Quality of drug treatment in older people

Focus on hip fracture patients and multi-dose drug dispensing

Christina Sjöberg

Department of Internal Medicine and Clinical Nutrition
Institute of Medicine
Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

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“I pray you, in your letters,
When you shall these unlucky deeds relate,
Speak of me as I am; nothing extenuate,
Nor set down aught in malice. Then must you speak
Of one that lov'd not wisely but too well…”

William Shakespeare: Othello Act 5, scene 2

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firstname.lastname@gu.se

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To my beloved Magnus, Cecilia, Annika and Johan

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Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

ABSTRACT

The aim of this thesis was to describe the quality of drug treatment (QDT) regarding fall-risk increasing (FRIDs) and fracture-preventing (FPDs) drugs in older hip fracture patients, to evaluate a method for improving such treatment, and to study the effects of multi-dose drug dispensing (MDD) on drug treatment changes and on QDT.

A descriptive study of FRIDs and FPDs in a cohort of older hip fracture patients preceded a randomised controlled trial, in which the effects of an intervention regarding FRIDs and FPDs were investigated. A case-control study compared drug treatment changes of drugs prescribed via MDD or via ordinary prescriptions. In a register-based cross-sectional study QDT was compared in patients with or without MDD regarding five indicators of prescribing quality.

In older hip fracture patients FRIDs were common, whereas FPDs were scarce. Medication reviews performed by a physician improved the treatment with FPDs after one year, but did not affect the treatment with FRIDs. The odds for a drug to remain unchanged after six months was greater for drugs prescribed via MDD. Potentially inappropriate drug treatment according to indicators for prescribing quality was more common for patients with MDD, also after adjustments for important covariates.

QDT in older hip fracture patients may be improved regarding FPD, whereas extensive use of FRIDs is more difficult to affect. MDD is associated with poor QDT, *i.e.* fewer drug treatment changes and higher prevalence of potentially inappropriate drugs. These findings need to be further evaluated and taken into account when designing MDD systems.

Keywords: older people, hip fracture, osteoporosis, medication review, prescribing, multi-dose drug dispensing, drug treatment, quality indicators
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SAMMANFATTNING PÅ SVENSKA

Ju äldre en människa blir, desto mer komplicerad blir läkemedelsbehandlingen. Det beror att kroppen reagerar annorlunda på läkemedel, men också på att sjukdomarna och läkemedlen blir fler, vilket gör att risken för biverkningar ökar. Patienter som drabbats av höftfraktur är ofta äldre och har många sjukdomar. Vissa läkemedel kan öka risken att falla, medan andra läkemedel förebygger frakturer. I den första studien (Paper I) visades att användningen av fallriskökande läkemedel är hög hos äldre höftfrakturpatienter och att frakturförebyggande läkemedel ofta saknas. I en efterföljande randomiserad studie (Paper II) fick äldre höftfrakturpatienter antingen intervention eller vanlig vård. Interventionen bestod av råd till behandlande läkare om patientens läkemedel. Dessa utarbetades av en geriatriker och förmedlades muntligt och skriftligt till läkaren på sjukhuset vid ett tillfälle och till läkaren på vårdcentralen vid två senare tillfällen. Efter ett år hade inte antalet fallriskökande läkemedel förändrats nämnvärt, medan användningen av frakturförebyggande läkemedel i form av så kallade benaktiva läkemedel nästan hade fördubblats i interventionsgruppen jämfört med gruppen som fick vanlig vård. I enkätsvar från de läkare som tagit emot råden bedömdes uppskattningen och användbarheten av dessa råd bedömdes som hög.

Dosexpedition (ApoDos) används till äldre som inte själva kan klara sin läkemedelshantering. Alla läkemedel ordineras på ett särskilt dosrecept, och läkemedlen fördelas sedan av en maskin i portionspåsar. I en fall-kontrollstudie (Paper III) jämfördes läkemedelsbehandlingen hos höftfrakturpatienter vid utskrivning och sex månader senare. ApoDos-läkemedel var oftare oförändrade efter sex månader jämfört med läkemedel som ordinerats på vanliga recept. I en registerstudie (Paper IV) jämfördes äldre patienter som led av minst två vanliga sjukdomar (hjärtkärlsjukdom, diabetes, astma och KOL). Patienter med ApoDos hade oftare olämplig läkemedelsbehandling än patienter med vanliga recept, när fem nationella indikatorer för kvalitet på läkemedelsbehandling undersöktes.

Sammanfattningsvis ökade användingen av frakturförebyggande läkemedel, medan den höga användningen av fallriskökande inte påverkades av metoden med individuella råd till patientens läkare. Dosexpedition visade sig vara associerat med färre läkemedelsförändringar och med lägre kvalitet på läkemedelsbehandlingen. Dosexpeditionssystemet behöver förbättras för att motverka dessa kvalitetsbrister.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Sjöberg C, Bladh L, Klintberg L, Mellström D, Ohlsson C, Wallerstedt SM. Treatment with fall-risk increasing and fracture-preventing drugs before and after a hip fracture: an observational study.

Drugs Aging 2010;27(8):653-61

II. Sjöberg C, Wallerstedt SM. Improving treatment with fracture-preventing and fall-risk increasing drugs in older hip fracture patients: effects of medication reviews performed by a physician – a randomised controlled study.

Submitted

III. Sjöberg C, Ohlsson H, Wallerstedt SM. Association between multi-dose drug dispensing and drug treatment changes.

Eur J Clin Pharmacol 2012;68(7):1095-101

IV. Sjöberg C, Edward C, Fastbom J, Johnell K, Landahl S, Narbro K, et al. Association between multi-dose drug dispensing and quality of drug treatment - a register-based study.

PLoS One 2011;6(10):e26574

CONTENTS

ABBREVIATIONS

ACE	angiontensin converting enzyme
ADL	activities of daily living
ARB	angiotensin receptor blockers
ASA	American Society of Anesthesiologists physical status classification system
BAD	bone-active drug
Ca+D	calcium plus vitamin D
CI	confidence interval
DXA	dual x-ray absorptiometry
eGFR	estimated glomerular filtration rate
FASS	Farmaceutiska Specialiteter i Sverige (the Swedish Physicians' Desk Reference)
FPD	fracture-preventing drug
FRAX	the WHO Fracture Risk Assessment Tool
FRID	fall-risk increasing drug
GEE	generalised estimating equations
ICD 10	the International Statistical Classification of Diseases and Related Health Problems (10th revision)

KOL	kroniskt obstruktiv lungsjukdom (chronic obstructive pulmonary disease)
MDD	multi-dose drug dispensing
NA	not applicable
NORGEP	the Norwegian General Practice criteria
NSAID	non-steroid anti-inflammatory drug
OP	ordinary prescribing
RCT	randomised controlled trial
SBU	Statens beredning för medicinsk utvärdering (Swedish Council on Technology Assessment in Health Care)
SD	standard deviation
SERM	selective oestrogen receptor modulator
SoS	Swedish National Board of Health and Welfare (Social-styrelsen)
SPDR	Swedish Prescribed Drug Register (Läkemedelsregistret)
SRDD	Swedish Register on Dispensed Drugs (Läkemedels-förteckningen)
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool for Older Person's Prescriptions

DEFINITIONS IN SHORT

ASA	Classifies the status of a patient before surgery as normal healthy (1), mild systemic disease (2), severe systemic disease (3), severe systemic disease that is a constant threat to life (4), or moribund (5)]
ApoDos	The system for multi-dose drug dispensing provided by Apoteket Farmaci, presently the only system in Sweden
Bone-active drugs	Drugs involved in the turnover of bone; in this thesis: bisphosphonates, selective oestrogen receptor modulators, strontium ranelate, and parathyroid hormones
Estimated glomerular filtration rate	calculated from the plasma creatinine level by use of the Cockcroft-Gault formula
Fall-risk increasing drugs	As defined by the Swedish National Board of Health and Welfare in *Indicators for appropriate drug therapy in the elderly* – mainly psychotropics, cardiovascular drugs, and opioids (Table 1).[1] In this thesis also urinary spasmolytics, other parasympatico-mimetics, and beta-blocking eyedrops
Fracture-preventing drugs	Bone-active drugs (bisphosphonates, selective oestrogen receptor modulators, strontium ranelate, and parathyroid hormones) and supplementation with a combination of calcium and vitamin D
Multi-dose drug dispensing	System where all drugs which should be ingested concomitantly are machine-dispensed into labelled unit bags, one for each dose occasion. Special prescriptions

	containing all prescriptions for each patient are used in the Swedish system ApoDos
Ordinary prescribing	Prescribing by use of ordinary prescriptions, different from multi-dose drug dispensing
Social Service Register	Socialtjänstregistret. Holds information on individuals receiving certain municipal services provided for older people and people with functional impairments
Swedish Prescribed Drug Register	Läkemedelsregistret. Holds information on all prescribed drugs that are dispensed to a specific individual at Swedish pharmacies
Swedish Register of Dispensed Drugs	Läkemedelsförteckningen. Holds information on all prescribed drugs that are dispensed to a specific individual at Swedish pharmacies during the preceding 15 months
Vega database	The health care consumption database of Region Västra Götaland

1 INTRODUCTION

Drug treatment in older people is a delicate matter. Not only do these people have numerous diagnoses, which urge for treatment with drugs, but their many drugs may cause side effects and may interact with each other. Furthermore, aging bodies interact differently with drugs, as regards both effects in different organs and drug turnover. Moreover, the patients' autonomy is often decreased, and not infrequently cognition is impaired. Will a further drug do good or will it add to the list of symptoms that may be caused by side effects? Will withdrawal of a drug result in poorer health or will it increase the patient's quality of life? Whether the consideration concerns a new or an existing drug treatment, these questions should arise.

According to the oath of Hippocrates, one of the essential rules of a physician is never to do harm. As patients age, focus is turned to quality of life rather than quantity, and treatment of symptoms gains priority over preventive treatment. Applying these aspects to drug treatment, individual consideration of the patient's condition is crucial. It cannot be done from checklists, but from adopting the art of medicine. Because patients are unique, they must be treated individually based on thorough knowledge and an empathic attitude. The essential basis for decisions on drug treatment is accomplished diagnosing and careful consideration of other treatment alternatives, combined with a flexible attitude to treatment guidelines. Since there are few evidence-based medical studies regarding the oldest old a substantial portion of humbleness must be applied.

