The phenotype and outcome of patients with a recent fracture at the Fracture Liaison Service

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Colofon

ISBN: 9789090377964

Cover design and layout: © evelienjagtman.com
Production: Gildeprint

The work described in this thesis was supported by the Stichting De Weijerhorst.
The printing of this thesis was financially supported by Maastricht University.

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Pamela Habibović
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 22 november 2023 om 13.00 uur

door

Lisanne Vranken

Promotoren
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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Burden of fractures

Fractures constitute a major public health concern. In 2000, an estimated 9 million fractures occurred worldwide, of which 1.6 million were hip fractures, 1.4 million clinical vertebral fractures and 1.7 million forearm fractures.[1] Fracture rates are highest in the Caucasian population, and approximately one-third of all fractures occur in Europe.[2] The annual incidence of fragility fractures, *i.e.*, fracture occurring after a fall or lesser trauma, will double between 2010 and 2040 mainly due to aging of the world population.[2] At the age of 50 years, the remaining lifetime risk of fractures is reported to be approximately 50% for women and 20% for men.[3-5]

In The Netherlands, approximately 120,000 fractures occur annually in patients aged 50 years or older.[6,7] Of all registered fractures in The Netherlands, 32% was attributed to osteoporosis, resulting in an incidence of osteoporosis-related fractures of 1018 per 100,000 for women and 260 per 100,000 for men. It has been estimated that between 2010 and 2030 the incidence of osteoporosis-related fractures will increase by 40%, and the related costs by 50%.[6]

Fractures, especially hip and vertebral fractures, but also non-hip, non-vertebral fractures, are associated with increased morbidity and have a substantial impact on patients' quality of life.[8-10] Fractures diminish patients' quality of life as much or even more than diabetes mellitus, arthritis and lung disease.[11] Further, many patients do not return to their pre-fracture performance status.[9,12]

A fracture indicates an increased risk of subsequent fractures. Within 5 years after a fracture, 19-24% of women and 13-20% of men sustain a subsequent fracture.[13,14] Fractures are associated with a 2-fold increased subsequent fracture risk.[15] However, approximately 41% of all subsequent fractures in women and 52% of all fractures in men occur within two years after the index fracture.[16] Therefore, subsequent fracture risk is not constant over time, but is highest immediately after a fracture [16-18], and this short-term high risk is referred to as imminent fracture risk.[17,19,20] Subsequent fractures contribute substantially to the overall fracture burden. After the age of 40 years, 40% of low-trauma fractures in women and 24% in men are subsequent fractures.[21]

Fractures after the age of 60 years have been associated with excess mortality in women and men.[22,23] Patients with a fracture have a 2-fold increased mortality risk compared to those without a fracture.[23-25] Mortality risk has been reported to be increased following all fractures across all ages, except for minor fractures for which increased mortality was only apparent for those older than 75 years.[23] Increased mortality risk persists for 5 years for all fractures and up to 10 years for hip fractures [23], but is highest in the first year after the fracture.[14] It remains unclear

what drives the fracture-mortality association. Some suggest the association is related to underlying health and comorbidities [26,27], whereas other found little or no evidence for this.[24,28]

As subsequent fracture and mortality risk are highest immediately after a fracture, patients with a recent fracture need to be assessed and when needed treated as soon as possible after the fracture.[29]

Fracture Liaison Service

Since effective treatment of osteoporosis is available, several guidelines recommend secondary fracture prevention in all men and women aged 50+ years who recently sustained a clinical fracture.[29–34] Nevertheless, the majority of patients presenting with a fracture do not receive appropriate assessment and treatment.[35,36] In order to increase the number of patients receiving appropriate fracture risk evaluation and treatment, and to reduce subsequent fractures and mortality, a service to facilitate case finding of patients aged 50+ years with a low-trauma fracture in order to provide routine assessment and, if indicated, treatment for osteoporosis, was designed and implemented in 1999 in Glasgow, called: Fracture Liaison Service (FLS).[37]

The FLS has been identified as the most successful organizational approach for secondary fracture prevention in patients aged 50+ years with a recent fracture by working groups of the American Society for Bone and Mineral Research (ASBMR), the International Osteoporosis Foundation (IOF), and the European League Against Rheumatism (EULAR)/European Federation of National Associations of Orthopedics and Traumatology (EFFORT).[29,33,34] The effectiveness of the implementation of a FLS in terms of subsequent fracture as well as mortality reduction has been summarized in several reviews [38–41], showing variable impact on subsequent fracture risk and mortality risk. In a recently published meta-analysis, FLS care was associated with a lower subsequent fracture risk in the overall comparison as well as in the post- versus pre-FLS comparison.[41] Further, FLS care was associated with a reduced mortality risk in the post- versus pre-FLS studies, but not in the overall comparison.[41] However, previous FLS studies varied in study design (*i.e.*, before and after the implementation of a FLS in the same hospital (post- versus pre-FLS), and between hospitals with and without a FLS), study population (*i.e.*, proportion of women, and index fractures included), and length of follow-up, and were of varying quality. Furthermore, in most of the FLS studies, the competing risk of mortality was not taken into account when analyzing subsequent fractures risk.

A 5-step procedure that could be implemented in FLS care has been proposed (see Figure 1).[42] As a 1st step, all patients aged 50+ years with a recent fracture should be identified and invited to the FLS for fracture risk evaluation and treatment. The 2nd

step includes a detailed evaluation of medical history, medication use, clinical risk factors, vitamin D status, dietary calcium intake, known contributors to secondary osteoporosis and metabolic bone diseases (SECOB) and fall risk should be performed, in addition to assessment of bone mineral density (BMD), and vertebral fracture assessment (VFA). In the 3th step, patients need to be further evaluated for undiagnosed contributors to SECOB. The 4th step, includes a multifactorial intervention, including lifestyle management recommendations, calcium and vitamin D supplementation as required, treatment of contributors to SECOB, and anti-osteoporosis treatment according to national guidelines. In the 5th and last step, adequate follow-up should be organized, checking treatment adherence and response, and adverse events, as well as new contributors to SECOB, falls and fractures.

Osteoporosis and bone mineral density

Osteoporosis is defined as a systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[43] This definition, developed by international consensus in 1993, captures the effect on bone mass and microarchitecture, and the clinical outcome fractures. Diagnostic criteria were developed in 1994 by the World Health Organization (WHO), based on areal bone mineral density (aBMD) measurements.[44] Dual-energy X-ray absorptiometry (DXA) is the most widely used bone densitometric technique. aBMD is preferentially measured at the lumbar spine, total hip and femoral neck, and converted to a T-score. The T-score is the number of standard deviations by which the aBMD in an individual differs from the mean value expected in young healthy women.[44] A patient is diagnosed with osteoporosis when the T-score is equal to or below -2.5, with osteopenia when the T-score lies between -1.0 and -2.5, and has a normal BMD when the T-score is equal to or higher than -1.0.

aBMD measured by DXA has its limitations. DXA scanners generate two-dimensional images of complex three-dimensional structures, and report aBMD as the quotient of the bone mineral content divided by the bone area. Consequently, a large bone will give a higher aBMD, but may in fact have the same bone density as a smaller bone. Further, DXA does not distinguish between cortical and trabecular components, which may contribute differently to bone strength and resistance to fracture. DXA-measured aBMD accounts for about two-thirds of the variance of bone strength, meaning that some important features of bone quality are not captured by DXA.[45]

