Aspects of fracture prevention

The role of fracture liaison services and alendronate

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An ounce of prevention is worth a pound of cure.

Benjamin Franklin

Abstract

Objective: In an ageing population, osteoporotic fractures become more common and cause increased morbidity, mortality and societal cost. This thesis aimed to determine the potential role of fracture liaison services (FLS) and alendronate treatment on fracture risk in those with a recent fracture, in the elderly and in those treated with oral prednisolone.

Methods: All four papers in this thesis are retrospective cohort studies. In the first two papers, we used regional electronic health records to study patients 50 years or older with a recent major osteoporotic fracture. Patients in FLS hospitals were compared to historic controls or patients at non-FLS hospitals. The chance of receiving examination with dual-energy X-ray absorptiometry (DXA) and osteoporosis medication was investigated as well as the risk of sustaining a recurrent fracture. In the last two papers, we used national registers to study the risk of fracture after alendronate treatment in elderly and prednisolone users respectively versus propensity score matched controls without alendronate treatment.

Results: Implementation of FLS was associated with an 18% reduced risk of recurrent fracture. Also, implementation of a minimal resource FLS increased the proportion of patients being investigated with DXA and the chance to receive osteoporosis medication after fracture reached levels comparable to FLS types using conventional coordinator-based models. Alendronate prescribed to older patients (≥80 years) with prior fracture was associated with reduced risk of hip fracture by 38% with sustained safety. Alendronate prescribed to patients 65 years or older treated with oral prednisolone was associated with a 65% reduction in hip fracture risk.

Conclusions: Preventive efforts such as FLSs and alendronate treatment in elderly and prednisolone users are associated with reduced risk of fracture. An increased use of FLSs and alendronate treatment would reduce fracture incidence, thereby mitigating suffering and costs resulting from fractures.

Keywords: Osteoporosis, prevention, fracture, fracture liaison service, alendronate, elderly, prednisolone.

Sammanfattning på svenska

Bakgrund: I en befolkning med ökande andel äldre blir osteoporosfrakturer som leder till ökad sjuklighet, dödlighet och kostnader allt vanligare. Denna avhandling syftar till att undersöka den möjliga preventiva nyttan med så kallade frakturkedjor och alendronatbehandling till riskgrupper såsom patienter med nyligen genomgången fraktur, äldre samt prednisolonanvändare.

Metoder: Alla fyra publikation i denna avhandling är retrospektiva kohortstudier. I de två första publikationerna använde vi regionala register med sjukhusdata för att studera patienter 50 år eller äldre med osteoporosfraktur. Patienter i sjukhus med frakturkedjor jämfördes med historiska kontroller och med patienter i sjukhus utan frakturkedjor. Chansen att få bentäthetsmätning och osteoporosläkemedel undersöktes, samt risken att få en ny fraktur. I de två sista studierna använde vi nationella register för att undersöka hur alendronatbehandling till två specifika riskgrupper, äldre respektive prednisolonanvändare, påverkade risken för fraktur jämfört med matchade kontroller med likvärdig sjuklighet.

Resultat: Införandet av frakturkedjor ledde till en minskning av nya frakturer med 18%. Dessutom ökade andelen frakturpatienter som erhöll bentäthetsmätning och osteoporosläkemedel vid en sekreterarbaserad frakturkedja till nivåer jämförbara med konventionella koordinatorbaserade frakturkedjor. Behandling med alendronat till patienter 80 år och äldre med tidigare fraktur var associerat med 38% minskad risk för höftfraktur. Behandling med alendronat till patienter 65 år och äldre med prednisolon var associerat med 65% minskad risk för höftfraktur.

Slutsatser: Preventiva åtgärder såsom frakturkedjor och alendronatbehandling till riskgrupperna äldre och prednisolonanvändare var associerat med minskad risk för fraktur. En ökad användning av frakturkedjor och alendronat-behandling skulle kunna minska frakturincidensen, på så vis minska lidandet och kostnader som orsakas av frakturer.

List of papers

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

I. **Axelsson K F**, Jacobsson R, Lundh D, Lorentzon, M.

Effectiveness of a minimal resource fracture liaison service

Osteoporosis International, **2016**. 27(11): p. 3165 - 3175.

II. **Axelsson K F**, Johansson H, Lundh D, Möller M, Lorentzon M.

Association Between Recurrent Fracture Risk and Implementation of Fracture Liaison Services in Four Swedish Hospitals: A Cohort Study.

Journal of Bone and Mineral Research, **2020**. 35(7): p. 1216 - 1223.

III. **Axelsson K F**, Wallander M, Johansson H, Lundh D, Lorentzon M.

Hip fracture risk and safety with alendronate treatment in the oldest-old.

Journal of Internal Medicine, **2017**. 282(6): p. 546 - 559.

IV. **Axelsson K F**, Nilsson A G, Wedel H, Lundh D, Lorentzon M.

Association Between Alendronate Use and Hip Fracture Risk in Older Patients Using Oral Prednisolone.

JAMA, **2017**. 318(2): p. 146 - 155.

Content

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
DXA	Dual energy X-ray absorptiometry.
ECM	Extra cellular matrix
FLS	Fracture liaison service
FRAX	Fracture risk assessment tool
MOF	Major osteoporotic fracture, i.e. fracture on hip, spine, upper arm or wrist and sometimes pelvic fractures
RANK	Receptor activator of nuclear factor-κB
RCT	Randomized controlled trials
SD	Standard deviation
TBS	Trabecular bone score
VFA	Vertical fracture assessment

1 Introduction

Fracture prevention is a broad subject including aspects such as pharmaceutical treatment, non-pharmaceutical efforts, patient motivation as well as organizational aspects. This thesis will concentrate on organizational efforts, particularly so-called fracture liaison services (FLSs), which aim to identify and reach patients at risk of fracture, and efficacy of pharmaceutical treatment in specific patient groups at high risk of fracture.

1.1 The skeleton

The oldest known animal with a skeleton is Coronacollina acula, a multicellular organism from around 550 million years ago.[1] The human skeleton has evolved into a complex multifunctional organ. The skeleton has obviously mechanical functions, but is also important for storing calcium and phosphate, housing the hematopoiesis process (formation of cellular blood components) and has endocrine and immunological functions.

The skeleton can be divided into the axial and the appendicular skeleton. The axial skeleton (the head, vertebra and rib cage) offers a protective shell for the vital organs such as the brain, spinal cord, heart and lungs, whereas the appendicular skeleton (the limbs and the pelvic) serves as attachment sites for muscles and tendons to enable body movement.

Histologically, there are two main types of mature bone: cortical (compact) bone with a dense ordered structure and, trabecular (cancellous) bone with a lighter less compact irregular structure.[2] Cortical bone is the most common bone type and consists of osteons, long cylindrical structures with dense bone matrix lamellae ordered parallel to the main compression. In the center of the osteon is the Haversian canal, harboring blood vessels and nerves. Trabecular bone consists of a sponge-like system of bars and plates aligned parallel to the lines of stress.

There are a number of different ways to classify bones; according to location, shape consistency or size. A common classification is flat bones and tubular bones.[3] Flat bones are thin, often somewhat curved, e.g. the ribs, sternum, scapula and the bones in the head. Flat bones consist mostly of trabecular bone with a thin cortical shell. The tubular bones include both the long tubular bones in the extremities and the short tubular bones in the hands and feet. Tubular bones have three distinct parts: (i) the diaphysis in the middle which is a hollow

shaft composed mostly of dense cortical bone, (ii) the epiphyses located at the ends of the bone as articular surface and (iii) the metaphyses in between. The epiphyses and metaphyses are mostly trabecular bone with a thin cortical shell.[4] The distribution of cortical and trabecular bone varies between and within the bones. For example, since trabecular bone is ideal for withstanding compressive stress, the proportion in the vertebra is high.

Bone strength depends both on material composition and structure.[5] Bones are subject to conflicting requirements.[6] Stiffness is needed to resist deformation and enable loading, yet flexibility (changing length and width) is needed to absorb energy upon tension or compression. Also, bones need to be light-weight for smooth mobility. These traits, including stiffness, flexibility, strength and lightness, are balanced for each bone to fulfill its specific requirements of compression, tension, shear and torsion. Exceeding the bone strength will result in a fracture.