Quality of drug treatment

The idea of *quality of drug treatment* refers to different objectives, such as extension of lifetime, higher quality of life, decreased morbidity, or decreased consumption of health care.[2,3] In everyday use, this notion is mostly discussed in terms of balancing the effects and side effects in the individual.[4-6] Nevertheless, the subject can be approached from different perspectives, *i.e.* medical, patients, carers, or economic perspectives.[1]

Many attempts have been made by researchers and other actors in the pharmaceutical area to define quality of drug treatment. But since the perspectives vary, a universal definition is elusive. Terms commonly used are (*in)appropriate prescribing* and *rational prescribing*. These terms do not have a formal definition, but appropriate prescribing sometimes represent an outcome whereas rational prescribing rather represent a process.[7]

When discussing quality of drug treatment in older people, certain themes may be identified, e.g. *overprescribing* of drugs, *underprescribing* of drugs, and *inappropriate prescribing*.[1,2,6] These may be considered with or without regard to the patient's condition. A number of sets of criteria have been established in order to identify such problems; for instance Beers criteria, developed in the United States of America, STOPP (Screening Tool for Older Persons's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment), set out in Ireland, NORGEP (the Norwegian General Practice criteria), and in Sweden: Indicators for appropriate drug therapy in the elderly, given by the Swedish National Board of Health and Welfare.[1,8-10] The Swedish indicators have become widely used for national comparisons of quality of drug treatment. These instruments mostly focus on overprescribing and inappropriate prescribing. They are often, but not always, correlated to diagnoses. Furthermore, many older patients lack treatment with drugs, which would possibly extend their lives or enhance their quality of life.[11-13] Very few criteria relate to such underprescribing. Such an instrument may be exemplified by the Irish START.[9]

Medication reviews

For a long time, geriatricians have focused on the need of clinical overall assessments in older people, including regular *reconsideration* of drug treatment.[4,13-15] Medication reviews imply methods of systematic assessments of patients' medications. Above all they focus on the medication list, checking whether these drugs are optimally prescribed with respect to dosage, side effects, indication, possible interactions, and the patient's pharmacokinetic function, and sometimes also on lack of drug treatment, *i.e.* over-, under- and inappropriate prescribing.[16] Very often instruments based on criteria such as mentioned previously, are used. The results of the medication review may be considered by the prescribing physician in dialogue with the patient, before final decision on *drug treatment changes*, which may be regarded as the outcome of a thorough reconsideration.[17-19]

Medication reviews have been investigated in many studies, usually performed by pharmacists or physicians. Whereas many of these have shown positive results, regarding surrogate endpoints, such as number of drugs, only a few also show positive results regarding hard endpoints, such as mortality, morbidity or admission to hospital.[20-22]

Hip fracture patients

The typical hip fracture patient is frail; he or she is old, suffers from a number of diseases, is treated with several drugs, and is often dependent on assistance on a daily basis.[23] Due to these conditions hip fracture patients

may constitute a model group for frail older patients. Furthermore, since most cases are low-energy fractures, two significant problems in older people are combined; fall accidents and osteoporosis.

Fall accidents are prevalent. Every year falls occur in one-third of people aged ≥65 years; the incidence increasing with patient age.[24] Serious consequences such as fractures and head injuries are frequent. Incidence rates range from 6-22%.[25] The causes of fall accidents are often multifactorial. Common risk factors for falls are old age, female sex, previous fall, impaired gait or balance, impaired vision, impaired cognition and dementia, certain acute and chronic diseases, and drugs.[26] The individual effect of drugs on risk of falls is difficult to estimate, but has been reported to be 8% in nursing homes,[27] whereas they have been estimated to be involved in more than one-half of the falls in demented inpatients.[28]

Fall-risk increasing drugs. Several drug groups have been identified as fall-risk increasing. In clinical studies, the most frequently occurring drug group is *psychotropic drugs*.[29-32] Antipsychotics, antidepressants and anxiolytics/sedatives are all associated with an increased risk of falls, whereas acetylcholinesterase inhibitors and memantine are not shown to have such a relationship. Antipsychotics and benzodiazepines seem to have the strongest correlation to risk of falls.[33]

Cardiovascular drugs are well-known to be associated with risk of falls. Numerous authors refer to the systematic review published by Leipzig et al in 1999, where digoxin, type IA antiarrhythmics, and diuretics were shown to be associated with falls in older people.[34] Due to the obvious risk of causing orthostatic hypotension all antihypertensives are considered as fall-risk increasing. Among the antihypertensives most researchers still consider diuretics to have the strongest association with risk of falls, whereas there is no evident consensus concerning the ranking of the other ones.[35-37]

In addition to psychotropic and cardiovascular drugs, analgesics are often referred to as fall-risk increasing. *Opioids* are commonly associated to falls, whereas non-steroidal anti-inflammatory drugs (NSAIDs) show such an association in some studies.[37,38] Besides analgesics, some other drug groups are often mentioned, e.g. urinary spasmolytics, antiparkinsonian drugs, anti-epileptics, and beta-blocking eye drops.[20,39-42] For Swedish purposes, drug groups associated with risk of falls are given by the Swedish National Board of Health and Welfare, presented in Table 1.[1]

Table 1. Fall-risk increasing drugs according to the Swedish National Board of Health and Welfare

Main drug groups	Drug group
Psychotropic drugs	Antipsychotics (not lithium) Anxiolytics Hypnotics and sedatives Antidepressants
Cardiovascular drugs	Vasodilators for cardiac diseases Antihypertensives Diuretics Beta-blocking agents Calcium channel blockers ACE-inhibitors, ARB
Analgesics	Opioids
Others	Alpha-blocking drugs for prostatic hyperplasia Antiparkinsonian dopaminergic drugs

ACE-inhibitors, angiontensin converting enzyme inhibitors; ARB, angiotensin receptor blockers

Fracture-preventing drugs. The diagnosis osteoporosis refers to decreased bone mineral density compared to that of young individuals of the same sex, and its clinical manifestations are low-energy fractures.[43] Clearly, in hip fracture patients osteoporosis is prevalent in most of the patients.[44]

Several drugs may increase bone mineral density and are also shown to decrease the risk of low-energy fractures. Drugs interfering with bone turnover have been shown to be effective, such as *bisphosphonates*, which inhibit the osteoclasts in the digestion of bone. These are usually given as weekly pills, but may also be administered intravenously once a year. Besides the first-line treatment with bisphosphonates, a number of other bone-active drugs are available: *selective oestrogen receptor modulators* (SERMs), *strontium ranelate*, and *parathyroid hormone*. The latter stimulate the osteoblasts, *i.e.* bone tissue is produced, as opposed to the other bone-active drugs, which slow down bone loss. Since our studies were performed, another bone-active drug has been introduced; *denosumab*, a human monoclonal antibody inhibiting the maturation of pre-osteoclasts into osteoclasts. In addition to these bone-active drugs, supplementation with *calcium plus vitamin D* has been shown to reduce the fracture incidence in females aged ≥80 years in nursing homes, whereas calcium or vitamin D given separately have not shown convincing results.[45-47] At the time of the studies in this thesis the Swedish Medical Products Agency recommended bone-active drugs combined with calcium plus vitamin D as first-line therapy. In women and men aged ≥80 years at high risk of fractures monotherapy with calcium plus vitamin D was recommended to be

considered in cases where bone-active drug treatment was not suitable (Table 2).

Table 2. Drug treatment recommended for patients at high risk of fractures according to the national guidelines published in 2007[48]

Patient group	**First-line therapy**	**Second-line therapy** (not in order of rank)
Women	Bisphosphonates*	Parathyroid hormone* Raloxifene (SERM) * Strontium ranelate* Oestrogen*
Men	Alendronate* Risedronate*	
Women and men ≥80 years, where bone-active drugs are not suitable	Calcium + vitamin D	

*All bone-active drugs should be combined with calcium + vitamin D as basic therapy
SERM, selective oestrogen receptor modulator

However much suffering low-energy fractures causes for the patients in terms of increased mortality and morbidity, decreased autonomy, and numerous inpatient days, osteoporosis is neither sufficiently diagnosed nor treated.[49,50] In part, this may be explained by the fact that the diagnosis is based on measurement of bone densitometry, *i.e.* dual x-ray absorptiometry (DXA), and equipment for such measurement is not available in every hospital. Moreover, according to the national guidelines, indications for drug treatment relate to the value of bone mineral density.[48] Besides the diagnostic procedure, the recommended drugs are associated with a number of contraindications and adverse drug reactions, as well as complicated dosing regimens. Thus, even if fracture-preventing drug treatment is initiated, compliance tends to be poor.[51-53] In addition to these circumstances, osteoporosis is strongly correlated to high age, and there may be a hesitation to add further drugs to the medication list of old patients, who have a short expected survival time, who suffer from several diseases, and who are already being treated with an ample number of drugs.[54]

For calculation of the fracture risk, the World Health Organization has developed FRAX (the WHO Fracture Risk Assessment Tool), unique for every country.[55] From this tool, the 10-year probability of a major osteoporotic fracture and that of a hip fracture may be calculated with or without knowledge of the patient's bone mineral density. The instrument has been emphasised by the Swedish National Board of Health and Welfare in

the National Guidelines for the Musculoskeletal Diseases, published in 2012, as the basis for decisions on further investigation concerning osteoporosis in every patient.[56]

In the treatment of patients who have sustained low-energy fractures like hip fractures, the quality of drug treatment becomes crucial. Such a life-threatening trauma calls for reconsideration of the drug treatment. Notwithstanding the fact that these frail older patients are often treated with several fall-risk increasing drugs, the same patients also tend to lack treatment with fracture-preventing drugs.[20,49,57] Drug treatment of frail older patients should be changed in order to minimise the risk of new falls and fractures while keeping other diseases adequately treated and preserving the patients' quality of life.

Multi-dose drug dispensing

Multi-dose drug dispensing is a system intended for patients on regular medication with difficulties in handling their own drugs owing to physical or cognitive impairment. The prescribed drugs are machine-dispensed into disposable plastic sachets, one for each dose occasion. Each unit bag is labelled with patient data, drug contents, and time for intake. However, almost half of the prescribed drugs may not be dispensed into the unit bags, such as chewing tablets and liquids, or due to the fact that they are intended for use as needed. Hence, they are delivered in original packages on request. Nevertheless, the ready-dispensed drugs facilitate the work for nurses, who save 10-20 minutes per patient and week.[58]

In Sweden, multi-dose drug dispensing is supplied by Apoteket Farmaci under the name of ApoDos. This system has become frequent in Sweden and is used by 185,000 inhabitants today. Many of the users are found among older people and residents in nursing homes. In Region Västra Götaland, 18% of the inhabitants aged 75 years and over use this system (L Gustafsson, personal communication, November 18, 2012).

In addition to the altered dispensing, the prescribing routine is different from that of ordinary prescribing. A specific multi-dose drug prescription is used, which contains all drugs prescribed to the same patient. This document, available electronically, but outside the medical record system, is used by all prescribers and may be also be accessed by nurses. In this way, the multi-dose drug prescription often serves as the medication list of the patient.

