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Medication in older hip fracture patients

Medication in older hip fracture patients

Falls, fractures, and mortality

Annika Kragh Ekstam, MD



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DOCTORAL DISSERTATION

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Faculty opponent

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Title and subtitle: Medication in older hip fracture patients – Falls, fractures, and mortality		
<p>Abstract</p> <p><i>Background and aim:</i> Due to an increasingly ageing population, the number of hip fracture patients, often with multiple chronic diseases and multiple pharmacotherapy, is set to rise. The high risk of adverse outcomes that hip fractures lead to in older individuals is well described, including high first-year mortality. This thesis aim to improve our knowledge of older hip fracture patients' treatment with drugs that potentially increases the risk of falls, fractures, bleeding, and death, in order to identify potentially effective interventions for preventing adverse outcome from the medication.</p> <p><i>Methods and results:</i> Three general population-based cohort studies and one observational cohort study, on medication in hip fracture patients, are included. National registry data for 2,043 patients (<i>I, II, III</i>) and medical journals for 255 patients (<i>IV</i>) were analysed.</p> <p><i>Paper I</i> aimed to describe the use of fall-risk-increasing drugs (FRID) and to analyse whether there were any changes in the prescribing six months after a hip fracture, compared to six months before. A majority was exposed to FRID prior to the fracture and an increase of thirty percentage-points in post-fracture prescribing was found. Anti-osteoporosis treatment increased only marginally, but in hospitals offering geriatric support the prescribing of anti-osteoporosis drugs increased significantly compared to hospitals without this support.</p> <p>In <i>Paper II</i>, first-year mortality was shown to be significantly higher in patients exposed to ≥ 4 FRID, polypharmacy, psychotropic and cardiovascular drugs. Regression analyses of treatment with FRID, adjusted for age, sex and any ≥ 4 drugs, showed higher mortality in patients exposed to ≥ 4 FRID compared to ≤ 3 FRID. In <i>Paper III</i>, exposure to potentially inappropriate medication (PIM) was found in 81% of the patients. Logistic regression, data adjusted for age, sex, and use of ≥ 5 drugs, indicated that exposure to any PIM and analgesic-PIM (tramadol, dextropropoxyphene) increased six months' mortality significantly. Exposure to other categories of opioids did not indicate higher mortality. Patients with a length of in-hospital stay (LOS) ≥ 10 days had a higher six months' mortality than patients with a LOS of ≤ 9 days.</p> <p>In <i>Paper IV</i>, regression analysis of hip fracture patients' exposure to low-dose acetylsalicylic acid (LdAA), adjusted for multiple confounders, showed higher first-year mortality and that more blood transfusions were given to patients treated with LdAA compared to non-users. Levels of coagulation factors were also significantly higher in the blood of patients treated with LdAA compared to unexposed patients.</p> <p><i>Conclusions:</i> The thesis proposes that older hip fracture patients are frequently exposed to FRID and PIM, that exposure to ≥ 4 FRID, any PIM, analgesic-PIM, LdAA, polypharmacy, and a LOS of ≥ 10 days are factors associated with higher mortality. Additionally was found that exposure to FRID increases significantly after the fracture and that anti-osteoporosis treatment is more frequently prescribed to orthopaedic patients when geriatric support is available. The overall conclusion lies in the identification of plausible ways to reduce adverse outcome and improve the care of hip fracture patients. Further studies on ways of improving the care of hip fracture patients should be explored by evaluating methods of preventing drug-related adverse outcome, as well as of strengthening the collaboration between orthopaedic and geriatric professionals.</p>		
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Medication in older hip fracture patients

Falls, fractures, and mortality

Annika Kragh Ekstam, MD



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“Every fall is an opportunity to prevent the next one!”

The Fragility Fracture Network

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List of publications

This dissertation is based on the following papers, which are referred to in the text by their Roman numerals. The original papers have been reprinted with the permission of the publishers.

- I. Kragh A, Elmståhl S, Atroshi I. Older adults' medication use 6 months before and after hip fracture: a population-based cohort study. *JAGS* 2011;59 863-868.
- II. Kragh Ekstam A, Elmståhl S. Do fall-risk-increasing drugs have an impact on mortality in older hip fracture patients? A population-based cohort study. *Clinical Interventions in Aging* 2016;11 489-496.*
- III. Kragh Ekstam A, Atroshi I, Elmståhl S. Mortality, inappropriate medication and length of hospital stay in older hip fracture patients: A general population-based cohort study. *Submitted, under review* 2017.
- IV. Kragh AM, Waldén M, Apelqvist A, Wagner P, Atroshi I. Bleeding and first-year mortality following hip fracture surgery and preoperative use of low-dose acetylsalicylic acid: an observational cohort study. *BMC Musculoskeletal Disorders* 2011, 12:254.

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Abbreviations

ADL	Activities of daily living
ANCOVA	Analysis of covariance
APTT	Activated Partial Thromboplastin Time
ASA	American Society of Anaesthesiologists
ASA score	American Society of Anaesthesiologists' classification of Physical Health
ATC	Anatomical Therapeutic Chemical Classification system
CI	Confidence interval
CVd	Cardiovascular cause of death
DDI	Drug to drug interaction
EBM	Evidence based medicine
FORTA	"Fit for the Aged" (Italian list of PIM)
FRAX®	Fracture risk assessment tool
FRID	Fall-risk increasing drug
HR	Hazard rate ratio
ICD ^{10th}	International Statistical Classification of Diseases and Related Health Problems – Tenth Revision
INR	International Normalized Ratio
LdAA	Low-dose acetylsalicylic acid
LOS	Length of in-hospital stay
NICE	National institute for clinical excellence
NNT	Numbers needed to treat
NNH	Numbers needed to harm
NOAC	New oral anti-coagulants
NSAID	Non-steroidal anti-inflammatory drugs
OBRA	Omnibus Budget Reconciliation Act
OR	Odds ratio
PIM	Potentially inappropriate medication
PRISCUS	Latin for "old and venerable" (German list of PIM)
RCT	Randomized controlled trial
SD	Standard deviation
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions

Background

In old age, the primary goals in life of maintaining good health, wellbeing, and autonomy are often linked to the use of medicines. In geriatric medicine, the necessity for individual adaptation and regular adjustment of older patients' drug use is essential to ensure the patient a safe and efficient pharmacotherapy. The studies included in this dissertation are based on an interest in upholding good quality and safety in older patients' drug use and in identifying possible ways to prevent adverse outcomes from the medication.

An ageing society at risk of hip fracture

The world's population is ageing and the frequency of hip fractures is increasing. During the last hundred years, the mean survival age in the Swedish population has increased by 25 years and is still rising (www.scb.se). This has led to an increase in the number of older persons at risk of sustaining a hip fracture. [1] In a study by Rosengren and Karlsson in 2014, it was found that the number of hip fractures in Sweden come 2050 might double and by then reach about 30,000 hip fractures annually. [2] A study from Taiwan, Chen et al. 2015, predicted a 2.7-fold increase of annual incidence of hip fractures from 2010 to 2035. [3] This epidemiological shift is a signal to alert health authorities to the important work of implementing preventive interventions to lower the risk of hip fractures. Plausible ways to reduce falls and fractures are to avoid the use of fall risk-increasing drugs and to evaluate more patients for anti-osteoporosis treatment.

Hip fractures – through the decades

With a gradually ageing population in many countries, the number of hip fractures is predicted to increase significantly over the next decades. [4] In Sweden, the mean age of hip fracture patients is over 82 years, higher in women and lower in men. In two studies, by Haleem in 2008 and Bergstrom in 2009, the mean age of hip fracture patients was shown to increase with one year every fifth year-period. [5, 6] This is one reason for the high mortality found in hip fracture patients, with numbers staying consistent through the years. [6]

Hip fractures have gone from being a nearly intractable condition 50 years ago to being an injury that can be treated with a mean length of in-hospital stay of 9 to 10 days. [7] During the last decades, considerable advances in the treatment of hip fracture patients have been made and implemented in Swedish hospitals. Among these are new techniques for surgery, fracture fixation implants modified to osteoporotic bone, and improved anaesthetic methods. In addition, interventions for optimal timing of surgery, early rehabilitation, improved nutrition, and fluid treatment pre- and postoperatively have proved to be beneficial. [8-14] In order to identify methods to improve the care of hip fracture patients, a national register of hip fracture patients (www.rikshoft.se) was started in 1988 and is one of several national quality registers. Here, data from 52 out of 54 Swedish hospitals with orthopaedic departments, are generated yearly to monitor and compare results in the care of hip fracture patients. A large number of national quality registers is currently being run with the aim of improving and upholding a high quality in Swedish health care. The collecting and use of data for these registers have been reviewed and evaluated to ascertain the effects they can have on health care. [15, 16]

Consequences of hip fractures

The consequences of hip fractures are serious and affect a significant number of patients and their relatives. Among the confirmed dysfunctions are incapacities to walk and move, to perform regular day-to-day activities, and to live independently without help from others, along with hip pain and lower quality of life. [17-25] Fear of falling, bringing with it the risk of losing independency and dignity, constitutes a threat to the quality of life in many hip fracture patients, as shown by Salkeld in 2000. [26] It was also concluded that the decline in quality of life could be on the same level as that of patients going through myocardial infarctions or suffering from breast cancer. [26, 27] In a majority of hip fracture patients the fracture itself, as well as the subsequent surgery, lead to substantial tissue damage and bleeding. The exposure to bleeding during the treatment of hip fractures increases with the use of drugs containing low-dose acetylsalicylic acid and other anti-platelet drugs that affect the coagulation process. [28-31]

In spite of improved surgical techniques, anaesthetic methods, care, nursing, and rehabilitation, long-term mortality is still high in hip fracture patients. [6, 32-34] Six-month mortality is reported to be between 11 to 23% and first-year mortality 22 to 29% and even higher in some countries, with one of the main reasons for this being the rapidly increasing mean age of the patients. Mortality in female hip fracture patients are alleged to be on the same average level as in patients with breast cancer. [35] Old age, male sex, type of fracture, and comorbidities have been identified as significant risk factors associated with increased mortality after a hip fracture. [35, 36]

In addition to the individual concerns a hip fracture causes, the socioeconomic consequences are also of high significance because of the expected dramatic demographic changes, both those currently happening and those of the near future. A cost increase of 50 to 100% is predicted for hip fractures alone, but the magnitude of the problem can reach beyond that when all osteoporotic fractures are included. [24, 32, 37]

Osteoporosis

The population's risk of developing osteoporosis in the Scandinavian countries is among the highest in the world. [38, 39] This is often explained by a high proportion of the population reaching old age, inadequate sun exposure during the long winters, low levels of vitamin D, and genetic disposition. [40-43] Hip fractures are one of the major fractures related to osteoporosis, along with fractures of the wrist, shoulder, and spine. [44-47] The costs of treating and caring for patients with osteoporotic fractures are expected to increase. A study by Burge et al. in 2007 predicted a probable 50% increase in costs of osteoporotic fractures between 2005 and 2025. [32] Hip fractures constitute 17% of osteoporotic fractures and account for more than 70% of the costs related to all osteoporotic fractures. Hip fractures are estimated to make up more in-hospital days in women over 45 years of age than diabetes, myocardial infarction, or breast cancer according to Kanis et al. [37]

Aside from post-menopausal osteoporosis, secondary osteoporosis caused by diseases and medications are frequent in hip fracture patients. In hip fracture patients, multiple comorbidity and polypharmacy are often prevalent and can constitute part of the problem. A number of frequently occurring chronic diseases in old people is connected to osteoporosis. Among the most common ones are rheumatoid arthritis, diabetes, chronic obstructive pulmonary disease, and inflammatory bowel disease, but the drug treatment of these conditions also constitutes a major risk of developing osteoporosis. Drugs known to increase the risk of developing osteoporosis are, among others, corticosteroids, proton-pump inhibitors, and older anti-epileptic drugs. [48-51] Other risk factors for osteoporosis and fractures are smoking, alcohol and a sedentary life-style. [52-54]

In *Paper I* of this thesis it was found that few of the patients were treated for osteoporosis at the time of fracture and that an insufficient number was prescribed anti-osteoporosis treatment subsequently. For various reasons, osteoporosis has on a global scale remained undetected and undertreated at all stages of the disease. Prognostic tools are available, such as the FRAX[®] instrument, with which it is possible to calculate the individual 10-year probability of a major osteoporotic fracture. This tool can aid physicians and patients in choosing appropriate preventive measures based on the 10-year risk of a major fracture. [55, 56]

Since the risk of a new fracture following an osteoporosis-related fracture is high, an estimated increased risk of 87%, according to Kanis et al. in 2004, the incitement for starting treatment is strong. [48] There are now sufficient data on the beneficial effects on bone quality and fracture reduction in individuals treated with bisphosphonates, calcium and vitamin D to initiate this treatment in hip fracture patients. [57-64] Although this has been discussed extensively, it has, likely due to divergent research results in different populations and countries, been difficult to reach a consensus. Even if anti-resorptive therapy with bisphosphonates has been shown to reduce both the number of fractures, and the mortality rate, there are often problems with compliance to oral treatment. [63-66] Treatment of older nursing home residents with vitamin D and calcium supplementation alone has proved beneficial in terms of reducing falls and fractures. [67-72]

The history behind PIM

In the mid-1980's, the necessity for evaluating the suitability of drug use in older people started to become apparent when it came to light that nursing home residents in the USA were commonly treated with psychotropic drugs without clear or valid reasons. This led in part to the launching of the Omnibus Budget Reconciliation Act (OBRA), along with concerns regarding the rising costs of health care for nursing home residents and the demographic shift towards an aging population. [73-77] OBRA brought about a significant reform for residents of nursing homes that at the outset focussed mainly on the use of antipsychotic drugs, which was found in 23% of the residents. Physicians were asked to justify the prescribing of antipsychotics for each individual and to re-evaluate the therapy based on explicit diagnostic criteria. Within the subsequent three years, the prescribing of antipsychotic drugs in nursing home residents decreased to 15%. [78, 79]

In the wake of OBRA, quality assessments and drug reviews in people living in nursing home facilities were introduced in other countries and the Beers' explicit criteria became a major support in this regard. In order to improve safety and efficacy of drug use in older patients, a list of inappropriate medicines was compiled in the USA by a group of experts led by doctor Mark Beers and published in 1991. [80] The list of PIM was intended as a guideline in order to alert physicians to the high risk of adverse reactions related to these drugs in older patients. Beers' list has mainly been used as a tool to compare the appropriateness of medication in nursing homes, focusing not only on the quantity of drugs but also on the quality and safety of the drug treatment. These guidelines have since been revised repeatedly, with the latest version released in 2015, and followed by several European lists in different countries such as Sweden, the Netherlands, and the United Kingdom. [81] Among these are the STOPP list (Screening Tool of Older Person's Prescriptions), and START list (Screening Tool to Alert doctors to Right Treatment) which not only

intend to identify PIM but also to draw attention to the under-use of potentially more effective and safe drugs. These lists were then followed by the German PRISCUS list (Latin for “old and venerable”) and the Italian FORTA list (“Fit for the Aged”). [82]

Swedish national registers

Under strict control, exceptions to the Public Access to Information Secrecy Act were allowed as of July 2005, and data from national databases in Sweden became more accessible for research. It became legally allowed to perform research that enabled researchers to link together individual information from national registers based on each citizen’s unique civic number. The rationale for researching database-compiled information is to take advantage of this major source of data and to use it to continuously improve healthcare.