1.2 Bone biology

Bone is a connective tissue where approximately 10% of the bone volume constitute bone cells, and 90% is extracellular matrix (ECM) of which 65% is inorganic, 20% organic and 15% lipids and water. The inorganic (mineral) matrix is mainly in the form of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, important for bone strength and stiffness to withstand compressive forces and stores 99% of the calcium, 85% of the phosphorus and around half of the magnesium and sodium in the body. The organic matrix is primarily type I collagen (90%) providing bone its form and resistance to tensile forces.[3]

Bone tissue renews itself constantly through bone remodeling to maintain stability and integrity.[7] There are three types of cells involved in the process: osteoblasts (4-6%), osteocytes (90-95%) and osteoclasts (1-2%).[8]

Originating from mesenchymal stem cells, osteoblasts have recently been associated with regulation of osteoclast formation and multiple endocrine functions, but their traditional role is to build bone, a process (osteogenesis) involving secretion of organic matrix, i.e. dense collagen layers alternately parallel and orthogonal to the axis of stress loading.[9] This matrix is filled with extremely dense hydroxyapatite-based mineral, a process driven by both active and passive transport as well as by pH control.[10] At the end of their approximately three months long life, osteoblasts can evolve in four different ways: (i) transform into inactive osteoblasts covering the bone surface as bone-lining cells, (ii) become trapped in the bone as osteocytes, (iii) undergo

apoptosis (programmed cell-death) or (iv) transdifferentiate into cells that deposit chondroid or chondroid bone.[11]

Osteocytes are spider shaped cells coordinating the bone remodeling. With the cell body trapped in a lacuna (small spaces inside the lamellae), and dendritic processes reaching far into the bone's canaliculi, the osteocyte is well positioned to detect shifts in loading through fluid shear stress and orchestrate bone remodeling when appropriate.[12]

The osteoclast are the only cells which can resorb bone, which is achieved by secreting H+, Cl−, cathepsin K and matrix metalloproteinases into the resorption area. Unlike the osteoblast and the osteocyte, the osteoclast has a hematopoietic origin. Monocytes differentiate into osteoclast progenitor cells which express the receptor RANK (receptor activator of nuclear factor-κB), a receptor essential for further differentiation. Many different cells produce the ligand to RANK, in order to stimulate osteoclastgenesis. The mature osteoclast is multinuclear and formed through the fusion of multiple precursor cells.[13]

1.3 Dual energy x-ray absorptiometry (DXA)

Bone strength depends on both bone mineral density (BMD) and bone quality. Since introduced in the 1980, Dual energy X-ray absorptiometry (DXA) has become the golden standard for measuring BMD.[14] Its key feature is the usage of two x-ray beams with different energy levels, enabling separation of dense tissue from soft tissue. This is based on differences in attenuation. Low energy x-rays are attenuated more by bone than soft tissue, whereas high energy x-rays are attenuated equally regardless of tissue type. By measuring how much of each beam has passed through a certain area of the body, BMD can be calculated and expressed as a two-dimensional measurement in g/cm^2. Normally, this value is translated into a T-score, which is the difference from the mean of a population of young adult women, expressed in standard deviations (SD). DXA is used to measure BMD in order to diagnose bone fragility and estimate fracture risk, and to facilitate decision making regarding osteoporosis treatment initiation and follow-up. The radiation emanating from a measurement is very low, allowing operators to remain in the room during measurements, and without any requirement to wear any type of protective clothing or other methods of shielding.[15] Interpretation of the result must be performed together with visual assessment in order to account for confounding factors such as aortic calcification, arthritis and scoliosis.[16]

Vertebral fracture constitutes both a common consequence and an important risk factor for new fractures. Conventional x-ray assessment is the accepted

standard for diagnosis. However, this is often omitted in clinical practice, resulting in a large underdiagnosis of vertebral fracture. Modern DXA machines provide lateral spine densitometry, or vertebral fracture assessment (VFA), a low-radiation dose method providing the means to diagnose vertebral fractures with high specificity and sensitivity.[17] Diagnosing vertebral fractures using VFA is particularly important since vertebral fractures are strong predictors of future fractures, independently of other relevant clinical risk factors.[18]

A limitation of DXA is that BMD is a two-dimensional measure, not accounting for three-dimensional aspects such as bone microarchitecture. To this end, trabecular bone score (TBS) was developed and included in most modern DXA machines. TBS measures gray scale differences between two adjacent two-dimensional images of the lumbar spine, resulting in information on skeletal microarchitecture.[19] The TBS is associated with incidence of new fracture independently of BMD and FRAX.[20]

While TBS focuses on trabecular information, there are other methods that investigate bone strength through cortical properties. Cortical micro-indentation measures the indentation after a probe with a predefined force and frequency has been applied to the cortical surface.[21] The measured bone material strength is decreased in patients with fracture independently of BMD.[22] However, its place in clinical practice is yet to be determined.[23] Investigation of cortical and trabecular micro-architecture using high-resolution peripheral quantitative CT (HR-pQCT) is another method that improves prediction of fracture, independently of BMD and FRAX alone.[24]

To summarize, there are other methods that can complement DXA to assess bone strength, but despite its limitations, BMD predicts 60-80% of the bone strength in ex vivo studies.[25,26] And BMD alone is better at predicting fractures than blood pressure is at predicting stroke.[27]

1.4 Osteoporosis

The definition of osteoporosis has evolved over the years.[28] The most recent definition was issued in 2011 by a consensus panel defining osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.[29] Furthermore, bone strength was used in the definition to reflect the importance of both BMD and bone quality. BMD varies with age (Figure 1) and increases during childhood until peak bone mass, which is the measure of maximal acquired bone mass at the end of skeletal maturation.[30] Peak bone mass is obtained at different ages depending

on sex and skeletal site, but generally occurs around the age of twenty.[30] After reaching peak bone mass, there is a gradual biological loss of bone. Among women, peak bone mass fails to reach as high as in men, and during menopause, bone loss is accelerated resulting in lower BMD among women than in men. When BMD falls below one standard deviation below the mean of a reference population of young white adult women, it is referred to as osteopenia, while BMD at or below 2.5 standard deviations still is referred to as osteoporosis, based on the 1994 definition from the World Health Organization.[31] Notably, osteoporosis is not just the result of bone loss, it can also be a consequence of a low peak bone mass.[32] Furthermore, osteoporosis can be classified as primary, i.e. as a consequence of normal ageing or menopause, or secondary, when due to medication or illness.[33]

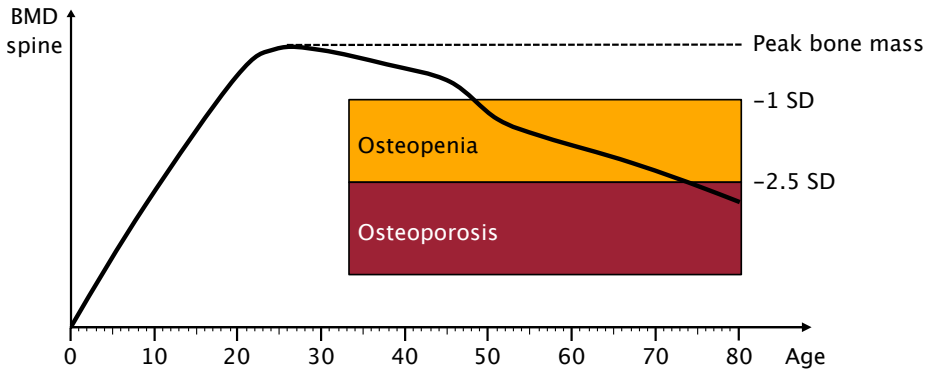


Figure 1. Schematic presentation of the development of BMD for women.

