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Cardiovascular Risk Factors for Falls and Fractures in the Elderly

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Cardiovascular Risk Factors for Falls and Fractures in the Elderly

Maria Härstedt



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DOCTORAL DISSERTATION

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Faculty opponent

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| Title and subtitle: Cardiovascular Risk Factors for Falls and Fractures in the Elderly | | |
| <p>Abstract</p> <p>Background: The population is getting older and low-energy falls and fractures are a growing health challenge as their incidence increase with advancing age. With the ageing population follows an alternation in physiology and an increased number of comorbidities and medications. These comorbidities and medications may constitute an increased risk for fall and fracture. Low-energy fractures are associated with great suffering and death among the elderly, a great cost to society and a challenge to the health care systems.</p> <p>Aims: The overall objective was to investigate correlation between cardiovascular risk factors for low energy falls and fractures. The risk factors analyzed were comorbidities, medications and polypharmacy, orthostatic hypotension and resting heart rate and cardiovascular biomarkers.</p> <p>Material and methods: Study I and II are prospective case series. We analyzed the same cohort of 272 consecutive patients who underwent acute hip fracture surgery. Analysis of how comorbidities at baseline and alterations among medications might affect readmission and mortality during the 6 month follow up. Study III and IV were retrospective population-based studies. In study III we analyzed if orthostatic hypotension (OH) and resting heart rate at baseline among a cohort of 33000 patients enrolled in Malmö Preventive Project (MPP) study, might increase the incidence of first low-energy fracture during a follow up period of 25 years. In study IV we investigated whether cardiovascular biomarkers at baseline among 5291 patients in Malmö Diet and Cancer (MDC) study could increase the incidence of first low-energy fractures during the follow-up of 21 years.</p> <p>Results: Among hip fracture patients in Study I, hypertension and ischemic heart diseases, as well as cognitive disorders were the most common comorbidities in hip fracture patients. Hypertension and pacemaker treatment increased the risk of readmission, whereas mortality increased with ischemic heart disease and malignancy. In Study II, the total number of medication, anti-osteoporotic agents, SSRI and eyedrops were associated with higher rate of readmission, whereas vitamin K antagonist, thiazides and tramadol were associated with readmission due to a new fall. In Study III, orthostatic decline in blood pressure and elevated resting heart rate independently predicted increased incidence of low-energy fractures. In Study IV, higher levels of circulating levels of the cardiovascular biomarker MR-pro-ADM predict low-energy falls among middle-aged men, but not women.</p> <p>Conclusions: Common cardiovascular comorbidities among the ageing population increase the risk of hip fracture, readmission and mortality and certain medications also increase the risk of readmission. Suffering from OH and elevated resting heart rate constitute an increase risk of suffering from a low-energy fracture. In Study IV, higher levels of the cardiovascular biomarker MR-pro-ADM predicted low-energy fracture among middle-aged men, but not among women. These findings emphasize the importance of future collaboration between different specialities within hospitals and medical care to identify high risk patients, as well as the role of medication reviews to improve risk prevention.</p> | | |
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Maria Härstedt



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*To my beloved children Ellen and Filip,
you are my everything*

*Our generation is the first generation
with a possibility to live in equality.
Our generation is the last generation
that can save the great Arctic ices.*

Ellen Härstedt, age 17, April 2018

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List of papers

This thesis is based on the following four papers, referred to in the text by their Roman numerals. The papers are appended in the end of this thesis.

- I. Härstedt M, Rogmark C, Sutton, R, Melander O, Fedorowski A. Impact of comorbidity on 6-month hospital readmission and mortality after hip fracture surgery. *Injury* 2015;46:713-8
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- II. Härstedt M, Rogmark C, Sutton, R, Melander O, Fedorowski A. Polypharmacy and adverse outcomes after hip fracture surgery. *Journal of Orthopaedic Surgery and Research* 2016; 11:151
- III. Hamrefors V, Härstedt M, Holmberg A, Rogmark C, Sutton R, Melander O, Fedorowski A. Orthostatic Hypotension and Elevated Resting Heart Rate Predict Low-Energy Fractures in the Population: The Malmö Preventive Project. *PLoS One* 2016;11:e0154249
- IV. Härstedt M, Hamrefors V, Holmberg A, Rogmark C, Sutton R, Melander O, Fedorowski A. Cardiovascular Biomarkers and Risk of Low-energy Fractures among Middle-aged Men and Women – a Population-based Study. *Under review*

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Abbreviations

| | |
|---------------------|---|
| ADE | Adverse Drug Event |
| AHT | Anti hypertensive treatment |
| BMD | Bone Mineral Density |
| BMI | BODY Mass Index |
| CT-pro-AVP/Copeptin | C-terminal-pro-arginine-vasopressin |
| DBP | Diastolic Blood Pressure |
| DXA/DEXA | Dual Energy X-ray Absorptiometry |
| FRIDs | Fall Risk Induced Drugs |
| MDC | Malmö Diet and Cancer |
| MPP | Malmö Preventive Project |
| MR-pro-ADM | Mid-regional-fragment of pro-adrenomedullin-peptide |
| MR-proANP | Mid-regional-fragment of pro-atrial-natriuretic-peptide |
| NT-pro-BNP | N-terminal pro-brain natriuretic peptide |
| OH | Orthostatic hypotension |
| OP | Osteoporosis |
| QCT | Quantitative Computer Tomography |
| QUL | Quantitative Ultrasound |
| RHR | Resting Heart Rate |
| SD | Standard Deviation |
| SBP | Systolic Blood Pressure |

Abstract

Background: The population is getting older and low-energy falls and fractures are a growing health challenge as their incidence increase with advancing age. With the ageing population follows an alternation in physiology and an increased number of comorbidities and medications. These comorbidities and medications may constitute an increased risk for fall and fracture. Low-energy fractures are associated with great suffering and death among the elderly, a great cost to society and a challenge to the health care systems.

Aims: The overall objective was to investigate correlation between cardiovascular risk factors for low energy falls and fractures. The risk factors analysed were comorbidities, medications and polypharmacy, orthostatic hypotension and resting heart rate and cardiovascular biomarkers.

Material and methods: Study I and II are prospective series. We analysed the same cohort of 272 consecutive patients who underwent acute hip fracture surgery. Analysis of how comorbidities at baseline and alterations among medications might affect readmission and mortality during the 6 month follow up. Study III and IV were retrospective population-based studies. In Study III we analysed if orthostatic hypotension (OH) and resting heart rate at baseline among a cohort of 33000 patients enrolled in Malmö Preventive Project (MPP) study, might increase the incidence of first low-energy fracture during a follow up period of 25 years. In study IV we investigated whether cardiovascular biomarkers at baseline among 5291 patients in Malmö Diet and Cancer (MDC) study could increase the incidence of first low-energy fractures during the follow-up of 21 years.

Results: Among hip fracture patients in Study I, hypertension and ischemic heart diseases, as well as cognitive disorders were the most common comorbidities in hip fracture patients. Hypertension and pacemaker treatment increased the risk of readmission, whereas mortality increased with ischemic heart disease and malignancy. In Study II, the total number of medication, anti-osteoporotic agents, SSRI and eye drops were associated with higher rate of readmission, whereas vitamin K antagonist, thiazides and tramadol were associated with readmission due to a new fall. In Study III, orthostatic decline in blood pressure and elevated resting heart rate independently predicted increased incidence of low-energy fractures. In Study IV, higher levels of the cardiovascular biomarker MR-pro-ADM predict low-energy falls among middle-aged men, but not among women.

Conclusions: Common cardiovascular comorbidities among the ageing population increase the risk of hip fracture, readmission and mortality and certain medications also increase the risk of readmission. Suffering from OH and elevated resting heart rate constitute an increased risk of suffering a low-energy fracture. One known cardiovascular biomarker demonstrates an increased risk for having a low-energy fracture among men, but not among women. These findings emphasize the importance of future collaboration between different specialities within hospitals and medical care to identify high-risk patients, as well as the role of medication reviews to improve risk prevention.

Introduction

We have an ageing population, especially in the western countries. With older age follows more comorbidity, and thus more medications. This means great challenges for hospitals and medical care, including a greater economic burden.