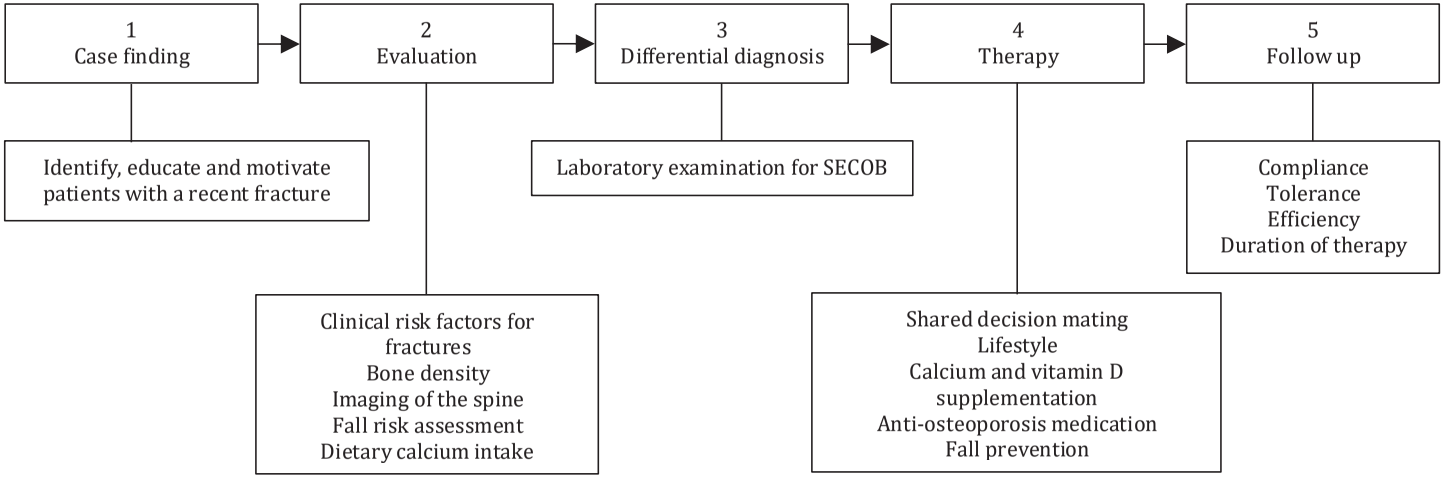

Figure 1. Secondary fracture prevention in patients aged 50 years or older: a five-step approach.[31]

The majority of patients with an age of 50 years and older, who sustained a fracture had an aBMD in the non-osteoporotic range.[46,47] Approximately 70% of patients with a fracture have an aBMD above the threshold for osteoporosis.[47,48] So, when fracture risk evaluation is only based on BMD measurements, many patients are classified incorrectly as having a low fracture risk. New technologies, such as high-resolution peripheral quantitative computed tomography (HR-pQCT) – described in more detail further on – can non-invasively determine volumetric BMD (vBMD), bone micro-architecture, and calculated bone strength.

Prevalent vertebral fractures and vertebral fracture assessment

Vertebral fractures are the most common osteoporotic fractures.[49–51] However, the majority of vertebral fractures occur without acute symptoms, and consequently do not come to medical attention and remain undiagnosed.[52] Vertebral fractures can be diagnosed on X-rays, DXA, computed tomography (CT) and magnetic resonance imaging (MRI), and imaging analysis for the presence of vertebral fractures is referred to as vertebral fracture assessment (VFA). DXA-VFA has the advantage of low radiation exposure and allows BMD measurement in the same session. Various methods can be used to determine the presence and severity of prevalent vertebral fractures. The most frequently used method is the semi-quantitative method according to Genant.[53] Vertebral fractures are assessed by visual determination of the degree of vertebral height loss and morphological changes, and are differentiated from other, non-fracture deformities, such as Scheuermann's disease or Schmorl's nodes. Height loss of 20-24%, 25-39% and ≥40% are classified as mild (grade 1), moderate (grade 2) and severe (grade 3) vertebral fractures, respectively.

In patients with a recent non-vertebral fracture, prevalent vertebral fractures are more common in those with more severe fractures, multiple fractures, and osteoporosis.[54,55] However, in a more recent study performed at 2 FLSs in the Netherlands, there was no difference in the prevalence of VFs between patients with a normal BMD, osteopenia or osteoporosis and no difference between various index fractures.[56] Moderate to severe vertebral fractures, even when asymptomatic, are predictors for subsequent vertebral and non-vertebral fractures.[57–60] The presence, number and severity of vertebral fractures have been associated with vertebral and non-vertebral fractures, independent of BMD.[54,59–62]

According to the Dutch guideline 'Osteoporosis and fracture prevention' released in 2011 [30], it is recommended to perform a systematic evaluation of the presence of prevalent vertebral fractures in patients with a non-vertebral facture and a T-score ≤ -1.0, and to start anti-osteoporosis treatment in patients with osteopenia and a vertebral fracture grade ≥ 2. By recommending anti-

osteoporosis treatment in osteopenic patients with a vertebral fracture, at the FLS the percentage of patients eligible for treatment increased by a quarter, from 31.0% in a pre-guideline to 38.4% in a post-guideline cohort.[56]

Increased fracture risk may be caused by factors not captured by aBMD, such as bone micro-architecture and bone strength. Compared to fracture-free controls, patients with prevalent vertebral fractures had an impaired bone micro-architecture.[63-66] Whether prevalent vertebral fractures are associated with impaired bone micro-architecture in the presence of a recent non-vertebral fracture remains to be evaluated.

Bone micro-architecture and strength, and High-Resolution peripheral Quantitative Computed Tomography

Bone consists of two compartments; cortical and trabecular bone, and these compartments have different micro-architectural properties. Cortical bone forms the compact outer layer of the bone and provides mechanical strength, while trabecular bone is located within the cortex and provides structural support as well as elasticity. Bone micro-architecture can be evaluated using high-resolution peripheral quantitative tomography (HR-pQCT). HR-pQCT has emerged as a non-invasive imaging modality with an isotropic voxel size of 82 µm (XtremeCT; XCT, Scanco Medical, Bruttisellen, Switzerland) or 61 µm (XtremeCT II; XCT II, Scanco Medical), which allows for assessment of volumetric bone density and bone microarchitecture of cortical and trabecular bone compartments.[67] Additionally, HR-pQCT images can be used in micro-finite element analyses (mFEA) to calculate bone strength indices.[68]

Previous cross-sectional studies have shown that, compared to fracture-free controls, patients with vertebral fractures have significantly impaired bone micro-architecture in the distal radius and tibia after adjustment for aBMD in the spine or hip.[63-65] Stein *et al*. reported a significantly greater deterioration of bone micro-architecture in the tibia, but not the radius in women with a vertebral fracture compared to those with a non-vertebral fracture.[65] Further, two previously published studies reported more deterioration of bone micro-architecture with increasing severity of prevalent vertebral fractures in women [63,64], whereas one study found no association between severity of prevalent vertebral fractures and HR-pQCT parameters after adjustments for aBMD.[66] Whether there is an association between the presence and severity of prevalent vertebral fractures and HR-pQCT parameters in patients with a recent non-vertebral fracture is unknown.

Comorbidities and medications

Comorbidities are prevalent in patients with a recent fracture, especially in those with a hip or vertebral fracture.[69-72] In hip fracture patients, 54% had 2 or more comorbidities [69], and 35% had 4 or more comorbidities.[70] In patients with a vertebral fracture, all patients had one comorbidity, and 75% of men and 78% of women had

more than 5 comorbidities.[72] The most common reported comorbidities in fracture patients are osteoarthritis, hypertension and cardiovascular disease.[71,73] Various comorbidities and medications contribute to increased bone loss or bone fragility or fall risk and consequently an increased risk of fracture.[74] If these contributors are not diagnosed and managed properly, fracture prevention may be suboptimal.

Guidelines advocate the careful evaluation of medical history and medication use, and laboratory test to identify contributors to osteoporosis and fractures in patients with osteoporosis. A distinction can be made between previously diagnosed (known) and newly diagnosed contributors to secondary osteoporosis and metabolic bone disease (SECOB). Previously diagnosed contributors to SECOB were identified in 23.0% of patients with a recent fracture at a FLS, and newly diagnosed contributors (excluding vitamin D deficiency) in 26.5% of these patients.[75] Additionally, more than 90% of these patients had a vitamin D deficiency (<50 nmol/l) and/or inadequate dietary calcium intake (<1,200 mg/day).[75] Interestingly, the presence of SECOB contributors was established in individuals of any age (over 50 years old) and gender, and across all BMDs and fracture types.[75] However, the prevalence of comorbidities and medication use associated with increased fall and fracture risk in patients' medical history and medication overview has not been systematically evaluated in FLS patients.