1.5 Fracture epidemiology

The clinical manifestations of osteoporosis are fractures. In Sweden, there are approximately 90.000 fractures in 80.000 patients, 50 years or older each year.[34] Hip fracture is the most severe fracture type and is associated with both increased morbidity and mortality.[35] Approximately 50% of hip fracture survivors will not recover to their pre-fracture level of mobility,[36] and the one-year mortality is increased 8-36%.[37,38] An estimated 2.7 million hip fractures occur yearly world-wide, and if osteoporosis were prevented, half of these would likely be avoided.[39] Vertebral fractures are also often severe with outcomes such as increased morbidity, hospitalizing pain and increased mortality, however only about a third are clinically recognized.[40] While other fracture types may have less severe clinical manifestations, they still cause substantial suffering, hospitalization and high societal and health-care costs. In Sweden, the yearly fracture related cost of osteoporosis has been estimated to around €2 billions.[41] According to Statistics Sweden, the number of persons

among the oldest old (80 years or older) will have doubled in 2040, reaching a million.[42] Since the fracture risk increases with increasing age,[43] this will lead to dramatic cost increases. In the United States the demographic trend is similar. The fracture related cost of osteoporosis was estimated to $17 billion in 2005,[44] and the number of the oldest-old is expected to increase from 11.7 million in 2012 to more than 20 million in 2030.[45]

In osteoporosis research, the term osteoporotic fracture or major osteoporotic fracture (MOF) is often used. Usually it refers to hip, vertebral, proximal humerus, and distal radius fractures and sometimes pelvic fracture are included as well.[28] However, in a large study of 9704 women, also other fracture sites, such as tibia, clavicle and patella were correlated to low BMD, not just those included in the MOF definition.[46] Thus, the term MOF is probably a consequence of those fractures being common, rather than their unique correlation to osteoporosis.

There is a noteworthy paradox regarding fracture risk and fracture prevalence. In a large population cohort of approximately 200.000 post-menopausal women aged 50-104 recruited in a primary care setting, less than 20% of the fractured patients had osteoporosis and approximately 50% were osteopenic.[47] In other words, while the risk of fracture increases dramatically with decreasing BMD (blue in Figure 2), the number of fractures occurring in patients with osteoporosis is relatively low (yellow in Figure 2). Thus, from a preventive perspective, the traditional osteoporosis definition (T-score less than -2.5) will only find a minority of the patients at risk of fractures. To find more patients at risk, other factors needs to be considered.

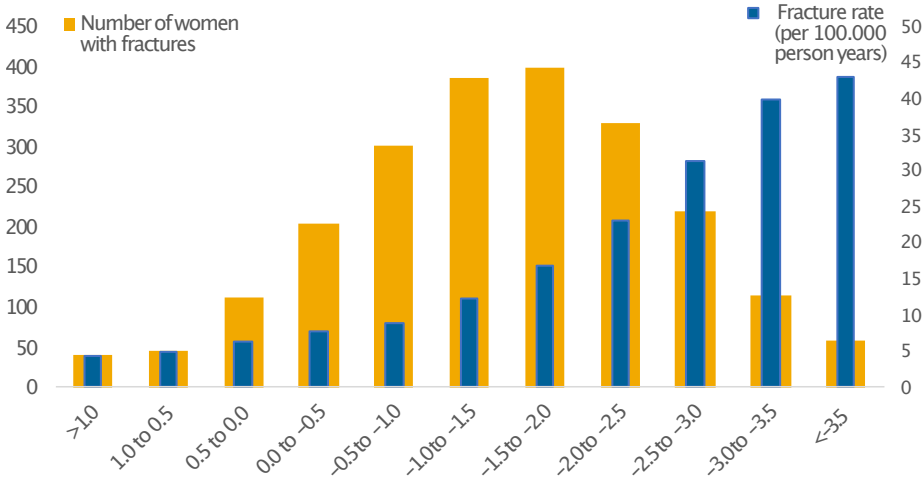


Figure 2. Fracture prevalence and fracture risk per BMD in post-menopausal women. Adapted with permission.[47]

1.6 Risk factors for fracture

Assessing a patient's risk of sustaining a fracture requires consideration of multiple risk factors, such as high age, female sex, low BMD, low body mass index (BMI) smoking, oral glucocorticoid intake, and history of fracture and falls.

1.6.1 Age and BMD

Femoral neck BMD is a strong predictor of hip fracture.[48] However this association is age dependent. For 65-year-old women, each SD decrease in BMD increases the risk of hip fracture by a factor three, more than three if younger than 65 years, and less than three if older than 65 years. Since BMD declines with increasing age, one might assume that the increased risk due to increasing age is due to the BMD decline. However, while the risk of different fracture types differs depending on age, the risk of any fracture increases with increasing age,[43] and is independent of BMD (Figure 3).

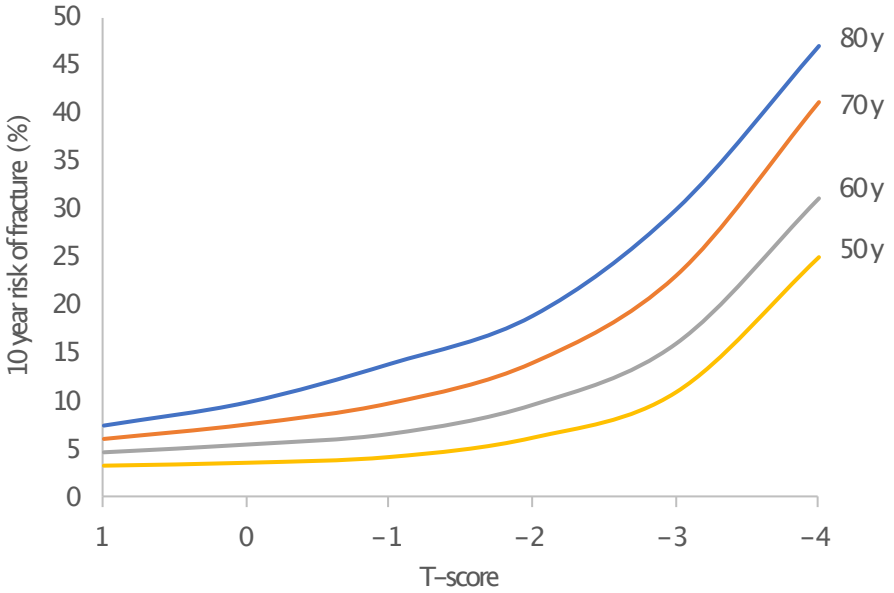


Figure 3. Age and BMD are strong and independent risk factors for fracture. 10-year fracture risk shown for a woman, 165 cm, 65 kg, with no other risk factors according to FRAX.

1.6.2 BMI

Body mass index (BMI = weight / height^2) is associated non-linearly with risk of fracture and dependent on BMD.[49] Low body mass index (below 25 kg/m^2) is associated to increased risk of fracture, an association which is attenuated but still remains after adjustment for BMD. Without adjusting for BMD, the risk of sustaining a hip fracture at BMI 20 kg/m^2 is almost doubled compared to BMI 25 kg/m^2.