As shown in figure 1, in Sweden in 1960, a woman lived approximately 75 years and a man 71 years. In 2016 a women lived 84 years and a man 81 years. In 2060, the life expectancy is expected to be 89 years for women and 87 for men. With this higher life expectancy, in Sweden in 2045 there are believed to be more than 1 million persons over the age of 80 years old in 2045, and in 2060 more than 1.2 million people. To be compared with a little less than half a million people over the age of 80 in 2014(1).

In the Nordic countries (Sweden, Norway, Denmark, Finland and Iceland) almost 9% of the population will be over 80 years old in 2030 and in Finland the population over the age of 65 will constitute more than 50% of the adult population that year(2).

In the European Union, the share of people aged 65 and over is projected to increase from almost 19 % in 2015 to over 28 % by 2050, with the share of people aged 85 and over more than doubling from 2.5 % in 2015 to 6.0 % by 2050(3).

Globally, the number of persons aged 60 or over is expected to more than triple by 2100, increasing from approximately 784 million in 2011 to 2 billion in 2050 and 2.8 billion in 2100. Whereas the number of persons aged 60 or over is expected to almost triple,, that of persons aged 80 or over (the “oldest-old”) is projected to almost eight-fold, to reach 402 million in 2050 and 792 million in 2100. Life expectancy is believed to grow even more rapidly in other parts of the world as well, especially China and India(4), as shown in figure 2. In The United States those over the age of 85, are the fastest growing segment in the population(5).

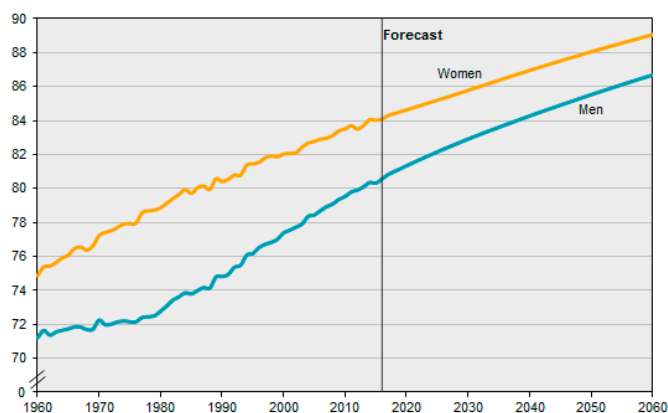


Figure 1. Life expectancy in Sweden by gender 1960–2016 and prognosis 2017–2060

Average life expectancy is a measure of how many years a new born child will live on average if mortality in different ages remained the same as during the year for the calculation. Source: Reprinted from SCB, Statistiska centralbyrån, Statistics Sweden, updated 2017-04-12, with permission from the publisher.

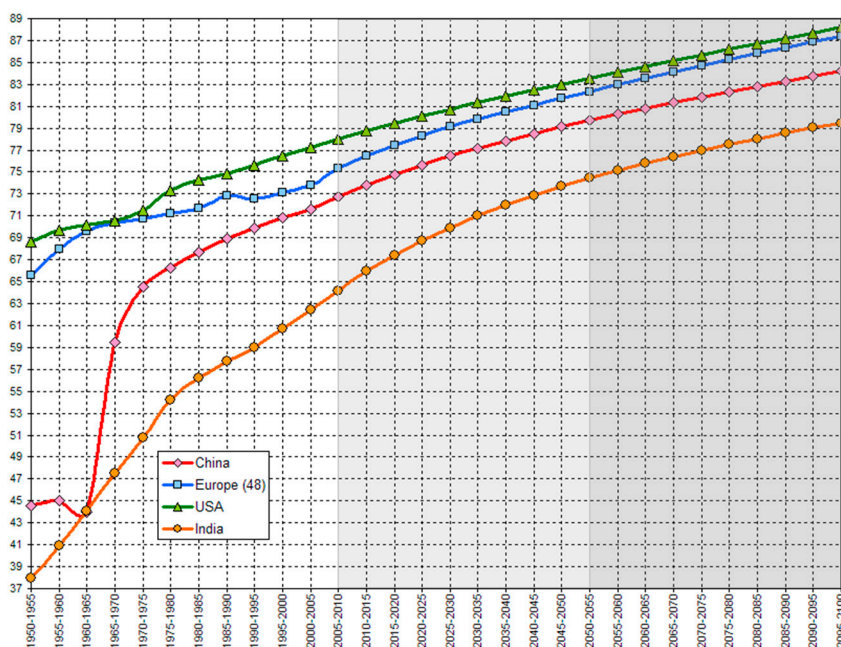


Figure 2. Life Expectancy at Birth in China, Europe, USA and India: 1950-2100 (Both Sexes)

Source: Reprinted from United Nations, Department of Economic and Social Affairs, Population Division (2011): World Population Prospects, the 2010 Revision. New York. See: www.unpopulation.org, with permission from the publisher.

Low-energy fractures

Osteoporosis

The word osteoporosis (OP), literally “porous bone”(6), is one of medical science newest words as it was first described in France and Germany in 1820, but medical researcher cannot say in what language the term first appeared, hence its origin remains a mystery. In its modern sense it has been known for a little over half a century, but the definition has constantly changed and has reflected medical progress and attempts to maintain a difficult balance between physiological and clinical criteria(7-10).

Osteoporosis can be defined as a skeletal condition characterized by a decreased density of normally mineralized bone (BMD) which leads to decreased mechanical strength and an increased risk of fracture. Furthermore, this skeletal disorder characterized by low bone mass and deterioration of bone tissue leads to a consequent increase in the fragility of bone and hence increased susceptibility to fractures (10, 11). Several methods to measure BMD and diagnose osteoporosis exist. Most common is Dual Energy X-ray Absorptiometry (DXA/DEXA), but also Quantitative Computer Tomography (QCT) and Quantitative Ultrasound (QUL) are being used. Often, a BMD measurements in women that fall 2.5 standard deviations (SD) below the normal young mean has been used as criteria to diagnose osteoporosis, so called T-score. The World Health Organisation, WHO has originally set the criteria for osteoporosis in 1994 and further updated them in 2004 (10, 12, 13). Over 200 million individuals are estimated to suffer from osteoporosis worldwide (12, 14, 15). In Sweden, every third woman between the ages 70-79 years has been diagnosed with osteoporosis(16).

Fragility fractures

According to the World Health Organisation, WHO, a fragility fracture is defined as a fracture occurring spontaneously or following a minor trauma such as a fall from standing height or less and includes vertebral fracture (spontaneous, without any trauma), that may result in spinal deformity. Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low-energy') trauma(17-19). Fragility fractures are a strong indicator of osteoporosis and are associated with an almost 10-fold increase in the risk of having a future fracture following a prior fragility fracture(20). Osteoporotic fractures are, as previously discussed, defined as fractures associated with low bone mineral density, BMD.

Fragility fractures occur most commonly in the spine (vertebrae), hip (proximal femur) and wrist (distal radius). They may also occur in the arm (humerus), pelvis, ribs and other parts of the body(17). According to the Swedish National Board of Health and Welfare fragility fractures are defined and diagnosed according to International Classification of Diseases 10, ICD-10 and comprise the following classifications, see table 1 below.

Table 1. Fragility fractures diagnosis according to ICD-10 version 2016

| | |
|--|-------|
| Fracture of lower end of radius | S52.5 |
| Fracture of lower end of both ulna and radius | S52.6 |
| Fracture of upper end of humerus | S42.2 |
| Fracture of shaft of humerus | S42.3 |
| Fracture of rib(s), sternum and thoracic spine | S22.X |
| Fracture of neck of femur | S72.0 |
| Pertrochanteric fracture | S72.1 |
| Subtrochanteric fracture | S72.2 |
| Fracture of shaft of femur | S72.3 |
| Fracture of lower end of femur | S72.4 |
| Fracture of upper end of tibia | S82.1 |
| Fracture of sacrum | S32.1 |
| Fracture of coccyx | S32.2 |
| Fracture of pubis | S32.5 |
| Multiple fractures of lumbar spine and pelvis | S32.7 |
| Fracture of other and unspecified parts of lumbar spine and pelvis | S32.8 |

Source: Reprinted from Socialstyrelsen: Återfrakturer inom 5 år efter fragilitetsfraktur. 2014-10-3.
<http://www.socialstyrelsen.se/indikatorer/sokiindikatorbiblioteket/utvardering>, with permission from the publisher

Low-energy fractures are a growing health challenge throughout the world, especially in the western countries. Sweden and Norway have the highest frequencies. In Sweden the number of fragility fractures is approximately 70.000, of these, 18.000 are hip fractures and the number is increasing(16, 21-23). Most common reason to hospital admission is hip fractures, followed by fractures to the vertebrae, see fig 3(24).