Celiac disease

Celiac disease (CD) is an autoimmune enteropathy induced by dietary proteins in wheat, rye, and barley. Symptoms vary widely resulting in a broad clinical presentation of CD. Classical CD presents with signs and symptoms of malabsorption. Besides malabsorption, other symptoms, such as diarrhea, steatorrhea, weight loss, or growth failure are required for diagnosing CD.[76] In the past, mainly malnourished children were diagnosed with CD, but now many patients are diagnosed later in life. Atypical presentations and subclinical CD in adults are increasingly recognized and represent a clinical challenge.[77,78]

Celiac disease is a known risk factor for osteoporosis and fractures, with a RR of 1.3-1.9 for fractures.[79–81] Appropriate treatment of CD relieves symptoms and can improve BMD.[82–84] However, even well-treated CD patients may have a lower BMD and more frequent fractures compared to healthy controls.[85,86]

The worldwide prevalence of CD based on serologic tests is reported to be 1.4% and of biopsy-proven CD 0.7%.[87] Rostami *et al.* reported a prevalence of biopsy-proven CD of 3 per 1,000 persons in a Dutch population of healthy blood donors.[88] In a population with a low BMD, the estimated prevalence of asymptomatic CD is 2-3%.[89] A meta-analysis showed a prevalence of biopsy-proven CD of 1.6% in osteoporotic patients.[90] The prevalence of CD has not been evaluated in patients aged 50+ years with a recent fracture attending the FLS. We hypothesized that CD would be more prevalent in a FLS population than in the general population.

Cardiovascular disease

Osteoporosis and cardiovascular disease (CVD) are both important causes of morbidity and mortality in older men and women. These conditions frequently occur in the same individual. CVD in a patient's medical history has important clinical consequences for osteoporosis and fracture treatment. For example, raloxifene is contraindicated in postmenopausal women with a history of or an increased risk for venous thromboembolic events (VTE).[91,92] Also, the recently new available osteoanabolic drug romosozumab is contraindicated in patients with a recent history of cardiovascular disease.[93,94] Further, nonsteroidal anti-inflammatory drugs (NSAIDs), prescribed for pain management, are contraindicated in patients with CVD or at risk of CVD, including those with hypertension, heart failure, and diabetes mellitus.[91,95]

Epidemiological studies indicate an association between CVD and osteoporosis. Low BMD is associated with more severe or advanced vascular calcifications.[96–99] Further, patients with a low BMD are at increased risk for new cardiovascular disease.[100,101] Conversely, in patients with CVD, bone loss and fracture risk were increased.[102–107] The prevalence of CVD has not been systematically studied in patients with a recent fracture at the FLS.

Falls

A fall is defined as an unintentional change in position resulting in coming to rest on the ground or at a lower level.[108] In community-dwelling individuals aged 70+ years, approximately 30% sustain at least one fall and 15% two or more falls during 1-year follow-up.[109–111] The consequences of a fall can be severe: approximately 20% need medical attention, 5% sustain a fracture, and 5-10% incur another injury, such as severe head injury, joint distortions or dislocations, or soft-tissue contusions or lacerations.[112–116] Conversely, up to 90% of all fractures were caused by a fall.[117,118]

Systematic reviews and meta-analyses show that at least 15% of falls in older people can be prevented, with individual trials reporting reductions of up to 50%.[119,120] Preventing falls is important, but the ultimate question is whether it also prevents fractures. Some studies reported that fall prevention in older individuals also reduces the numbers of fractures.[121–127] In addition, a meta-analysis of studies of interventions to prevent falls showed that the relative risk of injurious falls could be reduced by the same amount as falls alone (35%).[128] However, all these findings are preliminary and a large randomized controlled trial is needed to determine the effect of fall prevention on (subsequent) fractures.

Falls are an important risk factor for fractures, independent of age and BMD.[129–131] Patients who reported a fall in the previous year had a 6-fold increased risk of fractures in the previous year as compared to those without a fall.[132] Compared to women without osteoporosis and without a fall, women with osteoporosis without a

fall have an age- and BMI-adjusted fracture risk of 2.8, and women with osteoporosis and a fall have an adjusted-fracture risk of 24.8.[132] Guidelines on osteoporosis and fracture prevention recommend fall prevention in patients aged 50+ years with a recent fracture.[29,33,34,133,134] However, studies reporting falls in a FLS population are scarce, and it is not well known to what extent the imminent subsequent fracture risk after an index fracture can be attributed to incident falls.

AIMS AND OUTLINE OF THIS THESIS

In this thesis we aimed to study the phenotype and the outcome of patients aged 50+ years with a recent fracture at the FLS.

In the **first part (Chapter 2-6)** of this thesis we focused on the phenotype of patients at the FLS. In **Chapter 2**, we performed a literature survey on the phenotype of patients with a recent fracture at the FLS. In **Chapter 3**, we studied the comorbidities and medications associated with increased fracture risk in FLS patients. In **Chapter 4**, we focused on the prevalence of celiac disease in patients attending the FLS. In **Chapter 5**, the prevalence of cardiovascular risk factors was evaluated in patients with a recent fracture at the FLS. In **Chapter 6**, we studied the association between prevalent vertebral fractures and bone quality of the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture at the FLS.

In the **second part (Chapter 7-8)** of this thesis we focused on outcome of patients at the FLS. In **Chapter 7**, we evaluated the impact of FLS care on the 3-year risk of subsequent fractures and mortality of patients with a recent clinical fracture. In **Chapter 8** we studied the association between incident falls and subsequent fracture risk in patients attending the FLS.

Chapter 9 comprises a summary of the main results of this thesis. Finally, in **Chapter 10**, we provide a general discussion of our findings, including future perspectives for clinical practice and research.

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PART I

PHENOTYPE OF PATIENTS AT THE FLS

CHAPTER 2

THE PHENOTYPE OF PATIENTS WITH A RECENT FRACTURE: A LITERATURE SURVEY OF THE FRACTURE LIAISON SERVICE

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Calcif Tissue Int. 2017; 101(3):248-258

ABSTRACT

The etiology of fractures in patients aged 50 years and older is multifactorial, and includes bone- and fall-related risks. The Fracture Liaison Service (FLS) is recommended to identify patients with a recent fracture and to evaluate their subsequent fracture risk, in order to take measures to decrease the risk of subsequent fractures in patients with a high-risk phenotype. A literature survey was conducted to describe components of the bone- and fall-related phenotype of patients attending the FLS. Components of the patient phenotype at the FLS have been reported in 33 studies. Patient selection varied widely in terms of patient identification, selection, and FLS attendance. Consequently, there was a high variability in FLS patient characteristics, such as mean age (64–80 years), proportion of men (13–30%), and fracture locations (2–51% hip, <1–41% vertebral, and 49–95% non-hip, non-vertebral fractures). The studies also varied in the risk evaluation performed. When reported, there was a highly variability in the percentage of patients with osteoporosis (12–54%), prevalent vertebral fractures (20–57%), newly diagnosed contributors to secondary osteoporosis and metabolic bone disorders (3–70%), and fall-related risk factors (60–84%). In FLS literature, we found a high variability in patient selection and risk evaluation, resulting in a highly variable phenotype. In order to specify the bone- and fall related phenotypes at the FLS, systematic studies on the presence and combinations of these risks are needed.

