17) or nosocomial infections (18)), or lead to the prescription of more (appropriate and inappropriate) drugs. Even if drugs are used in a rational way they may cause unplanned healthcare (for example first-time allergic reaction to antibiotics).

2.3 Primary care and its key role in the care of older patients

Older patients with many comorbidities are often treated and followed up in primary health care (19). Primary health care in Sweden is provided by public and private general practices which both are publicly financed (20). Patients may consult a specialist without being referred from a GP, as primary care does not have a gate-keeper function (21). However, when people experience a health problem, they first of all consult a GP or nurse at a primary care practice. In Stockholm County, nine out of ten adults aged ≥ 65 are registered at a practice and meet a GP on average 3.8 times a year (22). All residents have access to health care for low patient fees. A considerable amount of prescribing to older patients is performed by primary care professionals (figure 2). Still, older patients even receive prescriptions from hospitals or specialists other than GPs (23). Formally, Swedish primary care is not responsible for the patient's drug list in its entirety (24).

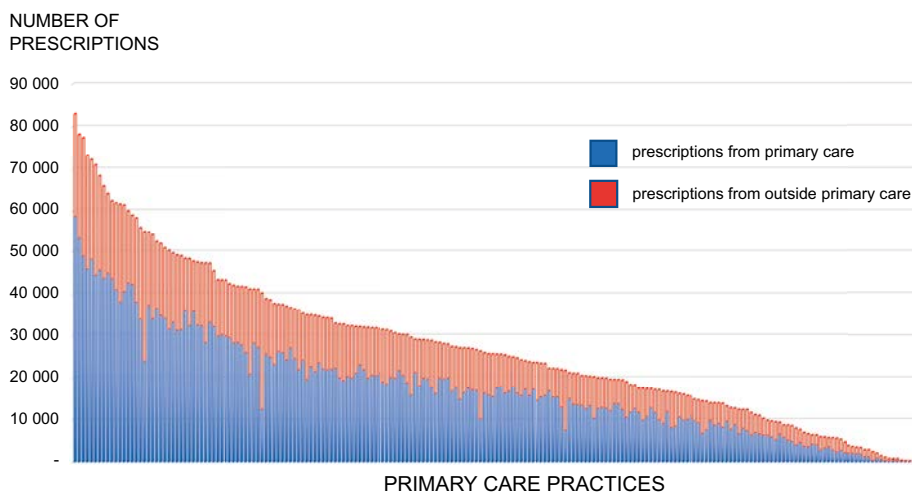


Figure 2. Who prescribes to older patients registered with a primary care practice in Stockholm County? Each bar corresponds to a primary care practice. (Data extracted from Stockholm County's Regional healthcare data Warehouse (25)).

2.4 What is potentially inappropriate prescribing, and why is it problematic?

Since the early 1990's up to now, the significance of the term "*potentially inappropriate prescribing*" has undergone a transformation. Initially, PIP referred to misprescribing and the use of "too many inappropriate drugs". The first criteria for PIP, the Beers Criteria from 1991, focused on misprescribing. These criteria included 30

indicators. Nineteen indicators related to drugs that should be avoided such as long-acting benzodiazepines, and eleven to inappropriate drug dosages, frequencies or durations of drug treatment such as “ranitidine at dose > 300mg/day and duration > 12 weeks” (26). Beers criteria were developed in the US based on expert opinions and thus do not entirely match European settings. Subsequently, other criteria were developed in different countries (27, 28) or original criteria were updated (29-31), reflecting a more holistic view on PIP.

Besides *misprescribing* even *overprescribing* and *underprescribing* (also called “*potential prescribing omissions*”) are now considered potentially inappropriate (27). In particular underprescribing has gained increased interest, as unplanned hospital admissions have been associated with under- rather than misprescribing (32). The term “*appropriate use of polypharmacy*” illustrates that polypharmacy does not *per se* have a negative significance (33). From a clinical point of view this holistic approach seems valid.

PIMs may be categorized into different groups: 1) drugs that should be avoided (such as longacting benzodiazepines, drugs with anticholinergic effects) 2) drugs that are inappropriate in impaired renal function (such as NSAIDs), 3) drug-drug interactions (such as warfarin and paracetamol), and 4) drug-disease interactions (such as betablocking agents in patients with asthma). Of note, there is overlap between the different PIM groups. For example, NSAIDs are contraindicated in severely impaired renal function (group 2), may interact with warfarin and increase risk for bleeding (group 3), and may worsen heart failure (group 4).

PIP criteria may be explicit or implicit (27, 34). Explicit criteria are developed based on consensus processes, literature searches and expert opinions. They comprise drug classes, drug dosages or drug combinations that should be avoided due to an increased risk for adverse effects, such as long-acting benzodiazepines. One important disadvantage of explicit criteria is that they do not consider the burden of comorbidity frequently present in older patients. Examples for explicit criteria are the abovementioned American Beers criteria (29), the German PRISCUS list (35), the Canadian McLeod criteria (36), the Irish STOPP/START criteria (37), the Swedish criteria (1, 38) or the European FORTA criteria (39).

Implicit indicators rely on the judgment of the clinician, and PIP is assessed at an individual level. One example is the *Medication Appropriateness Index* (MAI) (40), a weighted appropriateness score assessing several prescribing dimensions, such as the indication of drug treatment, drug dose and drug-disease interactions.

There are two important reflections in relation to different PIP criteria.

First, they are a collection of PIMs, drug combinations, and drug-disease combinations, but only few of them have been tested prospectively in older patients. In other words, it is uncertain to which extent adverse drug reactions will be pre-

vented if older patients' drug treatment follows the criteria. One exception are the Irish STOPP/START criteria containing 114 indicators whereof 80 refer to misprescribing (STOPP criteria) and 34 to underprescribing (START criteria) (37). Clinical outcomes seem to improve when drug treatment is optimized following STOPP/START criteria (41-43). Moreover, the complementary use of Beers and STOPP/START criteria has shown to have modest predictive validity in relation to the detection of adverse drug reactions and unplanned health care consumption (44).

Second, GPs face high demands of efficiency. They may find that extensive criteria are too detailed and time-consuming (45). Studies evaluating the clinical impact of PIP criteria often include pharmacist support, a resource which is rarely available in primary care. Positive results shown in studies including pharmacist support may therefore not simply be extrapolated to the primary care setting.

Table 1. Similarities and differences between the Swedish criteria (version 2010) and STOPP-START criteria (version 2015)

		Swedish criteria	STOPP-START criteria
Similarities	Overall construction of criteria	Two sections "stopp" (misprescribing) and "start" (mainly underprescribing)	
	Drug-disease interactions	No separate list of <i>drugs that may worsen a pre-existing condition</i> (quoted from (48)) (drug-disease interactions)	
Differences	Underlying approach	Rather pharmacological (indicators are grouped by pharmacological characteristics, for example separate chapter on drug-drug interaction)	Rather clinical (indicators are grouped by morbidity, for example "cardiovascular system criteria")
	Focus	Focus on "drugs to avoid" without taking into account morbidity	Focus on drug treatment in relation to morbidity
	Validity	Not prospectively validated	Validated in several studies
	PIP in relation to renal function	Separate list of 29 drugs/drug groups, but recommendations do not include concrete levels of renal function	Chapter E in STOPP includes 6 drugs that are inappropriate below a concrete level of renal function
	Specific recommendations	"concomitant use of potassium and potassium-sparing agents (for example, amilorid or spironolactone), if there are no special reasons for this combination (intolerance against spironolactone or amilorid)"	"Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months)."

PIP potentially inappropriate prescribing, ACEI Angiotensin-converting-enzyme inhibitor, ARB Angiotensin II Receptor Blockers.

2.4.1 The Swedish criteria of potentially inappropriate prescribing

In 2004, the Swedish National Board of Health and Welfare released the first version of the Swedish criteria of PIP (46) based on American Beers Criteria (26) and Canadian McLeod Criteria (36). This list was updated twice in 2010 (1, 38) and 2017 (47). The Swedish criteria comprise two sections, namely a misprescribing and an underprescribing section. For similarities and differences between the Swedish criteria and STOPP-START criteria see table 1.

Contrary to Beers Criteria, neither the Swedish criteria nor STOPP-START criteria include a specific list of drug-disease interactions defined as “*drugs that may worsen a pre-existing condition*” (quoted from (48)).

2.4.2 Potentially inappropriate prescribing in relation to renal function

Impaired renal function plays a major role in the context of adverse drug reactions (49, 50). Some PIP criteria (29, 37) include a section on PIP in impaired renal function, but the specific substances differ substantially. For example, Beers’ Criteria list 20 substances that should be dose-reduced or are contraindicated in renal impairment, yet a commonly used drug like metformin is not part of this list (29). Irish STOPP/START criteria include only six contraindicated drugs whereof one is metformin that should not be given below an eGFR of 30ml/min (37). Moreover, there are substantial differences regarding recommendations on drug dosing (51). Surprisingly, there is no internationally recognized list of renal PIMs.

From a clinical point of view, it seems important that the definition of renal PIMs not only includes drug dosing and contraindicated drugs (as is the case in the abovementioned criteria) but also: 1) follow-up of electrolytes and/or renal function (such as spironolactone) 2) nephrotoxicity (such as aminoglycosides), 3) harm by active metabolites (such as morphine), and 4) lack of effectiveness in highly impaired renal function (such as hydrochlorothiazide).

In order to create a list of renal PIMs that takes into account the different categorizations presented above, we compared seven literature sources (52-58). Finally, the attempt to create a synthetic list was abandoned due to two findings: 1) the majority of drugs included in the final list are only rarely used in primary care, 2) there is only limited overlap between the literature sources (52-58), implying that there is no clear-cut and generally applicable definition of renal PIP.

In Stockholm County, clinicians use “Janusmed Drugs and Renal function”, a comprehensive knowledgebase with evidence based recommendations on drug use in the context of impaired renal function. Janusmed relies on Finnish Renbase® and is integrated in the electronic medical record (see chapter 4.3.1 for details) (59).

2.4.3 Drug-disease interactions

According to Pugh et al (48), a drug-disease interaction is present when a drug prescribed to treat one of a patient's diseases at the same time may "*worsen a pre-existing condition*" (quoted from (48)). One example for such a DDSI is the use of NSAIDs against osteoarthritic pain in a patient who also has heart failure. This interaction may be critical as NSAIDs may worsen heart failure and cause unplanned healthcare (60).

Similar as for renal PIMs, there is no universally applicable list of DDSIs. Most PIP criteria do not include DDSIs as a specific category but have incorporated them in the overall list of PIMs (37). In Sweden, clinicians consult the Swedish medical products list (61) when they screen for DDSIs.

2.5 Prevalence of potentially inappropriate prescribing

The prevalence of PIP has been assessed in numerous settings, populations and countries. Every second hospitalized older patient (62), home care patient (63) and nursing home resident (64) may be exposed to PIP.

As the majority of prescribing to older patients happens in primary care (figure 2), it seems crucial to analyze the prevalence of PIP in an outpatient setting. Two systematic reviews conclude that approximately 20% of older community-living patients are exposed to PIP (65, 66). Drug groups commonly associated with preventable unplanned hospital admissions are antiplatelets, NSAIDs, diuretics (67), hypoglycaemic agents and central nervous system agents (68). Diagnoses that may evoke drug-related morbidity are for example hypotension, bleeding, heart failure, renal failure and electrolyte disturbances (68) (69). Of note, every second drug-related hospital admission may be preventable (70) (71).

Single-study prevalence rates of PIP in the outpatient setting vary considerably between 17 % (72) and 94% (73). There are two explanations for these heterogeneous results.

First, the definition of PIP differs substantially between studies. The majority of studies use explicit Beers (26, 29, 30) or STOPP/START criteria (37), whereas few studies use implicit MAI criteria (40). The prevalence of PIP tends to be higher when using implicit compared to explicit criteria (>90% vs. 20%) (65). Some studies only assess one category of PIP, as for example DDSIs (74) or renal PIMs (50). Another observation is that the majority of studies focus on misprescribing or overprescribing, whereas underprescribing is only rarely taken into account. This is partly explained by the lack of clinical data in many studies.

Second, different data sources are used such as medical records, insurance data, prescription databases or administrative healthcare databases. An important advantage of medical records data is that clinical and laboratory information is available. Many PIMs need clinical data for proper assessment. On the other hand, only small samples of patients may be analyzed which hampers generalizability. Advantages of the use of databases are the relative ease of data collection and the possibility to analyze large populations without selection or recall bias. Furthermore, such data can easily be reproduced and may serve as a valuable source for feedback on prescribing, as recently shown in a Scottish study in primary care (75). However, an important disadvantage of register data is that mainly explicit criteria may be analysed.

There have been conflicting results regarding the trend of the overall prevalence of PIP in older patients during the last two decades. According to a systematic review (65), it has remained stable around 20% which is somewhat surprising in view of numerous attempts to reduce PIP in older patients (76). Other studies suggest slight decreases (10) or increases (77, 78).

2.5.1 Prevalence of potentially inappropriate prescribing in relation to renal function

According to a recent systematic review (79), there are twelve studies on the prevalence of renal PIP in older community-dwelling residents with impaired renal function (79). Participants were in mean between 71 and 85 years old. Different definitions of renal PIP were applied, and the formula used to calculate eGFR varied. These differences in study design explain that the observed prevalences varied between 1% to 37%.

2.5.2 Prevalence of drug-disease interactions

Little is known on the prevalence of drug-disease interactions in older patients. We are aware of one systematic review from 2013 including eight studies (80) together with five studies published since 2013 (81-85). The heterogeneity of definitions of DDSIs as well as different settings are major explanations for the range in prevalence of 3% (86) to 50% (82). Nursing home residents are more often exposed to DDSIs (50% (82)) than community-dwelling older patients (15-20%) (81, 83).

2.6 Who is at risk for adverse drug reactions?

In order to target interventions aiming to reduce preventable drug-related morbidity in older patients, it is important to identify risk factors for PIP and adverse drug reactions.

PIP is associated with polypharmacy (65, 87). Parallel with the number of drugs the likelihood of PIP (65) and in particular drug-drug interactions increases (9, 88). Data regarding the association of sex, age and burden of comorbidity on the one hand and PIP on the other hand are conflicting (65). Examples for practice characteristics that are associated with PIP are male sex of the prescriber (89) and localisation in an urbanized area (90).

Observational studies in older adults visiting the emergency department for drug-related morbidity have shown that patients at risk are older, to a larger extent female (69), nursing home residents (91), have impaired renal function (92), are treated with more than five drugs (69) with prescriptions by multiple specialists (93), have recently started a new high-risk drug (69), or are treated with a PIP according to STOPP/START criteria (43).

2.7 How to address potentially inappropriate prescribing

2.7.1 Potentially inappropriate prescribing – general practitioners' perspective

GPs experience that single disease guidelines induce PIP (45, 94-96) because most of their older patients are multimorbid (6). GPs have to compromise between evidence-based and patient-centered care and may feel pressure from patients to prescribe, or pressure to please the patient (97). Furthermore, they may maintain PIP because they are aware of less-than-ideal care situations, such as the home-dwelling patient with mild dementia who has an indication for insulin treatment but refuses help of home care nurses (97). The communication between primary and secondary care are suboptimal making it difficult to question indications for drug treatment (96, 98, 99). Of note, GPs do not agree on their responsibility for the entire drug list and may not want to question drug prescriptions released by other specialists (24).

During the process of deprescribing, GPs evaluate risk and benefit of a drug treatment and take into account the patient's quality of life and life expectancy (100). However, GPs may have negative experiences in relation to deprescribing, especially when coming to e.g. hypnotics and sedatives (101). Thus, they may rather maintain the status quo of drug treatment than deprescribe (102).

GPs question the utility of criteria to measure PIP as these often do not take into account the complexity of prescribing (103). Furthermore, they experience that PIP criteria as for example STOPP/START criteria are not applicable in primary care, as they are too vast and time-consuming (45, 101). At the same time, GPs demand simple measures to reduce PIP (45).

2.7.2 Interventions to improve potentially inappropriate prescribing

In view of the gap between theoretical knowledge and its actual application by healthcare professionals (104) it is an interesting and highly relevant question what is likely to bring about change in clinical practice. This is what implementation research is about: *“to understand what, why, and how interventions work in “real world” settings and to test approaches to improve them”* (cited from (105)). Such interventions may be categorized into professional-oriented, organizational, financial or regulatory ones (106). Examples of professional and organizational interventions in the context of PIP in older patients are summarized in table 2. Of note, financial incentives and regulatory interventions are mainly used in combination with professional-oriented or organizational interventions. Financial incentives are a powerful tool to improve clinical performance, but changes tend to cease when the incentive is removed (107). Neither financial nor regulatory interventions increase understanding.

An important characteristic of professional-oriented interventions such as medication reviews is that the entire drug list is evaluated for PIMs, whereas organizational interventions rather focus on a limited number of severe and frequent PIMs.