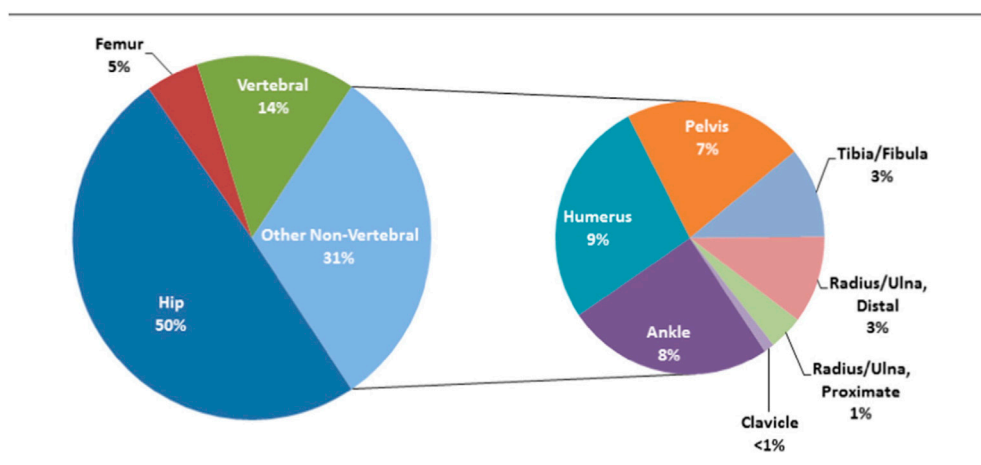


Figure 3. Distribution of admissions for treatment of osteoporosis-related fracture, by fracture type

Source: Reprinted from Weycker D, Li X, Barron R, Bornheimer R, Chandler D. Hospitalizations for osteoporosis-related fractures: Economic costs and clinical outcomes. *Bone reports*. 2016;5:186-91, with permission from the publisher.

In the year 2000, estimates showed almost 9 million osteoporotic fractures worldwide, of these 1.7 million fractures were at the forearm, 1.6 million consisted of hip fractures and 1.4 million were vertebral fractures. The estimated risk for a Swedish woman of 50 years of age to suffer a fragility related hip fracture is 23%, for a man 11%, fracture to the spine 15% (man 9%) and wrist fracture 22% (man 5%). The risk for a middle-aged woman to have any kind of osteoporosis related fracture during her life is 50 %, for a man the risk is 25%, and the risk for a woman to have a hip fracture are double that to men. The risk for both men and women to have a hip fracture doubles each five years(16, 25). Almost 35% of the osteoporotic fractures worldwide occurred in Europe(26). Globally, the annual number of hip fractures is predicted to increase from 1.7 million in 1995 to 6.3 million by 2050(27). The incidence of fragility fractures begin to increase in the middle-aged population(28) and are a burden for the patient and society. Hip fracture itself nearly always require hospitalization, is fatal in 20%, permanently disables almost 50% and only 30% of those affected fully recover(29, 30). Established consequences of fragility fractures are increased risk of subsequent fractures, hospitalization and institutionalization and mortality, decreased quality of life and an increased economic burden on healthcare systems throughout the world(31-35).

Society's cost of osteoporosis and osteoporosis related fractures have been subject to much research and many studies(16). In Sweden, cost related to osteoporosis are estimated at 4.6 billion SEK and related fractures at 3.5 billion SEK, with most of these costs related to hip, vertebral and wrist fractures(21, 36). Hip fractures itself

constitute more than half of all direct hospital related fracture costs. Among women over the age of 45, the yearly amount of emergency related days in hospitals are higher than for coronary infarction, breast cancer, chronic obstructive pulmonary disease (COPD) or diabetes mellitus(16).

Due to its impact and burden on society's economy, several attempts have been made to estimate threshold and present algorithms to improve selection of patients suitable for osteoporotic intervention and when it becomes cost-effective, but are difficult to implement(37).

Comorbidities and polypharmacy

As older patients move through time, often from physician to physician, they are at increasing risk of accumulating layer upon layer of drug therapy, as a reef accumulates layer upon layer of coral.

Jerry Avorn, MD

With an ageing population, and the elderly being the most rapidly growing proportion of patient population comes a dramatic change in the pattern of admitted patients to internal medicine wards. Constitutional changes due to ageing and diseases affect both turnover and effects of medications. This leads to an increased susceptibility and risk of side-effects(38, 39). Aging is often accompanied by several comorbidities and an increased frailty. With this increased amount of comorbidities there is a natural increase in the use of prescribed medications, so called polypharmacy(40, 41). Often seen, the use of the words frailty and comorbidity are used to identify or emphasize the vulnerability of the elderly. The more formal definition of the term comorbidity is the concurrent presence of two or more medically diagnosed diseases in the same individual(42).

There exists no formal definition of the term polypharmacy. Some studies define polypharmacy as the use of multiple drugs or more than are medically necessary; i.e. not indicated, not effective, interact with each other, or constitute a therapeutic duplication (41, 43, 44). Other define it as the use of five or more medications(43). In Sweden, the concurrent use of four or more prescribed drugs have been considered polypharmacy(45).

Common comorbidities

Older people often suffer from multiple chronic conditions simultaneously, comorbidity or multimorbidity, such as cardiovascular and mental diseases, arthritis, osteoporosis, cancer and diabetes mellitus. These diseases require multiple medications for proper treatment(46-48). Reports have emphasized the growing population of these older patients with multiple and chronic conditions, comorbidity, to be a future challenge to the physician and health care systems(42,

49, 50). In the United States, reports show that 70,2% at the age 80 years and older have two or more diseases (42). Apart from older age, female gender and lower education are associated with a more than 50% increased risk in multimorbidity(48). Comorbidity heightens the risk of disability and mortality over and above the risk from individual diseases(51-54), and there are pairs of chronic diseases that are synergistic in increasing risk for disability(47, 54).

Polypharmacy and adverse drug events (ADEs)

With several prescribed medications and the changing physiology in the ageing patient, complications are inevitable. Prescribed medications can lead to so called drug-induced symptoms. These symptoms can also produce prescribing cascades that develop when an adverse effect is misinterpreted as a new medical problem, leading to the prescription of additional drugs(39, 55). Adverse drug events (ADEs) are defined as injuries resulting from medical interventions related to a drug(56).

Two thirds of patients in Swedish nursing homes have been prescribed ten or more medications, on average twelve(57). Older people are more sensitive to side-effects than younger and research has shown that 22% of the elderly in primary care suffer from side-effects, and as many as 31% within hospitals(58). All medications have side effects, and with an increasing amounts of medications, both side-effects and the risk of interaction among medications increase.

Both internationally and in Sweden, side-effects such as vertigo and dizziness are common(59). Estimations show that 25% of people over the age of 65 years have fallen at least once during the last year, for persons between 80-84 years the number is approximately 40%. Medications related to these falls that cause fracture are drugs that affect consciousness and impaired vision(16). The Swedish National Board of Health and Welfare has created a list of medications that increase the risk of fall (FRIDs) and drugs that might cause and/or worsen orthostatic hypotension(38, 60).