Multi-dose drug dispensing has been identified as a factor of importance for the quality of drug treatment, both in research studies and by prescribers.[18,59-

[63] Evidence on disadvantages with this system exists regarding higher use of inappropriate drugs and higher number of medication errors at discharge from hospital.[61,63,64] For many years, the prescribers have called attention to the complicated and time-consuming handling of the system. In addition, the existence of a "renew-all-prescriptions button" in the multi-dose drug dispensing system has facilitated renewal of all the drugs of a patient by one click. Concerns have been raised that these properties of the system counteract reconsideration and changes of the drug treatment and hence contribute to a higher number of drugs in multi-dose drug users.[18,61,62,65] Indeed, these issues are discussed in two doctoral theses defended in 2012.[66,67]

2 AIM

2.1 Overall aim

To investigate the quality of drug treatment in older people as regards over- and underprescribing and the effects of medication reviews in hip fracture patients as well as drug treatment changes and inappropriate prescribing in patients with multi-dose drug dispensing

2.2 Specific aims

The specific aims of the four papers included in this thesis are:

I To describe the treatment with fall-risk increasing and fracture-preventing drugs before and after a hip fracture

II To investigate if medication reviews performed by a physician can improve the treatment with fracture-preventing and fall-risk increasing drugs in older hip fracture patients and to evaluate the targeted physicians' opinion on this intervention

III To elucidate if there is an association between drug treatment changes and multi-dose drug dispensing

IV To analyse if multi-dose drug dispensing is associated with inappropriate prescribing measured by established indicators for prescribing quality

3 PATIENTS AND METHODS

The studies in this thesis comply with the Declaration of Helsinki. Ethics approvals from the Regional Ethical Review Board in Gothenburg were obtained before recruitment of patients. Complete and detailed descriptions of patients and methods are provided in each publication or manuscript.

3.1 Patients and data collection

The patients in the four study cohorts and the sources for data extraction are briefly described in Table 3.

Table 3. Patients, settings, inclusion period, and data sources included in the four studies in this thesis

Study	**I**	**II**	**III**	**IV**
Number of patients	100	199	154	24,146
Patients	Hip fracture patients aged ≥65 years	Hip fracture patients aged ≥65 years	Hip fracture patients aged ≥65 years	Individuals aged ≥65 years with ≥1 drugs and ≥2 concomitant chronic diseases
Setting	Sahlgrenska University Hospital/ Mölndal	Sahlgrenska University Hospital/ Mölndal	Sahlgrenska University Hospital/ Mölndal	Region Västra Götaland
Inclusion period	March – April 2008	April – September 2009	March – April 2008 +April – Sept 2009	December 31st, 2007
Data sources	- Medical records at Sahlgrenska University Hospital - Swedish Register of Dispensed Drugs	- Medical records at Sahlgrenska University Hospital and in primary care - Interviews - Swedish Register of Dispensed Drugs - Vega database*	- Medical records at Sahlgrenska University Hospital and in primary care - Swedish Register of Dispensed Drugs	- Swedish Prescribed Drug Register -Vega database* - Social Service Register

* Vega database, the healthcare consumption database of Region Västra Götaland

For **Papers I, II** and **III** two cohorts of consecutively recruited hip fracture patients, aged ≥65 years, were used. The inclusion criteria were (i) hospitalisation at Sahlgrenska University Hospital after surgery, and (ii)

residence in the region of the hospital. Informed consent was obtained from the patients or by informing their next of kin. For Paper III, all patients alive at six months from the cohort in Paper I (Cohort I) and all control patients alive at six months from the cohort in Paper II (Cohort II) were included if they used the same prescribing mode (multi-dose drug dispensing or ordinary prescribing) at discharge from hospital and at six-month follow-up (Cohort III), as described in Figure 1.

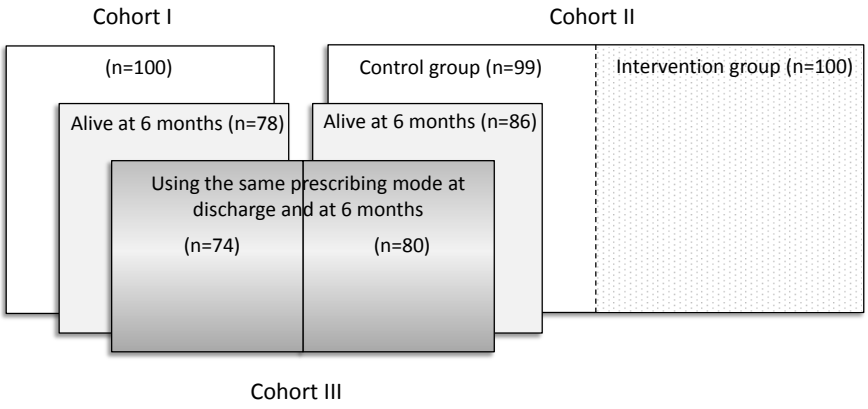

Figure 1. Description of patients included in the study of Paper III (n=154)

In **Paper IV**, a register study, all individuals aged ≥65 years living in the Region Västra Götaland on December 31st 2007 that had filled at least one drug prescription in the three month period preceding December 31st 2007, and if they had at least two diagnoses among specified common diseases (obstructive pulmonary disease, diabetes mellitus, and cardiovascular disease), which each had been the subject for at least two health care contacts (Cohort IV) (Figure 2).

Table 4. Data on burden of disease registered in the studies in this thesis

I	II	III	IV
- Diagnoses registered in the medical records - BMI - eGFR - Type of fracture - Risk factors for fractures - FRAX score	- ASA score - BMI - eGFR - Type of fracture - Risk factors for falls - Risk factors for fractures - FRAX score	-	- Number of diagnoses registered in the Vega database - Prevalence of any psychiatric diagnosis registered in the Vega database

ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index; eGFR, estimated glomerular filtration rate; FRAX, the WHO Fracture Risk Assessment Tool

Patient characteristics

For all four papers data on *age*, *sex*, and *residence* were collected. In Papers I, II, and III these data were derived from the medical records and from the multi-dose drug dispensing prescriptions, whereas they were obtained from the Swedish Prescribed Drug Register and the Social Service Register for Paper IV. *Burden of disease* was estimated in different ways in the studies, as described in Table 4. Furthermore, in Papers I, II, and III, *cognition* was estimated using a three-level scale (not impaired, impaired, or demented) based on status at inclusion and information from the medical records. No such information could be obtained for Paper IV.

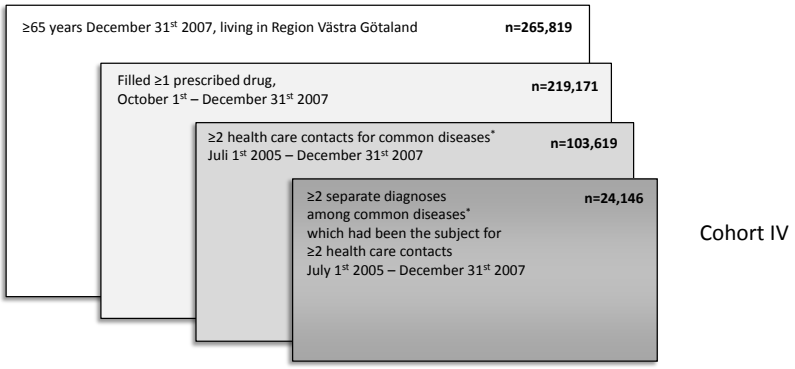

Figure 2. Description of patients included in Paper IV
**Obstructive pulmonary diseases, diabetes mellitus or cardiovascular diseases*

Drug treatment

Papers I, II, and III. At admission the medication list in the medical records was completed with information from the Swedish Register of Dispensed Drugs. At discharge the medication list in the medical records was used. At 6-month follow-up the Swedish Register of Dispensed Drugs was used. Drugs used regularly and as needed were included. Drugs for external use were excluded if they did not have systemic effects, *i.e.* tear substitutes, most topical medications, and preparations for treatment of xerostomia. A drug for regular use was considered to be in current use if the collected amount of the drug would last for treatment with the prescribed dose in 80% of the days covering the present date. A drug for use as needed was assessed to be in current use if the collected amount of drugs would last for treatment with at least one daily prescribed dose in 80% of the days covering the present date.

The selection of *fall-risk increasing drugs* used in this thesis is based on those identified by the Swedish national Board of Health and Welfare (Table 1) with addition of urinary spasmolytics and other parasympathicomimetics,

e.g. orphenadrine and chlorzoxazone, due to their potential to cause dizziness and confusion.[1] Furthermore, betablocking eyedrops were included because of their blood pressure lowering effects. *Fracture-preventing drugs*, *i.e.* bone-active drugs and supplementary calcium plus vitamin D according to Table 2, were also identified.

Paper IV. For collection of data on drug treatment the Swedish Prescribed Drug Register was used. An estimated medication list at December 31st, 2007 was constructed based on the drug prescriptions filled between October 1st and December 31st, 2007. This estimation was carried out by taking advantage of the method used by the Swedish National Board of Health and Welfare for calculation of the national yearly comparisons of results on indicators of prescribing quality.[68] By this method the drugs were estimated to be in current use if the date of filling the prescription and the amount dispensed was sufficient to cover December 31st. Incomplete or missing dosages were replaced by the mean daily dosage of the known dosages in the dataset. Drugs prescribed as needed were considered to be 50% of the dosage for regular use. For patients using multi-dose dispensed drugs, drugs dispensed every two weeks were judged to be in current use if prescribed within the last fourteen days, whereas the drugs delivered in original packages were managed in the same way as the ordinary prescribed drugs.

Mode of prescribing (multi-dose drug dispensing or ordinary prescribing) was collected from the Swedish Register of Dispensed Drugs in Papers I, II, and III, and from the Swedish Prescribed Drug Register in Paper IV.

3.2 Methods

Different methods were used in the four studies in this thesis, as shown in Table 5. The first observational study (Paper I) was performed to provide a basis for the randomised controlled trial in Paper II by observing the prescribing of fall-risk increasing and fracture-preventing drugs before and after a hip fracture. The interventional study (Paper II) was planned to be easy to integrate in clinical practice if successful and to be smooth for the patients. Hence the intervention performed in the patients allocated 1:1 consisted of medications reviews focusing on treatment with fall-risk increasing and fracture-preventing drugs. These were performed at three times (during the hospital stay and 3-5 months and 6-8 months after the hip fracture) by a geriatrician (the author) and forwarded orally and as a written document along with assessments of risk of falls and fractures to the prescribing physicians at the ward and at the primary health care centre. An

example of such a medication review is given in the Appendix. No further contact was made with the patients.