A systematic review identified 31 studies that analyzed the effectiveness of medication reviews as an isolated short-term intervention (109). In 26 out of 31 studies pharmacists performed the medication review and either gave prescribing recommendations to physicians, or acted as part of a multidisciplinary team (109). The physician finally decided if and in what way drug treatment should be modified. Only two out of 31 studies (109) dealt with physician-led medication reviews with the physician not being the researcher himself (117, 118). The way in which medication reviews were performed differed substantially between studies or was not sufficiently described. Four studies performing medication reviews based on STOPP/START criteria found a reduction of falls, delirium episodes, healthcare visits and length of hospital stay (42). However, according to two systematic reviews the clinical utility of medication reviews must be questioned despite slight improvements in prescribing and clinical outcomes shown in some single studies (108, 109).

Since 2012, physicians in Stockholm County have been required to perform and register medication reviews in older patients on a regular basis (see chapter 4.3.1). Collaboration with other healthcare professionals such as nurses, other specialists or pharmacists has been encouraged. The effects of such medication reviews on the quality of prescribing and patient-related outcomes have not been studied, and there is limited knowledge on how healthcare professionals in primary care in Stockholm experience the work with medication reviews.

Table 2. Examples of interventions that have been used to improve prescribing in older patients

	Intervention	Who intervenes	What is done and how	Studies or systematic reviews describing intervention
Professional-oriented strategies: How, when and where healthcare is organised and delivered, and who delivers healthcare ¹	Medication review	pharmacist alone or as part of a multidisciplinary team	pharmacist reviews medications and gives recommendations to physician who decides if changes in drug treatment are performed	Christensen 2016 (108) Huiskes 2017 (109)
		physician	physician reviews medications and changes drug treatment	Gallagher 2011 (41)
	Good Palliative-Geriatric Practice algorithm	physician	physician reviews medication and focuses on indication and effectiveness of drug treatment, possible adverse effects and dosing	Campins 2017 (110) Garfinkel 2010 (95)
	Computerized support systems	physician	computer applications that help clinicians to make therapeutic decisions, for example recommendations on drug dosing in patients with impaired renal function (111)	Grol 2003 (112) Bryan 2008 (113)
Organizational measures: Interventions that bring about changes in healthcare organisations, the behaviour of healthcare professionals or the use of health services by healthcare recipients ¹	Academic detailing/ educational outreach visits	tutors and healthcare professionals	tutor visits healthcare professionals at their working place and provides information on how to change practice, for example how prescribing may be improved	O'Brien 2008 (114) Grol 2003 (112)
	Feedback on performance	tutors and healthcare professionals	healthcare professionals are provided feedback on how they performed, for example their quality of prescribing	Ivers 2012 (115)
	Reminders	healthcare professionals	healthcare professionals are provided documents that remind them of an intended change in practice	May 2015 (116)
	Local consensus processes, interactive meetings	group of healthcare professionals with/without tutor	healthcare professionals agree on the necessity of a change of practice and on the way in which changes should be done	May 2015 (116) Grol 2003 (112)

¹ Cited from (106)

Medication reviews aim to achieve “pharmacological appropriateness”. In view of the complexity of PIP this implies a heavy workload which may be not be justified as one third of drug-related problems in older patients in primary care may be due to only three problems: 1) the absence of an indication for drug treatment; 2) a lack of effectiveness of drug treatment and 3) long-term drug treatment instead of short-term (73) (119). Garfinkel et al. recommend the use of the “*Good Palliative-Geriatric Practice algorithm*” (table 2). This algorithm may be considered as a “reduced version” of a medication review. It focuses on the evaluation of the indication of drug treatment when taking into account the patient’s age, comorbidity and possible adverse drug reactions (95). Consequently, on average 4.4 drugs per patient could be stopped, quality of life increased, and dementia symptoms improved (95, 120). Obviously, making sure that a drug has an indication and is effective seem to be the two most important steps during a medication review and may reduce a large proportion of all PIP. This corresponds well to the author’s clinical experience from the work with older patients. For example, drug-drug interactions are closely linked to the number of drugs which implies that the prescriber takes care of them *per se* when removing drugs without indication (88).

Computerized decision support systems that are linked to the electronic patient journal and alert physicians during the ordination process may enhance appropriate prescribing (table 2). This is particularly true for the hospital setting whereas effects are less certain in the outpatient or primary care setting (113). A common complaint from prescribers is that they are overrun by alerts (121).

Several educational strategies have successfully improved prescribing (see even chapter 2.7.3). Educational outreach visits have small but potentially important effects on prescribing (114) (122), and feedback on performance may effectively change clinical practice (123) (115). Moreover, it is effective to remind healthcare professionals of an intended action (“reminders”) (123). Interprofessional discussion may enhance agreement on the necessity of a change of practice and on the manner in which changes should be done (“local consensus process”). The combination of several evidence-based strategies increases effectiveness.

Several attempts have also been made to identify patients at risk for drug-related morbidity by means of regression models (124-126). This led to the development of screening tools forecasting adverse drug reactions similar to the Framingham risk score predicting the risk for cardiovascular mortality in patients with cardiovascular disease (127). For example, the GerontoNet ADR risk prediction tool (126) includes six risk factors: 1) \geq four chronic conditions, 2) heart failure, 3) liver disease, 4) renal impairment, 5) number of drugs, and 6) a history of ADR. However, these tools have not been implemented and tested prospectively (124).

2.7.3 Where and how are interventions aiming to improve potentially inappropriate prescribing conducted?

Research in this field increases which is illustrated by the growing number of studies included in three systematic Cochrane reviews on this topic (original review from 2012 and two updates from 2014 and 2018 (76, 106, 128) (figure 3).

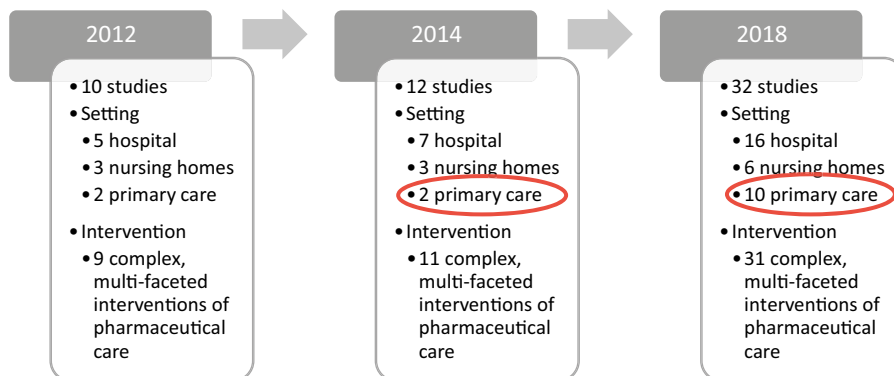


Figure 3. Original Cochrane review (2012 (128)) and two updates (2014 (76), 2018 (106)) that describe interventions aiming to enhance appropriate prescribing in older patients.

Most studies were conducted in an inpatient setting. However, the number of studies performed in primary care increased considerably from two in 2014 to ten in 2018. Moreover, the most recent review from 2018 identified 27 ongoing studies. The large majority of interventions are multifaceted and include medication reviews, educational interventions and financial incentives. The most important finding is that clinically relevant outcomes do not improve.

2.7.4 Multifaceted educational interventions in primary care

According to the most recent Cochrane review on interventions to improve PIP in older patients (106) (figure 3), ten studies were conducted in primary care settings with a total of 14 969 participants. Of these, only one used a multifaceted educational approach (129). Four other important studies (75, 130-132) have not been captured by the inclusion criteria of the Cochrane review (106) as they did not use validated PIP criteria (such as for example STOPP-START (37)). Table 3 summarizes the methods and findings from these five studies.

Table 3. Methods and results of five cluster-randomized studies on PIP in a primary care setting using multifaceted educational approaches. The descriptions of the interventions are in part quoted from the original articles.

Avery 2012 (131), UK	
Definition of PIP	3 PIMs: NSAIDs without proton-pump inhibitor, beta blockers and asthma, angiotensin converting enzyme inhibitor or loop diuretics without assessment of urea and electrolytes
Unit of allocation	Practice/patient
Follow-up	6 months
Participants	72 general practices with a combined list size of 480 942 patients
Intervention	Pharmacist-led, information technology-based intervention composed of feedback, educational outreach, and dedicated support
Controls	Simple computerized feedback + brief written educational material
Endpoints	Primary: % of patients at 6 months with at least one of three PIMs
Effects	Odds Ratios in favour of intervention patients (CI 95%): 1) NSAIDs 0.58 (0.58-0.91) 2) betablockers 0.73 (0.58-0.91) 3) angiotensin converting enzyme inhibitor/loop diuretics 0.51 (0.34-0.78)
Clyne 2015 (129), Ireland	
Definition of PIP	34 PIMs, for example "NSAID (>3 months) for relief of mild joint pain in osteoarthritis"
Unit of allocation/analysis	Practice/patient
Follow-up	After 4-6 months assessment of outcomes (depending on when the practice had performed medication reviews in 50 randomly selected patients)
Participants	21 GPs and 196 patients
Intervention	Pharmacist-led educational outreach visit on how to perform a medication review with a web-based pharmaceutical treatment algorithm
Controls	Usual care and one-time simple patient-level feedback on PIP
Endpoints	Primary: 1) % of patients with PIP and 2) mean number of PIMs in all intervention patients vs. all control patients group; Several secondary endpoints
Effects	Intervention patients ↓ odds (adjusted odds ratio = 0.32; 95% CI, 0.15-0.70) of having PIP; mean number of PIMs in intervention patients 0.70 vs. 1.18 in control patients Of note, the reduction in PIP was to a large extent due to the reduction of one indicator (Proton pump inhibitor at maximum therapeutic dosage for >8 weeks)

Dreischulte 2016 (75), Scotland	
Definition of PIP	9 PIMs: for example NSAIDs, antiplatelets, oral anticoagulant without gastroprotective drug, and 3 clinical outcomes: gastrointestinal bleeding, renal failure, heart failure
Unit of allocation/analysis	Practice/patient
Follow-up	48 weeks intervention + 48 weeks follow-up
Participants	34 primary care practices with 33 334 patients at risk (pre-intervention period) 33 060 patients at risk (intervention period)
Intervention	Complex intervention combining professional education, informatics, and financial incentives
Controls	Each practice was its own control due to stepped-wedge design
Endpoints	Primary: rate of patients with high-risk prescribing Secondary: rate of hospital admissions per 10 000 person-years for GI ulcer/bleeding, heart failure or acute kidney injury
Effects	Primary: ↓ from 3.7% to 2.2% Secondary: ↓ from 55.7 to 37.0 (gastrointestinal bleeding) ↓ from 707.7 to 513.5 (heart failure) not significant (renal failure)
Pit 2007 (117), Australia	
Definition of PIP	3 PIMs: NSAIDs, low-dose thiazide diuretics as first-line therapy for hypertension, and benzodiazepines
Unit of allocation/analysis	Practice/patient
Follow-up	4 and 12 months
Participants	22 GPs from 17 practices recruited 849 patients ≥ 65 presenting at practice during study period
Intervention	Education (academic detailing, prescribing information and feedback), financial incentives, medication risk assessment, and completion of a medication review checklist
Controls	Control doctors received no intervention except for completing a clinical audit to encourage participation in the study, which included feedback on the number of medication reviews and medication risk factors
Endpoints	Primary: number of patients with one of six possible outcomes (-2, -1, 0, 1, 2, 3) of an ordinal composite outcome measure of PIP; Secondary: ordinal outcome measures for each of the targeted drugs (neutral score (0), success (+1) (ie, recommendation was followed), or failure (-1) (ie, recommendation was not followed)
Effects	Intervention patients vs. control patients: 1) ↑ odds of having an improved composite score than patients in control group (Odds Ratio 1.86; 95% CI, 1.21–2.85) at 4 months, but not at 12 months 2) ↓ odds of using NSAIDs at 4 months, but not at 12 months No significant changes regarding benzodiazepines or thiazide diuretics at 4/12 months

Rognstad 2013 (133), Norway	
Definition of PIP	13 PIMs in patients aged ≥ 70 years
Unit of allocation/analysis	Peer continuing medical education groups with GPs/group of patients that were prescribed PIMs by specific GP
Follow-up	One year
Participants	449 GPs that were part of (pre-existing) peer continuing medical education groups who issued PIMs to 81 810 patients aged ≥ 70 years before and 80 521 patients after educational intervention
Intervention	Educational intervention composed of educational outreach visits, feedback, group discussion
Controls	Control group: usual care (remark: peer continuing medical education groups received a similar educational intervention but on the topic of prescribing practice for respiratory tract infections (134))
Endpoints	number of PIMs/100 patients issued by specific GP during pre-intervention period (year 2005) compared to post-intervention period (July 2006-june 2007)
Effects	$\downarrow 10.3\%$ PIMs/100 patients

CI confidence interval; GP general practitioner; PIMs/PIP potentially inappropriate medicines/prescribing.

The studies have several similarities. They all define specific subsets of PIMs, thus providing a very clear message to the prescribers. The interventions were very specific: drug treatment should be initiated or stopped, and the effects of changes in drug treatment may be observed within a few weeks. In all studies, clusters are randomised (practices or continuing medical education groups), but outcomes were assessed at patient level. Finally, all studies applied a combination of evidence-based educational strategies such as feedback on prescribing, educational outreach, reminders or group discussions.

The most distinct effect on clinical outcomes was achieved by Dreischulte et al. (75). The limited number of PIMs and the regular (every 8th week) feedback to prescribing GPs are important explanations for the decrease in drug-related hospital admissions.

Two studies (75, 131) had a “pragmatic” in contrast to an “explanatory” design (105, 135). Key characteristics of pragmatic trials are that they evaluate the “*effectiveness of an intervention in a normal practice setting with the full range of study participants*” (cited from (105)). Moreover, the intervention may be used in a flexible way as it would be in daily practice. Pragmatic trials may be considered as more “honest” than explanatory trials, as they are conducted within a “daily work” setting.

2.8 Process evaluation of complex trials

The design and analysis of complex trials such as the multifaceted interventions presented in table 3 are a challenge because the intervention is applied at cluster level whereas the outcomes (at least partly) are assessed at patient level. The following example may illustrate this challenge: An educational intervention is provided to primary care practices, and participating healthcare professionals are asked to review their patients' medicines according to a new method. In this context it is essential to measure not only if prescribing improves, but also to understand who participates in the educational sessions, who uses the new method and how, and if the new method is still used several months after the intervention, to give only some examples. A structured framework such as the one proposed by Grant et al. (136, 137) facilitates the planning and reporting of such a trial (138).

3 AIM AND RESEARCH QUESTIONS

3.1 Overall aims

- 1) To increase knowledge on *how commonly* older patients attending primary care use potentially inappropriate medicines in relation to their renal function, and how frequently they are exposed to drug-disease interactions.
- 2) To evaluate if an intervention on medication reviews combining several evidence-based educational strategies is a valuable measure *to address* potentially inappropriate prescribing in primary care, and
- 3) *To understand* GPs' and nurses' views on potentially inappropriate prescribing and medication reviews.

3.2 Contents of thesis

Figure 4 illustrates the contents of this thesis based on three published articles and one manuscript.

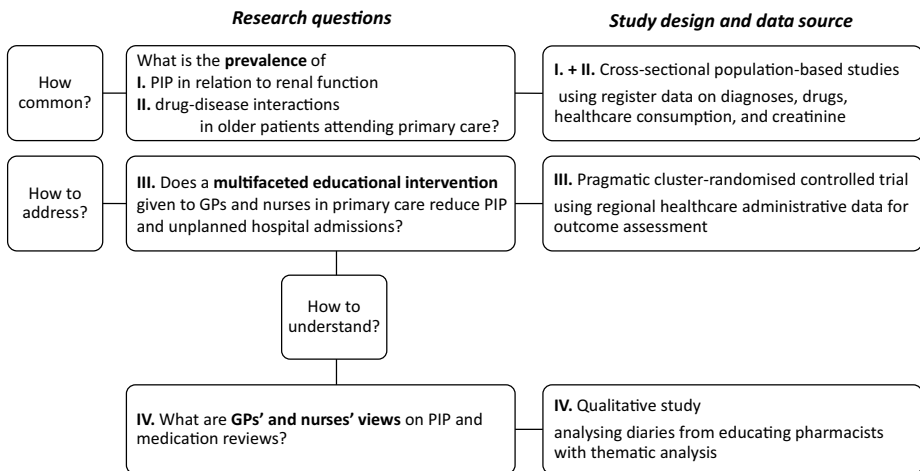


Figure 4. Contents of thesis.

GP general practitioner, PIP potentially inappropriate prescribing.

3.3 Research questions

- 1) *How common* is potentially inappropriate prescribing?
 - a. What is the prevalence of drugs that are contraindicated in relation to renal function in older patients who attend primary care and have chronic kidney disease stage 3 or 4? **(I)**
 - b. What is the prevalence of excessive dosing in relation to renal function in older patients who attend primary care and have chronic kidney disease stage 3 or 4? **(I)**
 - c. What is the prevalence of drug-disease interactions in older patients who attend primary care? **(II)**
- 2) *How to address* potentially inappropriate prescribing?
 - a. Does a multifaceted educational intervention given to GPs and nurses in primary care
 - i. reduce potentially inappropriate prescribing and unplanned hospital admissions? **(III)**
 - ii. increase the number of medication reviews? **(III)**
 - b. What are GPs' and nurses' views on potentially inappropriate prescribing and medication reviews? **(IV)**
 - c. Why did prescribing not improve after a multifaceted educational intervention in primary care? **(IV)**

4 RESEARCH METHODS AND MATERIAL

4.1 How common is potentially inappropriate prescribing?

4.1.1 Study design

The percentage of older patients currently exposed to PIP in relation to renal function (I) or drug-disease interactions (II) was assessed in two descriptive cross-sectional studies. The study period was one year (figure 5). In study I, the study period started at different dates for each participant depending on the date of creatinine assessment (index date) (figure 5), whereas the study period in study II was the same for all individuals (year 2016). One explanation for this long period is that an “average older patient” in the study population uses many drugs simultaneously (= polypharmacy), but drug dispense may happen at several time points during one year. Another explanation specific to study I was that drug doses were to be calculated based on the number of purchased drug packages during one year.