This research group took the opportunity to apply to the Swedish National Board of Health and Welfare for extraction of data on hip fracture patients. To be allowed to do so, a research plan including aims, methods, and ethical approval from relevant authorities was included in the application for assessment and authorisation. After evaluation of the study plan according to its clinical importance and strength, we were allowed access to coded, non-identifiable information on individuals from the geographical area of interest, which linked together three national databases, including the Swedish National In-patient Care Register, Drug Prescription Register and the Cause of Death Register.

These databases contain information on year, sex, age, and geographical data, which make follow-up on an individual and anonymous level possible. The Swedish National In-patient Care Register has a nearly 100% coverage of all hospital discharges since 1987 and are confirmed to have valid diagnoses in more than 85%. [83] Some diagnoses are more often omitted, mainly those regarding psychiatric disorders. Besides clinical findings, a hip fracture diagnosis requires confirmation by radiological examination, which forms the basis for choice of surgical treatment. For this reason, the risk of diagnostic errors in this group of patients is limited in comparison to other diseases.

Interventions to prevent falls

Injuries related to falls are a major health problem from the age of sixty-five. Especially in individuals 80 years and older, falls are a major concern for the healthcare sector and for the society at large due to the consequences for the individual and the high costs they entail. [84-91] Reviews on fall-risk reducing

preventive measures have shown that a multi-disciplinary approach and multi-interventional programs are the most effective methods of preventing falls. But also isolated interventions, such as eye surgery for cataracts, pacemaker treatment for arrhythmias, and to some extent reduced use of fall-risk increasing drugs, have proved to be effective in this aspect. [92-97] To start with, it is important to identify individuals at high risk of falls and fall-related injuries at an early stage. There are several fall-risk assessment methods available that can be an aid in intervening at the right time and in the right situation, both regarding to emergency care as well as for older people living at home. [98-107] Besides physical exercise, balance training, and nutritional reinforcement, other interventions aiming to reduce fall-risk in the home environment can be effective. It is also important to be extra alert when older patients are cared for in environments that involve extraordinary fall-risks, such as hospitals and other unfamiliar places. [108-112] More than a third of hip fracture patients experience some kind of confusional episode during their hospital stay. [113-116] The consequences for the delirium patient can be serious due to the risk of new falls, problems with nutrition and rehabilitation as well as the concealing of other serious perioperative complications. Confusion in hip fracture patients has also been singled out as an independent risk factor for six-month mortality. [113] This is another motivation for avoiding medication that can increase the risk for developing confusion in older patients. Many of the drugs included in PIM have strong anti-cholinergic effects and can increase the risk of delirium and prolong the time period of delirium.

Another significant intervention to lower fall-risk is drug reconciliations aiming at adjusting drug therapy and reducing the number of drugs used, as well as avoiding the use of certain drug classes, such as fall-risk increasing drugs. [117-119] However, according to a Cochrane review published in 2012, which covers both old people living in special care facilities and in the community, few studies on medication reviews fulfil the scientific criteria required. [120, 121] No solitary intervention can be expected to have a decisive role in improving medication for older patients due to the high complexity of the issue. Unless a broader multi-interventional approach is taken, an effect on falls cannot be fully anticipated, nor can physicians' actions be the only solution in this task, as care for older patients often requires a team-effort to succeed.

Introduction

In most health care settings, the most frequently used method of treatment is pharmacotherapy. As the presence of chronic diseases becomes more frequent with old age, the need for drugs to treat diseases and alleviate symptoms increases. According to statistics compiled by the Swedish Board of Health and Welfare in the last three decades, drug therapy for cardiovascular diseases, especially prophylactic use of anticoagulants, lipid-lowering drugs, and drugs acting on the renin system, has nearly doubled. Other drugs, the use of which has also increased dramatically in older patients during this timeframe, are proton-pump-inhibitors and antidepressants. The need to combine five or more drugs increases with age and the overall effect becomes more difficult to survey as side-effects, drug-drug interactions, and drug-disease interactions become more frequent.

Physiological changes with age and pharmacotherapy

The changes in pharmacological response in older patients must be taken into consideration in order to achieve efficient and safe drug therapy. In the ageing body, as degenerative changes in organ systems accelerate, drug therapy becomes more complex. Pharmacokinetic changes due to ageing, such as deteriorating functions of the gastrointestinal tract, the circulatory system, liver, and kidneys, lead to problems with absorption, distribution, metabolism and elimination of drugs, with the decline in kidney function being the principal reason for increased side-effects and drug-related morbidity. [122-130] Aside from the need to consider the pharmacokinetic changes, the aging person's susceptibility to adverse drug effects due to pharmacodynamic variations must also be considered. The increased sensibility in older people to both drug effects and to drug side-effects is caused by age-related degenerative changes foremost in the central nervous system, the circulatory system, the gastrointestinal tract, and in the homeostasis. This entails that meticulous risk-benefit assessments be carried out before prescribing drugs to older individuals and during regular follow-ups of the treatment.

Prescribing to older patients

When treating older patients with drugs, there are several aspects to take into account, such as individual physiological changes, comorbidities, cognitive abilities, side-effects, and the risk of interactions, both drug-drug and drug-disease related. The optimal way of treating older patients with drugs is based on an evaluation of the total effect on the patients' life situation, weighing the risks of adverse effects to the gains it can give the individual patient, while at the same time not withholding a potentially valuable pharmaceutical treatment from the patient. Such individual tailoring of drug therapy becomes even more essential in older people because of their high risk-profile.

The choice of treatment generally is ideally founded on evidence-based medicine (EBM), thereby combining findings in clinical research of high quality and the patients' own preferences. This may not always be an easy choice for physicians caring for geriatric patients since the numbers needed to treat (NNT) and the numbers needed to harm (NNH) seldom are available for older patients. One disadvantage of treating older patients with drugs according to EBM is that very little data on this category of patients are available from the preliminary studies. [131-134] This is partly due to patients over the age of 80 seldom being included, and older patients with coexisting conditions other than the one the drug is used for, or concomitant medications, often being excluded as well. Consequently, we often lack evidence-based data on a large proportion of future patients that will in fact often be using the drug. Another aspect of EBM is that geriatric patients generally have multiple diseases, and providing drug therapy according to the guidelines for each disease can lead to unwanted polypharmacy and increased risk of interactions.

Drug-related morbidity

The most frequently occurring adverse events connected with drugs are dizziness, nausea, fatigue, and blood pressure variations. These frequent symptoms increase the risk of falling in frail patients. [117] Drug-related morbidity has been calculated to constitute a major cost for health care worldwide, and older persons are at a higher risk of being afflicted. The most frequently occurring drug-related morbidity is known to be related to anticoagulants, antibiotics, anti-diabetics, and opioids. [135-137]

Among individual drugs, warfarin, insulin, and digoxin stand out as substances that often cause serious adverse events leading to emergency visits and hospitalisation. At the same time, these drugs are considered valuable to the patients and the adverse effects are more a sign of the difficulties involved in maintaining appropriate dosages and avoiding interactions. Since drug-related morbidity often is

preventable, it is essential to take action to make pharmacotherapy both safe and efficient in vulnerable patients. [138-142]

Polypharmacy

Treating a patient with multiple medications can be clinically sensible and in accordance with good clinical practise. But in the last decades, older patients have been exposed to an increasing quantity of drugs, and in a regularly issued report from the Swedish health authorities (www.socialstyrelsen.se) it was in 2015 established that more than 11% of the population over 80 years of age is prescribed ten or more drugs annually. Polypharmacy can potentially increase the number of adverse side-effects, harmful events caused by interactions and practical difficulties imposed on patients with multimедication. [143-149] Compliance also becomes a substantial problem when several drugs are used, and the complexity of the total medication increases. [150-153]

The demographic development with a larger group of the population reaching old age reinforces the necessity for treatment of chronic diseases as well as other ailments connected to old age. But less favourable prescribing also takes place, e.g. the prescribing of drugs to treat side-effects from already used drugs. This so-called “prescription cascade” can be another cause for polypharmacy as well. [154-159] Patients receiving drug prescriptions from several different physicians are also at a high risk of polypharmacy. [160] Harmful effects of polypharmacy may be the result of multiple clinicians prescribing drugs they are familiar with, but combining them with less well-known drugs from other physicians can make it nearly impossible to manage the therapy in an appropriate way.

Aims

General aims of the thesis

The primary aim of this thesis is to improve the knowledge of how older hip fracture patients are treated with drugs that can potentially increase their risk of falls, fractures, bleeding, and death. The secondary aims are to examine whether any actions are taken to reduce these risks by adjusting the use of potentially inappropriate medication and by prescribing anti-osteoporosis drugs, interventions that could potentially reduce falls, fractures, and mortality.

Specific aims of the included studies

Paper I. The primary objective was to describe the use of fall risk-increasing drugs in hip fracture patients aged 60 years and older, before the fracture. The secondary objectives were to study changes in use of fall risk-increasing drugs and anti-osteoporosis medication after the fracture as well as to analyse differences in drug prescribing between five health care districts in relation to access to geriatric support in the five hospitals.

Paper II. The purpose of this study was to explore any associations between older hip fracture patients' use of fall risk-increasing medication prior to the fracture and first-year mortality aiming to identify potentially unsafe drugs and drug combinations.

Paper III. The aim of the study was to assess older hip fracture patients' use of potentially inappropriate medication, including high-risk drug-drug interactions, and any related associations with mortality, cause of death, or length of in-hospital stay, in order to identify possibly avoidable risk factors for adverse outcomes.

Paper IV. The objective of this observational cohort study was to evaluate any relations between preoperative use of low-dose acetylsalicylic acid and intraoperative blood loss, blood transfusion, and first-year all-cause mortality in hip fracture patients aged 50 years and older.

Study population and methods

Study populations

This thesis is based on two different groups of hip fracture patients, one consisting of patients aged 60 years and older, the other group consisting of patients aged 50 and older. The patients included were all treated for hip fractures in Skåne County and sustained their fractures in 2005 and 2006. They were diagnosed with a hip fracture according to the International Classification of Diseases, 10 tenth revision (ICD^{10th}), with codes: S72.00, S72.10, S72.11, S72.20, and S72.21, registered in the administrative In-patient register for Swedish hospitals, and were residing in the county at the time of fracture.

Skåne County holds more than a tenth of the Swedish population and has five emergency hospitals that care for orthopaedic trauma patients, one in each health care district. These hospitals encompass both large university centres and medium-sized district hospitals and were at the time of the studies accountable for the residents of five administrative districts in the county. The residents of the county live in both urban areas, namely in Malmö, the third largest city in Sweden, in medium- and small-sized municipalities, as well as in rural areas. They make up the base for the included study patients and reflect a general varied population.

Papers I, II, and III

Paper I, II, and III included 2,043 hip fracture patients aged 60 and older, who underwent treatment in 2006 and were residents of Skåne, the southernmost county of Sweden, at the time of the fracture. Figure 1 and 2. Out of a total of 2,138 hip fracture patients in 2006, 95.6% of them were aged 60 and older, and only 95 patients did not meet the inclusion criteria. Of the study population, 1503 (73.6%) were women with a mean age of 83.8 years (SD \pm 7.9) and 540 (26.4%) were men with a mean age of 81.0 years (SD \pm 8.3).

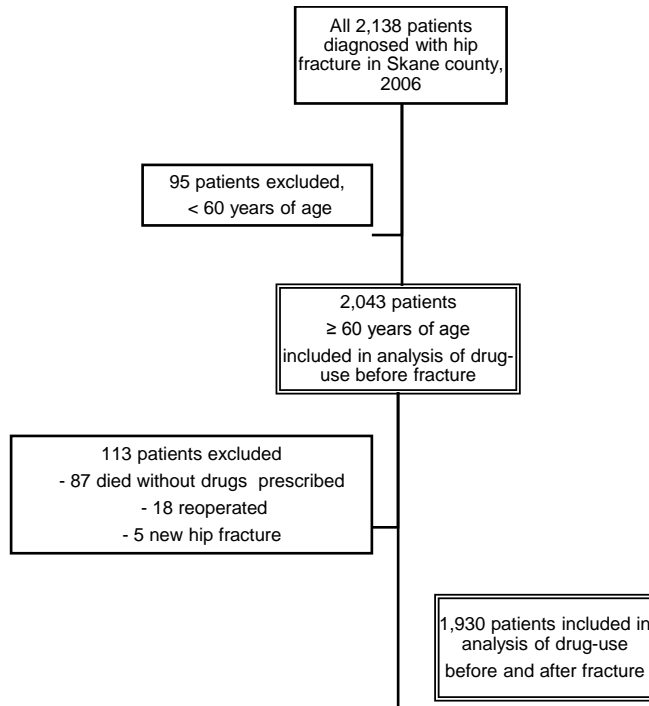


Figure 1. Participating patients included in *Paper I*.