Table 5. Description of study designs, outcomes and statistics used in this thesis

Study	**I** n=100	**II** n=199	**III** n=1980 drugs (in 154 patients)	**IV** n=24,146
Design	Descriptive	Randomised controlled trial	Case-control	Cross-sectional register-based
Follow-up period	6 months	12 months	6 months	NA
Comparison	NA	Intervention (medication review at 3 times to prescribing physicians) vs control (standard care)	Drugs prescribed via MDD vs drugs prescribed via OP	Patients using MDD vs patients using OP
Outcomes	Fall-risk increasing and fracture-preventing drugs - at admission to hospital - at discharge - at 6 months	(i) Fall-risk increasing and fracture-preventing drugs at 12 months (ii) Physicians' attitudes towards the intervention	Changed (added, dosage adjusted, withdrawn) and unchanged drugs from discharge to 6 months	Presence of (i) Ten or more drugs (ii) Long-acting benzodiazepines (iii) Drugs with anticholinergic action (iv) Three or more psychotropics (v) Drug combinations that should be avoided
Statistics	- Wilcoxon signed-rank test - Mann-Whitney U test	- Mann-Whitney U test - Chi-square test	- Multi-level regression analysis	- Logistic regression analysis

MDD, multi-dose drug dispensing; NA, not applicable; OP, ordinary prescribing

In Paper III we took advantage of the two cohorts of hip fracture patients, as previously described. Drug treatment ought to be changed in hip fracture patients after discharge from hospital, e.g. temporary drug treatment, such as pain treatment, low molecular weight heparin, and drugs for treatment of constipation have to be withdrawn, and the drug treatment should be reviewed to reduce the risk of new falls and fractures. Hence, their drugs were found to be suitable for investigating the expected association between multi-dose drug dispensing and a lower degree of changes in drug treatment.

This was performed by a case-control study of the drugs used by these patients.

Finally, a cross-sectional register-based study (Paper IV) based on more than 24,000 older individuals was performed to compare the prevalence of inappropriate prescribing in multi-dose drug dispensing users and in those using ordinary prescriptions.

4 RESULTS

4.1 Patient characteristics

The four papers in this thesis all focused on old and frail people. Whereas Papers I, II, and III concerned hip fracture patients, Paper IV investigated the drug treatment in old people suffering from at least two common diseases. As described in Table 6, these patients were at high age and use many drugs.

Table 6. Patient characteristics at inclusion in the four study cohorts

Study	**I** (n=100)	**II** (n=199)	**III** (n=154)	**IV** (n=24,146)
Mean age, years	84	84	84	77
Female sex, %	73	66	74	51
Impaired cognition, %	50	45	48	-
Living in a nursing home at inclusion, %	35	30	47*	6.1
Multi-dose drug dispensing, %	49	49	69**	20
Number of drugs, n	8.0	7.2	10.9**	7.4

* At six months
** At discharge from hospital

Papers I and II

Patient characteristics of the two hip fracture cohorts are presented in Table 6. Mean age in both hip fracture cohorts, as well as the cohort selected in Paper III, was 84 years. Females constituted 73% and 66% in the two cohorts. At admission to hospital approximately one third of the patients were living in nursing homes whereas this proportion had risen to more than half of the patients at discharge (66% and 55% respectively). Six months later some patients had returned to their own homes, but a larger proportion than at admission was still living in nursing homes (49% and 39%, respectively).

Concomitant diseases, as heart diseases, hypertension, current or past history of cancer, diabetes mellitus, past history of stroke, and hypothyreoidism were frequent. Impaired cognition was prevalent in nearly half of the patients out of which fully half suffered from dementia. Further data on burden of disease are given in Table 7. Whereas many patients had sustained a previous low-energy fracture in both hip fracture cohorts, the diagnosis osteoporosis was

Table 7. Patient characteristics regarding burden of disease

	Paper I (n=100)	**Paper II** (n=199)
Estimated glomerular filtration rate <40 ml/min, n/total n (%)	24/79 (30)	51/190 (26)
Body mass index <20, n/total n (%)	17/75 (23)	26/182 (13)
ASA ≥3, n (%)	-	103 (52)
Fall-risk factors, n (median [IQR])	-	4 (3-5)

ASA, American Society of Anesthesiologists physical status classification system [classifying the status of a patient before surgery as normal healthy (1), mild systemic disease (2), severe systemic disease (3), severe systemic disease that is a constant threat to life (4), or moribund (5)]; IQR, interquartile range, SD, standard deviation.

scarce in the discharge notes, as shown in Table 8. The fracture probabilities according to FRAX, requiring data on body weight and length for calculation, could be determined for 71 patients in Cohort I and for 190 patients in Cohort II.

Table 8. Patient characteristics regarding hip fractures and osteoporosis in Cohorts I and II

	I n=100	**II** **Intervention** n=100	**Control** n=99
Low-energy hip fracture, n	93	94	94
Previous low-energy fracture, n	43	54	58
Previous DXA, n	10	13	10
Diagnosis of osteoporosis in discharge notes, n	14	21	15
Referral to DXA at discharge, n	5	18	6
FRAX, 10-year probability of a major osteoporotic fracture, % (median)	35	34	35
FRAX, 10-year probability of a hip fracture, % (median)	18	18	20

DXA, dual x-ray absorptiometry; FRAX, the WHO Fracture Risk Assessment Tool

Fall-risk factors were investigated in Paper II. Median number (IQR) of the seven studied risk factors was 4 (3-5). The prevalence of the different risk factors is described in Table 9.

Table 9. Prevalence of fall-risk factors in Paper II

Fall-risk factor	**%**	**n/n of assessed patients**
Previous fall preceding year	71	128/181
Impaired gait or balance	86	171/198
Orthostatic reaction	32	44/139
Impaired vision	47	81/173
Impaired cognition/dementia	45	89/199
Need of assistance for ADL	51	99/196
Fall-risk increasing drugs	89	177/199

ADL, activities of daily living

In both papers *mortality* was high. In Paper I four out of 100 patients and Paper II seven out 199 patients were deceased during the hospital stay. After six months a further 18 patients were deceased in Paper I and a further 27 patients in Paper II (21 out of 100 patients in the intervention group and 13 out of 99 patients in the control group). After one year a total of 46 patients were deceased in Paper II; 27 out of 100 patients in the intervention group and 19 out 99 patients in the control group (P= 0.19). None of the deaths in the intervention group was judged to be associated with the intervention.

Mean number of *overall drug treatment* is presented in Table 10. In Paper I the mean number of drugs increased by just under three drugs at discharge from hospital. By six months the mean number of drugs had decreased and was slightly lower than at admission. In Paper II there were not any significant differences in mean numbers of drugs between the intervention and the control group. The development of number of drugs followed the same pattern as in Paper I, showing a considerable increase at discharge and an equivalent decline the following year.

Table 10. Mean number of drugs at admission, at discharge and at six-month and twelve-month follow-up in Cohorts I, II and III

Study	**I**	**II**		**III**
		Intervention	Control	
Mean number of drugs at admission	8.0	7.5	6.8	-
Mean number of drugs at discharge	10.8	11.4	10.2	10.9
Mean number of drugs at six months	7.4	9.2	7.2	7.8
Mean number of drugs at twelve months	-	7.8	7.1	-

Paper III

The cohort in Paper III constitutes about half of the patients from the cohorts in Papers I and II. Hence the patient characteristics are mainly corresponding

to these cohorts, which is evident from Table 6. However, due to the higher mortality in men than in women sustaining hip fractures, females constituted a larger proportion after six months than at admission to hospital. Hence the percentage of females was higher in Paper III. At admission to hospital 31% of the patients in this cohort were living in nursing homes and 63% were discharged to nursing homes. The mean total number of drugs at discharge and at six months was in concordance with those of Cohort I and II, *i.e.* 10.9 drugs at discharge and 7.8 at six months, as shown in Table 10.

Comparison between the multi-dose drug dispensing and the ordinary prescribing patient groups in Papers III and IV is presented in Table 11. Multi-dose drug dispensing patients were older, suffered more often from impaired cognition, lived more often in nursing homes, and used more drugs, whereas female sex was equally common. The subgroup analysis in Paper III, where only community-dwelling patients (n=81) were included, presented similar characteristics: they were older, suffered more often from impaired cognition, and had a higher total number of drugs, whereas female sex was equally common.

Table 11. Patients characteristics in multi-dose drug dispensing and ordinary prescribing groups in Paper III and IV

	Cohort III		**Cohort IV**	
	MDD (n=107)	**OP** (n=47)	**MDD** (n=4,927)	**OP** (n=19,219)
Mean age, years	87	79	81	76
Female sex, %	74	74	58	49
Living in nursing homes, %	67	2	28	0.6
Mean number of diagnoses, n	-	-	17	13
Mean number of drugs*, n	13.2	12.1	10.3	6.6
Impaired cognition, %	64	11	-	-

*For Paper III, total number of drugs
MDD, multi-dose drug dispensing; OP, ordinary prescribing

Paper IV

The cohort consisted of 24,246 patients, which implies that the study included about one eleventh of all inhabitants in the Region Västra Götaland at the end of 2007. As presented in Table 11, patient characteristics differed (all $P<0.0001$) between multi-dose drug dispensing users and users of ordinary prescribing regarding age, female sex, mean number of diagnoses, mean number of drugs, and residence in a nursing home. At the time of the study, multi-dose drug dispensing was more or less mandatory for people in

nursing homes, which is illustrated by the fact that out of the 1,475 individuals living in nursing homes only 113 used ordinary prescribing, *i.e.* 7.7%.

4.2 Fall-risk increasing drugs (Papers I, II)

In Paper I we found that fall-risk increasing drugs were common. This is shown in Figure 3, which presents the results of Paper I. The distribution of prevalence and mean numbers of subgroups of fall-risk increasing drugs correspond and point not only to the fact that the prevalence of these drugs was high, but also to that this treatment was extensive.

In both studies the prevalence and mean number of opioids increased considerably during the hospital stay, but decreased to the prefracture level after six months, due to opioid pain treatment after surgery. After six months the prevalence of opioid treatment had returned to the prefracture level. Regarding psychotropics and cardiovascular drugs, the prevalence and mean number of drugs did not change from admission to discharge or six months later. Furthermore, a subgroup analysis in Paper I did not find any significant changes in prevalence of any subgroups of psychotropics, cardiovascular drugs, or other fall-risk increasing drugs from admission to six months.

Table 12. Fall-risk increasing drugs at admission, discharge, 6 months, and 12 months I Papers I and II. Values are presented as mean (± SD)

	Paper I (n=100)	**Paper II** Intervention (n=100)	**Paper II** Control (n=99)
Admission	3.30 ± 2.05	3.08 ± 2.23	3.06 ± 1.89
Discharge	4.30 ± 2.12	3.86 ± 2.06	4.21 ± 1.99
6 months	3.08 ± 1.99	3.03 ± 2.15	3.33 ± 2.32
12 months	-	2.85 ± 2.05	3.09 ± 2.22

The mean number of fall-risk increasing drugs in the randomised controlled trial (Paper II) was corresponding to those in Paper I presented in Table 12. There were no significant differences in mean number of fall-risk increasing drugs between the intervention and the control group. Moreover, no significant differences were seen in major drug groups (psychotropics,

cardiovascular drugs, opioids, and other fall-risk increasing drugs) between the intervention and the control group.