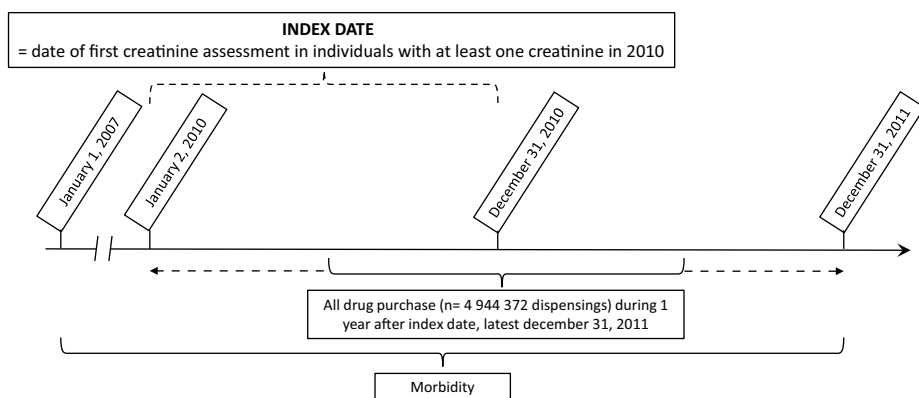


Figure 5. Illustration of time frames under which renal function, drug use and morbidity were assessed in study I.

4.1.2 Study population

The prevalence of PIP in relation to renal function (I) was analysed in patients aged ≥ 65 years who attended primary care at least once year 2010, with at least one creatinine assessment in 2010, and who had an eGFR of 30–59 mL/min (CKD stage 3) or 15–29 mL/min (CKD stage 4).

The prevalence of drug-disease interactions (II) was analysed in patients aged ≥ 65 years who were registered with a primary care practice in Stockholm County in December 2015.

People who died or moved in and out of Stockholm County were excluded.

4.1.3 Study I: Definition of potentially inappropriate prescribing in relation to renal function

In 2010, Stockholm County Council decided to integrate a computerized decision support system on drug prescription in impaired renal function in the electronic medical record (59). PIP in relation to renal function was defined with reference to the knowledgebase “*Janusmed Drugs and Renal function*” (version 2016). Janusmed is the Swedish adaptation of Finnish Renbase®, a comprehensive knowledgebase with evidence-based recommendations on drug use in patients with renal impairment. Renbase® refers to internationally accepted categories of CKD (139) and includes for every substance (a) a classification for each kidney function level (A: no need of dose modification. B: The information is not available or the recommendation is estimated based on the pharmacokinetic characteristics of the substance. C: Modification of the dose or dosage interval is needed. D: Use of the substance should be avoided.); (b) a short recommendation that may refer to dosing, but may also be a text suggesting to read the additional information; and (c) the additional information with the real recommendation in text. We analysed substances that should be dose-adapted (“C-substances”) and substances that are contraindicated (“D-substances”). C-substances were potentially inappropriate if 1) they were prescribed in a chronic manner. 2) their mean volume dispensed (Defined Daily Dose)/day exceeded the recommended dose. D-substances were considered as potentially inappropriate if dispensed at least once during the index year. For details, see methods section in paper I.

In 2011, physicians in primary care in Stockholm prescribed a total of nearly 700 different substances (ATC 5th level) to patients aged ≥ 65 . In order to delimit our analyses to a manageable amount of substances we applied the concept of “drug utilization 99%” (DU99) (140). This implied that we described the prevalence of PIP in relation to renal function within 99% of the total volume of all dispensed prescriptions measured as Defined Daily Doses in patients with CKD stage 3 or 4.

We adapted Janusmed for the purposes of study I according to figure 2 in the published paper (I), and analysed the prevalence of 45 C- and 5 D-substances in patients with CKD stage 3, as well as 41 C- and 25 D-substances in patients with CKD stage 4.

4.1.4 Study II: Definition of drug-disease interactions

Drug-disease interactions were chosen with reference to STOPP/START Criteria version 2 (37). As these criteria do not include a specific list of drug-disease interactions, we decided for each of the 80 STOPP-indicators if it is a drug-disease interaction according to the definition provided by Pugh et al. (48): “*drugs that worsen a pre-existing condition*”. Details on the selection process are shown in appendix of manuscript II. Finally, 33 drug-disease interactions were assessed for their prevalence.

4.2 Data sources

Sweden holds many registers that can be used for research purposes (141). The Swedish personal identity number (142) allows to link information from different registers and thus to create a complete “painting” of a patient taking into account sex, age, morbidity, drug use, healthcare consumption and laboratory data (figure 6).

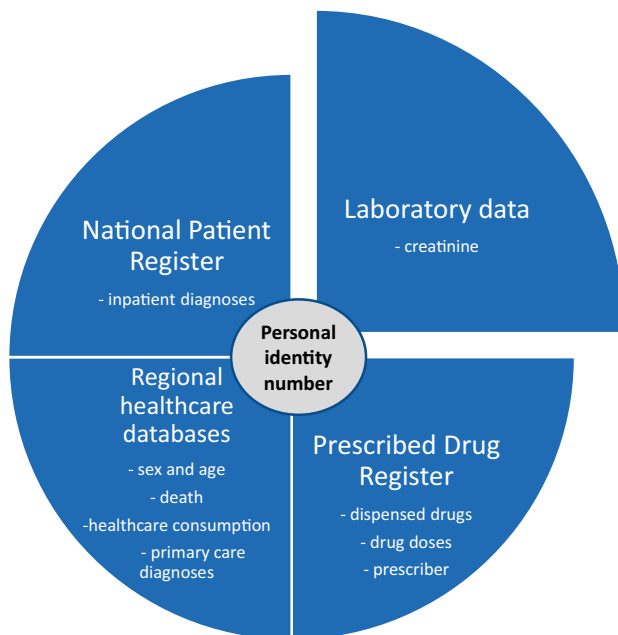


Figure 6. Illustration of registers and data that were linked using the personal identity number. Laboratory data were linked in study I only.

We linked information from:

- 1) Stockholm County’s regional healthcare databases (Stockholm regional healthcare data Warehouse (25), Vårdanalysdatabasen VAL). It contains all consultations in primary and secondary care as well as hospital admissions. Information on at least one diagnosis is available for more than 95% of primary care consultations.
- 2) The National Patient Register. Information on at least one diagnosis is available for 99% of outpatient specialist consultations, and for 99% of inpatient hospital admissions. With some exceptions (for example, cancer diagnoses), diagnoses in the national inpatient register have a positive predictive value of 85% to 95% (143).

- 3) The Prescribed Drug Register (144). It contains data on all prescription drugs dispensed in Sweden from July 2005 and later, their amounts and dosages, as well as prescriber information. The information has a high validity. Of note, neither in-hospital nor over-the-counter drugs are included.
- 4) For study I, data from the Stockholm CREATinine Measurements (SCREAM) database were retrieved (145). In addition to the registers described above SCREAM contains laboratory data from one of the three laboratories (Aleris, Unilabs or Karolinska University Laboratory) performing the majority of medical analyses in Stockholm County.

The estimated glomerular filtration rate was calculated with CKD-EPI formula based on creatinine values assessed during year 2010 (146). EGFR was categorized into (139): CKD stage 1 or 2: eGFR \geq 60 mL/min; CKD stage 3: eGFR 30–59 mL/min; CKD stage 4: eGFR 15–29 mL/min; CKD stage 5: eGFR < 15 mL/min.

4.2.1 Statistical considerations

I: The prevalence of PIP in relation to renal function was stratified by CKD stage 3 and 4. We calculated two-tailed 95% binomial confidence intervals for prevalences. We calculated the proportion of patients with potentially excessive doses as “number of patients with potentially excessive dose of specific substance/ number of patients with specific substance”. Data were extracted from SCREAM (145, 147) with R (<https://www.r-project.org>). Statistical analyses were undertaken with STATA version 14.

II: Three analyses were performed: 1) Prevalence of DDSIs in the entire study population; 2) Prevalence of the interacting drug in patients with interacting disease; and 3) Prevalence differences in two patient groups who all had a pain diagnosis: The prevalence of NSAIDs in patients with interacting disease was compared to the prevalence of NSAIDs in patients without interacting disease. Prevalence differences and two-tailed 95% confidence intervals were calculated. Data extraction was performed with SAS Enterprise Guide version 7.1, and statistical analyses were undertaken in STATA version 14.

4.3 How to address potentially inappropriate prescribing in clinical practice?

4.3.1 Study design and study population (III)

We designed a pragmatic cluster-randomised trial in primary care in Stockholm. The intervention was multifaceted and comprised several evidence-based educational strategies. The study period was originally planned to 12 months, but had to be shortened to 9 months (1st of January to 30th of September 2013) due to the financial incentives tied to basic medication reviews (see paper III, box 1 for details).

The clusters were primary care practices, and the individuals were patients aged ≥ 65 registered with the participating primary care practices. The multifaceted educational intervention should help GPs and nurses to develop a working procedure on medication reviews, and GPs and nurses were asked to perform medication reviews in their older patients.

As mentioned in chapter 2.8, the design, interpretation and reporting of multifaceted interventions with cluster-randomisation is complex because the intervention is applied at a cluster level whereas the outcomes (at least partly) are assessed at individual level. Therefore, the methods of study III are reported following the framework on process evaluations proposed by Grant et al. (137). Figure 7 illustrates the domains proposed in the framework, the corresponding framework questions, and which kind of collected data may serve as a source to answer the framework question.

Of note, we used the framework during the reporting but not the planning phase. When planning the trial, we used our “common sense” to decide which type of data material to collect at which time point. This allowed use to generate but not to test hypotheses (137). The time constraints we faced were the major reason for not using a framework in the planning phase already. The trial had to be prepared within four months (May 2012: decision to perform trial; September 2012: recruitment of practices started). The short time frame also partly explains the weaknesses of the process evaluation.

Besides the framework domains and questions illustrated in figure 7, the framework includes three more questions:

- 1) Are there unintended changes in processes and outcomes, both related to the trial intervention and unrelated care? We were not able to answer this question.
- 2) What theory has been used to develop the intervention?

In collaboration with two experienced clinical pharmacists working for the committee we developed a multifaceted educational intervention (see paper III: figure 3 and appendix) that comprised:

- a) A first educational outreach visit given to GPs and nurses at each practice with a powerpoint presentation including
 - i) theoretical knowledge on PIP according to the Swedish criteria (54)
 - ii) feedback on prescribing patterns on practice or county level:
 - (1) polypharmacy: number of patients aged ≥ 65 with 5-9 drugs or 10 and more drugs registered with the practice
 - (2) “drugs to avoid”: use of longacting benzodiazepines, anticholinergic drugs, tramadol and propiomazin among patients aged ≥ 65 registered with the practice

- (3) PIP in relation to renal function: top-10 PIMs in relation to renal function in Stockholm County, and information on the computerized decision support system (“Janusmed”, see chapter 4.1.3) that is integrated in the electronic medical record
 - (4) drug-drug interactions: 4-7 most prevalent drug-drug interactions in older patients in Stockholm County, and information on the computerized decision support system for drug-drug interactions that is integrated in the electronic medical record (148)
 - (5) drug-disease interactions: overall presentation of the “START”-section (“diagnose-specific” chapter) of the Swedish criteria (54) (see table 1), and presentation of the eleven diagnoses for which there are diagnose-specific recommendations on interacting drugs.
- iii) the development of a working procedure on medication reviews
- b) A second, reminding educational outreach visit three months after the first visit.
- 3) What is the wider context in which the trial is being conducted?

The primary care system in Stockholm is described in paper III, box 1.

Since the 1990’s, Stockholm County has built up a well-functioning organization promoting the rational use of medicines (149). The “Regional Drug and Therapeutics Committee” is part of this organization. It employs physicians and pharmacists who perform educational outreach visits in primary care in order to give feedback on prescribing patterns and to promote changes in prescribing.

In 2012, the Swedish legislation was updated, and Stockholm County issued new guidelines on the performance of medication reviews (see paper III, appendix). All levels of health care should perform medication reviews in older patients on a regular basis. The guidelines differentiated between “basic” and “comprehensive” medication reviews, and a financial incentive of 300 SEK (≈32 €) was tied with the performance of basic medication reviews. Stakeholders in Stockholm County assigned the Regional Drug and Therapeutics Committee to spread the knowledge on the new guidelines on medication reviews in primary care. We got the possibility to randomize primary care practices and applied for ethical approval.

In collaboration with two experienced clinical pharmacists working for the Regional Drug and Therapeutics committee (149) we designed a multifaceted educational intervention. The incentive was given independently of whether the practice was participating in the intervention or not or whether it had been randomized to intervention or control group.

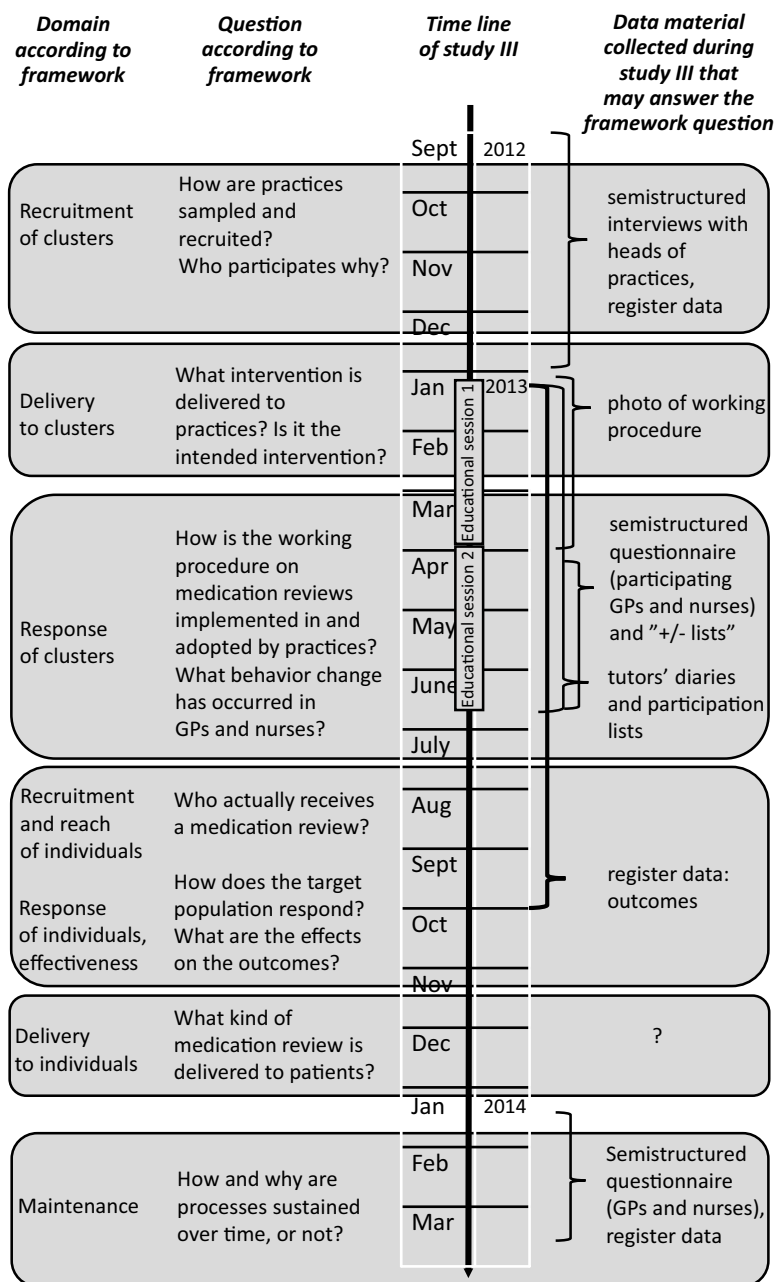


Figure 7. Illustration of the process evaluation for complex trials proposed by Grant et al. (137) in relation to study III.

4.3.2 Data material

This chapter describes the following data material shown in figure 7: 1) the working procedure on medication reviews created during the educational sessions; 2) the tutors' diaries; 3) and how the participation in the educational sessions was documented. Further data material shown in figure 7 is *not* described in this thesis.

4.3.2.1 Working procedure

Based on the new guidelines on medication reviews (150), relevant literature (27) and clinical experience, we developed a working procedure on comprehensive medication reviews (figure 8). During the education session, GPs and nurses discussed the "Who, How, When" of each step of a medication review.