INTRODUCTION

Fractures constitute a major health care concern worldwide, as 50% of women and 20% of men at the age of 50 years will sustain a fracture during their remaining lifetime.[1,2] Since the world population is ageing, the annual number of fractures is expected to increase from 3.5 million in 2010 to 4.5 million in 2025, corresponding to an increase of 28%.[3]

Fractures indicate an increased risk of subsequent fractures and premature mortality.[4-7] Current guidelines recommend secondary fracture risk evaluation in all men and women aged 50 years and older with a recent clinical fracture.[8-11] However, many fracture patients were not offered appropriate secondary fracture prevention, resulting in a care gap throughout the world.[12]

Fracture Liaison Services (FLS) have been designed and implemented to diminish the care gap.[13] The key components and objectives of a FLS are multiple. Firstly, case finding by systematic identification and selection of fracture patients. Second, to adequately evaluate subsequent fracture risk using clinical risk factors for fractures and falls, dual-energy X-ray absorptiometry (DXA) and imaging of the spine for detection of previously unknown vertebral fractures. Third, analysis for eventual underlying secondary osteoporosis and metabolic bone disorders. Fourth, adequate treatment in patients at high risk, and fifth, development of a follow-up program.[14]

Unfortunately, FLS are currently established in a small proportion of facilities that receive fracture patients worldwide.[15] The International Osteoporosis Foundation (IOF), American Society for Bone and Mineral Research (ASMBR), European League Against Rheumatism (EULAR), and European Federation of National Associations of Orthopaedics and Traumatology (EFORT) support the implementation of FLS as they identify this as the most successful approach for secondary fracture prevention.[11,15-18] In this literature survey, we investigate what has been published on components of the bone- and fall-related risk factor phenotype in patient attending the FLS.

METHODS

A literature search was conducted in PubMed/Medline, EMBASE and CINAHL to identify relevant publications up to and including October 2016 using the following search terms: Fracture Liaison Service, fracture prevention service, fracture prevention clinic, fracture prevention program, osteoporosis clinic, and secondary fracture prevention. The search was limited to human studies in adults (18-64 years) and aged (≥65 years) written in English. We specifically selected articles which reported components of the phenotype of patients at the FLS. Finally, additional relevant publications known to us were added.

RESULTS

Search results

After removing duplicates, our search resulted in 373 potentially relevant publications. Based on title and abstract screening, 270 publications were excluded. Based on full-text eligibility assessment, 80 publications were excluded, resulting in 23 being selected. The reasons for exclusion were no FLS population (n=40), and no components of the phenotype reported (n=40). In addition, manual searches through the reference lists were performed, resulting in 10 additional publications. In total, 33 publications were included in this literature review (Table 1).

Patient selection procedure

The patient selection procedure can comprise up to three steps: 1) the identification and selection of patients with a recent clinical fracture for evaluation at the FLS, 2) the patients' response to the FLS invitation (*i.e.*, the proportion of patients willing and able to attend the FLS), and optionally 3) the selection of a subgroup of FLS attenders to be included in the publication.

Identification and selection of patients for evaluation at the FLS

Patient identification and selection differed markedly across studies (Table 1 and Figure 1). Twenty-nine studies identified and selected in- and outpatients [13,19-46], two studies selected only inpatients [47,48], and two did not report this aspect of patient identification and selection.[49,50] With respect to age, 26 studies identified and selected patients age 50 years or older.[13,19-42,48] Five studies used other age criteria, namely patients aged 45 years and older [43,49], patients aged 75 years and older [44], or those who were postmenopausal.[45,46] In two studies, no age criterion was used.[47,50] Thirty-one studies identified and selected both men and women [13,19-44,47-50], whereas two studies selected only postmenopausal women.[45,46] Patients with any fracture were identified and selected in 31 studies [13,19-41,43-47,49,50], whereas only patients with a non-vertebral fracture were selected in 2 studies.[42,48]

Various additional exclusion criteria were used, such as high energy trauma fractures, pathological fractures and cognitive impairment. The total number of patients identified and selected for evaluation at the FLS was reported in 18 (55%) of 33 studies (Figure 1) [13,19-25,30,33-36,38,43,44,47,49], and ranged from 156 to 3057 patients (Table 1).

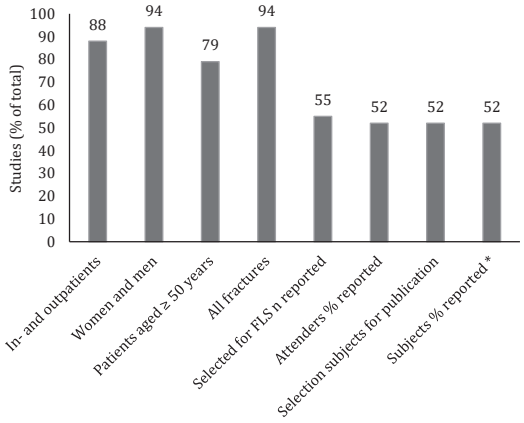

Figure 1. Percentage of studies reporting aspects of patient selection. * Subjects as percentage of patients selected for evaluation at the FLS.

Attendance

Selected patients were informed personally or through an information letter, except for the study by Fraser *et al.* [21], in which a letter was sent to the general practitioner informing them of the fragility fracture and invited referral to the fracture prevention clinic. In 17 (52%) of the 33 studies (Figure 1), 20-89% of the patients selected for evaluation at the FLS actually attended the FLS (Table 1 and Figure 2).[19-25,33-36,38,43,44,47,49,51]

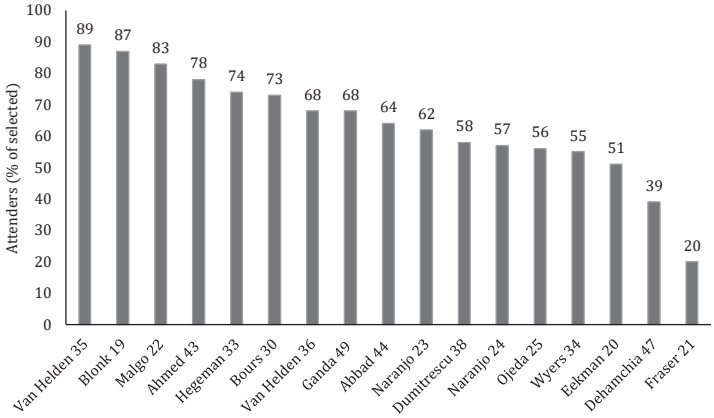

Figure 2. Patients attending the FLS as percentage of patients selected for evaluation at the FLS, reported in 17 studies.

Table 1. Patient selection procedure and number of identified patients, selected patients, attenders, and included attenders

Author	Country	Year	Patient identification and selection for FLS evaluation				
			IP/OP	Gender	Age	Fracture	Additional criteria[a]
Patient selection for FLS evaluation conform recommendations, all FLS attenders selected for publication (n=12)							
McLellan [13]	GBR	2003	IP+OP	F+M	50+	All	1
Blonk [19]	NLD	2007	IP+OP	F+M	50+	All	1, 2, 5
Eekman [20]	NLD	2014	IP+OP	F+M	50+	All	1, 9
Fraser [21]	AUS	2016	IP+OP	F+M	50+	All	1
Malgo [22]	NLD	2016	IP+OP	F+M	50+	All	2, 3, 5, 6, 7
Naranjo [23]	ESP	2014	IP+OP	F+M	50+	All	1, 2, 6
Naranjo [24]	ESP	2015	IP+OP	F+M	50+	All	1, 2, 6
Ojeda [25]	ESP	2010	IP+OP	F+M	50+	All	1, 2, 6
Woltman [26]	NLD	2010	IP+OP	F+M	50+	All	1,2
Ong [27]	GBR	2014	IP+OP	F+M	50+	All	1
Van den Berg [28]	NLD	2014	IP+OP	F+M	50+	All	8
Huntjens [29]	NLD	2011	IP+OP	F+M	50+	All	1, 2, 5
Patient selection for FLS evaluation conform recommendations, subgroup of FLS attenders selected for publication (n=12)							
Bours [30]	NLD	2011	IP+OP	F+M	50+	All	1, 2, 3
De Klerk [31]	NLD	2012	IP+OP	F+M	50+	All	1, 2, 5
De Klerk [32]	NLD	2013	IP+OP	F+M	50+	All	
Hegeman [33]	NLD	2004	IP+OP	F+M	50+	All	1, 5
Wyers [34]	NLD	2014	IP+OP	F+M	50+	All	1, 2, 3
Van Helden [35]	NLD	2008	IP+OP	F+M	50+	All	2, 8, 9
Van Helden [36]	NLD	2007	IP+OP	F+M	50+	All	2, 5, 8, 9
Langridge [37]	GBR	2007	IP+OP	F+M	50+	All	1
Dumitrescu [38]	NLD	2008	IP+OP	F+M	50+	All	2, 8
Gallacher [39]	GBR	2007	IP+OP	F+M	50+	All	1
Howat [40]	GBR	2007	IP+OP	F+M	50+	All	1
Gallacher [41]	GBR	2005	IP+OP	F+M	50+	All	1
Patient selection not conform recommendations (n=9)							
Huntjens [42]	NLD	2013	IP+OP	F+M	50+	NVF	2, 9
Ahmed [43]	IRL	2012	IP+OP	F+M	45+	All	1
Abbad [44]	FRA	2016	IP+OP	F+M	75+	All	1
Premaor [45]	GBR	2010	IP+OP	F	PM	All	1
Premaor [46]	GBR	2010	IP+OP	F	PM	All	1