1.6.3 Previous fracture

For a patient with a previous fracture, the risk of a new fracture is approximately doubled and independent of BMD.[50] The risk of a recurrent fracture is most pronounced immediately after the first, up to four times, and after about two years the risk levels off at about doubled risk, and remains increased after more than 10 years compared to patients without a previous fracture (Figure 4).[51] The risk depends also on the type of previous fracture, where prior vertebral fracture stands out with at least a fourfold increased risk of a subsequent vertebral fracture.[52]

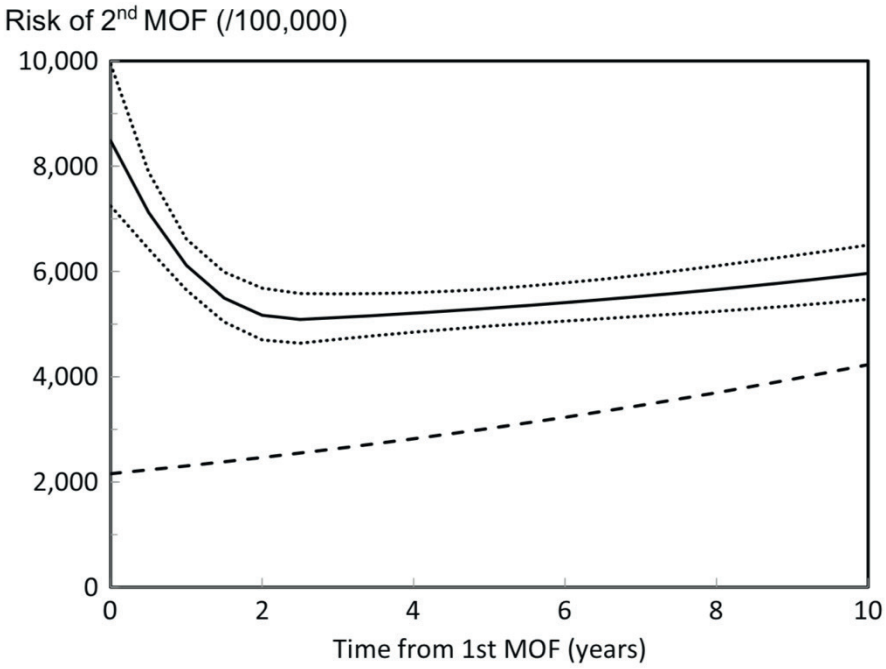


Figure 4. Risk of new fracture (2nd MOF) depending on time since last fracture (1st MOF) compared to unfractured controls (dotted line). Reprinted with permission.[51]

1.6.4 Heredity, smoking and alcohol

The risk of hip fracture increases by approximately 50% if a parental history of fracture is present and is more than doubled with a parental history of hip fracture.[53] With increasing age, this association is attenuated, much like most risk factors for fracture. Smoking increases the risk of hip fracture in a dose dependent manner. For current tobacco smokers the risk is almost doubled, a risk that is somewhat attenuated by BMD adjustment and for ever-smokers the risk is lower, yet significant.[54] A high alcohol consumption of 3 or more standard drinks per day,[55] doubles the risk of hip fracture but with lower consumption, no increased fracture risk was found.[56]

1.6.5 Glucocorticoids

There are a number of conditions (e.g. polymyalgia rheumatica, osteoarthritis, rheumatoid arthritis, inflammatory bowel diseases, gout) in which glucocorticoid therapy is used, making glucocorticoid use the most common cause of secondary osteoporosis.[57] In patients 65 years or older, treatment is especially frequent and occurs in about 2-3% of the population.[58] Oral glucocorticoid treatment affects the skeleton in several ways: decrease of osteoclast apoptosis, increase of bone resorption, and inhibition of osteoblast-mediated bone formation.[59] Thus, glucocorticoid treatment causes rapid bone loss and reduced BMD.[60] A large meta-analysis of 66 studies, with 2891 patients, averaging a daily dose 9.6 mg of prednisolone (or equivalent) with a cumulative dose of 17.8 g and duration of use of 5.4 years, showed that the risk of hip fracture is approximately doubled and for vertebral fracture nearly tripled.[61] The fracture risk increased quickly within a few months and was dependent on both time and dose, where no clear threshold for a low safe dose could be defined.[61] Among 80-year-old patients, in whom the absolute risk of hip fracture is very high, the relative risk increase for hip fracture risk was more than doubled and independent of femoral neck BMD.[62] Most studies and clinical guidelines attribute doses of 5 mg of prednisolone or more in older men and women as a risk factor for fracture.[61]

1.6.6 FRAX

Most known risk factors for fracture are age-dependent, i.e. stronger among younger men and women with lower absolute risk, and weaker among the elderly who have higher absolute risk. Some risk factors are dependent on BMD and many risk factors interact with each other. It is extremely difficult in clinical practice to account for many different risk factors simultaneously, consider potential interdependencies and estimate the absolute fracture risk of a patient. Therefore, a web-based algorithm to calculate total 10-year fracture

risk was created.[63] It can be used without BMD in order to assess fracture risk and provide guidance regarding the need for a BMD measurement with DXA. But most importantly, after BMD measurement it can provide information about the 10-year probability of hip fracture and MOF, risk estimates that can be used to aid in treatment decisions, in outlining guidelines and in health economic considerations regarding screening and treatment. At least 120 countries have incorporated FRAX in their guidelines and in 24 of them the treatment thresholds varied depending on age and/or BMD.[64,65]

The user-friendly design and in some cases simplistic assessment of known risk factors enables rapid and easy assessments of fracture risk, but also entails some tradeoffs, including an inability to adjust for dose in dose dependent risk factors such as glucocorticoid use, smoking and alcohol intake. In addition, multiple fractures, a recent fracture and a vertebral fracture all increases the risk of fracture more than any one fracture having occurred at any previous occasion. These prevalent fracture characteristics have not yet been incorporated in the FRAX tool. However, it is possible to adjust the FRAX risk manually based on (i) glucocorticoid dose,[66] (ii) type of recent fracture,[67] (iii) spine BMD,[68] and more adjustments will probably follow. It is clear that the FRAX tool can provide important guidance regarding fracture risk, though it cannot substitute an individual clinical assessment of fracture risk.

1.7 Pharmaceutical treatment

Current pharmaceutical treatment options include antiresorptive medications (reducing bone resorption), anabolic medications (increasing bone formation) and medications with dual effect.[69,70]

1.7.1 Bisphosphonates

Bisphosphonates are the most widely used osteoporosis medication and usually the first in line pharmaceutical option in treatment guidelines for most patients.[64] Key properties of the bisphosphonates include a high affinity for calcium hydroxyapatite and inhibitory effects on osteoclasts resulting in reduced bone resorption.[71] The affinity to calcium hydroxyapatite and effect on bone resorption vary by type of bisphosphonate, properties that affect treatment frequency and administration. The bisphosphonate group includes alendronate and risedronate normally administered orally once a week, ibandronate administered orally once a month, and zoledronic acid administered intravenously, once a year.[72] In Sweden, alendronate is the most commonly used bisphosphonate, accounting for about 95% of the approximately 90.000 Swedish bisphosphonate patients.[73,74] Treating

postmenopausal women for three years with alendronate increased BMD with 8.8% in the spine and with 5.9% in the femoral neck,[75] translating to a 45% reduction of new vertebral fractures and 40% reduction of hip fracture.[76] Zoledronic acid is a more potent bisphosphonate in terms of binding to calcium hydroxyapatite and effect on bone resorption. Compared to placebo, zoledronic acid, lead to a 70% reduction of vertebral fracture and 41% reduction of hip fracture among post-menopausal women.[77]

1.7.2 Evidence for treatment efficacy among older patients

Older patients often suffer from multiple comorbidities which prevent them from participation in clinical trials. Therefore, none of the large randomized controlled trials (RCTs) on anti-osteoporotic agents included a significant proportion of patients above the age of 80 years.[78] A trial testing the effect of risedronate in women aged 80 to 89, found no significant effect in reducing the risk of hip fracture.[79] However, the study included women with one non-skeletal risk factor for hip fracture or low BMD, whereas a previous fracture was not required, which could have affected the results. Regarding alendronate there are no studies with sufficient number of patients older than 80 years with sufficient power to investigate the effect on hip fracture risk.[78]

1.7.3 Evidence for treatment efficacy among glucocorticoid users

Bisphosphonates in glucocorticoid treated patients lead to a reduction of vertebral fracture risk by nearly 50%, but for non-vertebral fractures the evidence is inconclusive and for hip fracture, evidence is lacking, as a result of small randomized controlled studies without adequate statistical power to analyze effects on fractures with lower incidence numbers.[80,81] Despite this evidence gap, osteoporosis medications are frequently recommended to glucocorticoid treated patients in most clinical guidelines, including those in the US, EU and Sweden.[82-84]