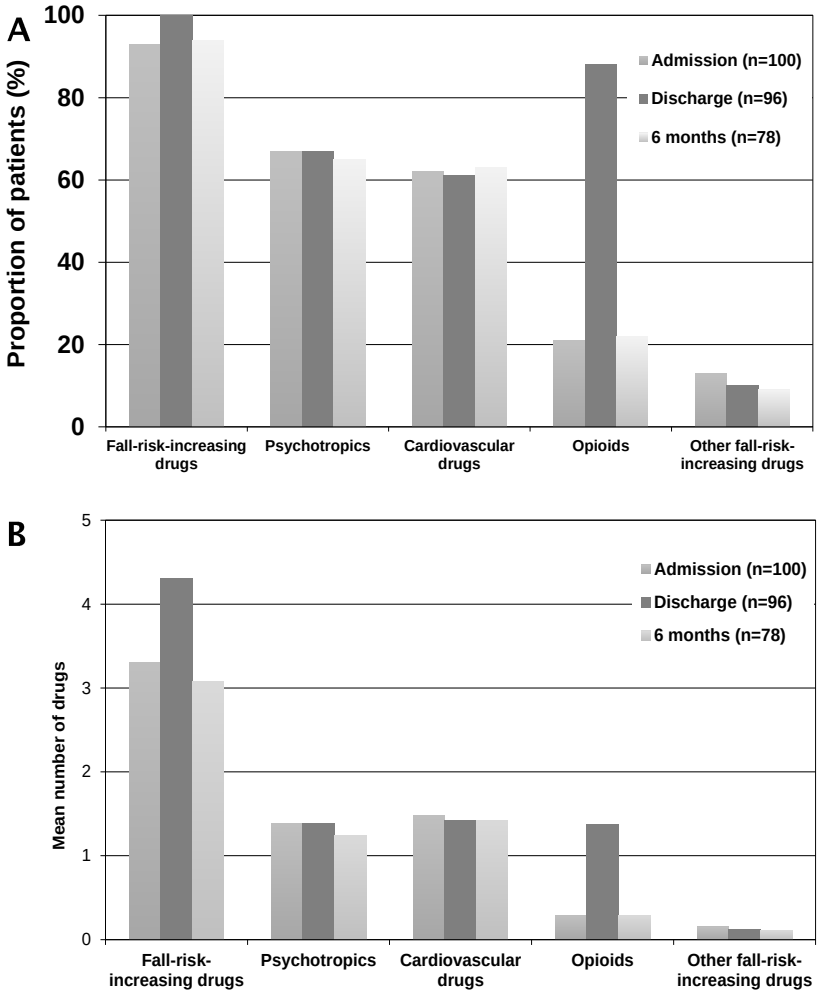

Figure 3. Proportion of patients (A) and mean number (B) of fall-risk increasing drugs and subgroups of fall-risk increasing drugs at admission to hospital, at discharge from hospital and at six-month follow-up in Paper I

4.3 Fracture-preventing drugs (Papers I, II)

Despite the fact that 43 patients (43%) were known to already have had sustained a previous low-energy fracture in Paper I, only 5% of the patients were treated with bone-active drugs at admission. In Paper II 112 patient (56%) were known to have sustained a previous low-energy fracture, and 12% used bone-active drugs at admission. Concerning any fracture-preventing drug, these drugs were used by 17% in Paper I at admission, and by 28% in Paper II.

In Paper I, no additional bone-active drugs were prescribed to patients during the hospital stay, whereas a further three patients in the intervention group and four patients in the control group had such drugs prescribed at discharge in Paper II, as presented in Table 13. According to the guidelines at that time, monotherapy with calcium plus vitamin D was used as fracture-preventing. Thus, in Paper I, 33% of the patients were prescribed any fracture-preventing drug at discharge, whereas these figures were 62% and 72% in the control and intervention groups in Paper II. Apart from this, the medication reviews identified contraindications for bone-active drugs in three patients on such treatment in the intervention group during the hospital stay. Hence this treatment was withdrawn. In the control group no such patients were identified, whereas two patients were not noticed to be on such drug treatment during the hospital stay. Accordingly these drugs were not included in the discharge notes. For this reason they were registered as withdrawn during the hospital stay and as newly prescribed at six months.

Table 13. Number of patients treated with bone-active drugs at admission, discharge, 6 and 12 months in the randomisation groups (Paper II)

	Intervention				**Control**			
	Addition	With-drawal	Deceased	Sum	Addition	With-drawal	Deceased	Sum
Admission				12				11
Discharge	+3	-3	-1	11	+4	-2	0	13
6 months	+6	-1	0	16	+4	-4	0	13
12 months	+6	-1	0	21	+2	0	-3	12

In Paper I, from discharge to six months a further four patients were treated with bone-active drugs, *i.e.* a total of 10%. The proportion of any fracture-preventing drug treatment had increased from 33% to 37%. In Paper II the corresponding figures at six months in the control and intervention groups of bone-active drugs were 15% and 20%, respectively. Regarding prevalence of any fracture-preventing drug at six months, the proportions were 53% and 70%, respectively, in the control and intervention groups.

In Paper II fracture-preventing drug treatment was studied at twelve months, as shown in Figure 4. In the control group 15% used bone-active drugs at twelve months, whereas 29% did so in the intervention group. This means that from admission to twelve months the absolute increase in percentage points as regards proportion of patients treated with bone-active drugs was 4% for control patients and 17% for intervention patients. Regarding use of any fracture-preventing drug, the proportion of patients had increased to 58% in the control group and to 77% in the intervention group.

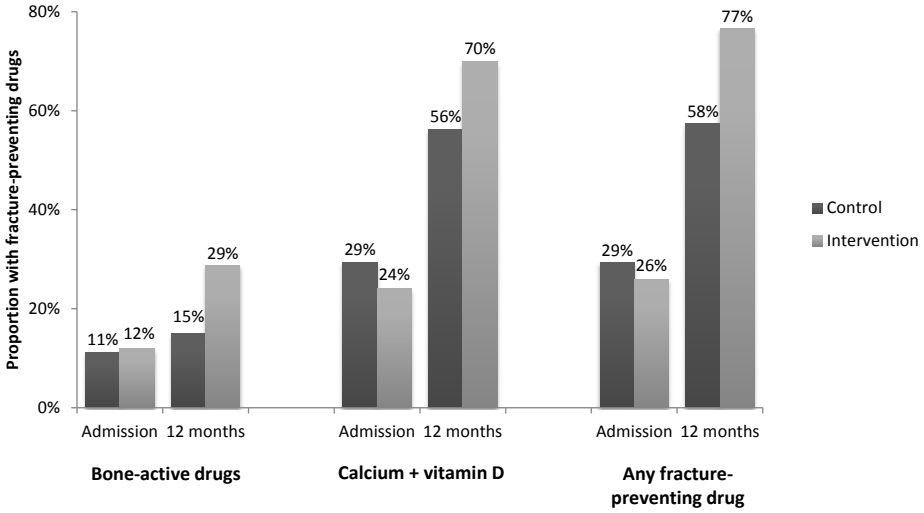

Figure 4. Proportion of patients treated with fracture-preventing drugs at admission and at 12 months in the randomisation groups in Paper II

In Paper I five patients were referred to dual x-ray absorptiometry (DXA) at discharge from hospital. The corresponding figures in Paper II were six patients in the control group and 18 patients in the intervention group. After discharge three more patients in the control group were referred to DXA and a further six patients in the intervention group.

4.4 Physicians' appreciation (Paper II)

A total of 88 questionnaires were distributed to the physicians who had received the feedback of the intervention (23 hospital physicians and 65 general practitioners). Eighty-one per cent of the questionnaires were returned. The physicians (75% consultants) graded their appreciation of the oral and written parts of the intervention as well as the usefulness on a scale of six, where 1 was the lowest score and 6 the highest score. The scores are presented in Figure 5.

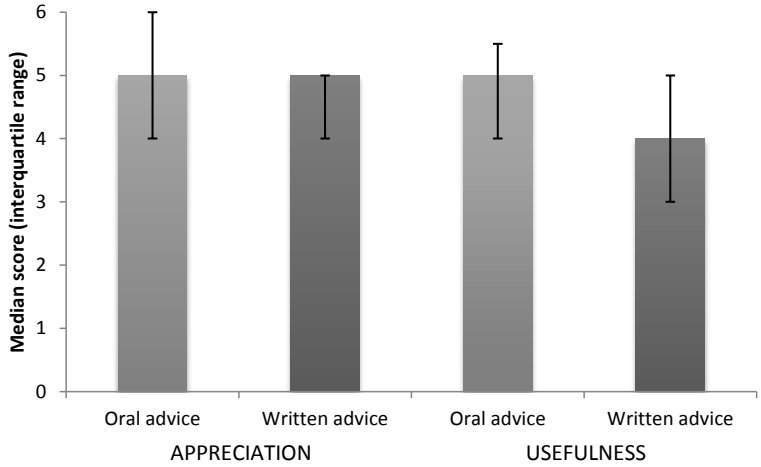

Figure 5. Physicians' scores on six-graded scale regarding appreciation and usefulness of the forwarded medication reviews

In the field for comments there were many notes on the appreciation of having direct contact with a hospital consultant, bridging the gap between the primary care and the hospital care. Another advantage that was highlighted was having contact with a geriatric consultant, knowledgeable on the matter of drugs in older people.

4.5 Drug treatment changes (Paper III)

Among the included 1,980 drugs, 1,217 were classified as changed (withdrawn, dosage adjusted or added) and 763 as unchanged. As presented in Figure 6, the proportion of unchanged drugs was higher in the multi-dose drug dispensing group. In the subgroup analysis, where all drugs prescribed to nursing home patients were excluded, these proportions remained, which is evident from Figure 6.