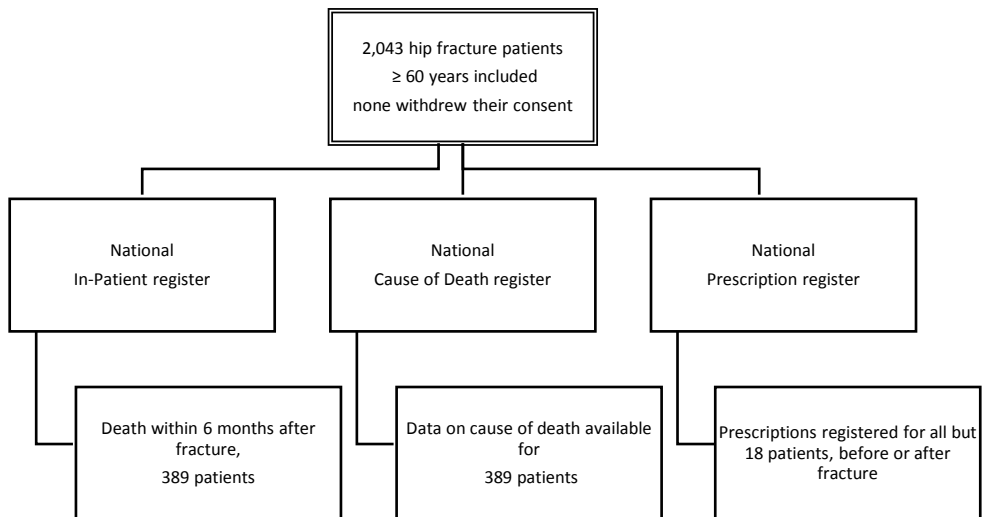


Figure 2. Participating patients and data from national registers in *Paper II* and *III*.

Paper IV

Paper IV included hip fracture patients aged 50 years or older, who underwent treatment in the Kristianstad emergency hospital in Skåne County from January 2005 through December 2006, and who resided in the county at the time of the fracture. The patients were treated for either cervical fractures requiring hemiarthroplasty or for pertrochanteric and subtrochanteric fractures requiring internal fixation. In the original study patients were screened for enrolment by an orthopaedic surgeon prior to the operation. Excluded were those patients with non-displaced cervical fractures (S72.00) that went through surgery with two hook-pins (since bleeding complications are very rare with this technique), patients with pathologic fractures due to malignancy, concomitant fractures, or other injuries that could require blood transfusion, and patients refusing blood transfusion. 555 consecutive eligible patients were presented at the emergency department during the course of the study, 333 patients were assessed, and 288 patients were included. Patients enrolled in the original study were randomly assigned to either the intervention group, where a compression bandage with pressure was applied over the fractured hip immediately post-operatively, or to the control group which received the same bandage but without any pressure applied. The evaluation of this bandage showed no significant effects on the measured bleeding parameters or the need for blood transfusion.

In this subsequent study, the 288 patients from both groups (intervention and control) were included, with the exclusion of 33 patients treated with warfarin (24), high-dose acetylsalicylic acid, dipyridol, and clopidogrel (9). The remaining 255 patients were divided into two groups depending on whether they were exposed to low-dose acetylsalicylic acid (LdAA) or not. Figure 3. We anticipated that the compression bandage did not have any bearing on bleeding factors, treatment, or mortality in the patients. Of the 255 included patients, 190 (74.5%) were women. The mean age of LdAA users was 84 years (SD \pm 7.6) and 81 years (SD \pm 9.5) in non-LdAA users.

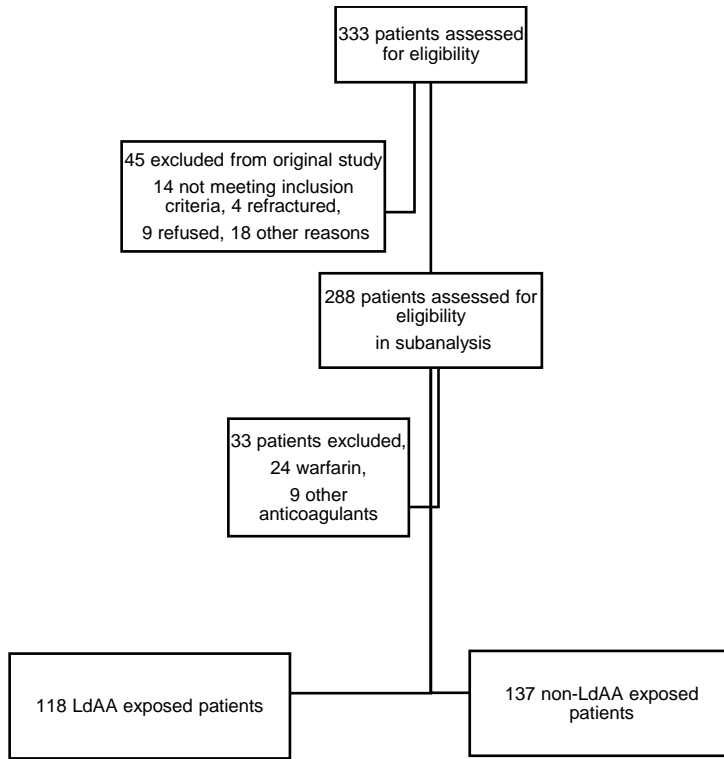


Figure 3. Participants included in *Paper IV*.

Data collection

Different sources of data were used for the two study populations included in this thesis. In *Papers I, II, and III*, three national registers formed the base of the collected data, and in *Paper IV*, the medical records for each patient constituted the source of the analysed information.

From the Swedish National Board of Health and Welfare’s statistics database, three national registers were used to assemble data for *Papers I-III*: the National Patient Register, the National Prescription Register, and the Cause of Death Register. The data on length of in-hospital stay in *Paper III* was drawn from the In-Patient Register.

Hip fracture

In *Papers I, II, and III*, information was drawn from the Swedish National Patient Register to identify all hip fracture patients from January 1 through December 31 2006. Hip fracture patients were identified using the International Statistical Classification of Diseases and Related Health Problems - tenth revision (ICD^{10th}) and were coded with S72.00, S72.10, S72.11, S72.20, and S72.21. In *Paper IV*, the included patients were those diagnosed with cervical fractures requiring hemiarthroplasty and patients diagnosed with pertrochanteric or subtrochanteric fractures requiring internal fixation, as identified by the orthopaedic surgeon at call.

Prescriptions

The Prescription register was used to link the patients' individual and anonymous codes with the register of In-patient care. The patients' prescribed and dispensed drugs were available for analysis, sorted by the Anatomical Therapeutic Chemical Classification system (ATC), as well as by the generic names of the substances included. Other available information was the number of times the drugs were dispensed within the time frame and the quantities prescribed.

Papers I-III and drug prescribing

Prescriptions filled six months before the hip fracture and six months after the fracture were collected. In *Paper I* all prescriptions issued six months before the fracture for 2,043 patients were analysed and compared with prescriptions six months after the fracture in 1,930 patients. In *Paper II*, prescriptions filled six months before the hip fracture were used for the analyses of FRID and mortality in 2,043 patients.

In *Paper III*, prescriptions that were filled at least twice six months before and after the hip fracture were included, covering twelve months or until death, in 2,043 patients. The rationale behind analysing only drugs that were prescribed at least twice was to increase the likelihood that the patients were in fact taking the drugs. An exception was made when analysing the presence of drug-drug interactions between e.g. antibiotics and warfarin or antibiotics and iron supplements. Here, antibiotics prescribed at least once during the year were included if they were presumably used at the same time that warfarin and iron were prescribed.

Use of low-dose acetylsalicylic acid (LdAA)

The information on drugs used by the patients' included in *Paper IV* was drawn from the medical charts assembled at the patients' arrival at the hospital. Here, we relied on information given by the patients and their relatives, and complementary information was collected from their general practitioners when needed. Users of low-dose acetylsalicylic acid were identified using the definition of lower than 320

mg as daily dosage. Other drugs with anticoagulant effects were also documented in the same way.

Fall risk-increasing drugs (FRID)

Fall-increasing drugs and drug combinations were identified from previous studies and included drugs with psychotropic, cardiovascular (excluding lipid-lowering drugs), anticholinergic, anti-epileptic, antiparkinson, and opioid effects. Also, a list compiled in 2010 by Swedish health authorities was used to assemble FRID. Included drugs are listed in Appendix A. Drugs for ophthalmologic use, intravenous fluids, and dermatologic use were not included.

Polypharmacy and potentially inappropriate combinations of drugs

Polypharmacy was defined as five or more drugs prescribed, and excessive polypharmacy as ten or more drugs, and were analysed for the patients in *Paper I*. Concomitant use of three or more psychotropic drugs was also studied in *Paper I* and *II*. In *Paper III*, a drug was included in the combinations when prescribed twice or more within a year. Drugs belonging to ATC codes D, P, and V (drugs for dermatological diseases, diagnostic use, and intravenous fluids) were not included in this analysis.

Potentially inappropriate medication (PIM)

Drugs categorised as belonging to PIM were identified from Beers' explicit criteria using the revised 2015 version and three additional drugs from a similar list compiled by the Swedish National Board of Health and Welfare in 2010. [161] Appendix B. These drugs are considered to be potentially inappropriate due to a high risk of adverse effects in the elderly and considered to have undesirable pharmacological effects in old age. The risk-benefit ratio of using PIM often incline towards being explicitly disadvantageous in older people.

In *Paper III*, the drugs belonging to PIM were divided into five separate therapeutic groups: analgesic, psychotropic, anticholinergic, cardiovascular, and various. The group labelled "various PIM" included drugs belonging to the following groups: antiparkinson, antispasmodic, non-steroidal anti-inflammatory drugs, antithrombotic, skeletal muscle-relaxants, gastrointestinal, endocrine, and antibiotic.

Anti-osteoporosis drugs

Included as anti-osteoporosis drugs analysed in *Paper I* and *II* were oral bisphosphonates and calcium as well as combinations of calcium and vitamin D supplements. No other categories of anti-osteoporosis drugs were prescribed to the patients included in these studies.

Drug-drug interactions (DDI)

Potentially clinically relevant drug-drug interactions included in the analysis were classified as D or C in Sweden (available at www.fass.se), see Appendix C. Interactions classified as D can generate serious clinical consequences for the patient and should be avoided, whereas interactions belonging to C can cause changes in the performance of the drugs or cause increased adverse effects and should therefore for safe use be carefully monitored and adjusted.

The Beers' explicit criteria (revision 2015, table 5, Appendix B) were used to identify DDI with high potential for adverse effects. Drugs with a narrow therapeutic range (mainly warfarin, digoxin, and antiepileptic drugs) with potential for serious adverse events due to interactions, was also identified and analysed. The most frequently prescribed medications, opioids, antidepressants, proton-pump inhibitors, angiotensin-converting-enzyme inhibitors, and antithrombotics were also analysed for DDI.

Length of in-hospital stay (LOS)

When analysing the patients included in *Paper III*, the median average stay in-hospital was nine days. The patients were then divided into two groups consisting of patients with 0-9 days and ≥ 10 days of LOS, for further analyses.

Blood tests, blood transfusion, and comorbidity

The results of blood tests and treatment with blood transfusions in *Paper IV* were obtained from the individual patients' medical records. In *Paper IV*, the data on comorbidities was drawn from the medical charts and assessed with reference to which diagnostic group they belonged to. For example, here the ICD^{10th} classification system was used with diagnostic codes I20-I25 and I30-I51 belonging to cardiovascular diseases, I60-I69 to cerebrovascular diseases, and hypertension with I10-I15.

Time and cause of death

Data on time of death in relation to the hip fracture was retrieved from the national registers. Cause of death was presented in accordance with the ICD^{10th} codes and divided into two categories and subsequently compared. One group contained deaths classified as belonging to I, which includes causes from the circulatory system of cardiovascular and cerebrovascular origin, and the other group contained all other causes.

Table 1.

Overview of the study populations and study designs.

Study	I	II	III	IV
Design	Population-based cohort	Population-based cohort	Population-based cohort	Observational cohort study
Sample	n=2,043 hip fracture patients \geq 60 years	n=2,043 hip fracture patients \geq 60 years	n=2,043 hip fracture patients \geq 60 years	n=255 hip fracture patients \geq 50 years
Data sources	Three national registers	Three national registers	Three national registers	Patients enrolled in RCT Medical charts
Data collection period	1 Jan 2006 through 31 Dec 2006	1 Jan 2006 through 31 Dec 2006	1 Jan 2006 through 31 Dec 2006	During 2005 and 2006
Main analysis methods	χ^2 –test t-test Odds ratio	χ^2 –test t-test Cox regression Hazard rate ratios	χ^2 –test t-test Logistic regression Odds ratio	Fisher's test Kaplan-Meier Cox regression Hazard rate ratio
Main objectives	Changes in FRID Differences in prescribing/district	Use of FRID, drug combinations First-year mortality	Use of PIM, DDI LOS, days Six-month mortality	Use of LdAA, Blood transfusions First-year mortality
Outcome	Descriptive Analytical	First-year mortality	Six-month mortality	First-year mortality Transfusions

Study design and statistical analysis

The study design used for *Papers I-III* is a population-based cohort study with data derived from national registers. For *Paper IV* an observational cohort study-design was used with data collected from medical records and time-of-death from the In-patient register. An overview of the included papers is compiled in table 1. Analyses in *Papers I, II, III, and IV* were performed using SPSS (Statistical Package for the Social Sciences) versions 15.0, 21.0, and 22.0.

Statistical analysis

Patients exposed to low-dose acetylsalicylic drugs, fall risk-increasing drugs, combinations of drugs, and potentially inappropriate medication were compared to unexposed patients and adjusted for confounders as possible and appropriate for the different studies. The performed analyses were adapted to the relevant research questions and the available data. Data were reported as numbers and proportions or mean and standard deviation (SD) as appropriate. Baseline differences in the patients were analysed using the t-test for continuous variables and the χ^2 -test for categorical variables and thus identifying probable confounders. Associations with

confounding factors were adjusted for by multivariate regression analyses. The results of the regression analyses were presented as odds ratios (OR) or hazard rate ratios (HR) with the confidence interval (CI) set at 95%. All tests were 2-sided and a P-value of <0.05 was considered statistically significant.