	Selected patients n	**Attenders** n (%)	**Selection for publication**[b]	**Subjects**[c] n (%)	**Subjects**[d] %
	4671				
	1,220	1,058 (87)		1,058 (100)	87
	2,207	1,116 (51)		1,116 (100)	51
	841	166 (20)		166 (100)	20
	856	709 (83)		709 (100)	83
	532	330 (62)		330 (100)	62
	1,324	759 (57)		759 (100)	57
	683	380 (56)		380 (100)	56
		523		523 (100)	
		4,288		4,288 (100)	
		1,898		1,898 (100)	
		7,199		7,199 (100)	
	893	656 (73)	A	626 (95)	70
		194	A	176 (91)	
		541	A	499 (92)	
	156	116 (74)	A	100 (86)	64
	3,057	1,694 (55)	A	1,359 (80)	44
	797	708 (89)	A	568 (80)	71
	425	288 (68)	A, B	277 (96)	65
			A	2,489	
	1,013	590 (58)	A, D	100 (17)	10
			A, E	337	
			E	577	
			D, E	50	
		834		834 (100)	
	158	124 (78)		124 (100)	78
	176	110 (64)		110 (100)	64
		1,641		1,641 (100)	
		1,641	F	1,005 (61)	

Table 1. Continued

Author	Country	Year	Patient identification and selection for FLS evaluation				
			IP/OP	Gender	Age	Fracture	Additional criteria[a]
Dehamchia [47]	FRA	2014	IP	F+M	No limit	All	1, 5, 8, 9
Nassar [48]	FRA	2014	IP	F+M	50+	NVF	1, 2, 5
Ganda [49]	AUS	2015	NR	F+M	45+	All	1, 2, 4, 10
Beringer [50]	GBR	2006	NR	F+M	No limit	All	1

[a] 1: High energetic trauma, 2: Pathological fracture, 3: Periprosthetic fracture, 4: Metabolic bone disorder, 5: Cognitive impairment, 6: Poor medical status/severe functional disability, 7: Patients who had osteoporosis screening in another hospital, 8: Already on osteoporosis treatment, 9: Patients residing outside the hospital's postal area, 10: Nursing home or hostel residence.

[b] A: All assessments completed, B: Follow-up data, C: Patients aged ≥65 years, D: Patients with osteoporosis, E: Patients with non-vertebral fracture, F; Patients aged <75 years, G: Pregnant women (n=1), patients with primary hyperparathyroidism (n=2), H: Non-hip fracture patients.

FLS attenders included in the publication

Of the 33 studies, 16 (48%) included all FLS attenders [13,19-29,42-45], whereas 17 (52%) included a subgroup of the attenders (Figure 1): patients aged <75 years [46], patients aged 65 years or older [37], patients diagnosed with osteoporosis [38,41], patients who completed all assessments [30-36,38,39,48,50], and those of whom follow-up data were available.[36,49] In 12 of the 17 studies that included a subgroup, the study population was composed of 20-99% of patients attending the FLS (Table 1).[30-34,36,38,46-49] Seventeen (52%) of the 33 studies reported patients included in the study as percentage of those selected for evaluation at the FLS (Figure 1). As a result of patient identification and selection, and study inclusion criteria, the study population was composed of 10-87% of those selected for evaluation at the FLS (Table 1 and Figure 3).

Components of the phenotype

Age and gender

In 29 of the 31 studies in which both men and women were included, the proportion of men ranged from 13 to 30% (Table 2).[19-36,38-44,47-50] As shown in Table 2, 25 of those 31 studies reported mean age, ranging from 64 to 80 years.[19-27,29,31-38,41,42,44,47-50] Mean age was also reported separately for men and women, ranging from 63 to 70 years in men [28,30,34,35,40,43,50] and from 62 to 77 years in women (Table 2).[28,30,34,35,40,43,45,46,50] The proportion of patients aged 50-59, 60-69, 70-79, and ≥80 years were, respectively, 33-35%, 32-35%, 23-27%, and 6-9%.[19,34] In both men and women, mean age was highest in hip fracture patients.[40]

Selected patients n	Attenders n (%)	Selection for publication[b]	Subjects[c] n (%)	Subjects[d] %
872	338 (39)	G	335 (99)	38
	528	A	362 (69)	
828	560 (68)	B	234 (42)	28
		A, H	86	

[c] Presented as % of FLS attenders.

[d] Presented as % of patients selected for FLS evaluation.

Abbreviations: FLS, Fracture Liaison Service; IP, inpatients; OP, outpatients; F, female; M, male; PM, postmenopausal; NVF, non-vertebral fracture

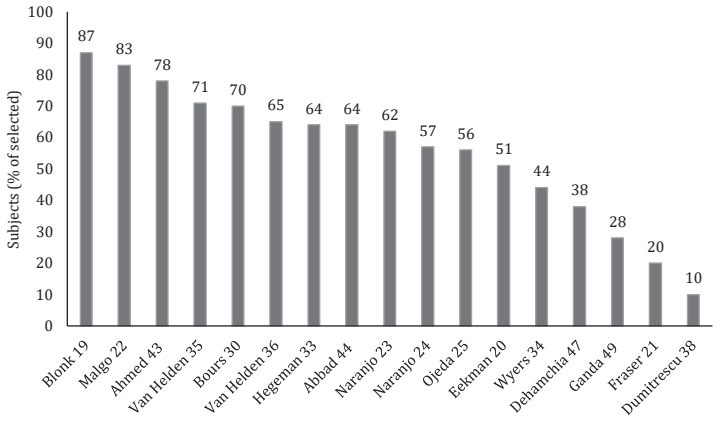

Figure 3. Patients selected for publication (subjects) as percentage of patients selected for evaluation at the FLS, reported in 17 studies.