The odds ratio (95% confidence interval) for a drug to be classified as unchanged when prescribed via multi-dose drug dispensing compared with

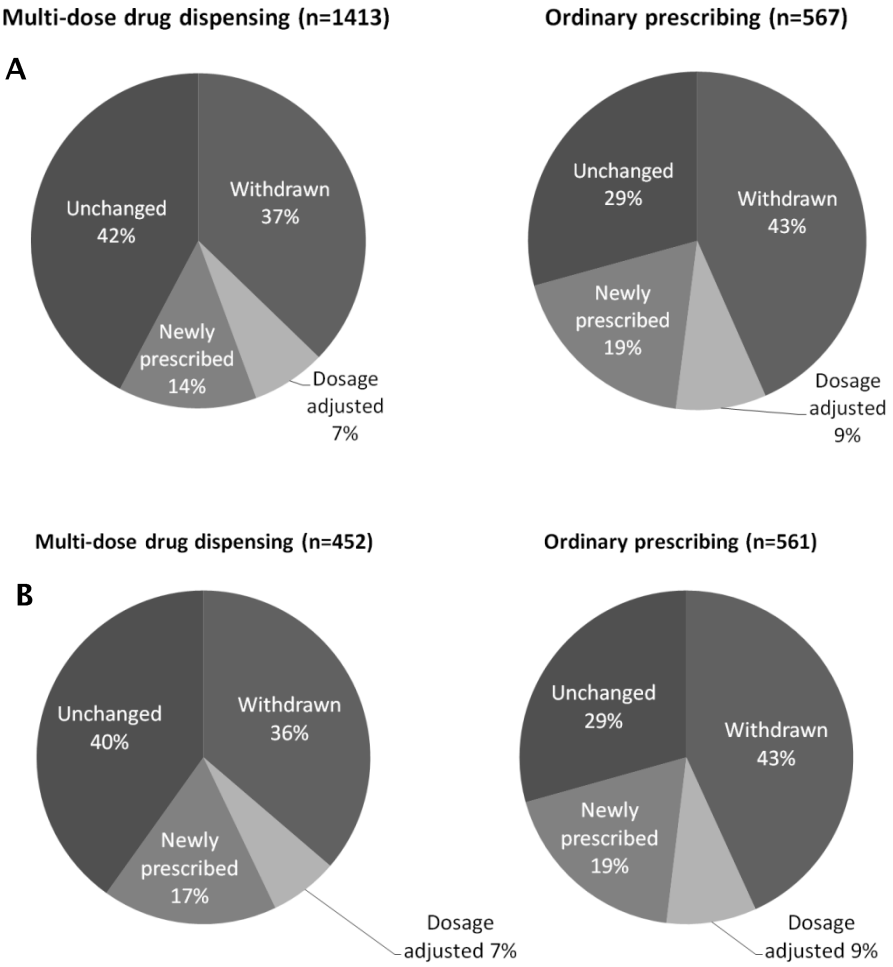

Figure 6. Classification of drugs as unchanged, withdrawn, dosage adjusted, or newly prescribed, at six months as compared to discharge

ordinary prescribing was 1.71 (1.38-2.27). The association remained when the other variables (age, sex, cognition, study year, and subgroup of drugs – fall-risk increasing, fracture-preventing, or other) were included in the model: 1.66 (1.20-2.31). Fracture-preventing drugs had higher odds to be unchanged compared with other drugs: 3.37 (2.28-4.98), respectively. Regarding the other variables there were no conclusive associations. The subgroup analysis of the drugs prescribed to community-dwelling patients showed results of the same magnitude as the main analysis.

4.6 Inappropriate prescribing (Paper IV)

Patients with multi-dose drug dispensing showed higher prevalence for inappropriate prescribing according to the five indicators of prescribing quality used I Paper IV than patients with ordinary prescribing (all P<0.0001), as presented in Figure 7.

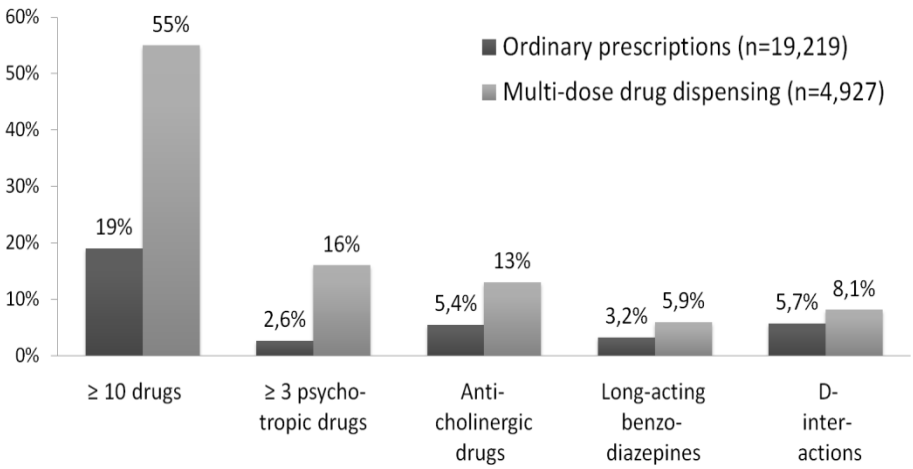

Figure 7. Proportion of patients with multi-dose drug dispensing or ordinary prescribing having inappropriate prescribing according to indicators of prescribing quality

The unadjusted odds for inappropriate prescribing according to the five indicators for prescribing quality were between 1.47 and 7.08 times higher in patients with multi-dose drug dispensing. After adjustments for age, sex, burden of disease, and residence, the odds were between 1.36 and 5.48 (Figure 8); the greatest odds were found for indicators concerning polypharmacy. For all indicators, the odds for inappropriate prescribing were greater for multi-dose drug dispensing than for the other variables included in the model, and in three out of five indicators, the confidence intervals between multi-dose drug dispensing and the other variables did not overlap.

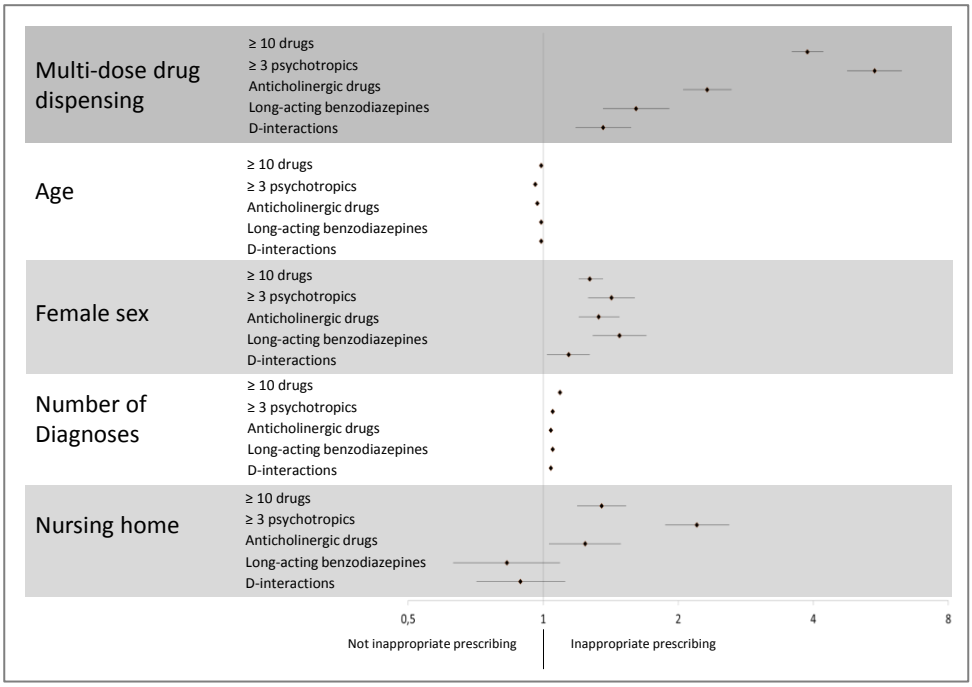

Figure 8. Odds ratios for inappropriate and not inappropriate prescribing (95% CI) according to indicators for prescribing quality among patients with or without multi-dose drug dispensing and for other variables included in the analysis

When the results were also adjusted for *Any psychiatric diagnosis*, the odds ratio (95% confidence interval) for inappropriate prescribing was changed marginally (Figure 9).

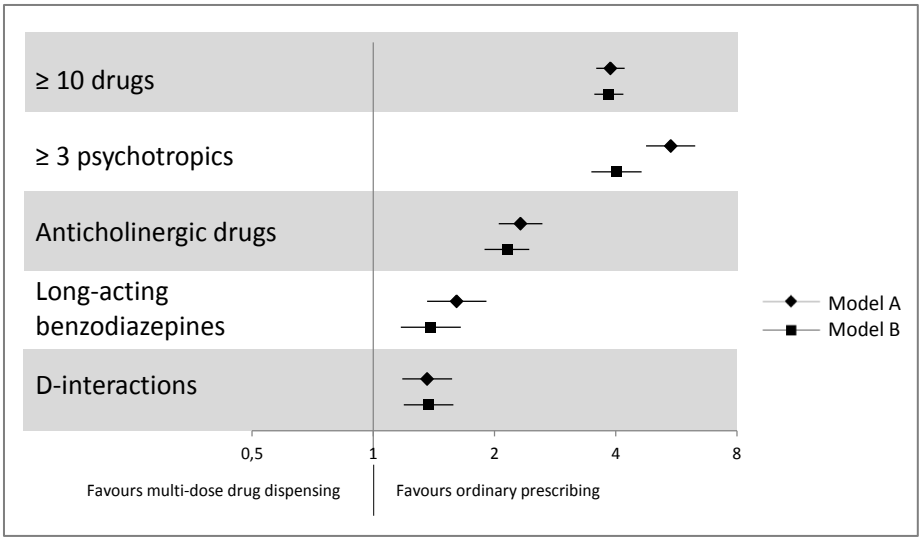

Figure 9. Odds ratios (95% confidence interval) for inappropriate prescribing according to indicators for prescribing quality, patients with multi-dose drug dispensing vs patients with ordinary prescribing. In Model A adjustments were made for age, female sex, number of diagnoses, and residence in a nursing home. In Model B prevalence of any psychiatric diagnosis was added to the adjustments in Model A

5 DISCUSSION

5.1 Main results

The results of the first study in older hip fracture patients (Paper I) support the comprehension that treatment with fall-risk increasing drugs is abundant ant that fracture-preventing drugs are underprescribed. Thus in order to improve the drug treatment in these patients, the next study (Paper II) investigated the effects of medication reviews. Compared to patients receiving standard care we found that in patients where the prescribing physicians had received feedback at the hospital and at the primary health care centres, treatment with fracture-preventing drugs increased: four times as many additional patients received treatment with bone-active drugs, and twice as many additional patients received treatment with any fracture-preventing drugs. Interestingly, the intervention did not significantly affect the prescribing of fall-risk increasing drugs. Indeed, the intervention was well appreciated by the targeted physicians.

The following two papers examined the association between quality of drug treatment and multi-dose drug dispensing, a system with limited scientific evaluation. The results of these studies confirm the assumption that drugs prescribed via multi-dose drug dispensing are less often changed, *i.e.* withdrawn, dosage adjusted or added, compared to ordinary prescribed drugs (Paper III). Furthermore, the results of Paper IV support previous findings regarding an association between inappropriate prescribing and multi-dose drug dispensing; five indicators for prescribing quality (*Ten or more drugs*, *Three or more psychotropics*, *Anticholinergic drugs*, *Long-acting benzodiazepines*, and *D-interactions*) were all more prevalent in patients with multi-dose drug dispensing, also after adjustment for important covariates.

5.2 Fall-risk increasing drugs

The results presented in Papers I and II confirm previous findings that fall-risk increasing drugs are frequent among patients sustaining hip fractures and are not significantly changed after the hip fracture. Furthermore, these drugs were not decreased by medication reviews performed by a physician.