The risk of being admitted to hospital due to a drug related side-effect is at least 4 times bigger among older than younger persons(61). Reports in Sweden show that each year at least 35000 individuals are so affected by side effects of prescribed medications that they are admitted to hospitals due to drug related problems. With proper counteractions this number could be lowered by 60%. Furthermore, Swedish reports show that as much as 8 % of patients that are admitted to hospital due to emergency causes are related to their medications(38, 62-67). Internationally, this is also established through several studies(61, 68-73). Leendertse et al showed in 2008 that almost half of the admissions to hospital due to adverse drug events (ADEs) were potentially avoidable(74). This has been confirmed in a study by

Hakkarainen et al in 2012(75). Risk factors associated with an increase amount of admissions to hospitals due to side effects are; gender, older age, polypharmacy and affected kidney function(76, 77). Female gender has been showed to be associated with a higher risk of admission to hospital due to drug related side effects(78, 79). There are several studies that investigate the association between old age and hospital admission due to drug related side effects, in one, the age of 75 years show a four-time increased risk(80). A patient with 11 or more prescribed medications has a 93% higher risk of being admitted to hospital due to an ADE, especially if combined with affected kidney function(76).

According to the Swedish National Board on Health and Welfare and confirmed internationally the most common side-effects causing admission to hospitals were falls and fracture, dizziness, heart related and bleedings(38, 81). Followed by deranged fluid- and electrolyte balance, cardiac arrhythmias, affected consciousness or confusion, cardiac failure and hypoglycaemia(61). For a more detailed list, see table 2.

Table 2. The most common side-effects causing admission to hospital according to the Swedish National Board on Health and Welfare. In a falling order.

| Side effect |
|--|
| Fall/fracture |
| Dissines |
| Heart related unspecified |
| Bleeding (including cerebral bleeding) |
| Deranged electrolytes |
| Bradycardia |
| Cardiac failure |
| Kognitive disorder |
| Low bloodpressure |
| Intestinal bleeding |
| Hypoglycemia |
| Skin reaction |
| Kidney failure |
| Colitis |
| Nausea |
| Fever |
| Allergi, unspecified |
| Depression |
| Respiratory difficulties |
| Bone marrow disorder |

Source: Reprinted from Socialstyrelsen. Läkemedlesorsakad sjuklighet hos äldre. 2014;2014-12-13, with permission from the publisher.

According to the Swedish National Board on Health and Welfare the most common drug classes shown to cause admission to hospital, related to side-effects, both in Sweden and internationally are listed in table 3. They are listed according to their ATC-code. They were medications against cardiovascular diseases (ATC-groups beginning with the letter C), anticoagulants, medications affecting the central nervous system (CNS) such as psychotropic and antidepressants, antiepileptic and opioid related, antibiotics, cytostatic, anti-inflammatory (NSAID) and medications against diabetes(38, 61).

Table 3. The most common groups of medication according to their ATC-code related to side-effect related admissions to hospital. In a falling order.

| ATC-code | Group of medications |
|----------|--|
| B01 | Anticoagulants |
| C03 | Diuretics |
| N06A | Anti-depressants |
| J01 | Systemic antibiotics |
| A10 | Diabetics |
| L01 | Cytostatic |
| M01 | Antiinflammatory (NSAID) |
| N03 | Antiepileptic |
| C09 | Drugs affecting the renin-angiotensin system |
| C07 | Beta blockers |
| C01A | Cardiac glycosides (digoxin) |
| N02 | Analgetics (especially opioids) |
| C08 | Calcium antagonists |

Source: Reprinted from Socialstyrelsen. Läkemedelsorsakad sjuklighet hos äldre. 2014;2014-12-13, with permission from the publisher.

Physiology of standing

Assumption of the upright posture requires an immediate physiological adaptation to gravity. Short term cardiovascular responses to postural change from sitting to standing involve complex interactions between the autonomic nervous system, which regulates blood pressure, and cerebral autoregulation, which maintains cerebral perfusion in the face of blood pressure changes(82, 83).

There is an instantaneous descent of approximately 500 ml of blood from the thorax to the lower parts of the body and legs, due to gravitational forces, i.e. venous pooling within the capacitance vessel below the diaphragm(84). In addition, there is a 10-25% shift of plasma volume out of the vasculature and into the interstitial tissue.

Two types of control mechanisms are involved: 1.) Autonomic regulation mediated by sympathetic and parasympathetic responses, affecting heart rate, cardiac contractility, resistance and compliance, and 2.) Cerebral autoregulation mediated by responses to local changes in myogenic tone, metabolic demands and CO₂ concentration that affect cerebrovascular resistance. This shift of blood to the lower extremities when standing up decreases venous return to the heart, resulting in a transient decline in cardiac filling and hence reduced cardiac stroke volume and a decline in arterial pressure and an immediate decline in blood flow to the brain. A reduction in arterial blood pressure unloads the baroreceptors located in the carotid and aortic walls, leading to parasympathetic withdrawal and sympathetic activation through baroreflex-mediated autonomic regulation. The parasympathetic withdrawal induces a fast increase in heart rate, whereas the sympathetic activation leads to a slower increase in capsular resistance, vascular tone, cardiac contractility and a further increase in heart rate. Hence, assumption of the upright posture results in a 10-20 beat per minute increase in heart rate, a negligible change in systolic pressure and an approximate 5 mmHg increase in diastolic blood pressure, countering the initial decline in blood pressure. During standing, contraction of the lower body skeletal muscle prevents excessive pooling and augments venous blood return to the heart (82, 85-88).

In table 4, there is a summary of the responses/physiology of standing.

Table 4. Summary of responses to standing (see text for further details)

| <u>Parameter</u> | <u>Immediate response</u> | <u>Compensatory response (</u> |
|--------------------------|---------------------------|--------------------------------|
| Arterial blood pressure | ↓ | ↑ (normalizing) |
| Heart rate | – | ↑ |
| Cardiac output | ↓ | ↑ (normalizing) |
| Stroke volume | ↓ | ↑ (normalizing) |
| Total perifer resistance | – | ↑ |
| Central venous pressure | ↓ | ↑ (normalizing) |

Orthostatic hypotension

A normal hemodynamic response to changes in posture, as mentioned above, requires normal function of the cardiovascular system, the autonomic nervous system and cerebral autoregulation(85, 89).

Failure of the regulatory mechanism, to respond properly to the circulatory redistribution may lead to orthostatic intolerance disorders such as orthostatic hypotension and/or tachycardia. Thus, compromising cerebral blood flow with symptoms such as blurred vision, fatigue, dizziness, syncope, fall and even mortality(90-94). It may also be asymptomatic(95, 96).

Orthostatic hypotension (OH) is a common manifestation of blood pressure dysregulation, hence failure in autonomic regulation. OH is caused by an excessive fall of cardiac output or by defective or inadequate vasoconstrictor mechanism(88). They are patients with low blood pressure when standing, usually normally blood pressure while seated, and sometimes high blood pressure while lying down(95, 97, 98). OH has been defined by international consensus as a fall of systolic blood pressure of at least 20 mmHg or a fall of diastolic blood pressure of at least 10 mmHg within 3 minutes of standing(88, 90, 99). An alternative criterion for OH is a standing systolic blood pressure (BP) of < 90 mmHg(100). However, it is not unusual for patients with autonomic failure (OH) for the decline in blood pressure to be much greater than this(85).

Orthostatic hypotension occurs in patients with neurodegenerative disorders such as Parkinson's disease and in individuals with disorders affecting the autonomic nerves. The prevalence of OH increases with age and is more common, up to 70%, in institutionalized elderly(88).

Cardiovascular biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacological responses to a therapeutic intervention(101). In different settings and research, the words neuropeptide and biomarkers are used for the same purpose.

The history of the research on the natriuretic peptides can be traced back to 1956(102) and in the early 1980's the atrial natriuretic peptide hormones was discovered. It is a circulating peptide with natriuretic/diuretic and vasorelaxant properties(103, 104). These cardiac biomarkers have been regarded as gold standard in diagnosing heart failure (HF)(105, 106) and strong prognosticators of other cardiac conditions(105, 107, 108).

Midregional fragment of proadrenomedullin, MR-pro-ADM

Adrenomedullin (ADM) was discovered in 1993 and was first described as having effects on blood pressure(109, 110). Newer research has shown that ADM is a 52-amino-acid peptide with a wide range of functions, from being a vasodilator, to regulating cellular growth and differentiating, modulating hormone secretion to having antimicrobial effects(109). Its widespread production in the tissues helps to maintain a blood supply in every organ.