Step	What?
1	initiate review
2	prepare review
	check current drug list
	order blood sample
	screen for side effects
	blood pressure, weight
3	estimate renal function
4	review with checklist
5	follow-up of review
6	document review

Figure 8. Suggested working procedure for medication reviews.

4.3.2.2 Tutors' diaries written after both educational sessions (IV)

The tutors who performed the educational outreach visits had several years of experience with academic detailing in primary care [19]. The writing of diaries after each educational session was a standardised part of their work. The purpose of the diaries was to document and structure the pedagogical process of academic detailing. The tutors were not steered in their reporting and had the maximum freedom of writing whatever they considered to be important regarding their purpose. In the context of our trial, they had decided to do the same after every educational session. When the tutors presented their diaries for the research group, we discovered they contained unexpectedly rich and extensive data. As we were not aware of any study analysing GPs' and nurses' views on medication reviews according to the Swedish legislation (151), we decided to analyse the diaries by a qualitative approach and obtained ethical approval.

We hoped to find a hint in the diaries regarding the question to why the trial did not improve prescribing. When the analysis progressed, the initial aim was modified into the final aim, which was to analyze GPs' and nurses' views on PIP and medication reviews in older patients in primary care.

4.3.2.3 Participation in educational sessions

The participating GPs and nurses signed the participation lists during the first and second educational sessions, and stated their profession. The “sums of participating physicians/nurses” were divided by the “number of employed physicians and nurses according to register data obtained prior to the study”. We analysed participation on a group level only and did not take into account if the same person participated both educational sessions.

4.3.3 Definition of potentially inappropriate prescribing (III)

Despite several disadvantages with the Swedish criteria (38, 54) (table 1) healthcare professionals in Stockholm County should refer to them when they perform medication reviews in older patients. We therefore assessed PIP in relation to five categories proposed in the “misprescribing” section (table 1) of the Swedish criteria version 2010 (54): polypharmacy, drugs to avoid, PIP in relation to renal function, drug-drug and drug-disease interactions. As the Swedish criteria do not contain a specific list of drug-drug and drug-disease interactions, we created a detailed list of potentially inappropriate interactions with reference to published literature (for details see paper III, appendix).

It is important to mention that we were not able to assess the Swedish criteria in their entirety, as we neither had access to clinical data nor written information from the electronic medical record. This implied that we could not measure 1) the indication for drug use (chapter 1.2 in Swedish criteria), 2) inappropriate drug regimen (chapter 1.3 in Swedish criteria), 3) inappropriate dosing (chapter 1.4 in Swedish criteria) and 4) PIP in relation to specific symptoms such as hypotension (chapter 1.8 in Swedish criteria).

4.3.4 Outcomes

The effects of the intervention were assessed at practice (number of registered medication reviews) as well as patient level.

The primary combined outcome was the number of patients with \geq one unplanned healthcare consultation defined as “unplanned hospital admission and/or emergency department visit” assessed at patient level. A selection of important secondary outcomes are presented in figure 9.

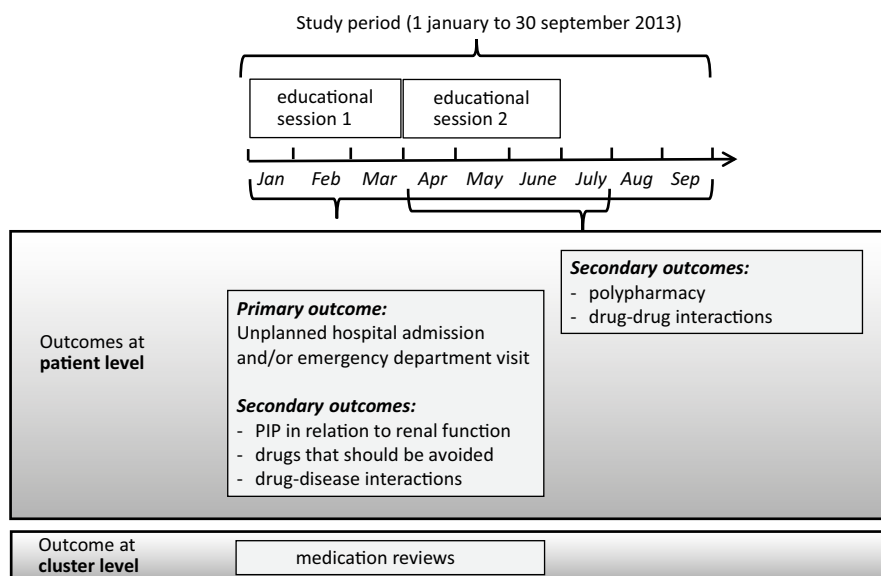


Figure 9. Which outcomes were assessed in study III, and when? See paper III, appendix, for details on the definition of PIP.

PIP: potentially inappropriate prescribing

4.3.5 Statistical considerations

Details on the calculation of the sample size are reported in the methods section in paper III.

The main post-intervention analysis assessed differences between patients aged ≥ 65 in intervention and control group. Risk differences between binary outcomes at patient level were calculated using a generalized linear model with binomial distribution and identity link. The difference in rates of medication reviews/registered patients were evaluated with a t-test. Supplementary analyses included a before-after analysis (difference-in-differences). This approach decomposes outcomes into a group effect (difference between intervention and control group), a period effect (difference between after and before the intervention, time trend), and an intervention effect (difference-in-differences) estimated as the period \times group interaction. Results are reported with a 95% confidence interval (95% CI).

For the patient-level outcomes, we took into account the clustering of patients within practices. All analyses were undertaken in Stata version 14.

4.4 Ethical considerations

In papers I and III and in manuscript II, epidemiological data from different registers were analyzed. The personal identity number that is specific for each individual was replaced by a random number which implies that it was not possible to identify individuals. Furthermore, all analyses were performed at group level only. Both procedures protect the individual's integrity.

Differences in quality of health care in relation to caregivers, sex, age or socio-economics may cause debate. Still, it is important to illuminate if such differences exist in order to improve the quality of health care.

Data for papers III and IV were collected during the cluster randomized controlled trial (paper III). This design was chosen because it permits to answer the research question in an efficient manner. The study was performed according to scientific recommendations on the performance of cluster randomized trials. All medical directors of participating primary care practices were informed about the aim of the study and that confidentiality was ensured. Participation in the trial was voluntary. The medical directors of the participating practices signed informed consent. Medication reviews are a part of routine health care offered by primary care. There was a risk that patients at control practices may have felt their rights to receive equal care curtailed, as GPs and nurses in control practices were educated >9 months later than GPs and nurses in intervention practices. Still, we considered the risks with randomization as minor and thus acceptable. All data from practices and registered patients were analyzed confidentially, and identifying information was not possible to anyone who was not directly involved in the study.

Regarding paper IV, the tutors consented to the analysis of the diaries. As the GPs and nurses who attended the educational sessions were not aware that the diaries would be analysed we applied and obtained ethical approval to analyse them in addition to the earlier approval for study III (152). Moreover, GPs and nurses were anonymous to the researchers, and it was not possible to identify them based on the tutors' diaries.

We considered that the benefits with this research project outweighed possible harms.

5 RESULTS

5.1 How common is potentially inappropriate prescribing?

5.1.1 Prevalence of potentially inappropriate prescribing in relation to renal function (I)

In 11% of older patients an eGFR ≤ 59 ml/min was observed (figure 10). Among these, 30 372 patients had CKD stage 3, and 2161 patients had CKD stage 4. Contraindicated medicines were used by 9 vs. 38% of patients with CKD stage 3 vs. 4. Excessive dosing was present in 43% of patients with CKD stage 3, and in 58% of patients with CKD stage 4.

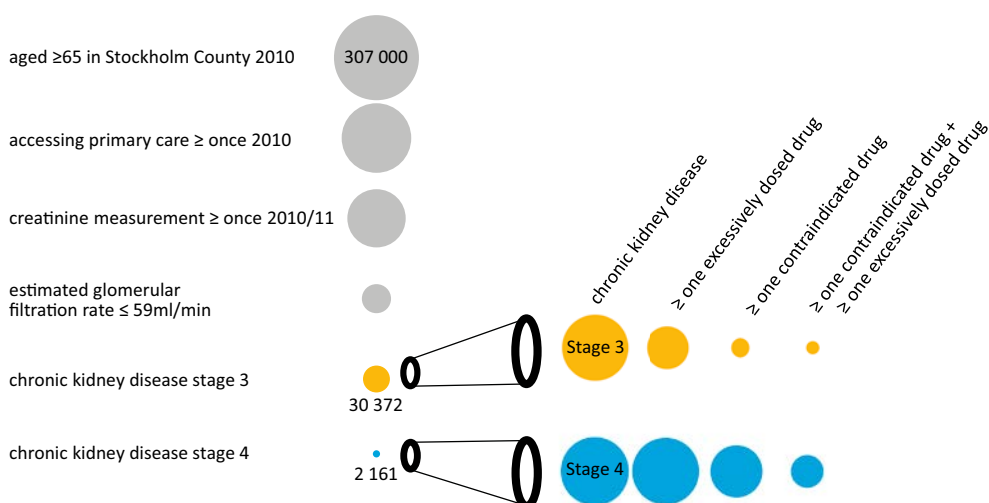


Figure 10. Study population (yellow and blue) and prevalence of potentially inappropriate prescribing in relation to renal function.

In both CKD stage 3 and 4, NSAIDs and antidiabetics were the most frequently encountered contraindicated drug groups. The three most prevalent contraindicated drugs are shown in table 4.

Table 4. Most commonly dispensed contraindicated drugs in patients with impaired renal function

% of patients with CKD stage 3 (95% CI) n=30 372		% of patients with CKD stage 4 (95% CI) n=2 161	
nitrofurantoin	4.9 (4.7 to 5.2)	codeine	9.4 (8.2 to 10.8)
dextropropoxyphene	3.0 (2.9 to 3.2)	diclofenac	7.0 (5.9 to 8.1)
methenamine	1.8 (1.7 to 2.0)	dextropropoxyphene	4.8 (3.9 to 5.8)

CKD chronic kidney disease, CI confidence interval.

Among the ten most commonly overdosed substances were drugs acting on RAAS (3 substances among top-10, in both CKD stage 3 and 4) and opioids (3 substances among top-10 CKD stage 3, 2 substances among top-10 in CKD stage 4) (figure 11). At the same time, drugs acting on RAAS were much more commonly overdosed than opioids (yellow-colored part of bar in figure 11). In patients with CKD stage 4, simvastatin and zopiclone were commonly used and in more than 30% of cases excessively dosed.

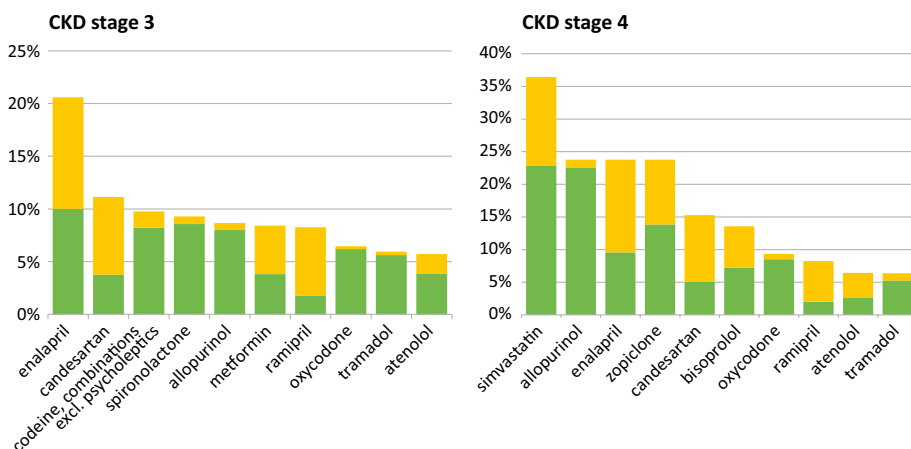


Figure 11. Graphical illustration of the ten most prevalent C-substances that were correctly (green) or excessively (yellow) dosed in patients with impaired renal function. (CKD chronic kidney disease.)

We found that only a few C-substances accounted for the majority of excessive dosing, meaning that there was a long “tail” of C-substances used by less than 5% of the study population (figure 11 and also paper I, figures 4a and 4b).

5.1.2 Prevalence of drug-disease interactions (II)

Among 336 295 older patients registered in primary care in Stockholm, 10.8% had at least one DDSI. Most common was the use of NSAIDs in patients with hypertension (figure 12). It explained more than 75% of the prevalence of all DDSIs. In total, NSAIDs were implicated in five out of a total of 31 DDSIs.

The most common interacting diseases were cardiovascular diseases, benign prostatic hyperplasia, urinary incontinence and dementia. In particular patients with constipation were treated possibly inappropriately as half of them received a drug (mainly opioids) that may worsen their constipation.

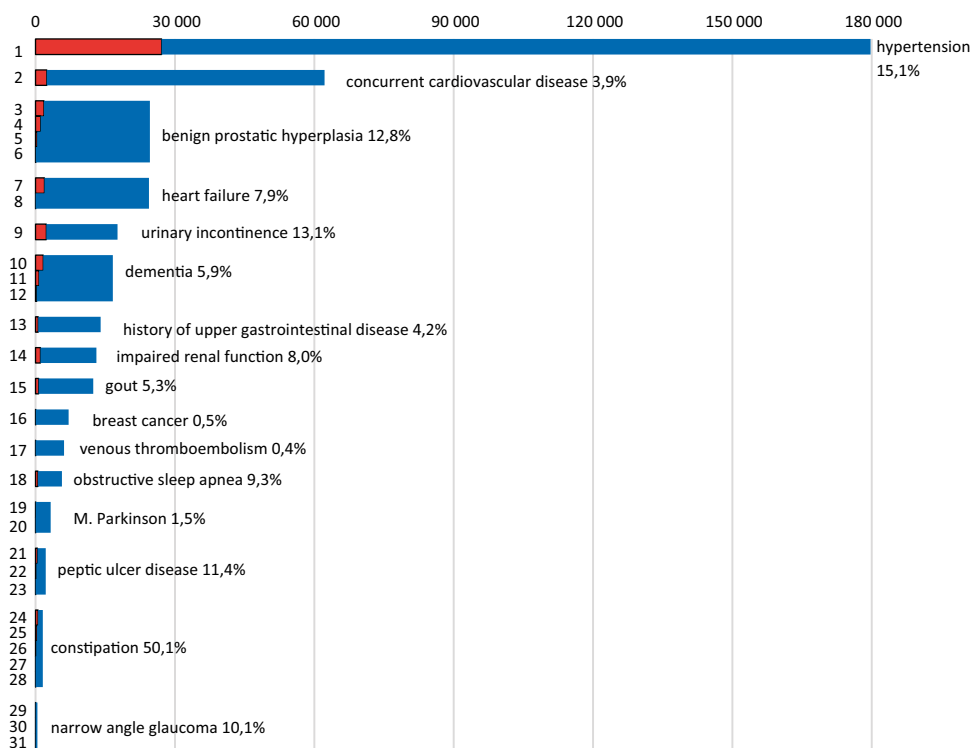


Figure 12. Number of patients with an interacting drug (red) grouped by the prevalence of the interacting disease (red+blue). The percentages indicate the prevalence of the interacting drug among patients with the interacting disease. The numbers to the left relate to the legend.

1 NSAID, 2 COX-2 selective NSAID, 3 antimuscarinic drug, 4 anti-muscarinic bronchodilator, 5 tricyclic antidepressant, 6 neuroleptic, 7 NSAID, 8 thiazolidinedione, 9 loop diuretic, 10 antimuscarinic drug, 11 antimuscarinic drug, 12 tricyclic antidepressant, 13 oral bisphosphonate, 14 NSAID, 15 thiazide diuretic, 16 oestrogen, 17 oestrogen, 18 benzodiazepine, 19 prochlorperazine or metoclopramide, 20 antipsychotics, 21 low-dose acetyl salicylic acid without proton-pump-inhibitor, 22 non-COX-2 selective NSAID without proton-pump-inhibitor or H2-blocker, 23 high-dose acetyl salicylic acid without proton-pump-inhibitor, 24 opioid, 25 antimuscarinic/anticholinergic drug, 26 oral iron, 27 verapamil, 28 aluminium antacid, 29 anti-muscarinic bronchodilator, 30 antimuscarinic drug, 31 tricyclic antidepressant

We compared the prevalence of NSAIDs in two patient groups all having a pain diagnosis: those with an interacting disease (such as heart failure) and those without (figure 13).

We found that patients with an interacting disease less commonly use NSAIDs. For example, patients with heart failure had a 15% lower prevalence of NSAIDs than patients without heart failure.