The extensive use of fall-risk increasing drugs among older patients is well-known.[20,57] Since cardiovascular diseases, psychiatric symptoms and diseases, and pain are common in older patients, a high prevalence of such drugs is expected.[69] These conditions are evident in our studies. According to Paper I the prevalence of fall-risk increasing drugs was not changed after the hip fracture. Furthermore, no significant changes were seen in mean number of these drugs. Concerning the main drug groups of fall-risk increasing drugs (cardiovascular drugs, psychotropics, opioids, and other fall-risk increasing drugs), opioids increased in median number by one during the hospital stay, but had returned to the prefracture level after six months. Cardiovascular drugs and psychotropics remained essentially unchanged during the study period. Interestingly, a Swedish register study showed increases of all these drug groups in hip fracture patients after six months.[57] However, this study started off six months before the hip fracture. Hence, the number of drugs at the time of the fracture was not known.

The intervention in Paper II did not succeed in affecting the number of fall-risk increasing drugs. There may be several reasons for this outcome. First, due to the concomitant diseases and symptoms, rationales for withdrawal of drugs may have been few or risky. Thus withdrawal advice may have been cautious or omitted. Even so, the targeted physicians may have assessed treatment of concomitant diseases more important than the risk of further falls. Moreover, attempts to withdraw drugs may have failed. Lastly, the physicians or the patients may have refrained from the process of withdrawal for certain reasons.

Whereas other studies most often have shown positive results in decreasing fall-risk increasing drugs, just a few have been able to decrease the number of falls.[20,70,71] A number of meta-analyses have studied different interventions directing risk of falls. Summarised, multifactorial measures have shown most favourable effects, but even these results are modest.[24,72] Furthermore, whether such a decrease of falls may also decrease the number of injuries is still to be proven.[72] Indeed, the comorbidity in hip fracture patients is high, making withdrawal of effective drugs difficult .[73] Besides, it is important to emphasise that drug treatment also has beneficial effects. For example, antihypertensive drugs have been shown to reduce mortality and morbidity even in the oldest old.[74] Hence, prioritising treatment of diseases before risk of falls may be adequate, not least since the risk of falls may be due to the diseases rather than to the drugs.[75,76] Furthermore, some previous studies concerning psychotropic drugs managed to reach an initial reduction in the number of such drugs. However, some of these drugs were restarted later on.[19,32,70] Moreover, nowadays people live longer and experience a better

quality of life despite several chronic diseases.[77] This fact may at least partially be explained by the access to effective drugs.[78] What is more, even if the number of drugs in older people in Sweden has increased, as has the number of older people; the number of hip fractures has been constant for the last decade. [56,79]

5.3 Fracture-preventing drugs

From Paper I and II it may be concluded that fracture-preventing drugs are underused but may be improved by medication reviews. Indeed, the percentage increase in use of bone-active drugs was fourfold in the intervention group compared to the control group.

By taking advantage of the results at six months, increases by the intervention may be compared to the observational study of Paper I as well as to a register-based study from the southern part of Sweden based on data from 2006, as shown in Figure 10.[57] The latter study shows about the same development of prevalence of bone-active drugs as Paper I. Hence, the starting point for the study of Paper II may be the fact that the treatment levels were probably not much different from that of other parts of Sweden.[80]

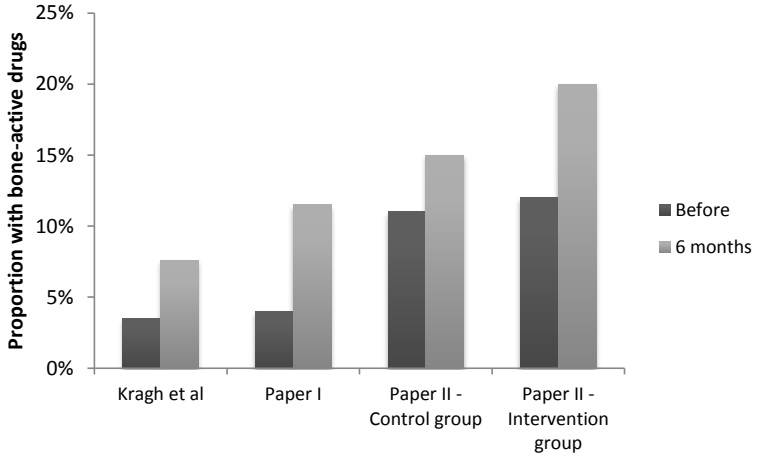

Figure 10. Comparison of prevalence of bone-active drugs between the observational study performed by Kragh et al, the observational study presented in Paper I, and the control and intervention groups of Paper II before and six months after the hip fracture

Compared to Paper I, even the control group in Paper II showed an increase of bone-active drugs. Reasons for this development may be the enhanced focus on fracture-preventing drugs caused by the results of the observational study one year previously as well as the higher attention on such treatment due to the on-going intervention. On the other hand, no such improvements were made regarding referrals to dual x-ray absorptiometry (DXA) in the control group, whereas such a recommendation was often given in the medication reviews. Indeed, the increase of referrals to DXA may also be seen as an improvement, since these often function as a step towards bone-active drug treatment.

The intervention in Paper II took place before a paradigm shift in fracture-preventing drug treatment. Previously, despite the weak evidence of the effectiveness of calcium plus vitamin D, monotherapy was recommended in older people at high risk of fractures having contraindications for bone-active drugs, since the side effects were regarded as relatively harmless. Such treatment was widely recommended in various countries world-wide – not only in Sweden. [9,48,81] However, in 2011 a meta-analysis showed higher incidence of cardiovascular events in women treated with calcium plus vitamin D.[82] As a consequence, the guidelines have changed. In 2012, the Swedish National Board of Health and Welfare published National Guidelines for Musculoskeletal Diseases, including guidelines for osteoporosis.[56] According to these guidelines, monotherapy with calcium plus vitamin D should never be used unless the person has a known lack of calcium or vitamin D. Hence, fewer patients will receive monotherapy with these drugs in the future. However, since lack of vitamin D is common in older people, many patients will possibly receive such treatment.[83,84]

At twelve months we reached a proportion of patients treated with bone-active drugs of 29% in the intervention group. In consideration of the fact that almost three out of ten of these patients had contraindications against bone-active drugs due to insufficient glomerular filtration rate, and that the expected survival time is short in a number of these patients this may be regarded as an achievement.[73] Furthermore, no patients in the intervention group on treatment with bone-active drugs were diseased at twelve months. This may indicate that the intervention targeted the right patients. The result of this intervention may be compared to the total Swedish figure of 13.8% from this period of time, but also to a population-based follow-up from Pennsylvania, where a drug treatment project raised the proportion of hip fracture patients receiving such drugs from 7% to 31% over seven years' time.[80,85]

The mortality in hip fracture patients is high.[73] Indeed, previous studies show figures on higher risk of death than of new fractures.[54] Hence, physicians may question adding of bone-active drugs in patients with short expected survival time, *i.e.* serious coherent diseases. Even so, bisphosphonate treatment given to hip fractures patients irrespective of bone mineral index, is shown not only to reduce the incidence of new fractures, but also to decrease mortality.[86,87]

5.4 Multi-dose drug dispensing

In Paper III, multi-dose drug dispensing was shown to be associated with fewer changes in drug treatment compared to ordinary prescribing, *i.e.* fewer drugs were dosage adjusted, withdrawn, or added within six months after a hip fracture. In Paper IV, multi-dose drug dispensing was shown to be associated with a higher probability for inappropriate drug treatment.

Though frequently stated by Swedish physicians, to our knowledge, this is the first study to demonstrate fewer drug treatment changes within in multi-dose drug dispensing system.[61,62,88] Reasons for this may be the prescribing system, since it is regarded as complicated and time-consuming.[89] Hence, prescribers sometimes refrain from making new prescriptions or drug treatment changes. In addition, the possibility available in the multi-dose drug dispensing system to renew all prescriptions in one click may decrease the reconsideration of the drug treatment, and thereby the number of drug treatment changes.[90]

Furthermore, the multi-dose drug dispensing system is developed to enhance patient safety and drug compliance in patients with difficulties in handling their own drugs. The alternative would be manual dispensing by nurses. Manual dispensing of drugs is related to a higher degree of medication errors than the automated multi-dose drug dispensing process.[58] Nevertheless, in studies on medication errors, the prescribers are found not only to make the most errors, but also to cause the most dangerous errors compared to nurses and pharmacies.[91,92] Hence, the producers of dispensing systems are advised to pay close attention to the prescribing procedure when developing such systems.

Within the multi-dose drug dispensing system drug treatment changes are made in mean more than two times per month.[58] Whereas this may be seen as a high number, it may be argued that it is too low in the light of the results of Paper III. According to the producer and to the guidelines for multi-dose drug dispensing – for instance in the Region Västra Götaland – a regular drug treatment is a prerequisite for prescribing within this system.[93,94] Hence, it is not adopted for acute illnesses, *i.e.* when the regular drug treatment turns irregular. This is the case in hip fracture patients, where a number of drugs and dosages will be changed during the hospital stay and the following months.

The results of Paper IV point to the fact that inappropriate prescribing is more common in people using multi-dose drug dispensing than in people using ordinary prescribing. These results confirm those of a previous study.[61] We adjusted for important covariates, such as age, sex, residence (community-dwelling or living in a nursing home), and number of diagnoses. Unlike Johnell et al, we chose to adjust for number of diagnoses rather than number of drugs, since one pronounced hypothesis is that multi-dose drug dispensing *per se* tend to augment the number of drugs.[61,65] Moreover, since the mean number of drugs per diagnosis, as may be calculated from Table 11, is 30% higher in patients using multi-dose drug dispensing, an association between this system and a higher number of drugs may be indicated.

The findings presented in Papers III and IV may be explained by the characteristics of the multi-dose drug dispensing system. Besides the complex prescribing routine, the facilitating of the dispensing itself may contribute. Patients, relatives, and nurses involved in the dispensing process may have less attention to the separate drugs.[60,90,95] Furthermore, less effort is needed to keep the prescriptions in order. In brief, there is general confidence in the system regarding a safe drug treatment making all concerned less observant. Another explanation may be the fact that patient information leaflets are not provided along with the dispensed drugs. Accordingly, no information on effects and side effects of the drugs is given. As a consequence, the knowledge of the drugs and the watchfulness on possible side effects may fade.[60,90] Furthermore, the ready-made medication list may abridge the patient interview on the drug treatment during the appointment. Thus, less information on drug related problems may reach the prescriber.

6 METHODOLOGICAL CONSIDERATIONS

Papers I and II

The first two studies in this thesis concerned drug treatment in hip fracture patients. The descriptive study (Paper I) was performed to form the basis of the randomised controlled trial (Paper II). Since so, the intervention study was based on good knowledge of the patients and their drug treatment. For this reason, the number of 100 consecutively recruited patients was found to be sufficient. The inclusion criteria were chosen to not exclude patients due to medical or cognitive function. Furthermore, the study design implied no further engagement for the patients to minimise the declination of participation. This turned out to be successful in both studies, hence the generalisability is good. Moreover, the intervention was practice-orientated, *i.e.* it was based on clinical experience from these patients, and it would be simple to transfer into clinical practice if successful, without strains of the patients or addition of ample resources.