In *Paper I*, the χ^2 -test was used to compare changes in the prescribing of drugs after the fracture as well as differences between the five healthcare districts regarding drug use before and after the hip fracture. Because sex-specific differences in the prescribing of drugs could reflect differences in morbidity, age-adjusted OR with 95% CI for exposure to dispensed drugs was calculated for women with men as reference.

In *Paper II*, we analysed associations between baseline differences by using t-test or χ^2 test. A Cox survival model was used to estimate survival in patients exposed to four or more FRID compared to those treated with three or less FRID. In the regression analyses, adjustments were made for age, sex, and exposure to any kind of four or more drugs, the categorical variables being sex and four or more FRID.

In *Paper III*, a logistic regression analysis was applied in order to determine whether or not use of PIM had any association with mortality or cause of death. Length of in-hospital stay was analysed separately. We adjusted for age, sex, and polypharmacy, with 30-, 90-, and 180-day mortality as the dependent variables. As a measure of association between exposure to PIM and death at these time intervals, we calculated OR with a 95% confidence interval to estimate the precision.

Finally, in *Paper IV*, baseline characteristics of patients preoperatively exposed to LdAA were compared with non-exposed patients using t-test for continuous variables and Fisher's exact test for proportions. The Fisher's exact test was also used to compare the presence and category of postoperative complications in LdAA users and non-users. Blood loss and transfusion-related variables were compared between the two groups using logistic regression or analysis of covariance (ANCOVA) adjusting for age (as continuous variable), sex, baseline haemoglobin, and type of fracture/surgery. To illustrate the first-year survival distribution between patients exposed to LdAA and non-exposed patients, the Kaplan-Meier method was applied. A Cox regression analysis was used with first-year mortality as the dependent variable with the independent variables being age, sex, LdAA at the time of fracture, type of fracture/surgery, baseline cardiovascular and/or cerebrovascular disease, and renal dysfunction.

Ethical considerations

When applying for ethical approval of the study design and procedures involved in *Paper I-III*, the regional research ethics committee in Lund gave directions to publish the intentions with the research in a newspaper covering the geographical area where the study group came from. This was a way to inform and gather responses from the prospective patients before collecting data. Three patients contacted us for more information but none withdrew their consent.

In *Paper IV*, each capable patient included gave their informed consent orally and in writing for the original study, after which the gathered data was used for this analysis. Since the co-morbidity panorama in hip fracture patients also includes varying degrees of cognitive dysfunction and dementia, the consent given in this category of patients was often given by a relative. All studies were carried out in accordance with the Declaration of Helsinki and approved by the regional ethics committee of Lund University. Study registration number 239/2008 for study I, II, and III, and 704/2004-11-30 for study IV.

Results

Patients' characteristics in Papers I, II, III, and VI

Baseline characteristics of the study population in *Papers I, II, and III* are described in table 2 and those in *Paper IV* are described in table 7. In *Papers I, II, and III*, the included patients were aged 60 years or older, and in *Paper IV* they were aged 50 years or older. In the study population of *Papers I-III*, women constituted 74% and men 26% of the population, and the mean age was 83 years. Male patients were younger than the female patients with an average of 2.8 years. Of the 2,043 patients, 1,062 (52%) had a cervical hip fracture, 839 (41%) a trochanteric fracture, and 142 (7%) a subtrochanteric fracture. A total of 150,289 prescriptions were dispensed during the observation period, and after the exclusion of drugs belonging to ATC codes D, P, and V (drugs for dermatological diseases, diagnostic use, and intravenous fluids) 143,110 prescriptions remained and were included in the analyses. Of the 255 patients included in *Paper IV*, 75% were women, the mean age was 82.4 years and 24% lived in nursing homes before the hip fracture.

Table 2.Baseline characteristics for the study population in *Papers I, II and III*, 2,043 patients.

	All 2,043 N (%)	Male 541 (26) N (%)	Female 1,502 (74) N (%)	P-value
Age (mean ± SD)	83.0±8.1	81.0±8.3	83.8±7.9	<0.0001
LOS (mean ± SD)	9.9 ±5.75	10.2 ±6.3	9.8 ±5.5	0.17
<i>Type of fracture</i>				
cervical fracture	1,062 (52)	272 (50)	790 (53)	0.5
perthrochanteric	839 (41)	231 (43)	608 (40)	0.29
subtrochanteric	142 (7)	39 (7)	103 (7)	0.64
<i>First year mortality</i>				
30-day	173 (8.5)	62 (12)	111 (7)	0.004
90-day	304 (15)	97 (18)	207 (14)	0.02
180-day	389 (19)	124 (23)	265 (18)	0.07
365-day	503 (25)	170 (31)	333 (22)	<0.0001
<i>Drugs 6 months before fracture</i>				
FRID, combinations	1,375 (67)	349 (64)	1,026 (68)	0.07
≥ 5 drugs	990 (48)	246 (45)	744 (49)	0.09
≥10 drugs	354 (17)	79 (15)	275 (18)	0.05
≥3 psychotropics	242 (12)	51 (9)	191 (13)	0.04
sedative/hypnotics	736 (36)	161 (30)	575 (38)	<0.001
anticholinergics	273 (13)	63 (12)	210 (14)	0.17
bisphosphonates	71 (3.5)	6 (1)	65 (4)	<.0001
calcium+ vitamin D	174 (9)	14 (3)	160 (11)	<.0001

Paper I

For the inclusion of patients, see Figure 1, page 20. The main results in *Paper I* included that exposure to FRID in 1,930 older hip fracture patients was high, with 68% being treated before the fracture, and the number increasing substantially afterwards with approximately 30 percentage points. The prescribing of sedatives, hypnotics, antidepressants, and polypharmacy increased substantially after the hip fracture. Table 3. These results point at that the potentially harmful consequences of using fall risk-increasing drugs and combinations of drugs, in this group of high-risk patients generally goes unattended by their physicians.

Table 3.

Number of patients dispensed fall-risk increasing drugs (FRID) six months before fracture compared to six months after. 1,930 patients. *Paper 1.*

	Before N (%)	After N (%)	Differences, in percentage points
FRID, including combinations	1,308 (68)	1,855 (98)	+ 30
Sedative/hypnotic	709 (37)	997 (52)	+ 15
≥ 5 drugs	942 (49)	1,700 (88)	+ 39
≥10 drugs	334 (17)	1,036 (54)	+ 37
≥3 psychotropic	234 (12)	399 (21)	+ 9
Cardiovascular drugs	850 (44)	1,243 (64)	+ 20
Opioids	407 (21)	1,421 (74)	+ 53
Bisphosphonates	68 (3.5)	146 (7.6)	+ 4.1
Calcium+ vitamin D	174 (9)	535 (28)	+ 19

Key results in *Paper 1* were that the prescribing of anti-osteoporosis drugs was low before the hip fracture, with only 3.5% being treated with bisphosphonates and that the number of treated patients increased only marginally by 4.1 percentage points in the six months following the fracture. The number of patients prescribed calcium and vitamin D supplements after the fracture increased by approximately 19%.

There were differences seen in the prescribing of anti-osteoporosis drugs to hip fracture patients between the five health care districts in the county. In the hospitals where geriatric support was available to the orthopaedic patients (northeast and southeast), anti-osteoporosis drugs were prescribed with a significantly higher frequency. Table 4.

Table 4.

Drugs dispensed 6 months before and after hip fracture in five health care districts, (n=1,930). Geriatric support was available in the orthopaedic wards of the Northeast and Southeast districts. *Paper 1.*

	Northeast (n=316) N (%)	Northwest (n=450) N (%)	Midmost (n=374) N (%)	Southeast (n=156) N (%)	Southwest (n=634) N (%)	P value
≥ 5 drugs						
before	123 (39)	192 (43)	153 (41)	64 (57)	410 (65)	0.23
after	288 (91)	390 (87)	337 (90)	143 (92)	542 (85)	0.02
≥ 10 drugs						
before	50 (16)	81 (18)	59 (16)	41 (26)	103 (16)	0.06
after	178 (56)	220 (49)	200 (53)	98 (63)	340 (54)	0.04
Opioids						
before	63 (20)	107 (24)	78 (21)	46 (29)	113 (18)	0.01
after	270 (85)	349 (77)	267 (71)	101 (65)	434 (68)	<.001
Bisphosphonates						
before	12 (4)	10 (2)	9 (2)	9 (6)	28 (4)	0.09
after	22 (7)	19 (4)	27 (7)	32 (21)	46 (7)	<.001
Calcium/Vit. D						
before	35 (11)	26 (6)	33 (9)	16 (10)	64 (10)	0.06
after	227 (72)	59 (13)	61 (16)	64 (41)	124 (20)	<.001

Paper II

For the inclusion of patients, see Figure 2, page 21. The main results in *Paper II* propose that exposure to four or more FRID, five or more drugs, ten or more drugs, and cardiovascular drugs is possibly associated with increased first-year mortality in older hip fracture patients, when adjusted for differences in age and sex. Table 5. Exposure to FRID, polypharmacy, and excessive polypharmacy is known to be harmful in terms of increasing the number of adverse drug events, drug-drug interactions, and in reducing survival. [148, 162, 163]. In this study we found another potentially unsafe combination of drugs, consisting of the concomitant use of four or more FRID. The combination had a two-fold increased risk of 30-day mortality compared to patients not exposed, and the increased risk persisted throughout one year after the fracture. Compared to patients exposed to polypharmacy or excessive polypharmacy, the patients exposed to ≥ 4 FRID had a similar or higher mortality risk at 30-day, and this remained up to 180 days after the fracture.

Table 5.

Comparisons between exposure to fall-risk increasing drugs and combinations, six months before a hip fracture, and 1-year mortality, *Paper II*.

Drug exposure	All exposed 2,043 patients N (%)	30-day mortality 173 (8.5%) HR [95% CI]	90-day mortality 304 (14.9%) HR [95% CI]	180-day mortality 389 (19.0%) HR [95% CI]	365-day mortality 503 (24.6) HR [95% CI]
FRID 1	249 (12)	0.85 [0.51-1.42]	1.04 [0.71-1.52]	1.24 [0.88-1.74]	1.18 [0.86-1.62]
FRID 3	315 (15)	0.89 [0.57-1.40]	1.10 [0.79-1.53]	0.92 [0.67-1.27]	1.11 [0.84-1.48]
FRID ≥ 4	518 (25)	2.01 [1.44-2.79]	1.56 [1.19-2.04]	1.54 [1.2-1.97]	1.43 [1.13-1.80]
Polypharmacy (≥ 5 any drugs)	990 (49)	1.62 [1.17-2.24]	1.48 [1.15-1.91]	1.45 [1.15-1.82]	1.5 [1.21-1.85]
Cardiovascular drugs	894 (44)	1.67 [1.21-2.29]	1.55 [1.21-1.99]	1.46 [1.16-1.83]	1.43 [1.16-1.76]
Psychotropic drugs	928 (45)	1.33 [0.97-1.82]	1.30 [1.02-1.67]	1.24 [0.99-1.55]	1.33 [1.08-1.63]

After adjusting for differences in age, sex, and use of any four or more drugs, the patients exposed to four or more FRID were at a significantly higher risk of dying at 90- and 180-day after the fracture ($p=0.015$ and $p=0.012$) than patients exposed to three or less FRID. Using a Cox regression survival model showed that exposure to \geq FRID may be a predictor for increased mortality. Figure 4. Polypharmacy, with the use of five or more drugs, has previously been identified as an independent risk-factor for falls and mortality in frail people. [134, 164-166]. This effect can

furthermore be explained by the high risk of adverse events and drug-drug interactions in patients treated concomitantly with five or more drugs. Use of multiple drugs also increase the risk that patients will be exposed to one or more FRID, with less beneficial outcome.

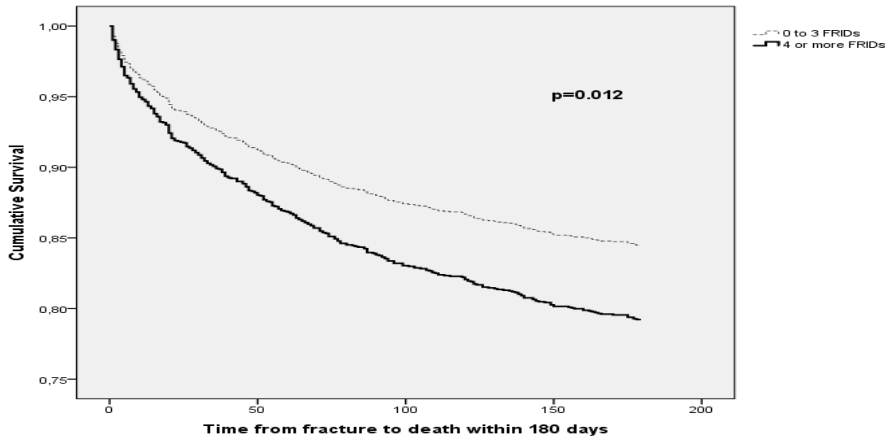


Figure 4. Time from hip fracture to death within 180 days in patients treated with four or more fall-risk-increasing drugs (FRID) compared to patients treated with three or less FRID. *Paper II.*

Paper III

For the inclusion of patients, see Figure 2, page 21. In analysing older hip fracture patients' use of potentially inappropriate medication, using Beers' explicit criteria and three drugs from a Swedish list in *Paper III*, it was found that a majority (81.5%) of hip fracture patients aged 60 and older was exposed to PIM of any kind. The most frequently used category of PIM (1,233 patients, 60 %, exposed) were two analgesic drugs listed as PIM by Swedish health authorities, tramadole and dextropropoxyphene, followed by psychotropic drugs (601 patients, 29 %) which mainly included anti-psychotics and long-acting benzodiazepines.