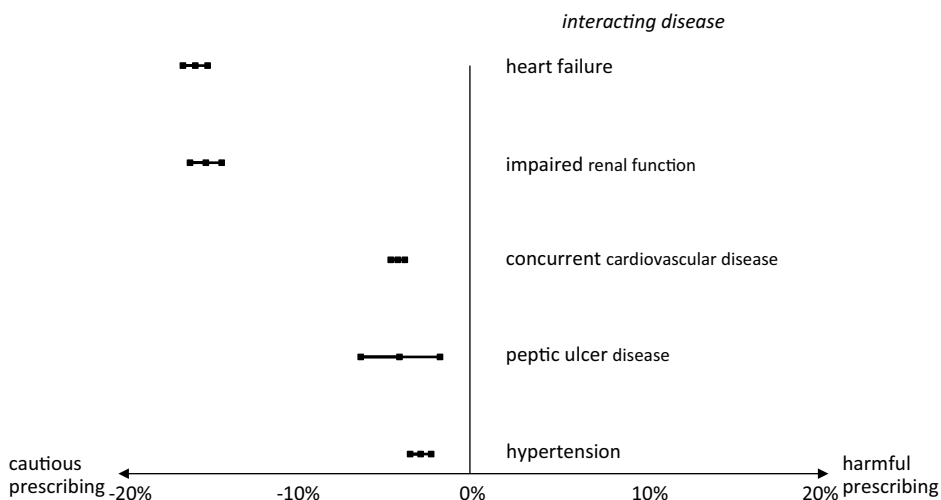


Figure 13. Prevalence differences and 95% confidence intervals of NSAIDs in patients with one or several pain diagnoses and with/without an interacting disease.

5.2 How to address potentially inappropriate prescribing?

5.2.1 Effects of multifaceted educational intervention (III)

In total, 69 practices were recruited corresponding to one third of all practices in Stockholm County. We randomized 34 practices to the intervention group. The tutors performed educational outreach visits in 33 intervention practices, as one practice dropped out.

The primary outcome was observed in 22.8% of patients in intervention practices and 22.0% of control practices (non significant) (figure 14, data points year 2013 in the right part of the graph).

Patients in the intervention group had a higher prevalence of the primary outcome already during 2012, the year before the trial (figure 14, data points year 2012 in the left part of the graph). Still, even when performing a difference-in-differences analysis taking into account this imbalance we did not find a significant difference between intervention and control practices.

Moreover, we observed neither a significant difference in the rates of medication reviews (intervention vs. control 0.13 vs. 0.16) nor a decrease in PIP in the intervention practices (table 5).

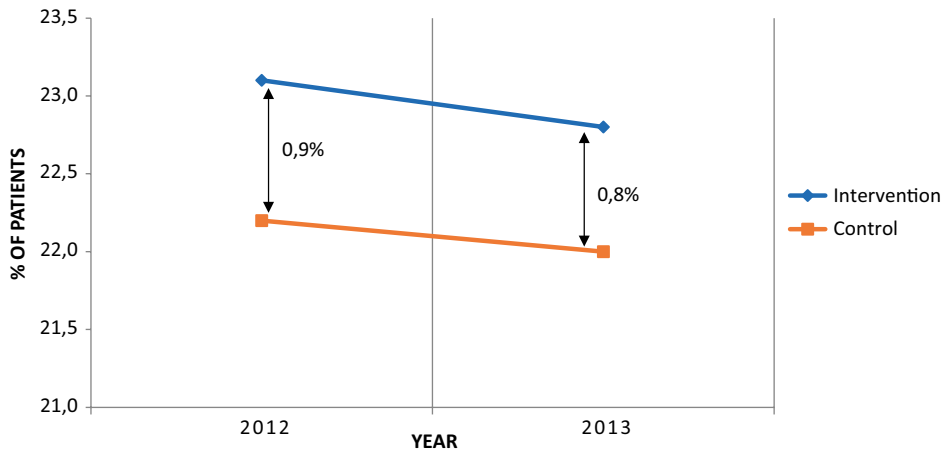


Figure 14. Prevalence of the primary outcome (= at least one unplanned hospital admission or emergency department visit) year 2012 (left) and 2013 (right).

Table 5. Effect of multifaceted intervention in 69 primary care practices (34 intervention and 35 control practices) on patient-level outcomes. Intervention effect measured with difference-in-differences analyses¹.

		Risk difference in % (95% CI) in 34 intervention vs. 35 control practices ²
Primary outcome	≥1 unplanned hospital admission and/or emergency department visit ³	-0.1 (-0.7 to 0.4)
Secondary outcomes	≥1 unplanned hospital admission	-0.5 (-0.96 to 0.03)
	≥1 emergency department visit	-0.2 (-0.7 to 0.4)
	Number of deaths	-0.08 (-0.28 to 0.12)
	Minor polypharmacy ⁴	0.06 (-0.01 to 0.12)
	Major polypharmacy ⁴	-0.1 (-0.5 to 0.3)
	≥1 drug to avoid/anticholinergic	0.4 (-0.1 to 0.9)
	≥1 drug-drug interaction	-0.1 (-0.6 to 0.3)
	≥1 drug-disease interaction	0.16 (-0.07 to 0.40)

¹ The difference-in-differences approach decomposes outcomes into a group effect (difference between intervention and control group), a period effect (difference between after and before the intervention, time trend), and an intervention effect (difference-in-differences) estimated as the period × group interaction

² Intention-to-treat-analysis: 34 randomized practices were analysed including one drop-out practice

³ Intracluster-correlation coefficient: 0.00464 (0.00273–0.00645)

⁴ Minor: 5-9 substances, major: ≥10 substances during April 1 – July 31, 2013

Among 33 intervention practices that completed the study, 74% of GPs (n=194) participated in the first educational session and 62% (n=189) in the second one. The corresponding percentages for nurses were 54 (n=113) and 46% (n=89), respectively.

We observed that the working procedures on medication reviews which GPs and nurses filled out during the educational sessions differed substantially, as illustrated in figure 15. Some practices were able to define the “Who, How, When” of the different steps during a medication review (left part of figure 15), whereas other practices were not (right part of figure 15).

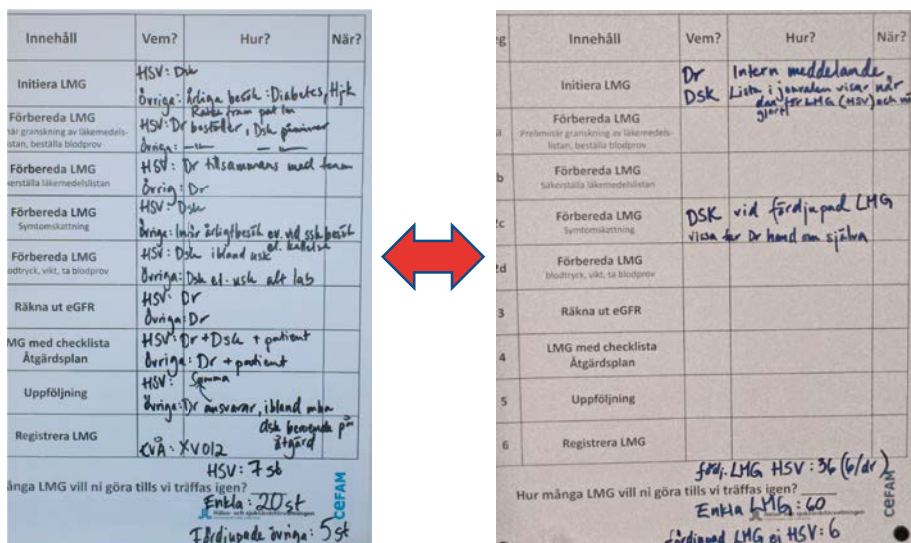


Figure 15. Examples of two working procedures on medication reviews developed by GPs and nurses in two intervention practices (see figure 8 for translation to English).

5.2.2 GPs' and nurses' views on potentially inappropriate prescribing and medication reviews (IV)

We identified five themes: 1) Complexity in 3 ‘P’: patients, pharmacotherapy, and primary care; 2) What, when, who? Clash between GPs’ and nurses’ experiences and guidelines; 3) Real-world problems and less-than-ideal solutions; 4) Eureka? Experiences with different steps during a medication review; and 5) Threats to GP autonomy.

We found several areas of accord where GPs and nurses shared the same view (themes 1 and 5), but even areas of conflicting views (themes 2-4).

GPs and nurses agreed that the clinical evaluation of older patients and their drugs is complex (theme 1) (figure 16). Drug treatment was only one piece of the complicated puzzle of medical care in older patients. To evaluate if an older patient's symptom is due to the underlying disease or a side effect of drug treatment was also challenging.

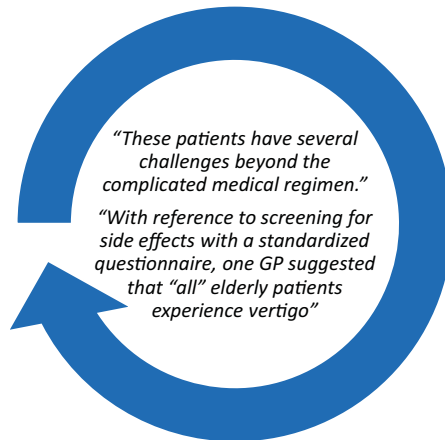


Figure 16. Complexity of clinical evaluation of older patients. Example from theme 1.

GPs' and nurses' did not agree with the guidelines' definition of medication reviews (theme 2) (figures 17 and 18). They expressed that medication reviews are a natural part of every consultation, and that they did them continuously and when required (figure 17). Furthermore, they shared views regarding the segmentation of medication reviews into 'basic' and 'comprehensive': this did not comply with their clinical experience (figure 18).

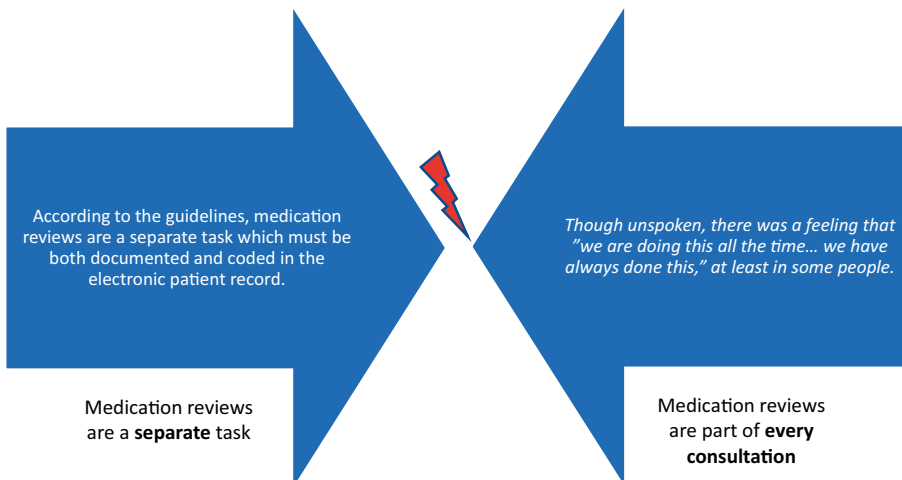


Figure 17. Are medication reviews a separate task or part of every consultation? Example from theme 2.

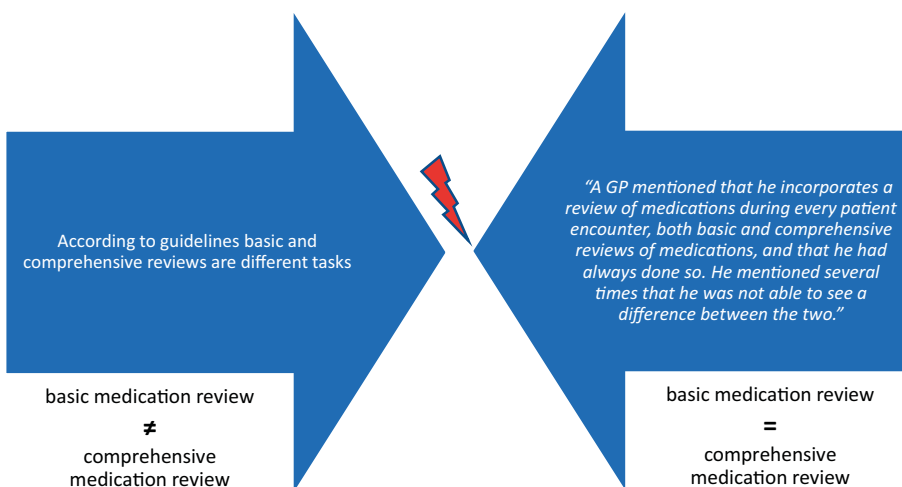


Figure 18. How do basic and comprehensive medication reviews differ? Example from theme 2.

6 DISCUSSION

6.1 Main findings

Older patients with impaired renal function are *commonly* exposed to PIP in relation to renal function. Excessive dosing is more common than the use of contraindicated drugs (CKD stage 3: 43 vs 9%; CKD stage 4: 58 vs 38%). A few drug groups were overrepresented: drugs acting on the RAAS and opioids among excessively dosed drugs, and NSAIDs and antidiabetics among contraindicated drugs. Only a minority of excessive dosing is likely to cause severe adverse drug reactions, such as codeine.

Drug-disease interactions are *less common* than PIP in relation to renal function. At least one DDSI was observed 10.8% of older patients in primary care. The most common DDSI was NSAIDs/hypertension (8.1%). We found that NSAIDs were prescribed cautiously to patients with interacting diseases.

It is unclear *how* GPs and nurses in primary care should *address* PIP in older patients. The multifaceted educational intervention neither reduced PIP nor unplanned healthcare. Moreover, intervention practices did not perform more medication reviews compared to control practices. Major reasons for these results may have been “complexity” and “dilution”.

We *understood* more about GPs’ and nurses’ views on PIP and medication reviews. We found several areas of accordance where GPs and nurses expressed the same views, but even areas of conflicting views. GPs and nurses agreed on the complexity of the clinical evaluation of older patients, PIP and medication reviews. Both GPs and nurses expressed that guidelines clash with clinical practice in primary care.

6.2 How do the main findings fit in?

6.2.1 Prevalence of potentially inappropriate prescribing

The observed prevalence of PIP in relation to renal function was higher than in former studies in community-living older adults (153, 154), whereas the prevalence of DDSIs was within the frame of prevalences found in former studies ranging from 3% (86) to 50% (82). However, it does not seem reasonable to compare overall prevalences at all, as the differences between our and former studies as well as between former studies are too substantial.

Regarding studies on renal PIP, these differences refer to the definition of PIP, the data sources used to assess the prevalence, the formula used to estimate eGFR, the categorization of eGFR, and the way drug doses were calculated. For example, Chang et al. (153) identified the most commonly prescribed drugs in the study population, chose 40 renal PIMs that should be dose-adapted with reference to a

consensus validation list from 2009 (155), calculated eGFR with the Modification of Diet in Renal Disease (146) equation, and categorized patients with impaired renal function according to “30-49 ml/min” and “15-29 ml/min”. Instead, we evaluated 50 renal PIMs in patients with CKD stage 3 and 66 in patients with CKD stage 4, used CKD-EPI formula to calculate eGFR, and classified eGFR into “30-59ml/min” and “15-29 ml/min”. Erler et al. calculated drug doses with reference to the maximum drug dose, whereas we used the Defined Daily Dose (“*the assumed average maintenance dose per day for a drug used for its main indication in adults*”, quoted from [18]) which implies a lower reference dose.

We also observed substantial design differences in between studies on DDSIs. To our knowledge, the study by Lau et al. (85) is the only one besides ours that defines DDSIs with reference to STOPP version 2. Still, Lau et al. considered only 25 STOPP indicators to be DDSIs whereas we concluded that 33 STOPP indicators were DDSIs. Lau et al. did not include the interaction NSAIDs/hypertension whereas we did. Furthermore, the settings and methods of assessment differ: Lau et al. used clinical information from 182 patients discharged from hospital in Hongkong, whereas we used register data from community-living older patients registered with 206 primary care practices in Stockholm County.

Due to the differences in definitions of renal PIMs and DDSIs in our study compared to former studies, even the specific substances figuring as PIMs differed. For example, Chang et al. defined renal PIMs with reference to a consensus list (155) that did not include drugs acting on RAAS, whereas we defined renal PIMs according to Janusmed that includes drugs acting on RAAS, and found that these were highly prevalent. Chang et al. reported moreover that ranitidine, allopurinol and metformin were the most commonly overdosed substances. In our study, allopurinol and metformin were among the top-10 renal PIMs in CKD stage 3, and allopurinol among the top-ten in CKD stage 4. Regarding specific DDSIs, we found that the interaction between NSAIDs/hypertension was far more prevalent than all other DDSIs, whereas Lau et al. describe that DDSIs including anticholinergic drugs were most prevalent; at the same time, Lau et al. did not assess NSAIDs/hypertension.

However, despite all these differences there is one common finding. In general, only a few substances account for the majority of PIP, and there is a long tail of renal PIMs and interacting drugs that are only rarely used. This finding is encouraging as it shows that the complexity of PIP may be reduced by focusing on the most common PIMs in the underlying population. This may in turn be used to create concise feedback on prescribing which was shown in a Scottish primary care study that used similar educational approaches as we did (75) (table 3). During the intervention, feedback on prescribing of a selection of clinically important PIMs that cause preventable drug-related morbidity was provided. Consequently, PIMs and unplanned hospital admissions decreased. In Norway, PIP improved

after feedback on prescribing given to GPs (130) (table 3). The study applied a colleague-to-colleague model and focused on 13 PIMs. The two most important explanations for the favourable results in both studies are the concise definition of PIP and the repeated feedback.

6.2.2 Physicians prescribe carefully, but there is room for improvement

We found that physicians prescribe cautiously to their older patients.