1.7.4 Other osteoporosis medication

Denosumab is a monoclonal antibody to the RANK ligand,[85] an important regulator of bone resorption affecting osteoclast development, function and survival.[86-88] When 60 mg denosumab was administered subcutaneously biannually for three years to postmenopausal women with osteoporosis, BMD increased by 9.2% in the spine and 6.0% in the hip translating to relative risk reductions of 68% for radiographic vertebral fractures, 40% for hip and 20% for nonvertebral fractures.[89] While the increase in BMD from bisphosphonates gradually level off and reaches a plateau after 4-5 years,[90,91] treatment with denosumab increases BMD continuously.[92] After 10 years of

denosumab, BMD in the spine and total hip increased 21.7% and 9.2% respectively.[92] Unlike bisphosphonates, denosumab's effect on the skeleton is reversible and discontinuation of treatment results in rapid BMD loss and a rebound phenomenon with increased bone turnover markers.[93] Upon discontinuation, the risk of multiple rebound associated vertebral fractures is increased, and more so in patients with prior vertebral fractures.[94-96] Therefore, unless an alternative treatment is available, discontinuation is not recommended.[97]

While continuously raised levels of endogenous parathyroid hormone as observed in primary hyperparathyroidism are associated with BMD reductions and fractures,[98,99] intermittent subcutaneous administration of teriparatide (parathyroid hormone 1-34) stimulates bone formation which increases bone mass and strength.[100,101] Teriparatide is superior both to alendronate, and to the combination of teriparatide and alendronate.[102,103] In a 24 months head-to-head study comparing teriparatide to risedronate in women with severe osteoporosis, there were 12.0% new vertebral fractures in the risedronate group and only 5.4% in the teriparatide group.[104] Compared to placebo, the benefits of teriparatide are expected to be even greater.[69] Because of observations of osteosarcoma in mice, teriparatide is only approved for a maximum of 24 months of treatment once in a lifetime.[105] Due to high cost, the usage of teriparatide has been restricted to patients with severe osteoporosis in many countries, and while biosimilars have recently become available at a substantially lower cost, the indication for treatment has not yet changed.[106]

Romosozumab is a bone forming agent with a dual effect in increasing bone formation and decreasing bone resorption. Its conception originates from genetic studies of van Buchems disease and Sclerostosis, in which the SOST gene coding for the protein sclerostin was found.[107-109] The loss of sclerostin function through homozygous mutations caused severe progressive generalized osteosclerosis manifested as facial distortion and increased intracranial pressure.[110] However, patients with heterozygotic mutations (thus only decreasing the sclerostin functions) had higher BMD than age-matched controls, few fractures and normal life-spans.[111,112] Sclerostin, primarily expressed in osteocytes, inhibits the Wnt pathway leading to reduced bone formation.[113] A phase I study, testing of the monoclonal antibody to sclerostin (subsequently named romosozumab), revealed a dose-dependent relationship to bone formation (increasing) and resorption (decreasing) markers.[114] A 12 months phase II study showed large BMD increases in both spine and hip, superior to the controls with teriparatide, alendronate and placebo respectively.[115] In women with osteoporosis, a phase III study showed a 73% reduced risk of new vertebral fractures for romosozumab vs placebo.[116] And

in comparison to alendronate, 12 months of romosozumab followed by alendronate was associated with a 48% lower risk of new vertebral fractures.[117]

1.7.5 Sequential treatment

Both teriparatide and romosozumab treatment results in dramatically improved BMD primarily in the spine, but also in the hip. When treatment with teriparatide is completed, the BMD starts to decline.[118] However, with a switch to bisphosphonates, the antifracture efficacy can be maintained and the BMD even improved.[119] Should teriparatide be used as a "rescue"-treatment, i.e. after failing with anti-resorptive, the BMD increase will not be as rapid or great, especially apparent at the hip, as for treatment naïve patients.[120] Thus, the optimal treatment regime appears to be starting with a bone builder and then continue with an anti-resorptive drug.[69,121]

1.7.6 Future treatments

All current osteoporosis medications in use today have been approved after rigorous randomized placebo-controlled trials with fracture outcomes. However, requiring fracture outcomes requires the studies to be large, time consuming and expensive. Since changes in BMD, especially at the hip, correspond well to risk of hip and vertebral fracture, BMD measurements might be allowed as a proxy and sufficient for future drug approval which would reduce the cost and time to market for any new osteoporosis medications.[122]

1.8 Fracture liaison services

Despite the existence of many different and efficient treatment alternatives, there is an extensive underdiagnosis and undertreatment of osteoporosis. In the US, the chance of receiving osteoporosis medication after sustaining a hip fracture has declined rapidly from 40.2% in 2002 to 20.5% in 2011.[123] In a recent large population based study from Sweden, only 22% of elderly women eligible for treatment according to national guidelines actually received treatment.[124] Previous fracture is a strong risk factors and many patients suffer a first fracture every year.[50] Therefore, secondary prevention programs, so called Fracture Liaison Services (FLS), are increasingly present world-wide.[125] By identifying patients at risk and intervening after a first fracture, the objective is to prevent subsequent fractures. In a systematic review, FLSs were classified according to their organizational approach based on intensity of patient detection and intervention.[126] Type A is the most comprehensive model in which the FLS encompasses risk assessment, DXA examination and

treatment initiation. Type B starts as type A with risk assessment and DXA examination, but sends a treatment recommendation to the patient's general practitioner. Type C only informs the patient's general practitioner of the fracture. Type D solely informs the patient. The success in terms of patients being investigated by DXA and receiving osteoporosis medication after a fracture is best for a Type A service (Table 1).

FLS model	DXA measurement			Treatment rate		
	# studies	Intervention	Control	# studies	Intervention	Control
Type A	5	79.4%	23.8%	8	46.4%	17.9%
Type B	7	59.5%	9.2%	5	40.6%	19.9%
Type C	9	43.4%	13.5%	7	23.4%	7.5%
Type D				1	8.0%	11.4%

Table 1 Type of Fracture Liaison Service and effectiveness

There is insufficient evidence regarding the effect of different FLS types when risk of new fractures is the investigated outcome. Existing studies on recurrent fracture are small, have short follow-up time or are at high risk of various biases.[126-130] Still, the importance of FLSs is starting to receive national recognition. In order to increase and improve implementation of FLSs, the National Board of Health and Welfare in Sweden has recently assigned it a top priority,[84] and health economy estimates in the US and the UK have demonstrated that FLSs are cost effective.[131,132]

A key role in an FLS is the coordinator, selecting patients and managing the patient flow between clinical evaluation and treatment facilities.[133] However, the additional funds to finance this process is frequently not available. No evidence regarding the efficacy of an FLS without a coordinator, introduced with minimal organizational changes, is available.

2 Aim

The general aim of this thesis was to study aspects of fracture prevention, specifically through the study of organizational change with fracture liaison services and targeting specific groups at high risk of fracture with alendronate treatment.

The specific aims for each included paper were:

1. To investigate if a minimal effort FLS was associated with increased investigation and medical treatment in a large cohort of men and women with fracture.

2. To investigate if FLS implementation was associated with reduced risk of recurrent fracture, using data from four hospitals in Western Sweden, two with FLSs and two without.

3. To investigate whether alendronate prescribed to older patients (≥80 years) with prior fracture was related to a reduced risk of hip fracture and sustained safety in a large cohort of older men and women.

4. To investigate whether alendronate prescribed to patients treated with oral prednisolone was associated with reduced risk of hip fracture in a large cohort of older men and women.

3 Methods

3.1 Data sources

All studies were retrospective cohort studies based on health registers or hospital health record data. In the first two studies, electronic hospital records from local and regional databases were used. The third and fourth studies used data emanating from national health registers. Senior Alert provided information on clinical characteristics such as body composition (weight and height) food and liquid intake and mental status.[134] The Swedish Patient Register included both inpatient and outpatient visits with information regarding comorbidities, fractures and fall injuries.[135] Medication data were retrieved from the Swedish Prescribed Drug Register,[136] and data on migration and death was collected from Statistics Sweden. All Swedes are given a unique personal identification at birth or at the time of immigration, which enables linkage between the different registers.