Analyses of short-term mortality, six months post-fracture, showed that exposure to analgesic PIM (tramadole and dextropropoxyphene) suggested that a connection with higher mortality six months after the hip fracture existed, when adjusted for differences in age, sex, and use of polypharmacy. Table 6. When studying mortality, polypharmacy was used as a proxy for multiple comorbidity, since sufficient information on comorbidity was missing. When all-PIM was analysed, mortality significantly increased between exposed and non-exposed patients at 30- and 90-day ($p=0.002$ and $p=0.003$ respectively). Exposure to PIM-analgesics also showed higher mortality post-fracture at 30-, 90-, and 180-day, with OR 2.59, 1.94, and 1.62. Exposure to other opioids however did not have this effect on mortality. When all-PIM was analysed separately from PIM-analgesics, the effect on mortality was

reduced. At 180-day a small but significant reduction in mortality was seen in patients treated with psychotropic PIM and various PIM, $p=0.041$ and 0.015 respectively. Exposure to DDI was not found to have any significant impact on mortality in the patients.

We also analysed the length of in-hospital stay and its' potential effect on survival. It was found that a LOS of ten days or longer (942 patients, 46%) was likely associated with a higher six-month mortality ($p<0.001$ at 30-, 90- and 180-day respectively), adjusted for age, sex, and polypharmacy, compared to a ≤ 9 days of stay.

Table 6. Older hip fracture patients' exposure to Potentially Inappropriate Medication (PIM), mortality, and length of hospital stay (LOS), adjusted for age, sex and polypharmacy. Paper III.

Exposed to:	Exposed of 2,043 N (%)	Mortality 30 days 173 (8.5%) OR [95% CI]	<i>P</i>	Mortality 90 days 304 (15%) OR [95% CI]	<i>P</i>	Mortality 180 days 389 (19%) OR [95% CI]	<i>P</i>
PIM all	1,666 (81)	1.79 [1.25 – 2.57]	0.002	1.57 [1.16 – 2.12]	0.003	1.29 [0.97 – 1.71]	0.082
PIM (PIM-analgesic excluded)	1,085 (53)	0.91 [0.64 – 1.28]	0.572	0.81 [0.62 – 1.06]	0.118	0.74 [0.58 – 0.95]	0.017
PIM analgesic	1,233 (60)	2.59 [1.85 – 3.63]	<0.001	1.94 [1.50 – 2.51]	<0.001	1.62 [1.29 – 2.05]	<0.001
PIM psychotropic	601 (29)	0.91 [0.63 – 1.32]	0.627	0.79 [0.59 – 1.05]	0.099	0.77 [0.59 – 0.99]	0.041
PIM various drugs	408 (20)	0.83 [0.55 – 1.26]	0.385	0.79 [0.58 – 1.09]	0.148	0.70 [0.53 – 0.94]	0.015
PIM anticholinergic	276 (14)	0.93 [0.55 – 1.55]	0.776	0.90 [0.61 – 1.33]	0.607	0.81 [0.57 – 1.13]	0.210
PIM cardiovascular	140 (7)	0.93 [0.47 – 1.86]	0.839	0.93 [0.55 – 1.57]	0.786	0.82 [0.52 – 1.29]	0.393
Opioids, not PIM	645 (32)	1.36 [0.92 – 2.02]	0.123	0.84 [0.63 – 1.12]	0.211	0.72 [0.56 – 0.92]	0.010
DDI, all	533 (26)	1.52 [0.96 – 2.41]	0.720	1.21 [0.87 – 1.67]	0.256	1.06 [0.79 – 1.40]	0.698
LOS ≥ 10 days	942 (46)	3.94 [2.67 – 5.81]	<0.001	2.34 [1.78 – 3.07]	<0.001	2.09 [1.64 – 2.67]	<0.001

Paper IV

For the inclusion of patients, see Figure 3, page 22. In *Paper IV*, was found that LdAA-exposure in hip fracture patients aged 50 years and older was associated with significantly higher values in blood tests on coagulation factors, both of International Normalized Ratio (INR) and of Activated Partial Thromboplastin Time (APTT), than unexposed patients, with $p=0.01$ and 0.02 respectively. Table 7. Significantly more units of blood transfusions were administered to LdAA-exposed patients with HR 1.8 (95% CI 1.04-3.3), when adjusted for differences in age, sex, type of surgery/fracture, renal function, and baseline cardiovascular and cerebrovascular disease.

Table 7.

Baseline characteristics for the study population in *Paper IV*.

	LdAA users	Non-LdAA users	P-value
	118 (46) N (%)	137 (54) N (%)	
Female	82 (69)	108 (79)	0.11
Male	36 (31)	29 (21)	
Age, mean (SD)	84.0 (± 7.6)	80.8 (± 9.5)	<.001
Compression bandage	55 (47)	59 (43)	0.61
<i>Type of surgery (fracture)</i>			0.07
hemiarthroplasty (cervical)	51 (43)	43 (31)	
fixation (per-/subtrochanteric)	67 (57)	94 (69)	
<i>Medical history</i>			
cardiovascular disease	72 (61)	56 (41)	<0.01
cerebrovascular disease	16 (14)	3 (2)	<0.01
hypertension	46 (39)	33 (24)	0.01
renal dysfunction	31 (26)	15 (11)	<0.01
<i>Bleeding data</i>			
APTT (SD)	33.1 (± 5.9)	31.6 (± 4.1)	0.02
INR (SD)	1.07 (± 0.12)	1.04 (± 0.09)	0.01
patients transfused, post-op	74 (68)	76 (54)	0.04
<i>Post-op complications</i>			
thromboembolic events	6 (5.7)	1 (0.7)	<0.01
any complications	54 (46)	48 (35)	0.08
<i>First-year mortality HR (95% CI)</i>			
LdAA use	2.35 (1.23-4.49)		0.01

It was also found that LdAA-exposure was associated with significantly higher first-year all-cause mortality (HR 2.35 (95% CI 1.23-4.49)), when adjusted for age, sex, type of fracture/surgery, renal function, and baseline cardio- and cerebrovascular disease. Figure 5.

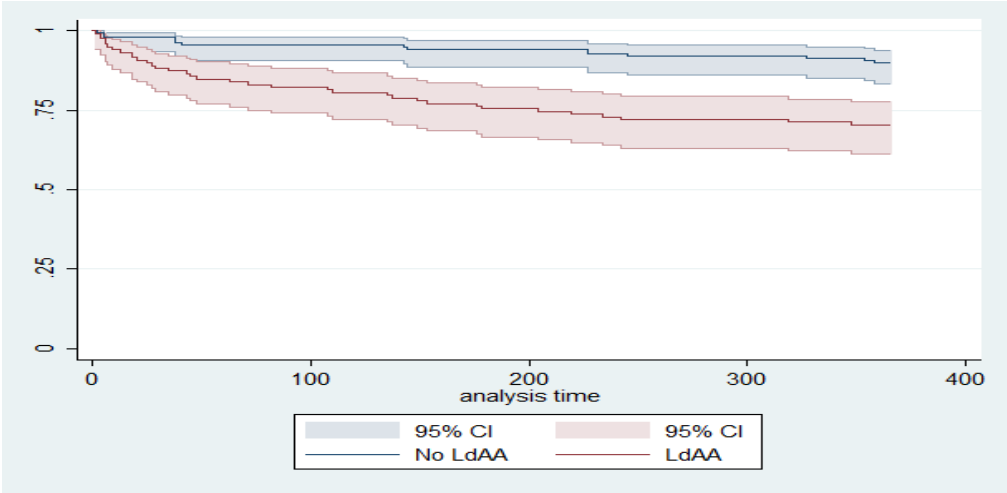


Figure 5. Kaplan-Meier survival estimate for one year after the hip fracture. Comparing exposure to use of low-dose acetylsalicylic acid (LdAA) preoperative to patients not exposed, number of days after surgery. *Paper IV*.

Discussion

Main findings and clinical implications

The studies included in this dissertation aimed to strengthen our knowledge of how medication in older hip fracture patients can be linked to potentially preventable adverse outcomes. We also studied whether any differences in drug prescribing were seen between patients treated in hospitals that offered geriatric support compared to patients in hospitals that did not. We found that exposure to LdAA, four or more FRID, PIM, PIM-analgesic and polypharmacy was likely to be associated with increased mortality in older hip fracture patients. Other relevant results were that the prescribing of FRID and PIM was high, whereas treatment with anti-osteoporosis drugs was notably low. No substantial evidence was found that prescribing of FRID was reduced after the fracture and the opportunity to intervene and lessen the risk of subsequent drug-related falls thus remained unexploited. Pain relief with analgesics may well have a beneficial effect on survival in older hip fracture patients but the choice of analgesics must be adapted to the individual. An additional result was that a hospital stay of ten days or longer had a seemingly negative relation to survival in older hip fracture patients.

Clinical implications

The strength of the three studies, *Paper I-III*, lie in the fact that the hip fracture patients were drawn from a general population cohort, in an appropriate number, as well as in the fact that all prescribed and dispensed drugs were included, thus making the results generalizable to similar populations. Some of the results in the dissertation confirm findings from earlier research, bearing in mind that these studies were mostly conducted in countries with different drug-prescribing traditions and in other study populations. A result from *Paper I* was that FRID frequently were prescribed before the hip fracture and that the prescribing of such drugs increased considerably after the fracture. This had, to our knowledge, at this time only been shown in one other study, a Swedish study from 2010 based on 100 patients from a single centre. [167] Later on, a study with comparable design was carried out by Rossini et al. in 2014, that showed changes in prescribing before and

after a hip fracture similar to our results. [168] In 2016, an American study was published which included more than 80,000 hip fracture patients. [169] The results from this study showed only a 3.4% increase in the prescribing of FRID but the definition of FRID differed somewhat from that used in *Paper I*. Since drug prescribing and clinical guidelines often differ between countries it can even so be of domestic interest to present results based on national research and this increases the potential of generalizing from these results.

In *Paper IV*, it was concluded that treatment with LdAA increased the all-cause first-year mortality, compared to mortality in unexposed patients. This had at the time of publication, to our knowledge, not been confirmed by other studies, when compared to studies by Marval et al. in 2004 and Kennedy et al. in 2006. [170, 171]

A unique finding in *Paper I* were the differences in drug prescribing in hip fracture patients treated in hospitals with geriatric support compared to that of patients treated in hospitals without this collaboration. This result may help strengthen the motivation for working towards closer collaboration between orthopaedic and geriatric units. Another clinically relevant result (*Paper III*) was that patients treated with a group of PIM with analgesic effects had a higher mortality than patients without this treatment, also when comparing with exposure to other opioids. This finding implicates that pain-relief is of utmost importance for the outcome of hip fracture patients' survival and that analgesics should be chosen carefully to suit each patients needs and conditions.

In *Paper III*, it was found that a LOS of 10 days or longer had a possibly unfavourable effect on survival. What clinical importance this result can have on the care of hip fracture patients is not within the scope of the study to identify. Length of in-hospital stay is a too complex topic to assess using an epidemiologic study design and it is not fully possible to explain the associations we have found. Even so, this result to some extent corroborates that concluded by Nikkel et al. in 2015 [172], in a large longitudinal studies on 30-day mortality after discharge from hospital.

Inappropriate drug prescribing

In this research both exposure to FRID and to PIM are studied. The reason for this is that drugs included as FRID are in many cases used as treatment for cardiovascular disease and besides reducing the dosage seldom can be avoided. Included in PIM however, are drugs with more varied effects and these are often possible to end or exchange for more appropriate drugs.

In *Paper I*, it was concluded that there were no substantial reduction in the prescribing of FRID, even though safer and non-pharmacological therapies were

available. Instead, FRID was used to treat morbidities that follows in the wake of the hip fracture, e.g. psychotropic, cardiovascular, and anti-cholinergic drugs. Included in the category of fall-risk increasing drugs are, among others, medication for cardiovascular diseases and psychotropic drugs. Some drugs may have health benefits for the patients that surpass the risks involved with the medication, and others may not. Many drugs used for inconveniences that follow with old age, such as insomnia and mild anxiety, can impose considerable risks to the individual patient. [94, 95, 173] Sedatives and hypnotics are drug classes that are considered to increase the fall-risk, and older hip fracture patients must be regarded as individuals at high risk of new falls and fractures. Other psychotropic drugs that are classified as FRID are antidepressants which are considered to nearly double the risk of falls in treated patients. [95, 174] In the study population included in *Papers I-III*, it was found that 36% of the patients were treated with sedatives or hypnotics and 21.5% with antidepressants. Here, a potential for modifying the drug regime and lower the fall-risk presents itself. The risk of a second hip fracture after the first one was shown, by Schroder et al. in 1993, to be 5-10% within three years and by Center et al. (2007) it was concluded that the increased risk of a subsequent fracture remains up to ten years after a low-energy fracture. [175, 176]

Included in PIM are drugs for psychiatric symptoms that are often prevalent in patients with dementia. Dementia is a frequently occurring comorbidity in patients with hip fracture, who are often prescribed antipsychotic drugs for disturbing behaviour related to dementia. Increased mortality in dementia patients has been linked to the use of antipsychotic drugs by, among others Ballard et al. in a withdrawal study in nursing home residents. [177, 178] The increased risk of developing delirium in hip fracture patients is one contributory factor for the higher mortality seen in this group of patients. [113, 115, 116] Here another possible way to reduce short-term mortality presents itself since 273 patients (13.4%) in the study population of *Paper II* were treated with strong anticholinergic drugs before the fracture. [179, 180] Since a connection has been established between delirium and the use of drugs with strong anticholinergic effect in geriatric patients, especially with concomitant use of two or more anticholinergic drugs, to reduce the prescribing can be a potential way of preventing delirium and reduce mortality. [181-189]

In *Paper III* a probable association between exposure to PIM and an increase in mortality six months after the fracture was found, which provides us with another opportunity to intervene in order to decrease fatal outcome in hip fracture patients. Exposure to DDI did in this study not show any impact on mortality but this does not imply that it is without risk to use such combinations of drugs to the individual patient.