The high prevalence of excessive dosing in patients with impaired renal function was mainly due to the prescription of drugs acting on RAAS. On the other hand, renal PIMs with a higher likelihood of causing severe harm such as opioids were only rarely overdosed. These findings are in line with former findings from outpatient populations (50, 154). Regarding the prescription of drugs acting on RAAS physicians are somewhat in an awkward position as patients with heart failure and renal impairment *should* receive ACE-inhibitors in high doses to treat heart failure but at the same time *not* because ACE-inhibitors in high doses may worsen renal function. Moreover, RAAS-active drugs are recommended as first line drugs in treating high blood pressure in patient with chronic kidney disease. A high prevalence of ACE-inhibitors in patients with renal impairment is thus not exceptionally “inappropriate”, as long as GPs follow up on renal function and electrolyte levels (which we did not to capture). Interestingly, ACE-inhibitors’ potential to induce a deterioration of renal function has been questioned (156).

Likewise, we found evidence that physicians are aware of severe DDSIs such as an aggravation of heart failure due to NSAIDs: these drugs were only rarely prescribed to patients with heart failure. These findings of “cautious prescribing” may explain why physicians who participated in the educational sessions on medication reviews (study III) expressed: “*We are doing this (=reviewing medicines) all the time, we have always done this*” (IV, figure 17). It is important to further elucidate to what extent physicians prescribe cautiously or harmfully even in relation to other DDSIs.

However, there is room for improvement of prescribing. Excessive dosing of opioids may cause substantial harm and is not acceptable even if only a few patients were exposed to it. It is neither acceptable that there were still 1920 older patients with heart failure who were dispensed NSAIDs at least once during 2016. Moreover, we may not have captured PIP in its wholeness as we only analysed prescribed drugs: Twenty percent of patients using NSAIDs buy them as over-the-counter drugs (157), making a higher prevalence of DDSIs with NSAIDs likely. To what extent GPs ask for over-the-counter drugs during their consultations and thus “prescribe cautiously” is poorly understood, but there is certainly room for improvement.

It is important to note that DDSIs are a direct consequence of single disease treatment guidelines (94). This means that GPs who follow guidelines will inevitably induce PIP. The prevalence of DDSIs therefore only partly reflects the responsibility of prescribing GPs, but rather the fact that guidelines do not meet the needs of multimorbid patients. Guidelines on the medical care of multimorbid older patients have been issued by the National Institute for Health and Care Excellence and The Royal college of GPs in UK (158, 159). Important suggestions are both a greater focus on the effectiveness of drug treatment and that the patient's needs should be prioritized during a medication review.

Finally, the presence of careful prescribing shown in our study may also be one explanation for the negative results of the multifaceted educational intervention (III). It evokes the question if there was enough potential to improve prescribing. However, the amelioration of clinical outcomes after an intervention aiming to reduce PIP (75) implies that there are still many possibilities to enhance appropriate prescribing.

6.2.3 Prescribing did not improve – why?

There are several studies using multifaceted educational approaches in primary care that showed a reduction of PIP (75) (table 3). We found neither a reduction of PIP nor unplanned healthcare. Major possible explanations are “complexity” and “dilution”.

6.2.3.1 Complexity

First, the definition of PIP may have been too complicated. It was based on the Swedish criteria and included five categories (polypharmacy, PIP in relation to renal function, drugs that should be avoided and anticholinergic drugs, drug-drug interactions and drug-disease interactions). During the educational sessions, we referred to certain of these PIP categories only in an ‘overarching’ manner as described in the methods part chapter 4.3.1. This information was too complex to be useful for GPs and nurses (see paper III, appendix: powerpoint presentation shown during educational session 1). We were for two reasons restricted as to the contents of the educational sessions: we should refer both to the Swedish criteria (54) as well as to the legislation defining two types of medication reviews: basic and comprehensive. Furthermore, the short time frame of 4 months to prepare the trial did not permit us to weigh PIMs in relation to their prevalence in the underlying population. Multifaceted educational studies in primary care that successfully improved prescribing (75, 129, 130) focused on 3-13 PIMs which probably is a major explanation for their positive results.

Second, complexity at different levels is reported by GPs and nurses participating in the educational sessions (IV) (figure 16). The clinical evaluation of older patients is complex, as chronic disease and side effects may cause the same symptoms. Furthermore, there is a narrow line between benefit and harm of certain drugs, such as ACE-inhibitors, as discussed in chapter 6.2.2. In such a context, it is a challenge to “improve” prescribing, which also explains the lack of effectiveness of our intervention.

Third, the working procedure for medication reviews which GPs and nurses were asked to fill out during the educational sessions may have been too complex (figure 14). The procedure was developed based on recommendations given in the official guidelines (150) and modified in relation to our clinical experience as GPs as well as relevant literature (27). As a consequence of their complexity, it is uncertain to which extent medication reviews actually were implemented. Independent of whether medication reviews are performed in an in- or outpatient setting, their effects on clinical outcomes are more than doubtful (108) (109), which puts our findings in line with those of other researchers. Of note, only Dreischulte et al. (75) found an improvement of clinical outcomes. The limited number of PIMs and the regular (every 8th week) feedback may be the two most important explanations for the decrease in drug-related admissions.

6.2.3.2 Dilution

We measured the effects of the intervention in all older patients registered with the practice instead of in those having an appointment with the GP or receiving medication reviews. This implies that the study population was too unspecific.

Furthermore, too few GPs and nurses may have participated in the educational sessions. The information provided during the educational sessions reached a total of two thirds of the intended recipients. Regarding future interventions with educational outreach visits, it is important to assure high participation.

Finally, the use of register data implied that certain effects of the intervention could not be captured. For example, it is possible that physicians to a higher extent calculated renal function in their older patients after the intervention.

6.3 Strengths and limitations

6.3.1 Study design (I–IV)

In studies I and II, we were interested in how many patients were exposed to PIP during the study period. A cross-sectional study is the design of choice when analysing a prevalence.

In study II, the cross-sectional design implied that drug exposure may have happened before the appearance of the disease, meaning that we assessed adverse drug reactions rather than DDSIs. However, as the prevalence of mainly chronic disease was assessed during 2012-2016 and drug use during 2016 this is rather unlikely. Still, to give a more accurate picture the prevalence of DDSIs should be reassessed using a prospective approach.

Study III was a cluster-randomized controlled trial in 69 primary care practices. In view of the work load and costs that come along with the planning, performance and analysis of such a trial the question arises if we should have chosen another study design, as evoked by one of the reviewers of paper III. An alternative approach might have been an observational before-after-analysis or a time series analysis. However, the level of evidence derived from observational studies is lower than from randomized trials. Moreover, the extra workload to randomise practices appeared manageable as the Stockholm County Council had decided that a campaign on PIP and medication reviews was to be launched with the task to visit all primary care practices. Ideally, a complex intervention should build on several steps: a preclinical theoretical step, a modelling phase, and an exploratory trial testing the feasibility of the intervention (160). Finally, a confirmative randomized trial may be launched. Due to the time constraints we faced (described in chapter 4.3.1) it was not possible to follow this ideal working process, which may be a limitation.

The multifaceted intervention did not improve PIP, which is why we decided to analyse the diaries the tutors had written after each education session (study IV). We were interested in GPs' and nurses' views on medication reviews and PIP in older patients and hoped to find hints to why the educational intervention had not produced the expected results. In this context, the diaries added important information. Documents such as diaries are valuable data sources in qualitative research and allow to generate hypotheses (161). However, interviews or focus groups with the participating GPs and nurses would have given us the possibility to ask follow-up questions and thus to gain deeper understandings. Still, due to time and financial constraints we were not able to collect such data.

6.3.2 Register data (I–III)

Feedback on prescribing derived from register data has previously successfully improved prescription patterns in the Stockholm region with 2.1 million inhabitants (149, 162).

This was an important reason to use register data in studies I-III. Figure 19 shows other advantages but even disadvantages with the use of register data.

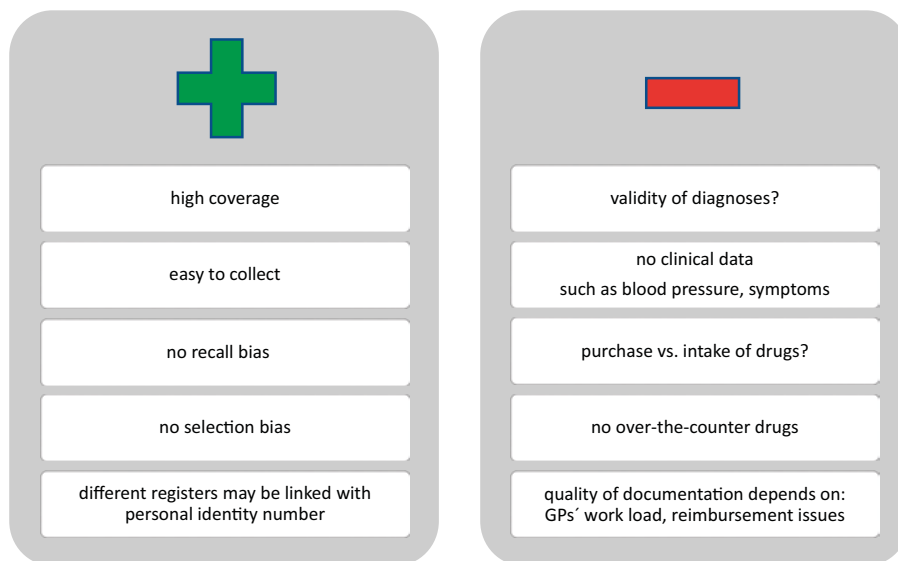


Figure 19. Advantages and disadvantages with the use of register data in studies I-III.

A complete documentation and registration of diagnoses and procedures is a prerequisite for reimbursement and assures high coverage. Moreover, register data are neither prone to recall nor selection bias and are easy to collect. In Sweden, register data may be linked via the personal identity number. However, data quality depends to some extent on healthcare professionals' work load and reimbursement issues which may induce registration bias. In study III, the financial incentives linked to the registration of medication reviews (143) may explain why there was no difference in the number of registered medication reviews between intervention and control practices.

The validity of coded diagnoses may differ. A systematic review from 2010 including 132 published articles concluded that hospital diagnoses derived from the National Patient Register have a high validity (143). However, for some diagnoses the sensitivity is lower, such as hypertension and hyperlipidemia. Patients with these diagnoses are rather followed up in primary care and outpatient settings. The coding of chronic diseases such as diabetes, hypertension (163) and heart failure (164) in primary care may be trusted; however, only few validation studies on diagnoses coded in primary care have been done, and in particular the validity of more uncommon diagnoses has not been sufficiently studied. Still, as we considered diagnoses that had been registered at all three sectors of healthcare, hospital, outpatient specialists and primary care, we believe that our findings are valid.

The validity of the prescribed drug register from which we collected dispensation data is high (144). However, the lack of clinical data and information on dispensation rather than intake of drugs is a limitation. For example, we were not able to correctly assess the DDSI “verapamil or diltiazem with NYHA Class III or IV heart failure” (37) as the NYHA class is not registered in a structured way. In study I, the mean-Defined Daily Dose for one third of dispensed C-substances could not be calculated due to the lack of clinical or laboratory information, implying an underestimation of the prevalence of excessive dosing. On the other hand, measuring dispensation rather than intake of drugs may imply an overestimation of PIP, as patients may stop taking a dispensed drug if they experience side effects. Finally, we only had access to prescription drugs but not over-the-counter drugs such as NSAIDs. This may have led to a substantial underestimation of both the prevalence of PIP in relation to renal function and drug-disease interactions.

6.3.3 Renal function (I)

Drug dosing guidelines have historically relied on Cockcroft-Gault formula (165). Janusmed recommends to use Lund-Malmö-formula for eGFR calculation which is a revised formula of CKD-EPI (166). In accordance with updated international recommendations (167) we used CKD-EPI formula. Compared to Cockcroft-Gault, CKD-EPI underestimates the prevalence of renal impairment (168) which may also imply an underestimation of the prevalence of PIP in relation to renal function. On the other hand, a sensitivity analysis performed by Chang et al (153) did not reveal important differences regarding the prevalence of renal PIMs when using Cockcroft-Gault vs. CKD-EPI. As a consequence, it is uncertain if the use of CKD-EPI rather than Cockcroft-Gault had significant impact on the observed prevalence.

Of note, we included only those patients whose creatinine had been measured (I). The disease burden in such patients may be higher than in the average older population. However, even the opposite is possible: patients without creatinine assessment are more frequently exposed to PIP in relation to renal function, because the GP is not aware of the impairment of renal function. Still, substantial selection bias seems unlikely as the large majority (95%) of older patients in another Swedish primary care population had their creatinine value checked [33].

6.3.4 Diaries as a data source (IV)

The diaries the tutors presented for the research group were unexpectedly rich and extensive. Four questions in relation to their validity arose.

- 1) In research, is it approved to qualitatively analyse data that have not been planned to be qualitatively analysed already from the beginning? Yes, in document analysis it may be: “*Documents contain text (words) and images that have been recorded without a researcher’s intervention.*” (quoted from (161)).

- 2) How trustworthy is information that is retrieved from documents whose collection has not been done for research purposes? *“Documents of all types can help the researcher uncover meaning, develop understanding, and discover insights relevant to the research problem”* (quoted from (169)). Findings retrieved from the qualitative analysis of documents should not be overstated but may be used to create hypotheses.
- 3) Are the diaries biased? It is unlikely that the tutors reported selectively, as they were not aware that the diaries would be analysed. Moreover, the diaries were written with the purpose to document what had been discussed during the sessions thus recording the pedagogical process and allowing a natural starting point for the follow up session. Documenting selectively would thus have impeded the usefulness of the diaries for the tutors.
- 4) Which qualitative approach should be chosen to analyse the diaries? We considered that thematic analysis would match our aim and also the character of our data material, as this approach permits to identify patterns in views, to discover similarities and differences in views, and to create hypotheses (170).

6.3.5 Definition of potentially inappropriate prescribing (I-III)

PIP in relation to renal function were defined with reference to Renbase®, a knowledge-database that relies on a thorough review of published literature. There were two reasons to choose Renbase®. First, it has a very inclusive approach to PIP in relation to renal function, comprising contraindicated drugs as well as dosing recommendations. Renbase® contains in its version from 2016 recommendations on more than 400 substances for CKD stage 3 or 4. Second, Swedish healthcare professionals consult this source when performing medication reviews in older patients (59). However, from a scientific point of view it must be criticized that Renbase® is not free of charge, which makes it impossible for interested readers to scrutinize the recommendations.

We derived 31 DDSIs from STOPP-START criteria (37) which have a high clinical validity (42). Five DDSIs could not be assessed by means of register data. The clinical relevance of certain STOPP-DDSIs may be questioned, such as the deterioration of hypertension in patients who receive NSAIDs (171). Interestingly, Beers criteria do not include this DDSI. As hypertension/NSAID explained more than 75% of the overall prevalence it would have changed our findings substantially if we had used Beers criteria instead of STOPP-START.

In study III, PIP was defined in relation to the Swedish criteria (54). Important differences between the Swedish criteria and STOPP-START criteria are shown in table 1. The main concern is that they are not validated prospectively, meaning that it is unsure if they are associated with drug-related morbidity. However, as

study III was performed in the context of an official campaign (chapter 4.3.1 and box 1 in article III), we were restricted to certain contents of the educational sessions, such as to refer to medication reviews according to the legislation (151) as well as to define PIP in relation to the Swedish criteria (54).

6.4 How may the findings be useful for general practitioners and nurses?

During a medication review, it is important to consider renal function and to adapt drug use accordingly. The most important drug groups to account for are NSAIDs, antidiabetics, drugs acting on RAAS, and opioids. If the eGFR is below 30ml/min, even simvastatin and zopiclone doses should be controlled. Computerized decision support tools may help to identify PIP in relation to renal function in patients using drugs that are less commonly prescribed.

Drug-disease interactions are less frequent than PIP in relation to renal function. However, if an older patient has cardiovascular disease, benign prostatic hyperplasia, urinary incontinence or dementia, GPs should be proactive and check for drugs that worsen concomitant diseases. Of note, NSAIDs are commonly implicated in PIP. They should only rarely be prescribed. As they are over-the-counter drugs, GPs and nurses should actively inquire their use.

GPs and nurses should be proactive and ask for education on PIP in older patients and feedback on prescribing, as both have the potential to improve prescribing. In Stockholm County, GPs and nurses may use the services offered by the Regional Drug Committee (162). Furthermore, the use of multimorbidity guidelines should be encouraged, and physicians should actively participate in the development of such guidelines, in order to assure their clinical usefulness. During medication reviews, benefits and harms of drugs should be weighted against each other. GPs and nurses should discuss all prescribing with their older patients and take into account the patients' drug treatment goals.

6.5 Future perspectives

6.5.1 Understanding

Qualitative research should be performed. It is important to understand more about older patients' views on their drug treatment. It should be elucidated what expectations they have in relation to the goals of drug treatment, and how primary care may meet these expectations. Furthermore, healthcare professionals who work with older multimorbid patients should be asked which kind of support they need in relation to prescribing. Interventions addressing PIP should be based on the needs of patients and healthcare professionals.