The prohormone fragments (pro-ADM) of ADM are more stable than the complete peptide. The midregional fragment of proadrenomedullin (MR-pro-ADM), included between amino acids 45–92, is the most stable part of the ADM(109, 111, 112). Its function has predominantly been used as a diagnostic marker in septic patients(112-114), but also in acute dyspnoea and heart failure(115-117), and more recently in Alzheimer's disease(118, 119). It has also been suggested to be a future predictor of cardiovascular events(120-122).

Midregional proatrial natriuretic peptide , MR-pro-ANP

Natriuretic Peptides consist of a family of peptides that are synthesized by three separate genes and then stored as three different prohormones, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-natriuretic peptide (CNP)(123). The first natriuretic peptide, atrial natriuretic peptide (ANP) was initially discovered in 1984, followed by B-type natriuretic peptide 4 years later(105, 124).

MR-pro-ANP, is mainly secreted by atrial myocytes(125). MR-pro-ANP is, like MR-pro-ADM, also increased under septic conditions(126), in patients suffering from acute dyspnoea(115, 127, 128), Alzheimers(118, 119) & useful as a predictor for coronary events(120, 122) and following myocardial infarction(122, 129). Studies has also shown increased levels among patients suffering from unexplained falls and syncope(130, 131).

N-terminal pro-brain natriuretic peptide, NT-pro-BNP

N-terminal pro-brain natriuretic peptide, NT-pro-BNP, is mainly synthesized by the ventricular walls of the heart(132-134).

Natriuretic peptides (B-type natriuretic peptide, BNP, and the N-terminal fragment of its prohormone N-terminal proBNP) are the gold standard biomarkers in determining the diagnosis and prognosis of heart failure(101, 134). However, it is also a predictor of first serious coronary event(122) and has been shown to be independently associated with cognitive impairment and dementia among an elderly population(135). NT-pro-BNP is also known to be increased under septic conditions(136).

Carboxy-terminal proarginin vasopressin , CT-proAVP; copeptin

Arginine vasopressin, AVP, also known as the antidiuretic hormone ADH, is a key peptide hormone in the human body, maintaining fluid balance and vascular tone(137). It is produced in the hypothalamus and secreted by the pituitary gland in response to hemodynamic and osmotic stimuli and changes in the body. Copeptin

is a stable fragment of the AVP precursor(138) and was first described in 1972(139). Copeptin is released together with AVP(140), and is, in contrast to AVP, very stable and is easy and robust to measure, therefore Copeptin is often used as a clinically relevant measurement for reliably assessing AVP(141, 142).

CT-proAVP has been shown to be an independent prognostic marker to predict outcome and mortality in patients with acute stroke(143, 144), following acute myocardial infarction (145, 146) and cardiac arrest(147), and under septic conditions, such as severe pneumonia(148, 149).

Present investigations

The following is an overview of the applied methods, study design and results from the papers included in this thesis. For further and more in depth information please refer to Papers I-IV.

Aims

The overall objectives

The overall objective of this thesis was to investigate correlation between different cardiovascular risk factors for low energy falls and fractures. The risk factors analysed were comorbidities, medications and polypharmacy, orthostatic hypotension and resting heart rate and cardiovascular biomarkers.

The specific objectives

There are five specific objectives in this thesis:

- To assess prevalence of coincident diseases among patients admitted for surgery of hip fracture (paper I).
- To analyse the impact of comorbidities on 6-month readmission rate and mortality among patients admitted for surgery of hip fracture (paper I).
- To study potential association of discharge medications with the postoperative readmission and mortality among patients admitted for surgery of hip fracture (paper II).
- To test the association between orthostatic hypotension, resting heart rate and incidence of low-energy-fractures in the general population (paper III).
- To investigate the associations between four cardiovascular biomarkers and the risk of low-energy fractures in a middle-aged population (paper IV).

Methods

Statistical analysis

Statistical analysis were performed using IBM SPSS statistical software version 22.0 and 24.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided whereby $p < 0.05$ was considered statistically significant.

Paper I and II

In paper I and II, patient characteristics were reported as mean and standard deviation or proportions.

In paper I, time to first readmission, number of and reasons for readmission within the first 6 months were determined. The relations of age, gender, type of comorbidity, length of hospitalisation with the readmission risk and mortality, as the categorical dependent variables, were assessed using a multivariate-adjusted (for age and gender) logistic regression model. Further, the relation between readmission and mortality was analysed using the same model with mortality as a dependent variable.

In paper II, proportions of specific drug use upon admission and their changes after medication review were calculated. The total number and reasons for readmissions as well as mortality within the first six months after discharge from hospital were determined. The relations of total number and type of discharge medications with readmission risk or death, as the categorical dependent variables, respectively, were assessed using a multivariable-adjusted (for age and gender) logistic regression model. In a subsidiary analysis, only readmissions due to fall injury, infection, or cardiovascular disease were assessed as a categorical dependent variable.

Paper III

The hemodynamic parameters recorded at baseline (supine SBP/DBP, Δ SBP/DBP, and RHR) were related to first incident low-energy fracture using multivariable-adjusted Cox-regression models. We tested models entering age, sex and BMI as covariates (Model 1) as well as more comprehensive models (multi-adjusted) including age, sex, BMI, AHT, diabetes, smoking, previous MI, and all measured hemodynamic parameters (supine SBP/DBP, Δ SBP/DBP and RHR) from the baseline examination. In order to evaluate the combined effect of RHR and OH on the risk of incident low energy fractures we constructed a combined RHR-OH-score for each individual subject. The score was constructed as follows: the study population was split into quartiles according to baseline RHR and Δ SBP, respectively. Thus, each individual was given a quartile number (1 for lowest, 4 for highest) for RHR and Δ SBP. The RHR-OH-score for each individual (range 2–8) was then constructed by summing the individual quartile number for RHR and Δ SBP, respectively. Additionally, in order to further investigate the specific contribution of RHR and Δ SBP and of their combined effect to the risk of incident low-energy-fractures, the 16 specific quartile combinations of RHR and Δ SBP that could be combined for the study subjects (i.e. subjects in [Q1 for RHR–Q2 Δ SBP], [Q1 for RHR–Q3 Δ SBP]. . . up to [Q4 for RHR- Q4 - Δ SBP] was tested in Cox-regression models in relation to the reference [Q1 for RHR–Q1 for Δ SBP]. The proportional-hazards assumption was confirmed by visual inspection of survival curves.

Paper IV (under review)

Group differences in continuous variables between low-energy fracture -positive and -negative individuals were compared using Student's T-test, whereas categorical variables were compared using Pearson's chi-square test. Levels of three of the four biomarkers, MR-pro-ANP, NT-pro-BNP and CT-pro-AVP, were log-transformed in all analyses due to skew deviation. MR-pro-ADM was normally distributed. The associations between levels of biomarkers at baseline and first incident fragility fracture during follow-up were tested in Cox regression models. We first used minimally (age and gender) adjusted models. If significant associations were found, we additionally tested the relation in models adjusted for smoking, systolic blood pressure, antihypertensive medication, BMI and previous low-energy-fracture. Potential interactions between gender and the each of the four biomarkers on incident fragility fractures were tested in the minimally adjusted models, with age and gender as covariates in addition to the biomarkers and the multiplicative interaction term [gender* levels of biomarker]. The proportional

hazard assumption was tested by visual inspection of survival curves of quartiles of the biomarkers.

Ethical aspects

Paper I and II

The ethical advisory board of Lund University approved the study protocol (Ref. No. 2010/273) and all patients gave their informed consent.

Paper III

Ethical approval for the Malmö Preventive Project, MPP, was approved by The Health Department of Malmö City in 1972. The retrospective analysis of the cohort was approved by IRB in Lund. All participants gave written informed consent and the data was anonymized before the analysis.

Paper IV

Ethical approval for the Malmö Diet and Cancer (MDC) study was approved by the ethical committee at Lund University. All participants in study IV provided written informed consent.

Experimental conditions and results

Paper I: Impact of comorbidity on 6-month hospital readmission and mortality after hip fracture surgery

In paper I we prospectively enrolled 281 consecutive patients who were admitted to the department of orthopaedics at Skåne University hospital in Malmö with a preliminary diagnosis of hip fracture between November 2009 and June 2011. Of these, we excluded 9 that did not meet the criteria of acute hip fracture surgery, and a total of 272 patients were included in our study after ethical approval and the patients accepting participation.