3.2 Ethical considerations

The ethical considerations entail personal integrity and data protection. All data was anonymized. When presenting the results, all results were presented on group level making it impossible to identify a specific individual. The anonymized data was kept at the universities locked computers ensuring no unauthorized access. All studies were approved by the regional ethical review board in Gothenburg.[137]

3.3 Study designs

Studies are traditionally ranked according to type and corresponding levels of evidence.[138] Level one, highest level of evidence, is randomized control trials (RCT), i.e. the participants are randomized to intervention or not. Preferably, the study is double blinded, meaning neither the study participant nor the responsible doctor knows about the group selection. Ideally, there will be no differences between the two groups other than the intervention. Level two includes cohort studies, retrospective (analysis of historic data) and prospective (different patient groups are followed over time). For retrospective studies, the challenge is to understand if findings are due to group differences or to the intervention. Level three includes case-control studies, i.e. a kind of exploratory study of a certain feature where differences between two groups with and without a specific feature (e.g. smoking) are analyzed. Level four and

five represent the lowest level of evidence, case studies and expert opinions respectively.

All four included papers here are retrospective cohort studies. In the first two papers (I and II), we studied patients 50 years or older with a major osteoporotic fracture. Patients in FLS hospitals were compared to historic controls (I and II) and to patients at non-FLS hospitals (II). In paper I, the primary outcomes were DXA examination and treatment initiation and secondary outcomes included fracture and death, although the study was not powered to investigate these outcomes adequately. In paper II, the primary outcome was recurrent fracture and secondary outcomes included treatment rates, non-skeletal fall injuries and death. In paper III and IV, patients with alendronate were compared to patients without. Paper III focused on patients 80 years or older with a previous fracture whereas paper IV focused on patients 65 years or older with current prednisolone treatment. The primary outcome in both papers III and IV was hip fracture. Secondary outcomes were major osteoporotic fracture, any fracture, non-vertebral fracture (only IV), death and known possible side effects from alendronate (mild gastro-intestinal symptoms, peptic ulcers and femoral shaft fractures). See Table 2 for a summary of study designs and outcomes.

	Paper			
	I	II	III	IV
Data source	Local hospital data	Regional hospital data	Senior Alert	Senior Alert
Study population	Patients ≥ 50 years with a fracture	Patients ≥ 50 years with a fracture	Patients ≥ 80 years with a fracture	Patients ≥ 65 years with prednisolone
Baseline	Fracture date	Fracture date	Date of inclusion in register	Date of inclusion in register
Case group	FLS period 2013-2014	Two FLS hospitals	Alendronate treatment	Alendronate treatment
Controls	Historic controls (2011-2012), same hospital	Both historic controls from same hospitals and other non-FLS hospitals	Propensity score matched patients without osteoporosis medication	Propensity score matched patients without osteoporosis medication
Primary outcome	DXA and treatment	MOF	Hip fracture	Hip fracture
Secondary outcomes	Recurrent fracture, death	Hip fracture, Treatment, fall injury, death	MOF, any fracture, adverse events, death	MOF, any /non-vertebral fractures, adverse events, death

Table 2. Summary of study designs and outcomes for the four papers

3.4 Variable definitions

The variable definitions were mainly the same in all four papers. Apart from skull and malignant fractures, all fracture diagnoses from hospital visits were collected using codes for the 10th revision of the International Classification of Diseases (ICD-10 codes). In order to exclude fracture diagnoses from revisits, the fracture data was refined. First, fracture diagnoses occurring together with code indicating a revisit (Z09, Z47, Z48) were discarded. Second, hip fracture diagnoses (S720-S722) without a code for surgical procedure (NFB, NFC or NFJ) were also discarded. Third, we used a washout period of five months, i.e. if a fracture diagnosis on the same skeletal site was repeated within five months, we excluded the latter diagnosis. The washout period length was defined by comparing a subset of the fracture diagnosis identified in the study presented in paper I to x-ray verified data in order to maximize accuracy. After this refinement, hip, major osteoporotic, non-vertebral and any fracture was defined. We defined a non-skeletal fall injury as a fall (W00-W19) on the same occasion as an injury (S00-T14). The fall had to occur at an occasion without a fracture diagnosis, in order to avoid overlap between the variables. Charlson

comorbidity index is strongly associated to the risk of death and was used in order to summarize comorbidity.[139] Prescription data was in most cases used to calculate repeated (more than one prescription) and recent (less than 90 days since last prescription was collected) treatment.

3.5 Statistics

Most of the statistical methods used in the papers are the same. However, during the progression of papers, the statistical methods have evolved and been refined. Below is a summary of all the statistics used followed by how it was implemented in each paper.

Group differences should be investigated using Fisher's exact test on categorical variables, Chi-square tests if multiple categories and t-tests for continuous variables if normally distributed; otherwise with the Mann-Whitney U-test. P-values less than 0.05 were considered significant. In large cohorts, a very small clinically negligent difference between groups could be significant, although not relevant. Therefore, using standardized difference is an option for quantifying group differences expressed as mean difference in terms of number of standard deviations:

$$standardized\ difference = \frac{mean_1 - mean_2}{\sqrt{\frac{SD_1^2 + SD_2^2}{2}}}$$

Incident rates and incident rate differences per 1000 person-years can be calculated in order to compare incidences during periods of different lengths. Incident rates do not distinguish between events occurring early from events occurring late during the follow-up. Yet, an early event reflects a higher risk than a late event during the same follow-up. To account for such differences, Cox regression models were used. Cox regression assumes proportional hazards during the follow up, which can be verified either visually or by using a time-dependent Cox model with a linear interaction term between time and group variable. Interaction terms can be added in a regular Cox model as well, together with the two potentially interacting variables, to investigate possible present interactions. For interaction terms, p-values lower than 0.10 were considered significant. See Table 3 for an overview of statistical methods used in the four papers.

	Paper			
	I	II	III	IV
Fisher			x	x
Chi-2	x		x	
T-test	x		x	x
Mann-Whitney U-test				x
Standardized difference		x		x
Incident rates		x		x
Incident rates differences				x

Table 3. Overview of statistical methods used in the four papers

3.6 Bias considerations

Due to the inherent study design, it is impossible to establish causality using register studies. The biggest challenge when comparing two groups in register studies, is the selection bias, i.e. systematic reasons for the group allocation to be unbalanced. To mitigate and minimize the risk of selection bias and other biases, we used a number of strategies.

3.6.1 Intention to treat

In papers I and II, we did not study the patients with fracture who actually were included in the FLS. We studied all those who were supposed to have been included, regardless if they were eventually included in an FLS or not, resembling an intention to treat approach, thereby avoiding any potential selection bias. There still might be differences between the groups, which is why we adjusted the analyses for baseline characteristics involving fracture risk and comorbidity.

3.6.2 Temporal bias

If there is a general trend in society reducing or increasing the risk of fracture, one needs to make sure that inclusion time (calendar year) does not affect the associations studied. In paper II, we investigated the secular trend of recurrent fracture in the two non-FLS hospitals as well as adjusted for index year in the main analysis.

3.6.3 Propensity score matching

In papers III and IV, we had sufficient numbers of potential controls, to select controls with similar baseline characteristics as the case groups. This was accomplished with propensity score matching. Ideally when matching, each control should only differ from its case by the variable being studied. However, that would require a near infinite number of possible controls to find suitable matches for every case. Instead, propensity score aims at finding a balance of means (or proportions) between the two groups. In the first step, logistic regression is performed with the group variable as outcome. For each variable describing the group, a beta value is calculated representing the tendency, or propensity, for that variable to affect group selection. In the second step, for each case or control, the propensity score is calculated as a sum of all the beta values (β_k) multiplied with the corresponding prevalence (x_k) for each variable.

$$Propensity\ score = \beta_1 \bullet x_1 + \beta_2 \bullet x_2 + \beta_3 \bullet x_3 + \ \ldots \ + \beta_n \bullet x_n$$

By doing this, instead of having dozens of variables to consider, the third step only needs to find the control closest to the case in terms of propensity score. We used the MatchIt package in R to perform propensity score matching.[140]

3.6.4 Multivariable adjustment

All four papers included analyses with multivariable adjustment. In theory, this excludes the influence of the adjustment variables on the outcome and any remaining association should be due to the group difference investigated. A limitation is of course the selection of variables. Differences between the groups not reflected in the variables selected, will not be accounted for. Furthermore, a linear relationship between the adjustment variables and the outcome is assumed by the statistical program (SPSS), and any other type of relationship would lead to sub-optimal adjustment. We selected variables with three different purposes: descriptive for the specific research question, representing general comorbidity or associated to fracture risk.