6.5.2 How common?

There is a need for increased knowledge on the actual harm of PIP. Several PIP criteria such as Beers (29) do not seem to predict clinical outcomes to a sufficient extent. In view of the time constraints GPs and nurses in primary care face, but even in relation to shared-decision making with older patients it is important to determine which PIMs really cause harm.

6.5.3 How to address?

There is no simple answer to how prescribing in older patients may be improved. Former interventional studies in primary care with the aim to improve prescribing in this patient group have shown negative or only decently favorable results. There is a need for multifaceted interventions in primary care combining several evidence-based implementation strategies such as feedback on prescribing and education on multimorbidity guidelines and PIP. Healthcare administrative data are a valuable data source to create feedback on prescribing that focuses on common and severe PIP. Furthermore, clinically relevant outcomes have to be defined and assessed, such as improvement of symptoms, attainment of patient-defined drug treatment goals, patient satisfaction with drug treatment, and reduction of drug-related morbidity and unplanned healthcare. PIP is only a process outcome and should be interpreted cautiously, taking into account if shared decision-making has taken place.

It is primary care's mission to offer medical care to the growing group of older multimorbid patients. Stakeholders need to emphasize primary care's authority in relation to other healthcare givers. This is particularly important in view of the uncertainty among GPs regarding their responsibility for the entire drug list. Last but not least, primary care needs financial support in order to meet the medical needs of older multimorbid patients.

6.6 Every coin has two sides

During the course of this research project and during my clinical work with older patients in primary care I have encountered many coins with two sides indeed (figure 20).

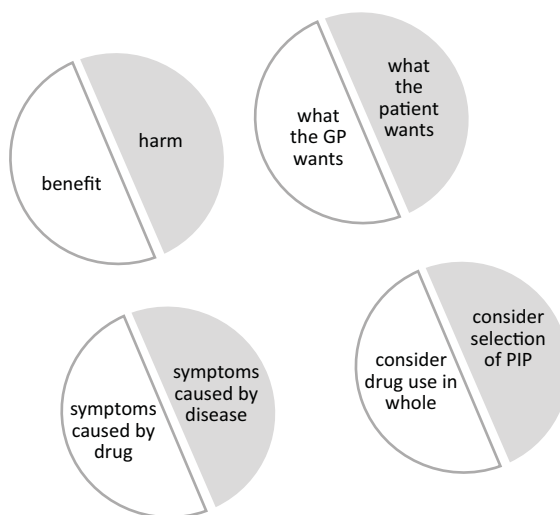


Figure 20. Every coin has two sides. PIP potentially inappropriate prescribing.

The line between benefit and harm of a drug is narrow, as shows the example of enalapril in a patient with heart and renal failure. To weight benefit against harm and to differentiate if symptoms rely on the disease or the drug are major challenges. To make decisions in close communication with patients is important, but may put me in the awkward position to continue harmful drug treatment “because the patient wants it”. Finally, approaches to address PIP in older patients take their departure from the whole drug list (such as medication reviews) or, on the other hand, from a selection of potentially inappropriate medications. Both approaches have advantages and disadvantages and should presumably be combined.

6.7 Conclusions

Potentially inappropriate prescribing in relation to renal function is found in every second to third older patient with impaired renal function in primary care. Excessive dosing was more common than the use of contraindicated drugs. Drug-disease interactions were seen in every tenth older patient, with a predominance of NSAIDs. In general, only a few drugs accounted for the majority of PIP, such as NSAIDs, drugs acting on the renin-angiotensin-aldosterone system, antidiabetics and opioids. Medication reviews that address PIP in its entirety are difficult to implement in primary care and may not improve prescribing in older patients. GPs and nurses expressed their concern that the complexity of care of older patients as well as PIP are a major challenges. They feel that their efforts to achieve appropriate prescribing are undermined by this complexity.

In view of the risks of PIP in older patients it is necessary to continue research into how prescribing may be improved.

7 EPILOGUE

One year ago, her eGFR had been 44 ml/min, but since then her creatinine had not been checked. I asked her to pass by the laboratory and ordered even a blood glucose and hemoglobin level. My plan was to increase the dose of enalapril in case her renal function would allow to do so. This would hopefully improve her heart function and even nycturia. Could I even reduce the dose of her diuretics, in case they worsened her incontinence? I shared my ideas with her. She agreed to a blood sample but was against changes of her heart treatment. “In hospital the doctor increased my heart medicine and the next day I fell because I was so dizzy! No, don’t give me more medicines, leave it as it is.”

Looking on my watch I realized that we had overrun the consultation time by four minutes. “Would it be okay for you to meet the nurse next week? I would like her to go through all your medicines, and to discuss if you have any difficulties in taking them”. I shared the daughters’ concerns about her getting forgetful, and wanted to make sure that she was capable to follow her medication regime. “I will give you a new appointment in four weeks to follow up on your complaints!”

8 ACKNOWLEDGEMENTS

Dear Jan, thank you for guiding me through my entire PhD project. I very much appreciate your kind, thoughtful and decent personality, and your ability to slow me down when I want to go to fast (which sometimes happens!). I liked our numerous discussions bringing me back to what is really important: doing research that is useful for clinicians in primary care.

Dear Björn, you are amazing when it comes to knowing the “right” people – whatever problem has to be resolved (Who may help with data extraction? Who may provide financial support for the participation in a conference? Who knows a jazz band for my party?!), you always establish the necessary contacts! You are really an impressive networker!

Dear Morten, thank you for many informative epidemiological discussions and numerous skype-meetings Sweden-Denmark when I got caught in apparently unresolvable STATA-troubles!

Dear Pia, discovering the richness of qualitative research together with you was a real pleasure! Your positive and encouraging feedback helped me a lot when research frustration took over... I am really looking forward to continue working with you!

In many other European countries, it is not self-evident to get payed for doing research. I therefore feel very privileged to have received generous financial support from Stockholm County Council and the Academic primary health care centre (“forskar-ST”, Pickup 20110538, ALF 20150287, PPG 20160501). Without this support my PhD project would not have been completed.

I would even like to acknowledge all help I received from the Regional Drug and Therapeutics Committee in Stockholm! Thank you, Christine Fransson and Kristina Persson for sharing your teaching experiences and your diaries, and for developing the educational intervention. Neither studies III nor IV would have been possible to perform without this help. Moreover, a big thank you to study nurse Eva Lindevall who recruited all participating primary care practices, and to Maria Juhasz-Haverinen who extracted prescription data. Likewise, I would like to thank the practices, GPs and nurses who participated in studies III and IV.

Bengt Sjöborg, thank you so much for helping me to reveal the secrets of VAL database, for writing numerous SAS enterprise programs, and for adding new variables all along the way...

To my co-authors Monique, Tero and Juan Jesus: Thank you for your important input, revision of paper I, but also practical help in defining “renal PIMs”. Monique, I hope there will be more opportunities to work together in an international research project!

Thank you Hans Lundin, Lina Forssell, Pia Frisk and Tomas Forslund, for sharing your PhD-experiences with me, helping me through some periods of research frustration.

A big thank you to my colleges at Torsviks Vårdcentral, in particular my chief Louise Eggimann – you are all very supportive when it comes to implement research ideas in clinical practice – I appreciate this very much!

Dear Hampus-group, you accompanied me on the last kilometres of this PhD-marathon. In particular, I would like to thank: Anikó Vég for important input regarding paper I, Birgit Eiermann for her comments on paper III, Monica Bergqvist for reviewing paper IV, and Lars L Gustafsson for his valuable comments on this thesis and for giving me the opportunity to present my PhD project. I am very pleased to plan future research projects with you!

As my clinical supervisor at Gärdets Vårdcentral, Ylva Tomson encouraged me to apply for a “forskar-ST”, and established the contact with Jan Hasselström who finally became my main supervisor. Ma chère Ylva – merci pour tout! Sans toi je n’aurais jamais suivi le chemin de recherche!

Liebe Frau Keller, indirekt sind Sie daran „schuld“, dass ich mein Interesse an Forschung überhaupt erst entdeckt habe. Ohne die Heidelberger Forschungserfahrungen mit Ihnen an meiner Seite wäre wohl meine „richtige“ Dissertation nie entstanden!

Dear Mom and Dad, thank you for giving me the opportunity to study medicine. I really love my work! Mom, you learned me how to best organize my work – without this skill I would never have been able to take care of my clinical work, my research interest and three small kids at the same time!

Dear Jan, Rasmus, Frieda and Martin, thank you for laughing with me every day. You remind me constantly of what is most important in life, namely: “eitta utti”!

9 REFERENCES

1. The National Board of Health and Welfare. National indicators for the quality of drug therapy in elderly persons. Stockholm, 2010. <http://www.socialstyrelsen.se/publikationer2010/2010-6-29>
2. World Health Organization. European Health Report. 2012.
3. Kok RM, Reynolds CF, 3rd. Management of Depression in Older Adults: A Review. *JAMA*. 2017;317: 2114-22.
4. Wright JT, Jr., Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373: 2103-16.
5. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation*. 2009;119: 515-23.
6. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380: 37-43.
7. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing*. 2013;42: 62-9.
8. Mangin D, Bahat G, Golomb BA, et al. International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. *Drugs Aging*. 2018.
9. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med*. 2015;13: 74.
10. Hovstadius B, Petersson G, Hellstrom L, Ericson L. Trends in inappropriate drug therapy prescription in the elderly in Sweden from 2006 to 2013: assessment using national indicators. *Drugs Aging*. 2014;31: 379-86.
11. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57: 6-14.
12. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci*. 2002;24: 46-54.

13. Kongkaew C, Noyce PR, Ashcroft DM. Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies. *Ann Pharmacother.* 2008;42: 1017-25.
14. Edwards IR, Biriell C. Harmonisation in Pharmacovigilance. *Drug Saf.* 1994;10: 93-102.
15. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ.* 1997;315: 1096-9.
16. Rochon PA. Drug prescribing for older adults. In: Schmader KE, ed., *UpToDate* edn, 2018.
17. Anderson DC, Postler TS, Dam TT. Epidemiology of Hospital System Patient Falls: A Retrospective Analysis. *Am J Med Qual.* 2016;31: 423-8.
18. Katz MJ, Roghmann M-C. Healthcare-associated infections in the elderly: what's new. *Curr Opin Infect Dis.* 2016;29: 388-93.
19. Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: implications for the importance of primary care in 'case' management. *Ann Fam Med.* 2003;1: 8-14.
20. Anell A. The public-private pendulum--patient choice and equity in Sweden. *N Engl J Med.* 2015;372: 1-4.
21. Masseria C, Irwin R, Thomson S, Gemmill M, Mossialos E. Primary care in Europe. In: Commission E, ed.: *The London school of economics and political science*, 2009.
22. Wandell P, Carlsson AC, Wettermark B, Lord G, Cars T, Ljunggren G. Most common diseases diagnosed in primary care in Stockholm, Sweden, in 2011. *Fam Pract.* 2013;30: 506-13.
23. Wettermark B, Bergman U, Krakau I. Using aggregate data on dispensed drugs to evaluate the quality of prescribing in urban primary health care in Sweden. *Public Health.* 2006;120: 451-61.
24. Rahmner PB, Gustafsson LL, Holmstrom I, Rosenqvist U, Tomson G. Whose job is it anyway? Swedish general practitioners' perception of their responsibility for the patient's drug list. *Ann Fam Med.* 2010;8: 40-6.
25. Forslund T, Wettermark B, Wandell P, von Euler M, Hasselstrom J, Hjemdahl P. Risk scoring and thromboprophylactic treatment of patients with atrial fibrillation with and without access to primary healthcare data: experience from the Stockholm health care system. *Int J Cardiol.* 2013;170: 208-14.

26. Beers MH, Ouslander JG, Rollinger I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med.* 1991;151: 1825-32.
27. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate prescribing: criteria, detection and prevention. *Drugs Aging.* 2012;29: 437-52.
28. Mimica Matanovic S, Vlahovic-Palcevski V. Potentially inappropriate medications in the elderly: a comprehensive protocol. *Eur J Clin Pharmacol.* 2012;68: 1123-38.
29. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63: 2227-46.
30. American Geriatrics Society. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2012;60: 616-31.
31. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med.* 1997;157: 1531-6.
32. Wauters M, Elseviers M, Vaes B, et al. Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalization in a cohort of community-dwelling oldest old. *Br J Clin Pharmacol.* 2016;82: 1382-92.
33. Cooper JA, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. *BMJ Open.* 2015;5: e009235.
34. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet.* 2007;370: 173-84.
35. Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int.* 2010;107: 543-51.
36. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ.* 1997;156: 385-91.
37. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44: 213-8.
38. Fastbom J, Johnell K. National indicators for quality of drug therapy in older persons: the Swedish experience from the first 10 years. *Drugs Aging.* 2015;32: 189-99.

39. Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) List: International Consensus Validation of a Clinical Tool for Improved Drug Treatment in Older People. *Drugs Aging*. 2018;35: 61-71.
40. Hanlon JT, Schmadler KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992;45: 1045-51.
41. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of Potentially Inappropriate Prescribing for Elderly Patients: A Randomized Controlled Trial Using STOPP/START Criteria. *Clin Pharmacol Ther*. 2011;89: 845-54.
42. Hill-Taylor B, Walsh KA, Stewart S, Hayden J, Byrne S, Sketris IS. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria: systematic review and meta-analysis of randomized controlled studies. *J Clin Pharm Ther*. 2016;17: 12372.
43. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Arch Intern Med*. 2011;171: 1013-9.
44. Brown JD, Hutchison LC, Li C, Painter JT, Martin BC. Predictive Validity of the Beers and Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) Criteria to Detect Adverse Drug Events, Hospitalizations, and Emergency Department Visits in the United States. *J Am Geriatr Soc*. 2016;64: 22-30.
45. Anthierens S, Tansens A, Petrovic M, Christiaens T. Qualitative insights into general practitioners views on polypharmacy. *BMC Fam Pract*. 2010;11: 65.
46. The National Board of Health and Welfare (Socialstyrelsen). National indicators for the quality of drug therapy in elderly persons [Indikatorer för utvärdering av kvaliteten i äldres läkemedelsterapi – Socialstyrelsens förslag]. Stockholm, 2003. http://www.demenscentrum.se/globalassets/myndigheter_departement_pdf/03_socialstyrelsen_indikatorer_lakemedel.pdf
47. National Board of Health and Welfare. National indicators for the quality of drug therapy in elderly persons [Indikatorer för god läkemedelsterapi hos äldre]. Stockholm, 2017.
48. Pugh MJ, Starner CI, Amuan ME, et al. Exposure to potentially harmful drug-disease interactions in older community-dwelling veterans based on the Healthcare Effectiveness Data and Information Set quality measure: who is at risk? *J Am Geriatr Soc*. 2011;59: 1673-8.
49. Hellden A, Bergman U, von Euler M, Hentschke M, Odar-Cederlof I, Ohlen G. Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. *Drugs Aging*. 2009;26: 595-606.

50. Khanal A, Peterson GM, Castelino RL, Jose MD. Potentially Inappropriate Prescribing of Renally Cleared Drugs in Elderly Patients in Community and Aged Care Settings. *Drugs Aging*. 2015;32: 391-400.
51. Khanal A, Castelino RL, Peterson GM, Jose MD. Dose adjustment guidelines for medications in patients with renal impairment: how consistent are drug information sources? *Intern Med J*. 2014;44: 77-85.
52. Haddad and Winchester's Clinical management of poisoning and drug overdose. In: Borron SW, Burns MJ, Haddad LM, Shannon MW, Winchester JF, eds., 4th ed. edn. Philadelphia :: Saunders/Elsevier, 2007.
53. Agency MP. Läkemedelsboken, 2014. <https://lakemedelsboken.se/kapitel/hjarta-karl/hjartsvikt.html>
54. The National Board of Health and Welfare (Socialstyrelsen). National indicators for the quality of drug therapy in elderly persons. Stockholm, 2010. <http://www.socialstyrelsen.se/publikationer2010/2010-6-29>
55. Davies DM. Davies's textbook of adverse drug reactions. 5.ed. ed. London: London, 1998.
56. Brenner BM. Brenner & Rector's the kidney. 7th ed. ed. Philadelphia, Pa. London: Philadelphia, Pa. London : W. B. Saunders, 2003.
57. Goldfrank LR. Goldfrank's toxicologic emergencies. 6. ed. ed. Stamford, Conn.: Stamford, Conn. : Appleton & Lange, 1998.
58. Goldfrank LR FN. Goldfrank's toxicologic emergencies. 6. ed. ed. New York: McGraw-Hill, 2006.
59. Shemeikka T, Bastholm-Rahmner P, Elinder CG, et al. A health record integrated clinical decision support system to support prescriptions of pharmaceutical drugs in patients with reduced renal function: design, development and proof of concept. *Int J Med Inform*. 2015;84: 387-95.
60. Arfè A, Scotti L, Varas-Lorenzo C, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ*. 2016;354.
61. FASS. [Swedish medical products list]. <https://www.fass.se/LIF/startpage>
62. Tosato M, Landi F, Martone AM, et al. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. *Age Ageing*. 2014;43: 767-73.
63. Fialova D, Topinkova E, Gambassi G, et al. Potentially inappropriate medication use among elderly home care patients in Europe. *JAMA*. 2005;293: 1348-58.