Fall prevention

From reviews on fall preventive measures it has been established that the most effective way to reduce falls and consequent injuries is a multi-interventional approach by a multi-professional team. [89] This reflects the complexity of the task of reducing falls that are often caused by the multiple fall-risk factors present in each individual person. The effects of varied interventions to reduce fall rates, number of falls, number of fallers, and number of fractures has been shown in several studies. [84, 93, 120, 190-193] Complex interventions are needed to reach this goal and in addition to identifying and handling the individual risk factors, actions such as public information campaigns and educational programs for healthcare personnel are also essential. This requires however substantial economic and workforce resources and a decisive effort must be put into the task. The increased risk of falling, leading to fractures in old people treated with FRID, has for long been recognised but so far, only few signs of reduced prescribing have been observed. [164, 165, 194-198] One way to improve drug safety is to implement current knowledge on how to avoid, adapt, and to discontinue treatment with FRID in patients considered to be at risk of falls and low-energy fractures. Since it is achievable to avoid prescribing combinations of FRID as well as to adjust dosages of FRID, prevent DDI, and to stop the prescribing of PIM, this is a potential foundation for further studies on fall prevention. In a review from 2012, by Gillespie et al., it was concluded that there is no strong evidence for the effect of medication reviews on reducing falls or fractures and that there is a need for further research to confirm whether this is a successful way of reducing falls or not. [1, 121] On the other hand adjusting medication towards safer and more appropriate therapeutic alternatives can be one of the most efficient ways of reducing falls but we have yet to reliably demonstrate this effect. [87, 92, 193, 199-201] In a study by Stenhagen et al. (2013) it was shown that the use of antipsychotics was a strong fall-risk factor. [96, 97] This is important to bear in mind when contemplating treating older patients with antipsychotics. Studies on dementia patients in care facilities who were treated with antipsychotic drugs indicate a significant reduction in mortality in a group of patients whose antipsychotic drugs were withdrawn, compared to a control group that continued the treatment. It was also concluded that in many cases antipsychotic drugs could be withdrawn without any problems for the patients. [177, 178, 202]

Anti-osteoporosis treatment and geriatric support

We found that anti-osteoporosis drugs aiming to reduce the risk of future fractures were not prescribed to an optimal number of patients. The appropriate amount of hip fracture patients that can gain from this treatment is considered to be at least twice the number that is prescribed anti-osteoporosis drugs today. The prescribing

of anti-osteoporosis medication (*Paper I*) increased marginally with anti-resorptive agents and only slightly more with calcium in combination with vitamin D, results that are confirmed in other studies. [47, 59, 203] The patients who more often were treated with anti-osteoporosis medication post-fracture were those treated in the two hospitals where collaboration between geriatric and orthopaedic physicians took place. Even if the increase in number of patients treated in two of the five districts was statistically significant, an ideal number of patients was not treated compared to the number that potentially stood to gain from such treatment. Several studies on the effect of geriatric care for hip fracture patients have shown beneficial effects on survival and on ADL functions compared to care in orthopaedic wards. [199, 204-208] Health authorities, such as the National institute for clinical excellence (NICE) in 2014 and the Royal College of Physicians in 2016, issued guidelines on how to improve the overall care of hip fracture patients where the importance of collaborative efforts between orthopaedic and geriatric departments are stressed.

These results imply that treating osteoporosis has the potential to prevent fractures as well as to lower the risk of fatal outcome in patients with osteoporotic fractures. The possible gains of reducing the risk of a second serious and costly fall-injury must be seen in the light of the fact that the risk of another osteoporotic fracture can be as high as 87% according to Kanis et al. in 2004. [48]

An important aspect of anti-osteoporosis medication is how to uphold compliance to the medication over a number of years and this is considered to be a serious problem due to the frequent adverse effects from the drugs. Compliance to both bisphosphonates and calcium supplements are low as has been confirmed in a number of studies and non-adherence can increase the risk of, possibly avoidable, further fractures. [65, 209-211] There are interventions evaluated as efficient to increase the adherence to anti-osteoporosis medication and they include improved patient-information on side-effects, regular follow ups, and fracture liaison services. [211-213]

Mortality and drugs

The influence on mortality in older hip fracture patients that arises from comorbidities and complications, from the fracture itself as well as from the emergency surgery, is substantial and must be taken into consideration when evaluating the impact of drug use on mortality. In *Paper IV*, a possible association between the use of LdAA and increased first-year mortality was established. This result could also be caused by the disease for which the drug was prescribed or by a lack of efficacy of the LdAA, but even so, the result remained significant after adjusting for several of these confounding factors. Since the time this study was conducted, a shift has been made in Sweden towards prophylactic anti-thrombotic

drugs more effective than LdAA for treating patients with varied cardiovascular and cerebrovascular disorders.

The LdAA percentage of all anticoagulants prescribed in the county has decreased by 20% in 2015 compared to 2006. (Information available at www.socialstyrelsen.se) Therapy with drugs like warfarin, clopidogrel, ticagrelor and new oral anticoagulants (NOAC) has since been introduced and are more frequently used. The LdAA-associated increase in mortality can also be explained by the added strain on the circulatory system that complications from increased bleeding and anaemia entails, with potentially harmful effects on cardiac function. The additional unsafe effects from blood transfusions in frail patients, with chronic heart failure and renal dysfunction, also add to the problematic task of handling perioperative anaemia. [214]

In *Paper II*, an increased risk of 90-day and 180-day mortality was found to be associated with the use of 4 or more FRID compared to the use of 4 or more drugs of any category. When matched to the increased mortality at 30-day connected to polypharmacy (HR 1.62 (95 % CI 1.17 – 2.24)) in these patients the use of 4 or more FRID brought with it a higher potential risk of death (HR 2.01 (95% CI 1.44 – 2.79)).

In *Paper III*, it was concluded that patients treated with any PIM and analgesic-PIM had a significantly higher mortality compared to unexposed patients. Tramadole and dextropropoxyphene are drugs with high potential risk for adverse reactions, especially in older patients, and Swedish health authorities in 2010 recommended that tramadole not be used in patients over the age of 75 years. At the time when data was collected for the study, this was however not yet an official recommendation. Even so, the number of patients receiving a prescription of PIM-analgesics at discharge from hospital do not necessarily reflect the amount of patients that were treated with tramadole or dextropropoxyphene during the hospital stay. There may have been a selection of patients who did not experience disturbing side-effects in-hospital whom were prescribed further treatment with tramadole or dextropropoxyphene after the discharge from hospital. This is, to some extent, confirmed by the fact that patients who were prescribed these drugs were significantly younger than those not prescribed them. However, to lessen the effect this could have on the result, the analyses were, among other confounding factors, adjusted for differences in age.

Mortality and length of in-hospital stay

In *Paper III*, it was found that the median length of in-hospital stay was nine days and that a LOS of ten days or longer was associated with higher mortality for up to six months after the fracture. There may be several reasons for a hospital stay longer

than the median, as this may either be due to the patients having longer time for recovery and rehabilitation in hospital wards with trained staff, or due to patients requiring longer hospital stays because of postoperative complications and other health problems. In our study, where we included deaths occurring in-hospital, there was no significant differences between the length of LOS and the patients' sex or age. It is likely that patients experiencing complications in-hospital are requiring a longer stay and that more fit patients can be discharged earlier. However, another category of hip fracture patients discharged after a shorter period of hospital care, are those residing in nursing homes, a category of patients with multiple diseases and short expected life-span. This was however not further studied because information on residency and health-status was not available wherefore the cause of the effect on mortality remains unknown. Our outcome opposes the results found in a longitudinal Swedish study covering 2006 to 2012, by Nordström et al. in 2015. [7] In their study they found that a stay of ten days or more in-hospital was related to higher survival 30 days after the hip fracture, however they excluded patients that died during the hospital stay. Their results are discussed and commented upon by Cram and Rush in 2015. [172] In an American longitudinal study from 2000 to 2011 by Nikkel et al., 2015 on 30-day mortality, after discharge, in 188,208 hip fracture patients, a result corroborating with ours was presented. [215] However there are major differences in the care of hip fracture patients between countries and hospitals that must be taken into account.

Generalizability and changes in drug prescribing

Even though the prescribing of inappropriate medication in the older population has been substantially reduced lately, every day new patients are started on inapt drug treatment regardless of the hazards this may bring. [216] In Swedish reports it has been shown that more than 25% of nursing home residents are still being treated with one or more PIM and that 8% of the total population 75 years or older are exposed. [217] It is important to be aware of the risks involved in treating older patients with FRID, PIM and LdAA, as well as the potentially serious outcomes they have been shown to bring. The results presented in this thesis and the aim to increase the knowledge of the consequences caused by inappropriate drug therapy, needs to be considered in its present day context. The changes in drug prescribing that has taken place over the past ten years can probably have impact on the clinical generalizability the results presented here can render. Some of the changes in drug prescribing between 2006 and 2015 in Sweden and the County of Skåne are presented in table 8. There have also been considerable changes in the national guidelines for therapy with anticoagulants, antithrombotic drugs, and PIM during the last ten years, whereas recommendations on drugs included in FRID have not changed accordingly. The use of cardiovascular drugs, for instance, has increased

due to the strengthened evidence for effects of drugs with prophylactic anti-thromboembolic effects, even in very old patients. Even though the guidelines differ as to when a patient is considered to be older, most consider 60 years or older to be the preferred age limit, few studies have been known to include patients over 80 years. [218-221]

Table 8.

Changes in drug prescribing from 2006 to 2015, comparison between Sweden and Skåne County. Patients/1,000 residents, 60 years or older.

	Sweden	2006	2015	Skåne 2006	2015
Osteoporosis, all drugs, M05		46	41	48	46
Antipsychotics (not lithium), N05A		43	26	39	24
Hypnotics + sedatives, N05CD, N05CF		232	211	232	203
Tramadole, N02AX02		87	31	115	35
All opioids, N02AA		34	91	31	100
SSRI, N06AB		109	101	115	108
Sedatives, N05B		137	119	156	135

The prescribing of PIM in Sweden has been reduced substantially in the last decade and is continuing to decrease. Figure 6 illustrates the trend of prescribing PIM to people 75 years and older during the last ten years in Sweden and Skåne County. (Personal communication, T Schöller, Läkemedelsrådet, Skåne). In the year 2006 a campaign was launched by Swedish authorities to alert physicians to the hazards of prescribing PIM to older patients and this has been helpful in reducing the use of PIM. For example, in the county of Skåne the use of tramadole has decreased from constituting 27% of all non-opioid prescriptions in 2006 to 11% in 2015, and the prescribing of dextropropoxyphene began to decline in 2009 before the drug was finally taken off the market in 2011. Figure 7. Propiomazin (N05CM06), a drug used for sleeping disorders, is one of the drugs listed as PIM and its' prescribing was reduced from 33 patients per 1,000 residents treated, to 24 in residents 60 years or older. On the other hand, the prescribing of bisphosphonates in patients over the age of 60 remained largely unchanged from 2006 to 2015, both in Skåne County and in Sweden. Table 8.

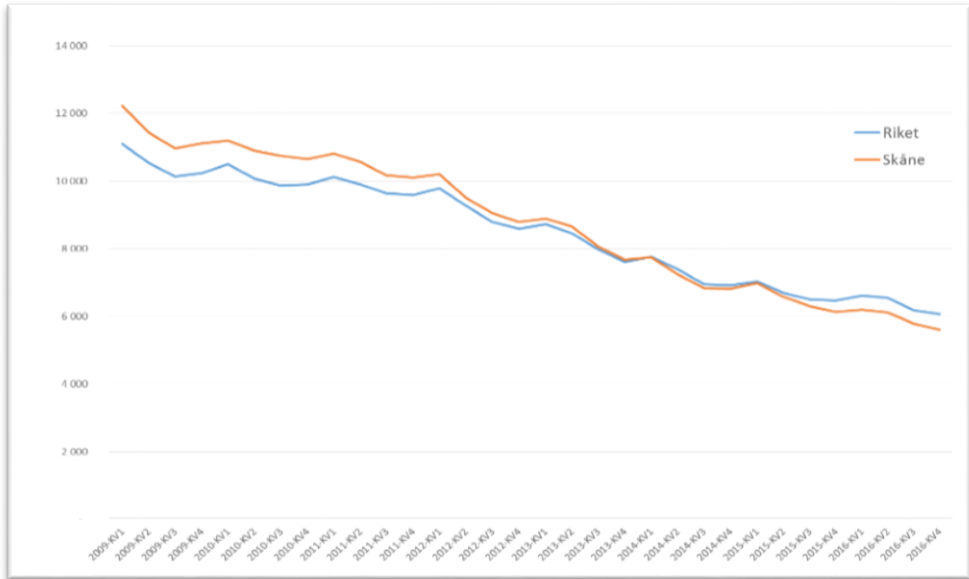


Figure 6. Trends in the prescribing of PIM in Sweden and Skåne County, 2009-2016. DDD/1,000 residents 75 years or older.

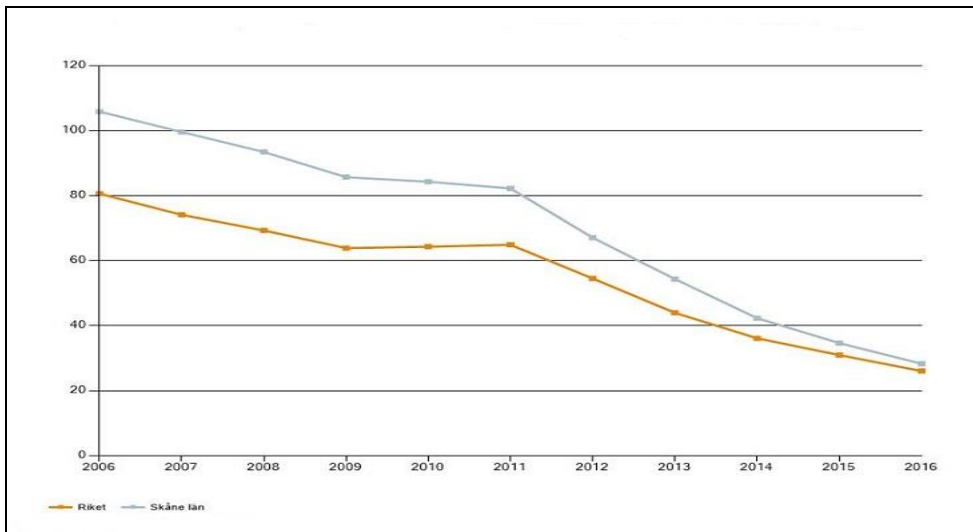


Figure 7. Trends in the prescribing of tramadol in Sweden (----) and Skåne County (----), 2006-2016. Patients/1,000 residents 60 years or older.