3.6.5 Healthy adherer effect

In spite of performing propensity score matching and adjusting the statistical models for baseline characteristics, there still might be some undocumented and unaccounted differences between the groups being compared. The healthy adherer effect was discovered in randomized trials when placebo patients were found to have mortality benefits.[141] Thus, the patients adhering to medicine, are likely more motivated patients with better health than the non-adherers. In order to check for this potential imbalance in the investigated groups, paper III included a persistence analysis of acetylsalicylic acid, a common medication

available in both the alendronate and non-alendronate group. This served as an extra verification that the groups were balanced in terms of comorbidity and that there was no healthy adherer effect.

3.6.6 Competing risk of mortality

In study populations with a high mortality rate, it is important to account for the competing risk of death. In short, death impedes the occurrence of the event of interest, possibly affecting the result. There are several different remedies. One is to just estimate if a difference in mortality rate would cause an over- or underestimation of the result. Another is using Fine-Gray competing-risk regression.[142] While Cox regression, focuses on the survival function, competing-risks regression focuses on the cumulative incidence function indicating the probability of the event of interest occurring before a given time. The result achieved is a sub-hazard ratio which is somewhat difficult to interpret intuitively, and even harder to explain, but can nevertheless be a useful complement to survival analysis.

3.6.7 Other subgroup and sensitivity analyses

In paper I, we investigated the subgroup of hip fracture patients 80 years or older. We expected strong associations between the FLS and receiving treatment after fracture in this subgroup since these patients followed a special track in the FLS with parental treatment at home. In paper II we investigated the risk of non-skeletal fall-injury. Since pharmaceutical treatment was the primary mediator of the FLS-effect, absence of association to non-skeletal fall injuries was expected. In papers III and IV, we analyzed not only alendronate treatment (yes/no) but also treatment duration and mean possession ratio in association to fracture outcomes.

4 Results

4.1 Paper I

In the first study, we found that implementation of a minimal resource FLS increased the proportion of DXA-investigated patients after fracture from 7.6% to 39.6% ($p<0.001$) and the treatment rate after fracture from 12.6% to 31.8%. This result is comparable to FLS types using the conventional coordinator-based model. The possible effect on recurrent fracture was not possible to evaluate in this study due to the relatively small number of included patients and short follow-up time. In fact, when reviewing the available literature, including the study presented in paper I, and assuming maximum effect from treatment, a normal delay in treatment initiation, we concluded that none of the previous studies reporting refracture effects were sufficiently powered.

4.2 Paper II

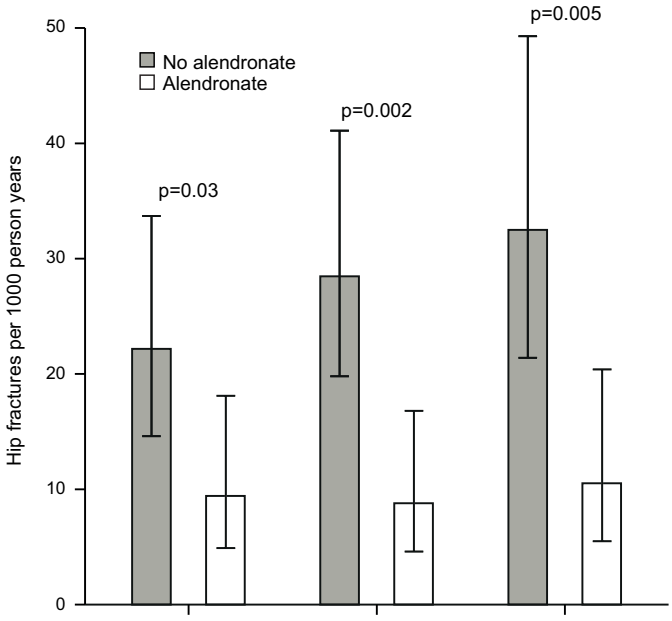
In this subsequent and much more comprehensive FLS study, additional years of follow-up became available from the first FLS cohort (paper I) and the possibility to include additional hospitals in the analysis arose, which enabled sufficient statistical power to study risk of recurrent fracture as the primary outcome. We found that FLS implementation in two of the hospitals in the region was associated with an 18% reduced risk of recurrent fracture. We compared the risk both with historic controls and with controls in non-FLS hospitals over the same time period. We could control for and report a large number of different baseline characteristics. Sensitivity analysis on fall-injury showed no difference in risk of fall injury between FLS and non-FLS patients, indicating that the association was due to increased osteoporosis medication, and not due to selection bias. Possible temporal trends were also investigated but not observed in the non-FLS hospitals. Given that the known efficacy of osteoporosis medication is to reduce the risk of hip and vertebral fractures by 40-50% and nonvertebral fractures by approximately 20-25%,[76] the expected risk reduction of 18% observed in patients included in the FLS periods was probable, considering that only a fraction of identified patients were prescribed treatment.

4.3 Paper III

In this study, alendronate prescribed to older patients (≥80 years) with prior fracture was associated with reduced risk of hip fracture by 38% with sustained safety, in terms of expected adverse events and mortality, compared to propensity score matched controls, with similar risk factors and comorbidities. Sensitivity analyses on treatment duration and mean accumulative dose of alendronate supported the main result. The use of propensity score matching as well as multivariable adjustment was used to minimize the risk of selection bias. Equal adherence in the groups to the commonly used drug acetylsalicylic acid, indicated that the analysis was not affected by healthy adherer bias. Alendronate use was associated with lower risk of hip fractures and to a lesser extent with other fracture types, such as major osteoporotic fracture and any fracture. As expected, a 58% increased risk of mild upper gastro-intestinal symptoms, a known alendronate caused side effect, was observed in the alendronate group.

4.4 Paper IV

In this study, it was concluded that alendronate prescribed to patients 65 years or older treated with oral prednisolone was associated with a 65% reduction in hip fracture risk. We excluded patients with other glucocorticoids and required recent and sufficiently long and high dosage of oral glucocorticoids. We defined alendronate users similarly. Sensitivity analyses on alendronate treatment duration and dose supported the main findings. Analyses per tertile of prednisolone dose revealed that the incidence of hip fracture among prednisolone patients with alendronate, was equally low in all three tertiles, while the hip fracture incidence among prednisolone patients without alendronate increased dramatically per tertile of prednisolone dose (Figure 5).



Cumulative prednisolone dose			
median (IQR), g	5.5 (3.8-7.5)	12.5 (10.8-14)	20.1 (17.5-24.8)
Number of patients	1196	1208	1200
No. hip fractures (alendronate users)	9	9	9
No. hip fractures (non-users)	22	29	22
Unadjusted Cox HR (95% CI)	0.43 (0.20-0.93)	0.31 (0.15-0.65)	0.33 (0.15-0.72)
30 months ARR (95% CI)	3.6 (1.8-5.3)	5.5 (3.5-7.4)	4.9 (3.1-6.8)
30 months NNT(95% CI)	28 (19-56)	18 (14-28)	20 (15-32)

Figure 5. Hip fracture incidence per tertile of prednisolone dos, with and without alendronate

5 Discussion

This thesis indicates that organizational change through fracture liaison services and alendronate treatment to specific risk groups can effectively prevent fractures. Paper I demonstrated that implementation of minimal resource fracture liaison service increased the rate of investigation and treatment and paper II showed that implementation of FLS also reduced the risk of recurrent fracture by 18%. Both studies were large and extensive information on risk factors and comorbidities allowed meticulous consideration of confounding factors. Paper III revealed that alendronate treatment to patients 80 years or older was associated with a 38% reduced risk of hip fracture. Paper IV found that alendronate treatment to prednisolone patients 65 years or older was associated with a 65% reduced risk of hip fracture. Both paper III and IV included multivariable propensity score matching and several sensitivity analyses to address potential sources of bias.