64. Morin L, Laroche ML, Texier G, Johnell K. Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. *J Am Med Dir Assoc*. 2016;17: 862 e1-9.
65. Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol*. 2015.
66. Opondo D, Eslami S, Visscher S, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. *PLoS One*. 2012;7: e43617.
67. Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol*. 2007;63: 136-47.
68. Salvi F, Marchetti A, D'Angelo F, Boemi M, Lattanzio F, Cherubini A. Adverse drug events as a cause of hospitalization in older adults. *Drug Saf*. 2012;35 Suppl 1: 29-45.
69. Kongkaew C, Hann M, Mandal J, et al. Risk Factors for Hospital Admissions Associated with Adverse Drug Events. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2013;33: 827-37.
70. Howard RL, Avery AJ, Howard PD, Partridge M. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. *Qual Saf Health Care*. 2003;12: 280-5.
71. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365: 2002-12.
72. Johnell K, Fastbom J, Rosen M, Leimanis A. Inappropriate Drug Use in the Elderly: a Nationwide Register-Based Study. *Ann Pharmacother*. 2007;41: 1243-8.
73. Bregnhøj L, Thirstrup S, Kristensen MB, Bjerrum L, Sonne J. Prevalence of inappropriate prescribing in primary care. *Pharm World Sci*. 2007;29: 109-15.
74. Lindblad CI, Hanlon JT, Gross CR, et al. Clinically important drug-disease interactions and their prevalence in older adults. *Clin Ther*. 2006;28: 1133-43.
75. Dreischulte T, Donnan P, Grant A, Hapca A, McCowan C, Guthrie B. Safer Prescribing--A Trial of Education, Informatics, and Financial Incentives. *N Engl J Med*. 2016;374: 1053-64.
76. Patterson SM, Cadogan CA, Kerse N, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2014;10: CD008165.

77. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. *BMJ Open*. 2015;5.
78. Perez T, Moriarty F, Wallace E, McDowell R, Redmond P, Fahey T. Prevalence of potentially inappropriate prescribing in older people in primary care and its association with hospital admission: longitudinal study. *BMJ*. 2018;363: k4524.
79. Dorks M, Allers K, Schmiemann G, Herget-Rosenthal S, Hoffmann F. Inappropriate Medication in Non-Hospitalized Patients With Renal Insufficiency: A Systematic Review. *J Am Geriatr Soc*. 2017;65: 853-62.
80. Gnjidic D, Johnell K. Clinical implications from drug-drug and drug-disease interactions in older people. *Clin Exp Pharmacol Physiol*. 2013;40: 320-5.
81. Lorgunpai SJ, Grammas M, Lee DS, McAvay G, Charpentier P, Tinetti ME. Potential therapeutic competition in community-living older adults in the U.S.: use of medications that may adversely affect a coexisting condition. *PLoS One*. 2014;9: e89447.
82. Aspinall SL, Zhao X, Semla TP, et al. Epidemiology of drug-disease interactions in older veteran nursing home residents. *J Am Geriatr Soc*. 2015;63: 77-84.
83. Hanlon JT, Perera S, Newman AB, et al. Potential drug-drug and drug-disease interactions in well-functioning community-dwelling older adults. *J Clin Pharm Ther*. 2017;42: 228-33.
84. Mand P, Roth K, Biertz F, et al. Drug-disease interaction in elderly patients in family practice. *Int J Clin Pharmacol Ther*. 2014;52: 337-45.
85. Lau M, Tenney J. Evaluation of Drug-Disease Interactions and Their Association with Unplanned Hospital Readmission Utilizing STOPP Version 2 Criteria. *Geriatrics*. 2017;2: 33.
86. Gellad WF, Good CB, Amuan ME, Marcum ZA, Hanlon JT, Pugh MJ. Facility-level variation in potentially inappropriate prescribing for older veterans. *J Am Geriatr Soc*. 2012;60: 1222-9.
87. Santos AP, da Silva DT, Dos Santos Junior GA, et al. Evaluation of the heterogeneity of studies estimating the association between risk factors and the use of potentially inappropriate drug therapy for the elderly: a systematic review with meta-analysis. *Eur J Clin Pharmacol*. 2015;71: 1037-50.
88. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf*. 2007;30: 911-8.

89. Guthrie B, Donnan PT, Murphy DJ, Makubate B, Dreischulte T. Bad apples or spoiled barrels? Multilevel modelling analysis of variation in high-risk prescribing in Scotland between general practitioners and between the practices they work in. *BMJ Open*. 2015;5: e008270.
90. Sinnige J, Braspenning JC, Schellevis FG, et al. Inter-practice variation in polypharmacy prevalence amongst older patients in primary care. *Pharmaco-epidemiol Drug Saf*. 2016;2.
91. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13: 57-65.
92. Hellden A, Bergman U, von Euler M, Hentschke M, Odar-Cederlof I, Ohlen G. Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. *Drugs Aging*. 2009;26: 595-606.
93. Calderon-Larranaga A, Poblador-Plou B, Gonzalez-Rubio F, Gimeno-Feliu LA, Abad-Diez JM, Prados-Torres A. Multimorbidity, polypharmacy, referrals, and adverse drug events: are we doing things well? *Br J Gen Pract*. 2012;62.
94. Dumbreck S, Flynn A, Nairn M, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *BMJ*. 2015;350: h949.
95. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med*. 2010;170: 1648-54.
96. Moen J, Norrgard S, Antonov K, Nilsson JL, Ring L. GPs' perceptions of multiple-medicine use in older patients. *J Eval Clin Pract*. 2010;16: 69-75.
97. Cullinan S, O'Mahony D, Fleming A, Byrne S. A meta-synthesis of potentially inappropriate prescribing in older patients. *Drugs Aging*. 2014;31: 631-8.
98. Spinewine A, Swine C, Dhillon S, et al. Appropriateness of use of medicines in elderly inpatients: qualitative study. *BMJ*. 2005;331: 935.
99. Herrmann ML, von Waldegg GH, Kip M, et al. [GP medication prioritisation in older patients with multiple comorbidities recently discharged from hospital: a case-based bottom-up approach]. *Gesundheitswesen*. 2015;77: 16-23.
100. Mantelli S, Jungo KT, Rozsnyai Z, et al. How general practitioners would deprescribe in frail oldest-old with polypharmacy – the LESS study. *BMC Fam Pract*. 2018;19: 169.

101. Voigt K, Gottschall M, Koberlein-Neu J, Schubel J, Quint N, Bergmann A. Why do family doctors prescribe potentially inappropriate medication to elderly patients? *BMC Fam Pract.* 2016;17: 93.
102. Cullinan S, Fleming A, O'Mahony D, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. *Br J Clin Pharmacol.* 2015;79: 860-9.
103. Clyne B, Cooper JA, Hughes CM, Fahey T, Smith SM. 'Potentially inappropriate or specifically appropriate?' Qualitative evaluation of general practitioners views on prescribing, polypharmacy and potentially inappropriate prescribing in older people. *BMC Fam Pract.* 2016;17: 109.
104. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *BMJ.* 1998;317: 465-8.
105. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ: British Medical Journal.* 2013;347.
106. Rankin A, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev.* 2018;9: CD008165.
107. Lester H, Schmittiel J, Selby J, et al. The impact of removing financial incentives from clinical quality indicators: longitudinal analysis of four Kaiser Permanente indicators. *BMJ.* 2010;340: c1898.
108. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev.* 2016;2: CD008986.
109. Huiskes VJ, Burger DM, van den Ende CH, van den Bemt BJ. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. *BMC Fam Pract.* 2017;18: 5.
110. Campins L, Serra-Prat M, Gozalo I, et al. Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling poly-medicated elderly people. *Fam Pract.* 2017;34: 36-42.
111. Hellden A, Al-Aieshy F, Bastholm-Rahmner P, et al. Development of a computerised decisions support system for renal risk drugs targeting primary healthcare. *BMJ Open.* 2015;5: e006775.
112. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *The Lancet.* 2003;362: 1225-30.

113. Bryan C, Boren SA. The use and effectiveness of electronic clinical decision support tools in the ambulatory/primary care setting: a systematic review of the literature. *Inform Prim Care*. 2008;16: 79-91.
114. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev*, 2008.
115. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev*. 2012;6: CD000259.
116. Grol R, Wensing M, Eccles MP. Improving patient care: implementing change in clinical practice. Oxford: Elsevier, 2004.
117. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust*. 2007;187: 23-30.
118. Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of "Fit for The Aged" (FORTA) on pharmacotherapy and clinical endpoints--a pilot randomized controlled study. *Eur J Clin Pharmacol*. 2014;70: 1261-7.
119. Rossi MI, Young A, Maher R, et al. Polypharmacy and health beliefs in older outpatients. *Am J Geriatr Pharmacother*. 2007;5: 317-23.
120. Garfinkel D. Poly-de-prescribing to treat polypharmacy: efficacy and safety. *Ther Adv Drug Saf*. 2018;9: 25-43.
121. Coleman JJ, van der Sijs H, Haefeli WE, et al. On the alert: future priorities for alerts in clinical decision support for computerized physician order entry identified from a European workshop. *BMC Med Inform Decis Mak*. 2013;13: 111-.
122. Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing". *N Engl J Med*. 1983;308: 1457-63.
123. Johnson MJ, May CR. Promoting professional behaviour change in health-care: what interventions work, and why? A theory-led overview of systematic reviews. *BMJ Open*. 2015;5: e008592.
124. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. *Ther Adv Drug Saf*. 2016;7: 11-22.
125. Alassaad A, Melhus H, Hammarlund-Udenaes M, Bertilsson M, Gillespie U, Sundstrom J. A tool for prediction of risk of rehospitalisation and mortality in the hospitalised elderly: secondary analysis of clinical trial data. *BMJ Open*. 2015;5: e007259.

126. Onder G, Petrovic M, Tangiisuran B, et al. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. *Arch Intern Med.* 2010;170: 1142-8.
127. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008;117: 743-53.
128. Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev.* 2012: Cd008165.
129. Clyne B, Smith SM, Hughes CM, et al. Effectiveness of a Multifaceted Intervention for Potentially Inappropriate Prescribing in Older Patients in Primary Care: A Cluster-Randomized Controlled Trial (OPTI-SCRIPT Study). *Ann Fam Med.* 2015;13: 545-53.
130. Straand J, Fetveit A, Rognstad S, Gjelstad S, Brekke M, Dalen I. A cluster-randomized educational intervention to reduce inappropriate prescription patterns for elderly patients in general practice - The Prescription Peer Academic Detailing (Rx-PAD) study NCT00281450. *BMC Health Serv Res.* 2006;6.
131. Avery AJ, Rodgers S, Cantrill JA, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. *Lancet.* 2012;379: 1310-9.
132. Guthrie B, Kavanagh K, Robertson C, et al. Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. *BMJ.* 2016;354: i4079.
133. Rognstad S, Brekke M, Fetveit A, Dalen I, Straand J. Prescription peer academic detailing to reduce inappropriate prescribing for older patients: a cluster randomised controlled trial. *Br J Gen Pract.* 2013;63: E554-E62.
134. Gjelstad S, Høy S, Straand J, Brekke M, Dalen I, Lindbaek M. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *BMJ.* 2013;347: f4403.
135. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ.* 2008;337: a2390.

136. Grant A, Dreischulte T, Guthrie B. Process evaluation of the data-driven quality improvement in primary care (DQIP) trial: active and less active ingredients of a multi-component complex intervention to reduce high-risk primary care prescribing. *Implementation Science*. 2017;12: 4.
137. Grant A, Treweek S, Dreischulte T, Foy R, Guthrie B. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. *Trials*. 2013;14: 15.
138. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337: a1655.
139. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63: 713-35.
140. Bergman U, Popa C, Tomson Y, et al. Drug utilization 90%--a simple method for assessing the quality of drug prescribing. *Eur J Clin Pharmacol*. 1998;54: 113-8.
141. [Läkemedelsverket] SMPA. Overview of data sources [Översikt över befintliga datakällor]. Uppsala, 2014.
142. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24: 659-67.
143. Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11: 450.
144. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16: 726-35.
145. Runesson B, Gasparini A, Qureshi AR, et al. The Stockholm Creatinine Measurements (SCREAM) project: protocol overview and regional representativeness. *Clin Kidney J*. 2016;9: 119-27.
146. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150: 604-12.
147. Guidelines for ATC classification and DDD assignment 2013. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2012. www.whocc.no
148. Andersson ML, Bottiger Y, Lindh JD, Wettermark B, Eiermann B. Impact of the drug-drug interaction database SFINX on prevalence of potentially serious drug-drug interactions in primary health care. *Eur J Clin Pharmacol*. 2013;69: 565-71.

149. Gustafsson LL, Wettermark B, Godman B, et al. The ‘wise list’– a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. *Basic Clin Pharmacol Toxicol*. 2011;108: 224-33.
150. The National Board of Health and Welfare (Socialstyrelsen). SOSFS 2012:9 Ändring i föreskrifterna och allmänna råden (SOSFS 2000:1) om läkemedels-hantering i hälso- och sjukvården [Changes in regulations and general advices regarding the handling of drugs in the health care system]. Västerås, 2012.
151. Swedish National Board of Health and Welfare. Läkemedelsgenomgångar för äldre ordinerade fem eller fler läkemedel – en vägledning för hälso- och sjukvården [Medication reviews for elderly persons prescribed five or more medications – guidelines for health services]. Stockholm: Socialstyrelsen, 2013. <http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19019/2013-3-18.pdf>.
152. Schmidt-Mende K, Andersen M, Wettermark B, Hasselstrom J. Educational intervention on medication reviews aiming to reduce acute healthcare consumption in elderly patients with potentially inappropriate medicines-A pragmatic open-label cluster-randomized controlled trial in primary care. *Pharmacoepidemiol Drug Saf*. 2017;26: 1347-56.
153. Chang F, O’Hare AM, Miao Y, Steinman MA. Use of Renally Inappropriate Medications in Older Veterans: A National Study. *J Am Geriatr Soc*. 2015;63: 2290-7.
154. Erler A, Beyer M, Petersen JJ, et al. How to improve drug dosing for patients with renal impairment in primary care - a cluster-randomized controlled trial. *BMC Fam Pract*. 2012;13: 91.
155. Hanlon JT, Aspinall SL, Semla TP, et al. Consensus guidelines for oral dosing of primarily renally cleared medications in older adults. *J Am Geriatr Soc*. 2009;57: 335-40.
156. Mansfield KE, Nitsch D, Smeeth L, Bhaskaran K, Tomlinson LA. Prescription of renin-angiotensin system blockers and risk of acute kidney injury: a population-based cohort study. *BMJ Open*. 2016;6: e012690.
157. Duong M, Salvo F, Pariente A, et al. Usage patterns of ‘over-the-counter’ vs. prescription-strength nonsteroidal anti-inflammatory drugs in France. *Br J Clin Pharmacol*. 2014;77: 887-95.
158. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management, 2016. <https://www.nice.org.uk/guidance/ng56/evidence/full-guideline-pdf-2615543103>
159. Royal College of General practitioners. Responding to the needs of patients with multimorbidity, 2016. <http://www.rcgp.org.uk/policy/rcgp-policy-areas/integration-of-care.aspx>

160. Campbell M, Fitzpatrick R, Haines A, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ*. 2000;321: 694-6.
161. Bowen GA. Document Analysis as a Qualitative Research Method. *Qualitative Research Journal*. 2009;9: 27-40.
162. Eriksen J, Gustafsson LL, Ateva K, et al. High adherence to the 'Wise List' treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines. *BMJ Open*. 2017;7: e014345.
163. Hjerpe P, Merlo J, Ohlsson H, Bengtsson Boström K, Lindblad U. Validity of registration of ICD codes and prescriptions in a research database in Swedish primary care: a cross-sectional study in Skaraborg primary care database. *BMC Med Inform Decis Mak*. 2010;10: 23.
164. Zarrinkoub R, Wettermark B, Wändell P, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail*. 2013;15: 995-1002.
165. Spruill WJ, Wade WE, Cobb HH, 3rd. Comparison of estimated glomerular filtration rate with estimated creatinine clearance in the dosing of drugs requiring adjustments in elderly patients with declining renal function. *Am J Geriatr Pharmacother*. 2008;6: 153-60.
166. Bjork J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmö Study cohort. *Scand J Clin Lab Invest*. 2011;71: 232-9.
167. Swedish Council on Health Technology Assessment (Statens beredning för medicinsk utvärdering). Methods to Estimate and Measure Renal Function [Skattning av njurfunktion. En systematisk litteraturoversikt]. Stockholm, 2012.
168. Christensson A, Elmstahl S. Estimation of the age-dependent decline of glomerular filtration rate from formulas based on creatinine and cystatin C in the general elderly population. *Nephron Clin Pract*. 2011;117: c40-50.
169. Merriam SB. Case study research in education: A qualitative approach. San Francisco, 1988.
170. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;3: 77-101.
171. Holmqvist L, Bostrom KB, Kahan T, et al. Prevalence of treatment-resistant hypertension and important associated factors-results from the Swedish Primary Care Cardiovascular Database. *J Am Soc Hypertens*. 2016;10: 838-46.



**Karolinska
Institutet**