Methodological considerations

Several methodological considerations are necessary to explore when evaluating the strengths and weaknesses of the studies on which this thesis is based. These includes, among others, the included study populations, register reliability, statistical methods used, and the risk of bias in connection with confounding factors.

Study populations

One of the most important factors that can bias the study results is the selection of study population. Two common denominators were present for the two included populations, a hip fracture diagnosis and an age within a set range, ≥ 50 years and 60 years and older, respectively. The patients included in the four studies were diagnosed with a proximal femur fracture, based on clinical as well as radiographic findings and the majority underwent surgery that confirmed this diagnosis. In comparison to other more complex diagnostic fields a hip fracture is easier to establish, which reduces the likelihood that any patients with hip fractures have been overlooked or wrongly diagnosed. There may have been undetected hip fractures patients who did not seek medical care, but this is not likely to be of such proportions that it could prejudice our results.

The included study patients in *Paper I-III* are drawn from a large sized county's population and represents and reflects a general population and can thus be considered a sound basis for generalizing the results to a wider elderly population. [222] The strength of studies based on population registers lies in the fact that participants are included regardless of cognitive status, language difficulties, or other incapacities which can be the case with RCTs. *Papers I-III* include patients from different living conditions in both urban and rural areas. In comparison with other studies on patients with proximal femur fractures the included patients are representative in terms of mean age, sex ratio, and distribution of cervical and non-cervical fractures. We considered the size of the study population to be adequate and that a p-value of <0.05 as a statistically significant indicator for differences. Patients who participated in *Paper IV* were likewise diagnosed with hip fractures, but in this case patients with one type of surgery were excluded due to the lower risk of bleeding in connection with undisplaced cervical fractures treated with pinning as the surgery procedure. This exclusion was made in the original study, in which it was evaluated whether placing a compression bandage over the fractured hip directly after surgery could reduce bleeding and the conclusion was that it did not.

Register consistency

When studying information from databases it is prudent to examine the reliability of the compiled data. In order to identify patients in the three different registers we used the Swedish personal identity number that is allocated to each individual resident. We consider the acuteness of this number to be very high in patients within the studied age range, who rarely change this number. [223] The registers used for *Paper I-III* (In-patient, Prescription and Cause of Death registers) are considered to be mostly consistent in terms of quality and inclusion of data. This has been studied by Ludvigsson in 2011. [83] Register studies, on the other hand, entail difficulties as the data required to cover all aspects of the patients' medical situation are not available.

The In-patient register has been discussed previously in the text regarding the reliability of diagnostic procedures of hip fractures. The impact of lack of data concerning comorbidities will be divulged upon later in the text, on the subject of confounding. The Prescription register has a high reliability since the purchases by law must be registered and form the base for pharmacies to receive economic compensation from the relevant authorities. For drugs to be included in this register they have to be prescribed by a physician and dispensed from a Swedish pharmacy.

Not all included data in the Cause of Death register used in *Paper III* can be considered explicitly reliable. Time of death is consistent, but cause of death is not established with correspondingly high precision. This derives from the fact that few deceased patients in Sweden are examined post-mortem to establish a more precise primary cause of death. Death certificates of older patients are subsequently based mainly on clinical findings out of or in-hospital. This is taken into consideration in *Paper III* where data on cause of death is divided into only two groups, death caused by diagnoses related to the circulatory system (ICD^{10th}, category I), present in 38 % of the patients, and the comparing group containing all other causes. In the last group the most frequent cause of death was from cancer (12%).

Drug prescribing and compliance

An important factor that can bias the results is the patients' exposure to drugs. In *Paper I-III*, drug exposure is based on the individual prescribing of drugs dispensed from a Swedish pharmacy. A central aspect of drug usage is that we do not know if the prescribed drugs are consumed or not. Studies have shown that it is quite common for patients to abstain from taking their prescribed medication. [153, 224-227] This has been taken into account in *Paper III*, where only drugs prescribed at least twice are included in the analysis in order to increase the reliability of drug exposure. In *Paper IV*, the current drug use was registered in the medical charts for

each patient, thereby to some degree confirming whether the drugs were used or not. One problem is the high prevalence of cognitive dysfunction in hip fracture patients. Reliable data concerning the medication taken by the patients with dementia, who with their next of kin giving informed consent for inclusion, participated in the study, was not easy to attain from the patients themselves. On the other hand patients with dementia often receive help with their medication, which can support the assumption that correct information on drug use was received. The consumption of over-the-counter, non-prescription drugs was not within the scope of the studies and neither was the use of herbal remedies nor medications prescribed before the data collection period, but this fact did not feasibly have any negative influence on the results. The use of calcium, vitamin D, a number of antihistamines, and other drugs with sedative effects could however be underrated due to the lack of access to data on consumption of over-the-counter drugs in the patients.

Identifying FRID, PIM, and DDI

When analysing FRID we used a list of drugs compiled by the Swedish Board of Health and Welfare in 2010, but no comparable Swedish list covering PIM was available at the time. Several studies on FRID, as well as reports by the Swedish Board of Health and Welfare, were accessible for identifying relevant fall-risk increasing drugs and these were used in *Paper I* and *II*.

The Beers' explicit criteria was used to identify drugs belonging to the different categories of PIM, making it possible to compare the achieved results with other studies, both nationally and internationally. The list of PIM according to Beers' explicit criteria has been difficult to use by European researchers since several substances are used only in the USA, leaving out inappropriate drugs used in other countries. [82] This was one of the underlying reasons for adding three drugs from a nationally compiled list of drugs identified as PIM in Sweden. [161] The other was to include other analgesics drugs (opioids) which are frequently used in the population of hip fracture patients.

No comprehensive list of clinically potentially relevant DDI of Swedish origin was available, and so a DDI list presented in Beers' list 2015 was used. Also DDI classified as D (must be avoided if possible) and C (must be dose-adapted when used in combination) for combinations of drugs were added. This can compromise the generalizability of the results outside of Sweden and make it difficult to compare these results with other studies on exposure to DDI and possible associations to adverse outcomes such as mortality. The included DDI in *Paper III* are compiled and presented in Appendix C.

Confounding or causality?

When confounding factors are identified their influence on the results can be diminished by using the appropriate statistical methods. In *Paper II*, it was identified that age and sex had influence on mortality but not on the type of fracture, as in other studies. Subsequently, we chose to adjust for age and sex in the analysis on mortality in connection with exposure to different categories of drugs identified as FRID. In *Paper II*, besides age and sex, adjustment for use of any four drugs was made when analysing the cumulative survival of patients treated with four or more FRID compared to those exposed to three or less FRID. This was done in order to reduce the risk of the total number of FRID interfering with the results on mortality at 90- and 180-day. Since we did not find a dose-response relation between the number of FRID and first-year mortality, this weakens the conclusion that patients exposed to four or more FRID have increased mortality. Recently a study by Zia et al. 2017, has been published, which shows a probable association between use of two or more FRID and increased falls but mortality was not studied. [164]

In *Paper III*, mortality and exposure to different categories of PIM were compared after adjusting for age, sex, and polypharmacy. In this case polypharmacy was used as a marker for multiple comorbidity in an attempt to decrease the risk for confounding by comorbidity. A weakness in the compiled data for *Paper II* and *III* was that comorbidity could not be analysed due to major differences in diagnostic registration practises between the five orthopaedic departments. This resulted in that more than a third of all patients, belonging mainly to two hospitals, did not have any registered comorbidities. Since this most likely primarily was a sign of variations in routines between the departments rather than differences in the disease burden of the patients, the data could not be used in the analyses in *Papers II* and *III*.

In *Paper IV*, we had access to information on comorbidities and were thus able to adjust the analysis concerning mortality in patients treated with LdAA. This was important since the drug itself signifies cardiovascular or cerebrovascular disease being the indication of the treatment, thereby making the results prone to confounding by indication. We were able to adjust for a number of confounding risk factors for increased mortality, such as cardiovascular or cerebrovascular disease, age, sex, baseline haemoglobin, type of fracture/surgery, and renal dysfunction. On the other hand, the risks associated with adjusting for multiple confounding factors are that the results might become attenuated and increase the risk of a type II error.

Selection of control patients

After contemplating using an external group of patients as controls to the hip fracture patients included in *Paper I-III*, we decided, after thorough consideration,

to use internal controls when relating drug exposure to adverse outcomes such as death, cause of death, and bleeding. It did not appear sufficient to use control cases from the general population, even when matched by age and sex, so we at first considered using external control cases consisting of patients with a corresponding disease burden. But it proved problematic to find external control patients with comparable age range, drug exposure, frailty, comorbidity, mortality, and severity of injury, in combination with exposure to an emergency surgical procedure with related anaesthesia, wherefore we decided to use internal control patients. In other studies, external control cases for hip fracture patients have been selected among patients with other diseases requiring in-hospital care, such as heart failure or pneumonia, but not among patients exposed to a degree of pain, stress, surgical intervention and anaesthesia similar to that of patients with proximal femur fractures. [228-232]

Study design

The studies included in the thesis are of descriptive and observational design aiming to identify risk factors to severe outcomes in older fracture patients, based on an epidemiological approach. Epidemiological methods are widely used in medical science and aim to study the distribution of diseases and events as well as to identify factors related to them. Epidemiological studies form a solid basis for research on health-related issues and can be used in a variety of research. The results from data analyses in epidemiological studies can supply important information upon which decisions on healthcare improvement can be based. In order to reach reliable results, it is crucial that the choice of study population, data collection procedures, and statistical methods are as unbiased as possible and adequately adapted to the aim of the research. Results from epidemiological studies can be difficult to interpret and draw conclusions from, especially when the results diverge from other studies. But the importance of epidemiological research must not be ignored since, with the increasing amount of data available in registers the opportunity to improve healthcare relatively cost-effectively must not go untried.

When performing research based on data on individuals from national registers, ethical considerations are of special concern. The risk of harming any individual patient with epidemiological studies may appear to be minimal, but in the light of the increasing amount of data being compiled, it must be carefully considered. Here, an important aspect is the purpose of the research as well as the potential for generalizability of the results.

Conclusions

The results of this thesis propose that exposure to four or more fall-risk increasing drugs, polypharmacy, potentially inappropriate medication (PIM), low-dose acetylsalicylic acid (LdAA) and a length of in-hospital stay (LOS) longer than ten days are factors associated with increased mortality in older hip fracture patients and that collaboration between orthopaedic and geriatric professionals can improve the treatment of osteoporosis. The overall conclusion lies in the identification of plausible ways to reduce adverse outcomes and improve the care of older hip fracture patients.

- A potential way to improve the outcomes for a majority of hip fracture patients is to reduce treatment with fall-risk increasing drugs. Prior to the fracture 64% were prescribed FRID, and this treatment was rarely discontinued despite of the risks involved. Rather, a 30 % increase in prescribing took place.
- Even though a close relation between low-energy trauma fractures and osteoporosis has been recognised, few patients were prescribed prophylactic anti-osteoporotic medication following the fracture.
- One possible way of improving anti-osteoporotic treatment is collaboration between geriatric and orthopaedic professionals. In orthopaedic wards offering geriatric support, more patients were treated with anti-osteoporotic drugs.
- Exposure to multiple FRID (≥ 4 FRID) prior to the fracture may be a potential risk factor for increased all-cause one-year mortality in hip fracture patients comparable to that of treatment with polypharmacy (combined use of ≥ 5 drugs), psychotropic and cardiovascular drugs, adjusted for age, sex and treatment with any ≥ 4 drugs.
- Drugs containing low-dose acetylsalicylic acid with anti-thrombotic effect, can have potentially serious effects on the outcome of hip fracture patients undergoing surgery. An increase in blood transfusions as well as a higher first-year mortality was found to be related to exposure to LdAA.
- Treatment with potentially inappropriate medication may have a significantly negative effect on short-term survival in older hip fracture patients exposed to any PIM.

- Patients that were receiving analgesics identified as PIM in Sweden (tramadol and dextropropoxyphene) had a considerably higher six-month mortality than unexposed patients. Analyses on exposure to other analgesics (opioids) did not show this effect which highlights the importance of individually adapted pain management in older fracture patients.
- In these analyses, exposure to drug-drug interactions (DDI) recognised as being of clinical importance did not show any significant impact on mortality, thereby confirming earlier research. The relevance of DDI must be studied in other settings and with different study designs to establish its impact on the health of older patients.
- The optimal length of in-hospital stay in older hip fracture patients is yet to be established, but indications are given here that a stay longer than the median of nine days can be linked to considerable negative effects on survival, compared to a shorter stay.

Since the effects of hip fractures carry such serious negative impact on both individual well-being and societal costs, procedures that can reduce falls, fractures, bleeding complications, and other serious outcomes, must be pursued. Identifying and introducing such interventions in the care of older hip fracture patients can potentially have substantially beneficial health effects. Drugs and drug combinations with potential for adverse effects in older patients can often be avoided and future studies should emphasise how to identify efficient methods of doing so.

Future perspectives

The results from this thesis focus on the possibilities of providing safer medication and care of older patients with proximal femur fractures and can in many ways also be applied to patients with other major osteoporotic fractures. Mortality in hip fracture patients is high compared to other severe injuries and diseases. In order to improve in-hospital survival, it is important to give priority to studies on interventions that may enhance drug-safety and reduce problems relating to falls, infections, pain, malnutrition, pressure ulcers and implant-related complications.

The risk of a second hip fracture is elevated for several years, and fall-preventive interventions can have a substantially favourable effect on reducing fall-related injuries in an older, high-risk population. We report that the prescribing of inappropriate drugs can have severe consequences for hip fracture patients and should be addressed accordingly. Efforts to reduce the risk connected with FRID and PIM should therefore be made by physicians, both in general and in-hospital health settings. Future research should focus on evaluating the effect of judiciously selected drugs and individually adjusted doses in high-risk patients in large populations and in randomized trials.

We have touched on the subject of osteoporosis, a common condition in hip fracture patients, and found that more can be achieved by a collaboration between orthopaedic and geriatric professionals. Collaborative efforts to care for patients with low-energy hip fractures, a serious complication to osteoporosis, have been shown to be beneficial. Specialised units working with standardised care procedures, earlier proved effective for optimizing the care of patients with other incapacitating conditions, such as stroke, is one way of improving the treatment for patients with osteoporotic fractures that ought to be further pursued. Randomised trials aiming to evaluate if individually modified drug use, with emphasis on minimizing the use of fall-risk increasing drugs and other inappropriate medication, may be effective in reducing falls and fractures, uphold autonomy, and improve quality of life.