We analysed the impact comorbidity has on the risk of readmission and mortality 6 months after acute hip fracture surgery.

Baseline characteristics of our study population, comorbidity and hospital stay among the patients were recorded. Number, timing and reasons for readmission, as well as mortality, were analysed within follow-up of 6-months after hospital discharge.

Results

Women were overrepresented, 72% and the mean age was 82.6 ± 8.9 years. The most common comorbidities among the 272 consecutive patients enrolled were cardiovascular diseases; hypertension (44%) and ischaemic heart disease (19%) and cognitive disorders (26%). The mean length of stay in hospital was 12.7 ± 7.9 days.

86 of the patients, 32% were readmitted 119 times within 6 months after discharge. Readmission was associated with hypertension (OR: 2.0, 95%CI: 1.2-1.9, $p = 0.009$) and patients with pacemaker (OR: 6.6, 95%CI: 1.7-26.3, $p = 0.007$). The most frequent cause of readmission was a new fall (26%), followed by an infection (23%). Other reason to readmission was inadequate care and unfavourable living conditions.

6-month mortality was predicted by ischemic heart disease (OR: 2.2, 95%CI: 1.0-4.9, $p = 0.005$) and malignancy. (OR: 2.5, 95%CI: 1.1-5.7, $p = 0.004$).

Paper II: Polypharmacy and adverse outcomes after hip fracture surgery

In paper II we prospectively enrolled 304 consecutive patients who were admitted to the department of orthopaedics at Skåne University hospital in Malmö with a preliminary diagnosis of hip fracture between November 2009 and June 2011. Of these, we excluded 32 patients that did not meet the criteria of acute hip fracture surgery, and a total of 272 patients were included in our study after accepting participation.

We collected information regarding lab results, comorbidity, assessed ASA grade (American Society of Anaesthesiologists)(150) and pharmacological treatment upon admission. An actual medication list was withdrawn from the Swedish National Pharmaceutical Register and verified by the patient, the patient's family and/or general practitioner. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. During the hospital-stay a pharmaceutical together with a consultant in internal medicine performed a medication review. Dosages and indications were checked, unsuitable drugs were withdrawn and dosages were adjusted, if appropriate. The patient's general practitioner received written information about alterations as did the patient and in some cases, the patient's family. Patients were followed up over a 6-month period after discharge from hospital.

Baseline characteristics of our study population and hospital stay among the patients were recorded, as mentioned above. The relations of total number and type of discharge medication with readmission risk and mortality were assessed during the 6 month follow-up.

We aimed at exploring the effects of polypharmacy and specific drug classes on readmission and mortality.

Results

Women were overrepresented, 72% and the mean age was 82.6 ± 8.9 years. Upon admission, the patients included had on average 6.2 ± 3.9 on discharge 7.8 ± 3.6 .

The most common medication group to be removed or modified was antihypertensive treatment and among them, diuretics and calcium channel blockers. During hospital stay; analgesics such as Paracetamol and Tramadol and low-molecular weight heparin (LMWH) were initiated.

32% of the patients was readmitted within the 6-month follow up, mainly due to a new fall or infection. The total number of medications were predictive of

rehospitalisation (OR: 1.08, 95%CI: 1.01-1.17, $p=0.03$). Anti-osteoporotic agents (OR: 1.86, 95%CI: 1.06-3.26, $p=0.03$), SSRIs (OR: 1.90, 95%CI: 1.06-3.42, $p=0.03$) and eye drops (OR: 4.12, 95%CI: 1.89-8.97, $p=0.0004$) were all predictive of rehospitalisation. Especially anti-osteoporotic agents and eye drops were associated with readmission due to a new fall, whereas SSRIs were associated with readmission due to an infection. Treatment with vitamin K antagonists (OR: 4.29, 95%CI: 1.19–15.39, $p = 0.026$), thiazides (OR: 4.10, 95%CI: 1.30–12.91, $p = 0.016$), and tramadol (OR: 2.84, 95%CI: 1.17–6.90, $p = 0.021$) predicted readmissions due to a new fall.

13% of the patients died during the 6-month follow-up. The total number of medications were not predictive of mortality. However, treatment with stronger opioid showed tendency towards increased mortality.

Paper III: Orthostatic Hypotension and Elevated Resting Heart Rate Predict Low-Energy Fractures in the Population

The Malmö Preventive Project (MPP) study is a population-based prospective cohort study of approximately 33000 (two third men and one third women) individuals in the city of Malmö, Sweden. The primary objective was to screen for CVD in the population. The subjects in MPP were between the age of 26 and 61 (born 1921-1948).

Baseline examination including orthostatic blood pressure and heart rate measurement were performed. The subjects were asked to fill a questionnaire regarding personal and family history of CVD, hypertension, diabetes, cancer, smoking and lifestyle pattern.

Paper III is a retrospective review of the prospective study of MPP. We included 33139 subjects from MPP with completed data on age, gender, BMI and follow-up data on low-energy fractures.

We investigated the association between orthostatic blood pressure response, resting heart rate and follow-up endpoint of first incident low-energy fracture. Testing included a model entering age, sex and BMI as covariates (model 1) and a more comprehensive model entering age, sex, BMI, antihypertensive treatment diabetes, smoking, previous MI and all measured hemodynamic parameters such as systolic blood pressure (SBP), diastolic BP (DBP), changes in BP and resting heart rate (RHR) (model 2 or fully adjusted model).

Results

The participants were followed for a median time of 25.1 years. The median follow-up time from baseline to first incident fracture was 15.0 years. The mean age at first incident low-energy fracture was 63.5 years (± 10.7).

An orthostatic decrease in systolic blood pressure of 10 mmHg at baseline was associated with 5% increased risk (95%CI: 1.01-1.10) of low-energy fracture during follow up in the fully adjusted model.

Resting heart-rate, independently of orthostatic response, predicted incident low-energy fracture in both models. In the fully adjusted model, the effect was an 8% increased risk of fracture per 10-beats per minute (95%CI: 1.05-1.12). Subjects with a resting heart rate exceeding 68 beats per minute (BPM) had an 18% increased risk (95%CI: 1.10-1.26, $p < 0.001$) of low-energy fracture during follow-up compared to the subjects with a resting heart rate below 68 BPM.

When analysing orthostatic response and resting heart rate combined, we found a 30% increased risk of low-energy fracture during follow-up.

Paper IV: Cardiovascular Biomarkers and Risk of Low-energy Fractures among Middle-aged Men and Women

The Malmö Diet and Cancer (MDC) study is a prospective population-based epidemiologic cohort study of approximately 30.000 persons who were enrolled 1991-1996 in the city of Malmö, Sweden. The subjects were born between 1926 and 1945, age 44-74 at inclusion. The overall aim of the MDC was to evaluate the impact of diet on cancer and mortality.

Baseline examination including blood pressure measurement, dietary assessment, questionnaires regarding smoking, medical history and medication were performed. Additional blood tests were analysed for a subgroup of 5540 persons.

In paper IV we (retrospectively) included 5291 individuals from the MDC study with data on baseline levels of at least one of four cardiovascular biomarkers; mid-regional-fragment of pro-adrenomedullin-peptide (MR-pro-ADM), mid-regional-fragment of pro-atrial-natriuretic-peptide (MR-pro-ANP), N-terminal pro-brain-natriuretic-peptide (NT-pro-BNP) and C-terminal-pro-arginine-vasopressin (CT-pro-AVP/Copeptin).

Associations between baseline levels of cardiovascular biomarkers and follow-up primary end-point of first incident low-energy fracture were analysed. Testing included a minimally adjusted model (aged and gender). If significant results we

additionally tested adjusting for smoking, systolic blood pressure (SBP), anti-hypertensive treatment (AHT), Body Mass Index (BMI) and previous low-energy fracture (multivariable adjusted model).

Results

The participants were followed for a median time of 21.0 years and during that time 19% experienced at least one low-energy fracture. The median time from baseline to the first incident low-energy fracture was 14.5 years. Patients with low-energy follow-up fracture tended to be older women, with lower BMI and higher prevalence of previous fracture.