Both paper I and II had a "intention to treat"-design. This means we included all patients who fulfilled the criteria for the FLS in the analyses, regardless if they were actually subjected to the FLS or not. This design is an important strength, limiting the risk of selection bias.

One important weakness in paper I is the relatively short follow-up. Due to a restricted budget, the minimal resource FLS distributed the referral power to approximately 30 secretaries as described in paper I. While this was an easy way to start, it might eventually cause problems. It is possible that the absence of a coordinator making individual considerations in the long term will result in unnecessary DXA referrals, worse adherence to DXA examination, longer waiting periods and an inefficient use of the DXA resource. This was not investigated in the studies, but the apparent decline in treatment rates in 2016 presented in paper II could be a sign of this. Therefore, the long-term effectiveness of a minimal resource fracture liaison services has not been established in this thesis.

Only 22% of older women eligible for osteoporosis treatment according to Swedish guidelines are actually receiving treatment.[124] While the guidelines differ slightly, the proportions in other countries are similar.[143,144] One reason for these low treatment rates might be lack of evidence in specific groups with comorbidities potentially making clinicians question if treatment is appropriate. Paper III and IV address the associations between alendronate treatment and fracture risk in two specific risk groups; elderly patients and

patients with prednisolone. With better evidence of indicated efficacy, treatment rates might improve.

All four papers are limited by being retrospective register studies which per design are not able to establish causality. However, it is not possible to answer the four research questions using randomized studies since the effect of osteoporosis medications is well known, and a placebo group would therefore not be an ethically viable option. And the use of the entire population as the sample is also a strength, since there is no selection bias.[145]

One important treatment barrier is fear of potential side effects, both among patients but also among prescribing doctors. Per-oral bisphosphonates are often associated with gastrointestinal events, especially among elderly.[146] Even though there are parenteral alternatives, peroral bisphosphonates are often the first line of treatment. Furthermore, all antiresorptive medications are associated with rare, but serious adverse effects such as atypical femur fractures and osteonecrosis of the jaw.[72] Atypical femoral fractures are subtrochanteric transverse minimal comminuted shaft fractures with focal lateral cortical thickening occurring after minimal trauma.[147] While the absolute risk is low (3-50 per 100.000 person-years) among bisphosphonate users, it is increased among long-term users (~100 per 100.000 person-years) and has raised skepticism regarding bisphosphonate treatment. In a large register-study, assuming all femoral shaft fractures and subtrochanteric fractures were atypical (definitely not true), bisphosphonates still prevented more hip fractures and demonstrated a very favorable risk benefit ratios, even for long term users.[148] The risk of atypical femur fracture appears to be most pronounced among Asians and during the first years after cessation.[149] Osteonecrosis of the jaw, i.e. exposed bone that does not heal within 8 weeks, occurs in approximately 1% of the oncology patients treated with antiresorptive medications, but in the osteoporosis patient it is only slightly higher than what is observed in the general population (<0.001%).[150] Yet, in spite of the low absolute risk and the clearly very positive benefit to risk ratio, fear of this side effect has probably contributed to the declining prescription rates in the US.[151] Other barriers for treatment include financial concerns, but also lack of information and personal motivation.[152,153]

Interestingly, bisphosphonates appear to be associated to several other positive effects as well. A role for bisphosphonates as adjuvant treatment of malignant tumors were presented more than 20 years ago.[154] Now, bisphosphonates are routinely prescribed to breast cancer patients with skeletal metastases in order to prevent or delay further metastases and improve pain control.[155] There is even some evidence of efficacy in a primary prevention setting where

zoledronic acid given to osteopenic healthy patients reduced the overall risk of cancer, however, cancer was not the primary endpoint.[156] Bisphosphonates might also have positive effects on the cardiovascular system. A systematic review of randomized studies showed that while no effect on cardiovascular events was seen, bisphosphonates reduce arterial wall calcification and reduce all-cause mortality in both osteoporosis and cancer patients.[157] Hence, there are indicative evidence of bisphosphonate use conferring a lower risk of cardiovascular disease and cancer resulting in reduced mortality, but possibly more extensive and larger studies will be presented.[158] Hopefully, more conclusive evidence of any additional potential positive effects would attract as much attention as the negative and balance the view on osteoporosis medication.

Naturally, this aim of this thesis is not to solve the mystery of underdiagnosis and undertreatment of osteoporosis. However, by illustrating potentially important specific benefits of fracture liaison services and treatment of high-risk groups, the thesis will hopefully contribute to promotion of fracture liaison services, and increased osteoporosis treatment, which could result in fewer fractures and reduced suffering for the affected patients.

In conclusion, secondary prevention through fracture liaison services increases the chance for a patient of being investigated and receiving treatment as well as it reduces the risk of recurrent fractures. Among elderly patients and oral prednisolone users, two groups with elevated fracture risk, alendronate treatment is associated with reduced risk of hip fracture with sustained safety.

6 Future perspectives

In the early days of fracture prevention, there was a discussion on shifting the BMD distribution of the entire population through lifestyle changes, but it was discarded as inefficient as opposed to pharmaceutical treatment to high risk individuals.[159] While the current guidelines for fracture prevention differ slightly over the world, a common denominator is pharmaceutical treatment focusing on high risk individuals and/or secondary prevention. However, this might be about to change. Primary prevention through screening of risk factors using FRAX was recently found to be associated with a reduction of refractures[160] and the relevance of an osteoporosis diagnosis for treatment decision is being questioned.[161] Since the majority of all fractures do not occur in osteoporotic patients,[47,162-164] treating osteopenic patients as well might have a great societal impact in preventing fractures. Furthermore, the emergence of sequential treatment will probably be key in the next decade in order to reduce the life-time risk of fractures.[121]

From a research perspective, there are a number of questions suitable for further epidemiology research. When new non-osteoporosis drugs are developed and approved, the trials are seldom large enough or designed to register adverse fracture events. Thus, register studies can fill an important role in investigating fracture safety after the introduction of new drugs. Furthermore, there are a number of conditions, (e.g. Parkinsson's disease, recent stroke, and heart failure) in which the efficacy of osteoporosis treatment is insufficiently studied.[165] Since many clinicians fear polypharmacy among the elderly with high morbidity,[166,167] they might find specific evidence for the efficacy and safety of osteoporosis medication in specific risk groups reassuring.[168]

Thus, this research field offers a number of important and relevant clinical challenges and research questions to address.

Related publications not included in the thesis

1. Wallander M, **Axelsson K F**, Nilsson A G, Lundh D, and Lorentzon M. Type 2 Diabetes and Risk of Hip Fractures and Non-Skeletal Fall Injuries in the Elderly: A Study From the Fractures and Fall Injuries in the Elderly Cohort (FRAILCO). J Bone Miner Res, **2017**. 32(3): p. 449-460.
2. **Axelsson K F**, Werling M, Eliasson B, Szabo E, Näslund I, Wedel H, Lundh D, Lorentzon M. Fracture Risk After Gastric Bypass Surgery: A Retrospective Cohort Study. J Bone Miner Res, **2018**. 33(12): p. 2122-2131.
3. Wallander M, **Axelsson K F**, Lundh D, Lorentzon M. Patients with prostate cancer and androgen deprivation therapy have increased risk of fractures-a study from the fractures and fall injuries in the elderly cohort (FRAILCO). Osteoporos Int, **2019**. 30(1): p. 115-125.
4. Larsson B A M, Sundh D, Mellström D, **Axelsson K F**, Nilsson A G, Lorentzon M. Association Between Cortical Bone Microstructure and Statin Use in Older Women. J Clin Endocrinol Metab, **2019**. 104(2): p. 250-257.
5. Larsson B A M, Johansson L, Johansson H, **Axelsson K F**, Harvey N, Vandenput L, McCloskey E, Liu E, Kanis J A, Sundh D, Lorentzon M. The Timed Up and Go test predicts fracture risk in older women independently of clinical risk factors and bone mineral density. Accepted October 9th, **2020**.
6. **Axelsson K F**, Litsne H, and Lorentzon M. Fractures and Fall Injuries after Hospitalization for Seasonal Influenza - a National Retrospective Cohort Study. Submitted **2020**.

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