Table 2. Reported components of the FLS patients' phenotype

Author	**Age,** mean	**Men,** %	**Fracture location**			**BMI,** mean
			Hip, %	**Clinical VF,** %	**NV/NH,** %	
IP+OP, F+M, 50+, all Fx						
McLellan [13]						
Blonk [19]	64	24	9	5	86	27
Eekman [20]	68	22				
Fraser [21]	70	14	8	10	82	
Malgo [22]	67	27	9	6	85	
Naranjo [23]	71	23	22	6	72	
Naranjo [24]	72	22	26			
Ojeda [25]	70	13	19	8	73	29
Woltman [26]	73	21	23	2	75	
Ong [27]	66	17				
Van den Berg [28]		20				
Huntjens [29]	67	23	6			
Bours [30]		23				
De Klerk [31]	67	21	8	13	79	28
De Klerk [32]	66	22				
Hegeman [33]	67	26	11	3	86	25
Wyers [34]	65	28	8			26
Van Helden [35]	67	28	13	3	84	
Range	64-73	13-28	6-26	2-13	72-86	25-29
IP+OP, F+M, 50+, NVF						
Gallacher [39]		23	5	Excluded	95	24
Howat [40]		21	13	Excluded	87	
Huntjens [42]	67	27		Excluded		
Range	67	21-27	5-13	Excluded	87-95	24
IP+OP, F+M, all Fx, various ages						
Langridge [37]	78		28			
Ahmed [43]		19	2	3	95	
Abbad [44]	80	21	45			
Miscellaneous						
Van Helden [36]	67	28				
Dumitrescu [38]	68	27	17	4	79	
Gallacher [41]	66	24	26	Excluded	74	
Premaor [45]		Excluded	6	<1	94	27
Premaor [46]		Excluded	10	<1	90	27

Table 2. Continued

Author	**Age,** mean	**Men,** %	**Fracture location**			**BMI,** mean
			Hip, %	**Clinical VF,** %	**NV/NH,** %	
Dehamchia [47]	67	25	28			
Nassar [48]	74	13	51	Excluded	49	24
Ganda [49]	65	20				
Beringer [50]	65	30	Excluded	41	59	
Range overall	64-80	13-30	2-51	<1-41	49-95	24-29

Abbreviations: IP, inpatient; OP, outpatient; F, female; M, male; NVF, non-vertebral fracture; Fx, fracture; VF, vertebral fracture; NV/NH, non-vertebral/non-hip; BMI, body mass index.

Fracture location

In 23 of the 32 studies that included hip fracture patients, the percentage of patients that had a hip fracture ranged from 2 to 51% (Table 2).[19,21-26,29,31,33-35,37-41,43-48] In 14 of the 28 studies that included patients with a clinical vertebral fracture, the percentage of patients with this fracture was reported, ranging from <1% to 41% (Table 2).[19,21-23,25,26,31,33,35,38,43,45,46,50] Most common were non-vertebral, non-hip (NVNH) fractures, of which the prevalence was reported in 18 of the 33 studies, ranging from 49 to 95% (Table 2).[19,21-23,25,26,31,33,35,38-41,43,45,46,48,50].Distal radius/ulna fractures were reported as the most common NVNH fracture (27-32%) [13,22,39,47], followed by humeral fractures (11-31%) [13,22,39,47], ankle fractures (11-16%) [13,22,39,47], and hand and foot fractures (6-16%).[13,39] Analyses for men and women separately showed that distal radius/ulna fractures were most common in women (21.8-38.7%), whereas hand (19.7%) [19], and ankle fractures [40] were most common in men. In 3 studies [29,30,34], fractures were classified according to Center *et al.*[6] Hip fractures were present in 1-8% of patients, major fractures in 13-33%, minor fractures in 58-79%, and finger or toe fractures in 1-13%.

Body mass index

Mean body mass index (BMI) was reported in 9 studies, ranging from 24 to 29 kg/m^2 (Table 2) [19,25,31,33,34,39,45,46,48], and was similar for men and women.[30,34] According to the World Health Organization (WHO) BMI classification, 2-6% of patients were classified as underweight (<18.50 kg/m^2), 31-33% had a normal BMI (18.50-24.99 kg/m^2), 35-38% were overweight (25.00-29.99 kg/m^2), and 26-30% were obese (≥30 kg/m^2).[27,39,46]

Bone mineral density

In all 33 studies, bone mineral density (BMD) measurement at the lumbar spine and hip was performed (Figure 4) [13,19-50], with additional measurements at the distal radius in one study.[33] Based on the lowest T-score, osteoporosis was diagnosed in 12-54% of patients in 22 studies [19,21-24,26,28-36,39,43-48], osteopenia was diagnosed in 29-

55% of patients in 18 studies [21-24,29-36,39,43-47], and 13-39% of patients had a normal BMD in 18 studies.[21-24,29-36,39,43-47] Osteoporosis was reported in 14-43% of women and in 6-28% of men.[13,28-30,32,34,35] Osteoporosis was most common in patients with a hip (36-63%) [13,19,29,48], and vertebral fracture [19], and least in patients with a foot, and clavicle fracture.[19] Classified according to Center *et al.* [6], osteoporosis was found in 31% of patients with a minor, in 49% of patients with a major, and in 58% of patients with a hip fracture.[30] Osteopenia was found in 49% of patients with a minor, in 39% of patients with a major, and in 42% of patients with a hip fracture.[30]

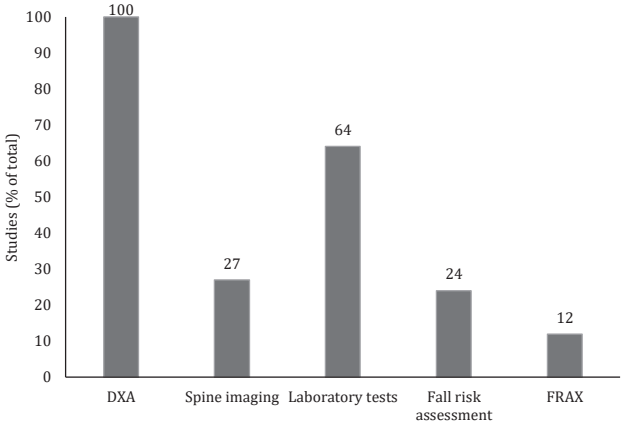

Figure 4. Percentage of studies reporting assessments for fracture risk evaluation.

Vertebral fracture assessment

Imaging of the spine was performed using densitometric vertebral fracture assessment (VFA) in four studies [38-40,48], and X-ray in five (Figure 4).[19,28,31,33,44] Classified according to Genant *et al.* [52], vertebral fractures (VF) were present in 20-57% of patients [31,33,38-40,44,48], with VF grade 2 or 3 in 55-73% of VF patients and 17-31% of all patients.[38, 39, 48] The prevalence of VF was similar for men (19-24%) and women (20-25%).[39,40] VF were present in 30% of non-vertebral fracture patients aged >75 years compared with 23% and 22% of patients aged 50-64 years and 65-75 years.[39] In contrast, Howat *et al.* [40] reported higher prevalence rates of VF with increasing age. The prevalence of VF varied by NVF location, with highest prevalence in hip fracture patients for both men (hip fractures 32% vs. ankle fractures 8%) and women (hip fractures 31% vs. humeral fractures 5%).[39, 40, 48] Patients with lumbar spine T-scores in the osteoporotic range were more likely to have VF (42%) than patients with T-scores in the osteopenic or normal range (20% and 16% respectively ($p<0.05$)).[39] Similar findings were reported for VF grade 2 or 3 (34% vs. 13% vs. 9% of patients with osteoporosis, osteopenia, and a normal BMD, respectively ($p<0.0001$)).[39]

Trabecular bone score

Only Nassar *et al.* [48] reported the trabecular bone score (TBS) in non-vertebral fracture patients at the FLS. Mean TBS was 1.201±0.113 and mean TBS was lower in patients with VFs than in those without VFs in VFA (1.156±0.108 vs. 1.227±0.107, p<0.0001).