There was no associations between levels of MR-pro-ADM and first incident low-energy fracture during follow-up among all subjects. MR-pro-ADM significantly predicted fractures among men (hazard ratio: 1.23, 95%CI: 1.09-1.40, $p=0.001$), but not among women. Among men, the association between MR-pro-ADM and first incident low-energy fracture remained significant in the multivariable adjusted model.

Levels of MR-pro-ANP, NT-pro-BNP and CT-pro-AVP/Copeptin did not predict first incident fracture during follow-up.

Discussion

Papers I and II

In paper I, our main findings were that hypertension and cognitive disorders were common comorbidities among the patients undergoing acute hip fracture surgery. One-third of the patients were readmitted to hospital and one of eight died within the 6 month follow-up after discharge. Hypertension and having a pacemaker were independently associated with this risk of readmission and the most common reason for readmission was a new fall. Ischemic heart disease and malignancy predicted mortality.

Much research has been done in the field of comorbidity/multimorbidity and its implications to the individual, to the health care systems and to society. In a review from 2011 Marengoni et al showed that multimorbidity affects more than half of the elderly population, with females and people from lower classes at higher risk(151). Not surprisingly, and according to our results regarding comorbidity, these studies have emphasized the growing population of older patients with multiple and chronic conditions, to be a future challenge to the physician and health care systems(42, 49, 50).

Hypertension, other cardiovascular, cerebrovascular diseases and cognitive impairment are common phenomenon among the elderly. According to previous studies, and according to ours, these disorders have a higher risk of an adverse complication or outcome after hip surgery(152-154).

Also, our finding that a previous fracture increases the risk of future readmission to hospital due to a new fall and/or a re-fracture was proved among 239 patients in a consecutive and prospective study in 2006(155). In a large study from 2006, 22066 patients with fractures were identified and had a relative risk of almost 4 of sustaining a subsequent low-energy fracture(156).

Common comorbidities are frequent in older patients and in patients admitted to hospital for hip fracture, and common reasons both to readmission and mortality following hip fracture surgery. In a study published in 2002, 82% of the study population had one or more chronic diseases, 65% had several(157). However, most current medical practice is based on one single disease model, failing to take into

consideration for the simultaneous presence of several conditions(157). New and further insights in this field can lead to the identification of preventive strategies and treatment of patients with several chronic diseases.

In paper II we showed that total number of medications, anti-osteoporotic agents, anti-depressants and eye drops predicted readmission to hospital 6 months after hip fracture surgery. Vitamin K antagonists, thiazides and tramadol were mainly associated with readmission due to a new fall.

Even though we today have available guidelines that have improved and rationalized drug prescription in many disease-oriented fields, there are still matters that can be improved. Polypharmacy is often a consequence of several chronic conditions, which lead physicians to prescribe more than one drug, and increasing the risk of hospitalization and sometimes mortality(40, 158). According to the Swedish National Board on Health and Welfare and confirmed internationally the most common drug-related side-effects causing admission to hospitals were falls and fracture, dizziness, heart related and bleedings(38, 81). Followed by deranged fluid- and electrolyte balance, cardiac arrhythmias, affected consciousness or confusion, cardiac failure and hypoglycaemia(61). These reasons for admissions are all well in line with our results.

Polypharmacy has been shown to increase during hospital stay. In a study by Nobili et al, the prevalence of polypharmacy was 51.9% upon admission, but 67% upon discharge from hospital(158). Upon admission, the patients included in our study, had on average 6.2 ± 3.9 prescribed medications upon admission and on discharge 7.8 ± 3.6 when discharged from hospital. The explanation to this was different kind of analgesics, anti-coagulants and antibiotics, naturally following hip fracture surgery.

Older people are known to suffer more from osteoporosis, hence they use more anti-osteoporotic medication and have higher risk of falling and fracture due to OH, weight loss, small muscle mass and strength and limited mobility(90, 159). Our finding that patients with anti-depressants readmitted more often is supported by research showing SSRI to cause urinary problems and an increased risk of falling(160, 161). Further it is known that, supporting our finding of thiazides causing readmission, well-known diuretics may cause electrolytic disorders that may contribute to the increased risk of falls(162).

Another way possible of looking at the increasing amount of prescribed drugs that we have seen during the last two to three decades is that it is a result of a positive development where new medications and treatment have made it possible to treat more diseases and conditions than before

Well-designed, interprofessional, including clinical pharmacists, intervention studies that focus on enrolling high-risk older patients with polypharmacy may

result in reduced unnecessary prescribing and may affect long-term health outcomes. One group of geriatric clinics within the European union uses The *GerontoNet ADR Risk Score*, a method for identifying older (≥ 65 years) patients at risk of suffering from adverse drug event. This instrument addresses at the following(38, 163):

- ≥ 4 diseases
- Affected kidney function (glomerular filtration ≤ 60 ml/min)
- Heart failure
- Amount of prescribed medications (≤ 5 , 6-7 or ≥ 8)
- Previous drug induced event

Hence, medication reviews and withdrawal or modification of drugs may be justified.

Strengths and weaknesses

Paper I

Strengths of study I are its prospective design allowing assessment of differences that may not be detected in retrospective case-control studies, and access to high-quality national and regional registers allowing detailed assessment of follow-up data including comorbidities, frequency, surgical and non-surgical causes of hospital readmissions and mortality. This study has also some limitations. Firstly, the study population was predominantly Caucasian, therefore, these results should be extrapolated with caution to other populations. Secondly, assessment and analysis of medical complications was limited to those that caused readmission. Less serious complications that did not lead to hospital readmissions were not considered. Thirdly, there are factors potentially associated with patient re-hospitalization that were not measured. These may include deficiency in the quality of care, medical errors, and unfavorable living conditions that may have influenced the readmission rate. Fourthly, orthostatic blood pressure measurements were not made and data concerning pacemaker analysis that might have demonstrated reasons for readmission are not available. Inclusion of these data should be planned in future studies.

Paper II

Strengths of paper II are that our catchment area is served by one university hospital, and all hip fractures were treated at the same study site. The hospital medical records were accessible and scrutinized by the researchers. Moreover, the Swedish record system is particularly appropriate for a study of this nature as the coverage of events

of interest has high efficacy and validity. However, medical records from primary care were not available; thus, primary care physicians may have introduced some post-discharge changes in medications that were unnoticed by the authors.

Originally this was supposed to be a case-control study but due to poor handling and not satisfactory data on the controls, the reviewers came with legitimate critics and we had to omit the controls from the article.

Paper III

In paper III we demonstrated that OH, elevated resting heart rate and their combination are strong independent predictors of future incident fragility fracture in a middle-aged population.

This is in line with a previous study in the same population(164). In an epidemiologic study from 2006, Rubenstein et al analysed risk factors for falls in older people. The most common causes were ‘accident’/environmental-related, followed by gait/balanced disorders or weakness and dizziness/vertigo, however the actual term orthostatic hypotension (as in our study) was not specified(165). Several studies have also analysed risk factors, such as medications, for falls and fractures among the elderly, such as antihypertensive treatment. It is likely that many low-energy fractures are caused by falls, and that these falls may in turn be provoked by a transient cerebral hypo perfusion due to impaired blood pressure response to OH(28, 166).

An explanation to why OH and RHR are associated with low-energy fractures could be that these variables are markers of poor physical condition or impaired health status, correlated with known traditional risk factors such as smoking or diabetes(28, 166). As discussed in previous sections, elevated RHR may also be a marker of subtle autonomic dysfunction.

These findings may have clinical implication that OH and resting heart rate may be used to sharpen clinical risk prediction of low-energy fractures, to better target subjects at highest risk.

Strengths and weaknesses Paper III

The main strengths of study III are the large number of subjects, long follow-up and access to reliable case data. The major limitation of this study is the lack of data on heart rate and 3-min BP on standing which were not recorded in MPP. Naturally, the current guidelines on OH were not available at the time of the baseline examination of MPP. Another limitation is that we assumed that most cases of low-

energy-fractures were indeed caused by a fall provoked by reduced cerebral circulation during a maladaptive BP response. However, some low energy-fractures are likely to occur in other settings. Finally, for the whole MPP cohort orthostatic response was examined only at baseline, indicating that we have been unable to evaluate how prospective changes in hemodynamic parameters were related to outcome.