The randomisation in Paper II was made on patient level, in preference of cluster randomisation, *i.e.* wards or health care centres, which would have been a weaker design. Due to this procedure, intervention and control patients were handled by the same hospital physicians parallelly, which may have decreased the differences of the results between the randomisation groups.

The choice of endpoints is a limitation. Hard endpoints, such as fractures or falls would have been advantageous. However, this would have demanded higher number of patients and longer follow-up periods.

The data on the drug treatment at six-month and twelve-month follow-ups are another limitation. Since these are derived from registers, they may have been both over- and underestimated. For instance, filled prescriptions may not have been in current use, and drugs used in hospitals or collected from nurses' acute drug supplies in nursing homes may be missing.

Paper III

In this case-control study patients were included from the two cohorts of hip fractures patients in Papers I and II. The hip fracture patient group is well suited for a study on drug treatment changes since several drugs are to be withdrawn between discharge and six-month follow-up and the drug treatment should be reconsidered due to the hip fracture, *i.e.* drug treatment

changes are common during the study period. Moreover, multi-dose drug dispensing is common in these patients and both multi-dose dispensing patients and ordinary prescribing patients use high number of drugs. Due to the fact that the patients were derived from two different cohorts, data on burden of disease were registered differently. Hence, it was not possible to adjust for this in the statistical model. Moreover, adjustment for cohort was made in the analyses and turned out to have little influence on the result.

Regarding categorisation of drugs as changed or unchanged, it may be argued that an exchange of a drug to another was overestimated, since it was registered as two events. However, two actions were taken, withdrawal and adding. Furthermore, it would have been arduous to clarify whether there was an association between two drugs when changed in a six-month interval. Moreover, since data on drug treatment at six months were derived from a register, this may be a limitation.

Paper IV

This register-based study took advantage of the national and regional high quality registers to compare quality of drug treatment in multi-dose drug dispensing patients and in patients using ordinary prescribing. Both the Swedish Prescribed Drug Register and the Social Service register are reliable. Data on diagnoses were derived from the regional Vega database. Its coverage is good, since it is used for reimbursements of health care costs to care providers.

Drugs may have been both over- and underestimated. Certain drugs are not registered in the Swedish Prescribed Drug Register; an example being drugs for inhospital use, *i.e.* if a patient spends much time in hospital the numbers of drugs may be underestimated. Furthermore, people living in nursing homes and those connected to the home nursing service may have certain drugs for acute need dispensed from the nurses' acute drug supply, *i.e.* antibiotic treatments and analgesics for short term use. These people more often use multi-dose drug dispensing, and therefore it may be presumed that the multi-dose drug dispensing use of drugs may be more often underestimated. In addition, drugs sold over the counter are not included.

Adjustments were made for important covariates, such as age, sex, and number of diseases. Psychiatric impairments, *i.e.* impaired cognition, abuse, or reduced compliance, are common causes to start multi-dose drug dispensing.[93,94] To target these confounders, we adjusted for impaired cognition in Paper III and for *Any psychiatric disease* in Paper IV. Other factors not included in the analysis may be of importance. As mentioned in

the Discussion section, we chose not to adjust for number of drugs, since (i) this has been done previously, and (ii) we hypothesise that the use of multi-dose drug dispensing in itself contribute to an increased number of drugs.

7 CONCLUSIONS

Fall-risk increasing drugs are common in hip fracture patients, whereas fracture-preventing drugs are not. A hip fracture does not change the number of fall-risk increasing drugs, whereas the prevalence of fracture-preventing drugs is increased a little after the hip fracture.

Medication reviews performed by a physician and fed back to prescribing physicians increase the use of bone-active drugs, but do not reduce the number of fall-risk increasing drugs. Such an intervention is appreciated by the targeted physicians. These results confirm the fact that optimising drug treatment in older hip fracture patients is a matter of adding bone-active drugs when suitable rather than withdrawing fall-risk increasing drugs – drugs often used for treatment of diseases or symptoms that affect the quality or length of life.

Multi-dose drug dispensing (ApoDos) is associated with fewer drug treatment changes than ordinary prescribing. Furthermore, this system is associated with inappropriate prescribing according to Swedish indicators of prescribing quality. Further scientific evaluation of such prescribing systems is required. In addition, development of the multi-dose prescribing system is advised in order to facilitate prescribing, *i.e.* drug treatment changes. Moreover, a more thorough consideration of the drug treatment in patients using the multi-dose drug dispensing system is needed.

8 FUTURE PERSPECTIVES

Medication reviews have been evaluated in numerous research studies. Despite the obvious problem with polypharmacy in older people, results on hard endpoints, such as mortality and morbidity are modest. This study adds to this list when it comes to withdrawal of drugs. However, the medication review method used in Paper II was successful in increasing treatment with bone-active drugs in older hip fracture patients. Further research assessing the effects of this method on other diagnoses that are undertreated could be valuable. Besides the positive effects on fracture-preventing drug treatment, the study indicated a way to improve the cooperation between hospital care and primary care. Lack of such cooperation is known to reduce the medical safety.[96] Development of effective methods for improving collaboration between different care givers is urged. Furthermore, more research on how to combine methods for improving the quality of drug treatment in older people is needed; preferably with focus on mortality and morbidity rather than on quality or quantity of drugs.

The drug treatment dilemma in older people is apparently not easily solved by medication reviews only, which is pointed out in the report of the Swedish Council on Technology Assessment in Health Care in 2009.[2] Several concurrent achievements are to be made to improve the drug treatment in older people. These measures concern education of prescribers, more overall assessments and thorough medical investigations of older people, regular consideration of drug treatment, and improved collaboration between stakeholders of the healthcare system.[2,97]

Since multi-dose drug dispensing is associated with fewer drug treatment changes and higher prevalence of inappropriate prescribing, actions to minimise such problems are urged. The prescribing system needs to be improved in order to facilitate prescribing, *i.e.* it has to be as easy to understand and to handle for the prescribers. Moreover, it is important that the system supplier and the care givers collaborate to provide adequate education to prescribers, including information about risks of the system. Existing knowledge on how to design digital systems to minimise safety risks has to be applied. Moreover, further research is needed tracing the effects of different prescribing systems on drug safety aspects.

In patients using multi-dose drug dispensing measures to make up for the decreased attention to the drugs and their effects are urged. Such steps need to include information on drug properties to the patients and their next of kin,

as well as increased education on drugs for the health care staff. Furthermore, regular and systematic search for side effects and other drug related problems is needed. Tools for such symptom assessments must be scientifically evaluated. Accordingly, these measures call for more time for the doctor's appointments for these patients, in order to evaluate the drug treatment more thoroughly.

New techniques, such as prescribing systems, are usually introduced to solve existing problems or to facilitate procedures. Nevertheless, new techniques may involve unforeseen problems. When concerning patient safety issues, it is of utmost importance that such problems be identified and early warnings be dealt with, *i.e.* the introduction of new prescribing systems has to be accompanied by thorough evaluation and openness for new and unexpected flaws.

The multi-dose drug dispensing system provides a complete medication list accessible for all prescribers. Such a complete medication list has been top priority in health care for long, since there are obvious medical risks for patients not receiving the right drug treatment. However, as described in the Discussion section, there may be a risk of decreased attention to the drug treatment by all concerned. This risk needs to be considered when designing and introducing such medication lists. While there are evident advantages, the disadvantages must be identified and resolved.

To conclude, the optimal quality of drug treatment in the older individual is literally individual. A focus on the patient rather than on the drug treatment yields a better approach. Not only is the physical and medical condition of a patient of importance for which treatment is the best for him, but also the patient's goals for the drug treatment. Does he prefer higher quality of life or longer life, or does he aim for both? What about his willingness to adhere to drug treatment? What is his pre-understanding? These issues may only be dealt with within a well-functioning doctor-patient relationship. Medication reviews or different criteria may serve as eye openers. Hence, the meeting between the patient and his ordinary physician is the right moment for reconsideration of the drug treatment. At the appointment the physician should investigate the patient's medical condition and thereafter assess the drug treatment bearing the Hippocratic Oath in mind: "I will prescribe regimens for the good of my patients according to my ability and my judgment and never to do harm to anyone".

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APPENDIX

Example of medication review

Risk assessment of falls and fractures and advice on drug treatment

_____ _____

Name Personal identity number

Risk assessment – fall	Yes	No
Previous fall preceding year?	□	□
Impaired gait/balance?	□	□
Orthostatic reaction?	□	□
Impaired vision?	□	□
Impaired cognition/dementia?	□	□
Need of assistance for ADL?	□	□
Fall-risk-increasing drugs?	□	□

Assessment: 30 % of community-dwelling people aged 65 and over sustain a fall every year. The risk factors mentioned above may be addressed. The patient suffers from an increased risk of falls.

Risk assessment - fracture	Yes	No
Previous fracture?	□	□
Parent fractured hip?	□	□
Current smoking?	□	□
Oral glucocorticoids >3 months?	□	□
Secondary osteoporosis?	□	□
Alcohol 3 or more units per day?	□	□
Reumathoid arthritis?	□	□
Inactivity?	□	□
Tendency to fall?	□	□
Weight loss5 kg or more preceding year?	□	□

Assessment: A woman/man aged 65 years of normal weight runs the ten-year-risk of sustaining an osteoporotic fracture or a hip fracture of 11/6 % and 3/2%, respectively, according to FRAX[1]. The risks of this patient are … **%** and … **%**, respectively.

[1] FRAX (WHO Fracture Assessment Tool). Ten-year-risk of a major osteoporotic fractures as well as of a hip fracture may be calculated. www.shef.ac.uk/FRAX

Current drug treatment

Cilaxoral (laxative)	dr	7,5 mg/ml	0+10dr
OxyContin	tabl	5 mg	1x2
Pamol (acetaminophen)	tabl	500 mg	2x3
Furix	tabl	40 mg	1x1
Zopiklon	tabl	5 mg	0+1

(**Bold** drug names are commented below)

Remarks on drug treatment

Estimated glomerular filtration rate **54** ml/minute

Fall-risk-increasing

OxyContin	Opioid. If possible withdraw by slowly decreasing the dose. If not possible, try to keep the dose as low as possible and/or on demand.
Furix	Diuretic. Not intended for treatment of hypertension. Increases risk of orthostatic reaction. Exchange to another antihypertensive drug treatment is recommended, for instance an ACE blocker.
Zopiklon	Hypnotic. Not intended for chronic use. Withdrawal is recommended. Try nonpharmacological treatment instead.

Fracture-preventing

Alendronate	weekly tablet 70 mg 1 per week is recommended.
Calcium + vitamin D	for instance **Kalcipos-D forte** 0+1 is recommended. If constipation add Laktulos eller Movicol. Dosages in the evening may decrease the risk of gastrointestinal adverse effects as well as interaction with other drugs ingested in the morning.

Kind regards,

Date Christina Sjöberg, consultant geriatrician, tel 031-343 08 97

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