Laboratory tests

Performance of laboratory test to investigate contributors to secondary osteoporosis and metabolic bone disorders (SECOB) was reported in 21 studies (Figure 4).[13,19-25,28-30,32-34,37-39,41,43,47,50] Two studies reported contributors to SECOB including vitamin D deficiency (<50 nmol/L), ranging from 50% to 70% [30,38], and three studies reported contributors to SECOB excluding vitamin D deficiency, ranging from 3% to 28% (Table 4).[22,30,32] The prevalence rates of contributors to SECOB were similar for men and women (28% vs. 26%) [30], were higher in patients with osteoporosis (33-35%) compared to 27-29% and 10-18% of those with osteopenia and a normal BMD, respectively [22,30] and were also higher in patients with more severe fractures according to Center.[23]

Four studies [21,38,41,50] reported mean vitamin D, ranging from 44-68 nmol/L and seven studies [22,30,33,38,41,43,50] reported vitamin D <50 nmol/L, ranging from 42% to 72% (Table 3). Mean vitamin D was lower in hip than in non-hip fractures patients (35 vs. 48 respectively, p=.019).[41] The prevalence of vitamin D <50 nmol/L was similar for men and women (62% vs. 53% respectively, p=.478) [50], for patients aged <75 years and those aged ≥75 years (53% vs. 61% respectively, p=.522) [50], and for patients with osteoporosis, osteopenia and a normal BMD (42% vs. 43% vs. 42% respectively).[22]

Daily calcium intake

Only three studies reported mean daily calcium intake [19,33,38], ranging from 759 to 912 mg/day, and two studies reported daily calcium intake <1200 mg/day, ranging from 86 to 91% of patients.[30,38] Daily calcium intake <1200 mg/day was similar for men and women, age decades, fracture location according to Center *et al.* [6], and patients with a normal BMD, osteopenia, and osteoporosis.[30]

Fracture risk assessment tools

FRAX score for major fractures was 8-13% in 4 studies, and for hip fractures 3-7% in 4 studies.[23-25,28] In 46-49% of patients, FRAX score for hip fractures was >3%.[23,24]

Fall-risk assessment

Fall-risk assessment was reported to be performed in 8 studies (Figure 4).[29,35-38,40,42,44] Only 4 studies [35,36,38,42] reported prevalence rates of fall-risk factors, with at least one fall-risk factor in 60-84% of patients (Table 3). All fall-risk factors were more frequently reported in women, with the exception of impaired vision, which was found in 25% of women and 31% of men.[35]

Table 3. Performance of assessments (DXA, VFA, laboratory tests, and fall risk assessment), and when reported, the results

Author	DXA	Normal BMD, %	Osteopenia, %	Osteoporosis, %	VFA	VF, Grade 1-3, %
IP+OP, F+M, 50+, all Fx						
Blonk [19]	+			37	+	
Van den Berg [28]	+			12	+	
Hegeman [33]	+	23	44	33	+	22
De Klerk [31]	+	35	38	27	+	42
Huntjens [29]	+	21	47	32	–	
McLellan [13]	+				–	
Eekman [20]	+				–	
Fraser [21]	+	19	45	36	–	
Malgo [22]	+	17	55	28	–	
Naranjo [23]	+	20	38	43	–	
Naranjo [24]	+	13	44	42	–	
Ojeda [25]	+				–	
Bours [30]	+	15	46	30	–	
De Klerk [32]	+	30	49	21	–	
Wyers [34]	+	23	48	30	–	
Van Helden [35]	+	21	44	35	–	
Woltman [26]	+			46	–	
Ong [27]	+				–	
Range		13-35	38-55	12-46		22-42
IP+OP, F+M, 50+, NVF						
Gallacher [39]	+	35	37	28	+	25
Howat [40]	+				+	20
Huntjens [42]	+				–	
Range		35	37	28		20-25
IP+OP, F+M, all Fx, various ages						
Abbad [44]	+	17	29	54	+	40
Langridge [37]	+				–	
Ahmed [43]	+	33	38	29	–	
Miscellaneous						
Dumitrescu [38]	+	Excluded	Excluded		+	57
Nassar [48]	+			52	+	37
Gallacher [41]	+	Excluded	Excluded		–	
Dehamchia [47]	+	19	45	36	–	

VF, Grade 2-3, %	Lab	SECOB, %	Vitamin D deficiency, %	Fall risk assessment	Fall risk, %
	+			-	
	+			-	
	+		69	-	
	-			-	
	+			+	80
	+			-	
	+			-	
	+			-	
	+	28	43	-	
	+			-	
	+			-	
	+			-	
	+	27[a], 70[b]	64	-	
	+	3/11[c]		-	
	+			-	
	-			+	75
	-			-	
	-			-	
		3-70	43-69		75-80
17	+			-	
	-			+	
	-			+	60
17					60
	-			+	
	+			+	
	+		64	-	
31	+	50[b]	62	+	79
21	-			-	
	+		72	-	
	+			-	

Table 3. Continued

Author	DXA	Normal BMD, %	Osteopenia, %	Osteoporosis, %	VFA	VF, Grade 1-3, %
Beringer [50]	+				–	
Van Helden [36]	+	24	47	29	–	
Premaor [45]	+	39	41	19	–	
Premaor [46]	+	39	41	19	–	
Ganda [49]	+				–	
Range Overall		13-39	29-55	12-54		20-57

Abbreviations: IP, inpatient; OP, outpatient; F, female; M, male; Fx, fracture; NVF, non-vertebral fracture; DXA, dual energy X-ray; BMD, bone mineral density; VFA, vertebral fracture assessment; VF, vertebral fracture; SECOB, secondary osteoporosis and metabolic bone disease.

DISCUSSION

This survey aimed to describe the bone- and fall-related components of the phenotype of patients attending the FLS based on 33 FLS related papers. The reported phenotypic characteristics varied widely among the various publications with regard to the mean age, proportion of men, and fracture location. In addition, the proportion of patients with osteoporosis, prevalent vertebral fractures, newly diagnosed contributors to secondary osteoporosis and metabolic bone disease, and proportion of patients with fall-related risk factors varied substantially across studies. Although, there is a great heterogeneity in components of the phenotype, the prevalence rates of these components were high.

The heterogeneity of reported phenotypes of FLS patients can be explained by several aspects. Firstly, the variability in the FLS patients' phenotype can be explained by differences in patient selection and FLS attendance. Positioning papers on secondary fracture prevention by the ASBMR, IOF, and EULAR/EFORT [11,15,18], recommended that all patients aged 50 years or older with a recent fracture should have their risk for subsequent fractures evaluated at the FLS. In three out of four studies, this recommendation was implemented successfully. Nine studies selected another group of patients for evaluation at the FLS based on different selection criteria (only inpatients, only women, only patients aged 75 years or older, only NVF patients). Additionally, various combinations of selection criteria were used, such as only low-trauma or fragility fracture patients, or excluded patients with pathological fractures. Further, FLS attendance rates ranged from 20 to 89%. This indicates that achieving adequate FLS patient selection and attendance is a major challenge and often hampered by logistic obstacles. It has been shown that FLS

VF, Grade 2-3, %	Lab	SECOB, %	Vitamin D deficiency, %	Fall risk assessment	Fall risk, %
	+		56	-	
	-			+	84
	-			-	
	-			-	
	-			-	
17-31		3-70	43-72		60-84

care with a central coordinator (often a specialized nurse) is the most appropriate clinical organization model for secondary fracture prevention.[11,15,18] Although capturing all fracture patients is the ultimate goal, it has been suggested that an FLS may initially focus on a subgroup.[15] Once secondary fracture prevention for these patients has been well-established, the scope of the FLS should be expended to eventually include all fracture patients. In addition, other approaches, such as an orthogeriatric service, may have been established in hospitals to systematically optimize care of hip fracture patients, including components covered by a FLS.[53] This type of service of course alters the phenotype of the patients attending the FLS. In our literature survey, all but 6 studies focused on all patients regardless of their fracture location. Of these 6 studies, one study [50] excluded hip fractures.

Second, as recommended in the positioning papers, risk evaluation should include dual-energy X-ray absorptiometry (DXA), and vertebral fracture assessment (VFA), and on indication, laboratory tests, and fall risk assessments.[18] DXA evaluation was performed in all studies, imaging of the spine in 9 studies, laboratory tests in 21 studies, and fall risk evaluation in 8 studies. Since these assessments often have to be justified through local business cases supported by solid health economic analysis, which are currently lacking, implementation of these assessments is not always feasible. Hence, the reported outcomes of the various bone- and fall-related components of FLS patients may be influenced not only by patients selection and attendance rates, but also by the possibility to perform additional assessments in all FLS patients.[53]

Based on these results in literature, it is difficult to describe the full spectrum of bone and fall risks in patients attending the FLS. In the context of fracture prevention, knowledge of the presence and combinations of the risk factors will

guide the need for evaluation and treatment. In this literature survey of FLS, we found a high variability in patient selection and fracture risk evaluation. In order to specify the bone- and fall-related phenotypes at the FLS, systematic studies on the presence and combinations of these risks are needed.