Paper IV

Our finding that circulating levels of MR-pro-ADM predict fragility fractures among middle-aged men is to our knowledge, the first of its kind.

As discussed in previous sections, several studies have shown correlations between cardiovascular biomarkers and more chronic diagnosis such as heart failure(101, 134). But, there has also been focus in different emergency settings on research of more acute events such as acute dyspnoea, pulmonary infections and sepsis(115, 127, 128). Correlations between cardiovascular biomarkers and dementia, such as Alzheimer's disease (118, 119) have been found, and previous studies have shown correlations and increased levels of biomarkers among patients suffering from falls and syncope(130, 131).

This may suggest a correlation of biomarkers and low-energy fractures, and suggests further research in the subject since our previous studies have shown correlations between both cognitive impairment and OH and fragility fractures.

In the last few years, several additional peptides/biomarkers have emerged, each reflecting different pathophysiological processes in the development and progression of heart failure: myocardial insult, inflammation, fibrosis and remodelling (101, 167). Their role in the clinical care of the patient is, however, still only partially defined and more studies are needed(101, 167).

Strengths and weaknesses Paper IV

The main strengths of this study are the large number of subjects, its reliable data and long follow-up. Our study has a number of limitations that should to be mentioned. First, the authors had little influence on the data collected and original study design. For the whole MDC cohort, cardiovascular biomarkers were only evaluated at baseline, indicating that we were unable to evaluate how any potential prospective change could be related to outcome.

Conclusions and Future perspective

The following conclusions can be drawn from the four papers included in this thesis:

1. Common comorbidities, such as hypertension and pacemaker treatment are associated with higher risk of rehospitalisation, while higher risk of mortality is associated with ischaemic heart disease and malignancy, following hip fracture surgery in the elderly.
2. The total number of medications, the use of specific drug classes such as antiosteoporotic agents, SSRIs, and eye drops predicted rehospitalization after hip fracture surgery. The use of vitamin K antagonists, thiazides, and tramadol were associated with readmissions due to a traumatic fall. Medication reviews and withdrawal or modification of drugs are justified.
3. Orthostatic blood pressure decline and elevated resting heart rate independently and combined predict low-energy fractures in a middle-aged population.
4. Higher circulating levels of MR-pro-ADM predict low-energy fractures among middle-aged-men, but not among women. Levels of other cardiovascular biomarkers are not associated, neither in males nor females, with these fractures.

General discussion and Future perspective

A fast growing elderly population means a growing number of patients with several comorbidities and thus a large numbers of prescribed medications. This implies more fragile patients with natural changes in physiology. But also, the suffering from both clinical diagnoses, such as cardiovascular diseases and osteoporosis, as well as interaction of prescribed medications, polypharmacy increases older peoples' frailty.

We need to get better at foreseeing patients at risk, and minimize risk factors. We know that osteoporosis leads to an increasing incidence of fragility fractures with age and Scandinavia has the highest incidence of hip fractures in the world. We tend to treat only the current fracture. Interventions in preventing falls, including fall

risk assessments are vital. Systematic attention to fall prevention should be a part of comprehensive care of older people. The increasing costs and suffering suggest that efforts should be focused on expanding the knowledge regarding benefits and risks of pharmaceuticals by including more elderly persons in clinical trials, especially patients with multiple comorbid conditions. We also need development of interdisciplinary teams to care for elderly patients inside and outside hospitals.

Swedish summary

Populärvetenskaplig sammanfattning

Visste du att ca en fjärdedel av de som trillar
och bryter höften inte lever efter ett år?

I takt med att befolkningen blir äldre och äldre kommer också antalet höftfrakturer att öka. Detta innebär ett stort personligt lidande och död, men även en stor kostnad för samhället i form av sjukhuskostnader, rehabilitering, vårdboende, och hemhjälp.

Bara i Malmö vårdades det nästan 750 personer för höftfraktur år 2007. Det är en av de högsta i landet. Många av dessa är äldre, över 80 år och en övervägande del kvinnor. Att framför allt kvinnor bryter höften beror på att kvinnor generellt lever längre och har skörare skelett (sk benskörhet) än män. Eftersom en övervägande del av de som bryter höften är äldre har de ofta också flera sjukdomar sedan tidigare och många äter därför flera olika mediciner.

Vanliga sjukdomar hos äldre är s.k. hjärta- kärlsjukdomar, som högt blodtryck och kärlkramp. Läkemedel mot dessa sjukdomar kan i sig ge biverkningar som gör att risken för att falla och därmed också bryta höften ökar.

Internationellt sett och nu även i Sverige används allt mer uttrycket ”polyfarmaci”, Med ”polyfarmaci” menas att en person samtidigt äter fyra eller fler läkemedel. Bland de äldre som bor på serviceboende eller behöver hjälp från kommunal hemtjänst är det vanligt med upp till 8–10 mediciner per person, ibland så många som 12. Att äta så många olika mediciner samtidigt ökar risken för interaktion mellan dessa olika läkemedel och en ökad mängd biverkningar. Denna risk ökar med varje ny utskriven medicin.

Många läkemedel har som känd biverkan blodtrycksfall vilket leder till yrsel, andra mediciner kan orsaka förvirring som oönskad bieffekt. Förvirring och yrsel kan leda till en ökning av fallskador och risken för höftfrakturer blir överhängande.

Vi har gjort fyra studier som resulterat i tre artiklar som publicerats i olika vetenskapliga tidskrifter.

I [artikel I](#) och [II](#) sammanställde vi samsjukdomarna hos ungefär 300 patienter som vårdats inneliggande på sjukhus i Malmö sedan de drabbats av en höftfraktur. I den

första artikeln/studien konstaterade vi att vissa sjukdomar såsom högt blodtryck och en kognitiv påverkan innebar en ökad risk att återinläggas på sjukhus inom 6 månader efter höftfraktur. Vissa sjukdomar såsom hjärtsjukdom och cancer innebar en ökad risk för att dö inom 6 månader.

I den andra studien granskade vi hur många och vilken typ av läkemedel som dessa patienter stod på och om det påverkade sjuklighet och dödlighet efter en höftfraktur. Vi gjorde en aktiv genomgång av dessa medicinlistor. Vi satte ut olämpliga mediciner (antingen var de felaktiga, interagerade på ett farligt sätt med andra mediciner eller så var där allvarliga biverkningar), justerade doser och/eller lämnade utan åtgärd. Resultaten visade att antalet läkemedel och vanliga mediciner påverkar hur ofta patienter återinläggs efter en höftfraktur.

I artikel III tittade vi på samband mellan en vanlig orsak till yrsel hos äldre, s.k. ortostatism (blodtrycksfall när man ställer sig upp) och höftfrakturer. Patientgruppen kom från en tidigare känd studie, Malmö Förebyggande Medicin (MFM) som vi kunde använda oss av. Patienter som drabbas av blodtrycksfall och ofta får yrsel i samband med detta drabbas oftare av höftfrakturer.

I artikel IV använde vi oss av blodprover tagna i en tidigare stor studie, Malmö Kost Cancer (MKC) studien. De blodprover vi var intresserade av är kända hormoner inom bl.a. kroppens blodtrycksreglering. Vi analyserade sambandet mellan dessa prover och en ökad förekomst av fallfrakturer. Resultatet här var skiftande och i ett av fyra prover såg vi ett samband hos män och en ökad risk för frakturer. Detta såg vi inte hos kvinnor.

Sammanfattningsvis, har vi konstaterat att hjärt- kärlsjukdom ökar risken för fall och bland annat höftfrakturer. Detta innefattar sjukdomarna i sig, symptom såsom blodtrycksfall och vissa blodprov. Flertalet mediciner som människor äter kan leda till komplikationer efter en höftfraktur och kan sättas ut eller justeras ner i dos.

Slutligen vill vi poängtera att vanliga sjukdomar och multimedcinering hos äldre är förenade med en högre risk för fall, en eventuell höftfraktur och därmed ökad risk för död. Genom att ställa krav på sjukvården att försöka förebygga dessa, optimera behandlingen, de mediciner våra äldre får utskrivet och aktivt rensa ut i läkemedelslistorna kan vi minska onödiga biverkningar, personligt lidande och död.

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I wish my parents were here

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It's never too late