Summary in Swedish

Populärvetenskaplig sammanfattning

Läkemedelsbehandling av äldre höftfraktur patienter – fall, frakturer och mortalitet

Den demografiska utvecklingen i Sverige och i flertalet andra länder går snabbt mot en allt större andel äldre i befolkningen, vilket inom en snar framtid kan medföra att även antalet höftfrakturpatienter ökar. Personer som får en höftfraktur är äldre, medelåldern omkring 82 år, och har ofta flera kroniska sjukdomar som behöver behandlas med flertalet läkemedel. Avhandlingen syftar till att öka vår kunskap om hur äldre höftfraktur patienter behandlas med läkemedel vilka potentiellt kan öka risken för fall, frakturer, blödningar och för tidig död. Fallet som ofta föregår en höftfraktur är delvis möjlig att förhindra, alternativt går det att minska dess skadeomfattning, genom att minska användningen av läkemedel vilka kan öka fallrisken. Läkemedel som ökar risken för fall (FRID), läkemedelsbehandling som bedöms vara generellt ogynnsam för äldre (PIM), osteoporosläkemedel och antikoagulantia analyseras i avhandlingens studier. Höftfrakturer ses som en av de allvarligare konsekvenserna av osteoporos, och precis som för andra typer av låg-energi frakturer kan medicinerings med anti-osteoporos läkemedel, i kombination med kalk och vitamin D, minska risken för nya frakturer och öka överlevnaden.

Studiedesignen för de fyra delarbeten som ingår i avhandlingen är kohortstudier utgående från en generell populationskohort av alla höftfrakturpatienter över 59 år under ett år i Skåne (studie I, II och III) samt från en kohort höftfrakturpatienter som ingick i en randomiserad kontrollerad studie på ett av Skånes akutsjukhus. Data från tre nationella register (patient-, recept- och dödsorsaksregistret) för 2 043 patienter, ingår i analyserna för studierna I-III samt data för 255 patienter hämtade från medicinska journaler i delarbete IV.

Syftet med *delarbete I* var att beskriva förskrivningen av FRID i en kohort av 2 043 höftfraktur patienter 60 år och äldre, genom analys av huruvida det utfördes några ändringar i läkemedelsförskrivningen sex månader efter en höftfraktur jämfört med sex månader före frakturen samt om det fanns skillnader i förskrivningen mellan de då fem ingående sjukvårdsdistrikten i Skåne. Vi fann att en hög andel (68 %)

behandlades med FRID före höftfrakturen och att det skedde en 30 procent enheters ökning i förskrivningen av FRID efter frakturen samt att det fanns delregionala förskrivningsskillnader, fr.a. av osteoporosläkemedel och opioder. Förskrivningsskillnadernas fördelning mellan sjukvårdsdistrikten pekade på att patienter som vårdades på sjukhus där specialister inom geriatrik och ortopedi samverkade, fick i större omfattning behandling mot osteoporos och opioder för smärta.

I *delarbete II*, analyserades ett-års mortaliteten hos patienter exponerade för FRID före frakturen jämfört med icke-exponerade patienter och vi fann att patienter behandlade med ≥ 4 FRID, polyfarmaci (≥ 5 läkemedel), psykofarmaka och hjärtkärl-läkemedel hade signifikant högre dödlighet än de som var oexponerade, justerat för ålder, kön och behandling med ≥ 4 läkemedel. Högre mortalitet sågs, efter justering för störfaktorer, även hos patienter med ≥ 4 FRID jämfört med dem som behandlades med ≤ 3 FRID.

Potentiellt ogynnsamma läkemedel för äldre och kliniskt betydelsefulla drog-drog interaktioner analyserades i *delarbete III* för att utröna om det förelåg skillnader mellan exponerade och oexponerade patienter samt om sjukhusvistelsens längd påverkade sex månaders mortalitet efter en höftfraktur. Analyserna visade att 81 % av patienterna behandlades med PIM och att ogynnsamma analgetika (tramadol och dextropropoxyfen) med hög risk för biverkningar hos äldre, minskade sex-månaders överlevnaden. Patienter som behandlades med PIM hade högre dödlighet vid 30- och 90-dagar justerat för ålder, kön och polyfarmaci. Behandling som medförde drog-drog interaktioner sågs inte påverka patienternas mortalitet. Vid analys av mortaliteten hos patienter som hade längre vårdtid än genomsnittet 9 dagar, justerat för ålder, kön och polyfarmaci, sågs en ökad dödlighet jämfört med patienter med kortare vårdtid.

I *delarbete IV* jämfördes höftfraktur patienter (≥ 50 år) som behandlades med lågdos acetylsalicyl syra (LdAA) med patienter utan denna behandling, avseende blödningsparametrar, blodtransfusionsbehov och ett-års mortalitet. Resultatet, efter justering för multipla störfaktorer, visade på signifikanta skillnader mellan patientgrupperna, med fler som fick blodtransfusioner efter operationen och en högre ett-års dödlighet i gruppen patienter som behandlades med LdAA.

Slutsatserna som kan dras från avhandlingens delarbeten är att åtgärder som minskar exponering för ≥ 4 FRID, polyfarmaci, PIM, PIM-analgetika, LdAA, och en vårdtid längre än nio dygn, kan potentiellt minska mortaliteten hos äldre höftfrakturpatienter. Förskrivning av FRID efter en höftfraktur ökade påtagligt medan osteoporos behandling förblev låg och genom ökad samverkan mellan specialister inom geriatrik och ortopedi kan sannolikt gynnsamma effekter för höftfraktur patienter uppnås. Förskrivningen av de studerade läkemedelsgrupperna har förändrats påtagligt under de gångna tio åren sedan studierna genomfördes och

allt färre äldre behandlas med PIM. Men fortsatt förskrivs dessa olämpliga läkemedel till 25% av alla boende på sjukhem och till cirka 11 %, av alla personer över 75 år i Sverige. Framtida studier bör fokusera på att identifiera och utvärdera effektiva metoder för att öka säkerheten i äldres behandling genom att minska förskrivningen av läkemedel vilka potentiellt kan öka riskerna för fall, frakturer, och blödning, samt för att minska potentiellt undvikbar överdödighet hos äldre höftfrakturpatienter.

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For the ones I have forgotten, I apologise in advance.

Appendices

Appendix A

Drugs identified as FRID, Papers I and II

Psychotropic drugs: sedative/hypnotic (N05B/N05C), antidepressives (N06A), antipsychotic (N05A), benzodiazepine (N05BA, N05CD), long-acting benzodiazepines (N05CD02/03, N05BA01)

Cardiovascular drugs (all included in class C, except for C10)

Anticholinergic drugs (A03AA, A03BA, A03AB, A03BB, A03C, A04AD, C01BA, G04BD, N02AG, N04A, N05AA, N05AB04, N05AC02, N05AF03, N05BB01, N06AA, R05CA10, R06AA02, R06AB, R06AD, R06AX02)

Antiepileptic drugs (N03A)

Antiparkinson drugs (N04B)

Opioids (N02A9)

Combinations of drugs: ≥ 5 drugs, ≥ 10 drugs, ≥ 3 psychotropic drugs.

Drugs with effects on bone metabolism, Paper I

Oral bisphosphonates (M05B)

Calcium and vitamin D supplement (A12A)

Non-steroid anti-inflammatory drugs (M01A)

Glucocorticosteroids (H02AB)

Appendix B

List of PIM to be avoided with a strong recommendation, according to Beers' criteria. Paper III.

Anticholinergics: brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyprohetadine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, promethazine, triprolidine

Antiparkinson agents: benzotropin, trihexyphenidyl

Antispasmodics: belladonna, clidinium-chlordiazepoxide, dicyclomine, hyoscyamine, propantheline, scopolamine

Antithrombotics: dipyridamole without aspirin

Antiinfective: nitrofurantoin

Cardiovascular: alpha1blockers; doxazosin, prazosin, terazosin
 alpha agonist, central; clonidine, guanabenz, guanfacine, methyl dopa, reserpine
Antiarrhythmic drugs: amiodarone, dofetilide, dronedarone, flecainide, ibutilide, procainamide, propafenone, quinidine, sotalol, disopyramide, digoxine (>0,125 mg/d)
 Nifedipine, spironolactone (>25 mg/d)
Central nervous system: tertiary TCA: amitriptyline, chlodiazepoxide-amitriptyline, clomipramine, doxepin (>6 mg/d), imipramine, perphenazine-amitriptyline, trimipramine
Antipsychotics: first and second generation: thioridazine, mesoridazine,
Barbiturates: all
Benzodiazepines: all, short, intermediate and long acting
Chloral hydrate, meprobamate
Nonbenzodiazepine hypnotics for chronic use: >90 days: eszopiclone, zolpidem, zaleplone
Endocrine: androgens; methyltestosterone, testosterone, estrogens with or without progestins

PIM included from a list by the Swedish National Board of Health and Welfare 2010. Paper III.

Propiomazin (N05CM06)
 Dextropropoxyphene (N02AC54)
 Tramadol (N02AX02)

Appendix C

Drug to drug interactions analysed in Paper III.

Beers' list on DDI:

- Angiotensin-converting-enzyme inhibitors and amiloride/triamterene
- Anticholinergic and anticholinergic
- Antidepressants and ≥ 2 other CNS-active drugs
- Antipsychotics and ≥ 2 other CNS-active drugs
- Benzodiazepines/nonbenzodiazepine benzodiazepine-receptor-agonist and ≥ 2 other CNS-active drugs
- Total of ≥ 3 CNS-active drugs
- Corticosteroids, oral or parenteral and NSAID
- Lithium and angiotensin-converting-enzyme inhibitors
- Lithium and loop diuretics
- Opioid receptor agonist analgesics and ≥ 2 other CNS-active drugs
- Peripheral Alpha-1 blockers and loop diuretics
- Theophylline and cimetidine

Warfarin and amiodarone

Warfarin and NSAID

Other DDI included:

Angiotensin-converting-enzyme inhibitors/angiotensin-receptor-inhibitors and potassium sparing diuretics

Beta-blockers and verapamil/diltiazem

Carbamazepine and risperidone

Carbamazepine/phenytoin and tramadol/dextropropoxyphene

Clopidogrel and omeprazole/esomeprazole

Dextropropoxyphene and alprazolam

Digoxin and beta-blockers

Digoxin and verapamil/diltiazem

Fluconazole and carbamazepine/erythromycin/cimetidine

Potassium and potassium sparing diuretics

Quinolone and calcium/iron

Selective-serotonin-reuptake-inhibitors and codeine/tramadol/tricyclic antidepressants

Simvastatin and erythromycin/fluconazole

Simvastatin and calcium receptor antagonists

Warfarin and erythromycin/quinolone

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Doctoral Dissertations in Geriatric Medicine at Lund University

Malmö 1987

Sölve Elmståhl

Hospital nutrition in geriatrics long-stay medicine. Dietary intake, body composition and the effects of experimental studies.

Malmö 1990

Marek Wróblewski

Clinical diagnosis in geriatric medicine. Clinical and clinico-pathological studies of myocardial infarction, ulcer disease and peritonitis in long-stay elderly patients.

Malmö 1992

Henrik Östberg

Retirement, health and socio-psychological conditions. A longitudinal study of 116 municipally employed women in Malmö, Sweden.

Malmö 1994

Barbro Sjöbeck

Aspects of quality and equality in dementia care.

Ann Månsson-Lindström

Urinary incontinence in the elderly. Aspects of knowledge and quality of aids.

Malmö 1995

Lena Annerstedt

On group-living care for demented elderly. Experiences from the Malmö model.

Malmö 1998

Berit Agrell

Stroke in geriatric patients - Aspects of depression, cognition and motor activity.

Malmö 2000

Arkadiusz Siennicki-Lantz

Cerebral blood flow and cognition. Clinical studies on Dementia and Cognitive Decline with special reference to Blood Pressure.

Malmö 2002

Mats Persson

Aspects of nutrition in geriatric patients - Especially dietary assessment, intake and requirements.

Malmö 2003

Marianne Caap-Ahlgren

Health-related quality of life in persons with Parkinson's disease- Aspects of symptoms, care-giving and sense of coherence.

Malmö 2006

Signe Andrén

Family caregivers of persons with dementia. Experiences of burden, satisfaction and psychosocial intervention.

Björn Albin

Morbidity and mortality among foreign-born Swedes.

Faina Reinprecht

Hypertension, blood pressure, cognition and cerebral blood flow in the cohort of "Men born 1914".

Ulla-Britt Flansbjer

Strength training after stroke: Effects on muscle function, gait performance and perceived participation.

Malmö 2009

Henrik Ekström

The influence of fracture on activity, social participation and quality of life among older adults.

Maria Wadman

Clinical presentation, prognostic factors and epidemiology of ischemic bowel disease in the very old.

Lund 2011

Ingela Steij Stålbrand

A matter of life and health. Life satisfaction, personality and mortality in two populations of elders.

Malmö 2013

Åsa Enkvist

Life Satisfaction and the Oldest-Old. Results from the longitudinal population study "Good Aging in Skåne".

Malmö 2014

Magnus Stenhagen

On Falls in the Elderly – Epidemiological Studies from the Longitudinal General Population Study 'Good Aging in Skåne' (GÅS), Sweden.

Malmö 2015

Beth Dahlrup

Family caregiving, a long and winding road. -Aspects of burden and life satisfaction among a general population of caregivers from the study "Good Aging in Skåne (GÅS)," and effects of psychosocial intervention for caregivers of persons with dementia.

Malmö 2016

Lena Sandin Wrangler

Gender perspectives among older people living with pain.

Malmö 2017

Terese Lindberg

Arrhythmias in older people-focusing Atrial Fibrillation. Epidemiology and impact on daily life.

Nivetha Natarajan Gavriilidou

Evolving geriatric anthropometrics- an interplay with lifestyle changes, birth cohort effects, and survival implications. Results from the general population study, "Good Aging in Skåne, Sweden".

Papers I, II, III, and IV