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CHAPTER 3

COMORBIDITIES AND MEDICATION USE IN PATIENTS WITH A RECENT CLINICAL FRACTURE AT THE FRACTURE LIAISON SERVICE

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Osteoporos Int. 2018;29(2):397-407

ABSTRACT

In this cross-sectional study, two-thirds of Fracture Liaison Service (FLS) patients had comorbidities and medications associated with increased bone- or fall-related fracture risk. Bone-related and fall-related fracture risk (BRR and FRR) were associated with age and fracture type, but not with gender or BMD. Systematic evaluation of these factors leads to a more profound assessment in FLS care.

Introduction: This study is a systematic evaluation of co-morbidities and medications associated with increased fracture risk in patients aged 50-90 years with a recent fracture visiting the FLS.

Methods: In this cross-sectional cohort study, comorbidities were classified according to the tenth revision of the International Classification of Disease (ICD-10) and medications according to the Anatomic Therapeutic Chemical (ATC) classification, and further categorized into those associated with BRR AND FRR.

Results: Of 1282 patients (72% women; 65±9 years), 53% had at least one BRR, 46% had at least one FRR, and 66% at least one BRR and/or FRR. At least one BRR, as well as at least one FRR were associated with age, BMI and fracture type, but not with gender or BMD. The proportion of patients with only BRR (±20%) or only FRR (±10%) was similar among ages, gender, BMI, fracture type and BMD. The combination of at least one BRR and at least one FRR was significantly associated with age, BMI and major fractures, but not with gender or BMD.

Conclusion: Comorbidities and medications associated with increased fracture risk are present in two-thirds of patients visiting the FLS. In addition, the proportion of patients having a combination of BRR and FRR increased significantly with age, BMI and fracture severity. This indicates that systematic evaluation of these factors is important for a more profound assessment of subsequent fracture risk in FLS care.

INTRODUCTION

Fractures constitute a major health concern, as the lifetime risk of a clinical fracture at the age of 50 years is 50% for women and 20% for men.[1,2] The annual number of fractures is expected to increase due to aging of the population.[3] It is well-documented that prior fractures in adulthood increase the risk of future fractures.[4-6] Prior fractures are associated with an approximately 2-fold increased relative risk (RR) for subsequent fractures.[6] Furthermore, the subsequent fracture risk is highest immediately after the fracture.[7] Hence, a fracture is an opportunity to prevent future fractures. Therefore, in current osteoporosis guidelines [8-12], secondary fracture prevention is recommended in all patients aged 50 years or older with a recent clinical fracture. The Fracture Liaison Service (FLS) has been identified as the most successful approach for secondary fracture prevention.[11-13]

Risk factors contributing to fracture are numerous and include factors with a deleterious effect on bone and that increase fall risk or both. Some of these risk factors are potentially modifiable. There are no studies that systematically evaluated all comorbidities and medication with an increased fracture risk in patients with a recent fracture. Systematic evaluation of comorbidities and medications could contribute to specify and quantify the presence of bone- and fall-related risk factors for fractures. In this study, we systematically evaluated comorbidities and medications with an increased fracture risk in patients aged 50-90 years with a recent clinical fracture visiting the FLS.

METHODS

Study design and population

A cross-sectional cohort study was conducted among women and men with a recent clinical vertebral or non-vertebral fracture who were evaluated at the FLS of the VieCuri Medical Center located in The Netherlands. Identified were all consecutive patients aged 50-90 years with a recent clinical fracture visiting the emergency department from January 2009 until June 2011. All fractures were radiologically confirmed. After fracture repair, a specialized nurse screened all patients and invited those eligible for fracture risk evaluation to the FLS. Patients with facial/skull and finger/toe fractures, metastatic cancer in bone, fracture due to high-energy trauma, osteomyelitis or failure of prosthesis were excluded. Those willing and able to be evaluated, visited the FLS approximately 3 to 4 months after the fracture event. According to the Dutch guideline for treatment of osteoporosis [8], patients received a detailed questionnaire for evaluation of risk factors for fractures and falls, including medical history and medication use. In addition bone

mineral density (BMD) measurement with dual-energy x-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck was performed, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease.[14] Laboratory tests included serum sodium, potassium, calcium, inorganic phosphate, albumin, creatinine, free tetra-iodothyronine (fT4), thyroid-stimulating hormone (TSH), serum aminotransferases (aspartate and alanine amino-transferase), alkaline phosphatase, intact plasma parathyroid hormone (iPTH), serum 25-hydroxyvitamin D (25(OH)D), and serum protein electrophoresis for all patients. At the FLS, a nurse measured height and weight and evaluated the questionnaire with special attention to medical history, medication use and calcium intake. Depending on the results of BMD measurements, 25(OH)D levels and calcium intake, patients were treated with calcium supplements, vitamin D supplements, and anti-osteoporosis medication according to the Dutch osteoporosis guideline.[8] Fractures were classified according to Center *et al.* [15] into hip fractures, major fractures (vertebra, multiple rib, humerus, pelvis, distal femur, and proximal tibia), and minor fractures (all remaining fractures except fingers and toes).

Bone Densitometry

BMD measurements were performed at the lumbar spine (LS; L1-L4), total hip (TH), and femoral neck (FN) using DXA (Hologic QDR 4500, Hologic, Bedford, MA, USA). According to the WHO criteria [16], patients were classified based on the lowest T-score in the LS, TH, and FN. T-scores of ≤ −2.5 standard deviations (SD) below the reference mean were classified as osteoporosis, T-scores between −1.0 and −2.5 SD were classified as osteopenia, and T-scores ≥ −1.0 SD were classified as normal.

Comorbidities

Chronic comorbidities in medical history and laboratory tests were classified according to the tenth revision of International Classification of Disease (ICD-10).[17] In current osteoporosis and fall guidelines [8-10,18-22], comorbidities with an increased bone- and fall-related (BRC and FRC) risk of fractures were identified (Table 1).

Medication use

Medications were classified according to the Anatomic Therapeutic Chemical (ATC) classification system.[23] In literature [24-27], medication with an increased bone- and fall-related (BRM and FRM) risk of fractures were identified (Table 1). Opiates were not included because we could not differentiate between those used chronically and those prescribed related to the recent fracture. Polypharmacy was defined as the use of at least 5 medications at ATC-3 level in which dermatological preparations and medication that was not used chronically were not counted in determining the number of medications.

Table 1. Bone- and fall-related comorbidities and medication.

Bone-related risk comorbidities (BRC)	**Fall-related risk comorbidities (FRC)**
Anorexia nervosa	Arrhythmia
Celiac disease	Arthritis
Chronic kidney disease (CKD)	Cerebrovascular accident (CVA)
Chronic obstructive pulmonary disease (COPD)	Cognitive impairment
Diabetes mellitus (DM)	Depression
Hemophilia	Diabetes mellitus (DM)
Hyperthyroidism	Dizziness
Hyperparathyroidism	Epilepsy
Hypogonadism	Incontinence
Inflammatory bowel disease (IBD)	Osteoarthritis
Leukemia	Parkinson's disease
Liver cirrhosis	Peripheral neuropathy
Lymphoma	Stroke
Malabsorption	Visual impairment
Monoclonal gammopathy of unknown significance (MGUS)	
Myeloma	
Rheumatoid arthritis (RA)	
Sarcoidosis	
Systemic lupus erythematosus (SLE)	
Bone-related risk medication (BRM)	**Fall-related risk medications (FRM)**
Anticonvulsants	Anti-arrhythmic drugs
Glucocorticoids, oral	Anti-Parkinson medication
Glucocorticoids, inhaled	Anti-psychotics
H2-receptor inhibitors	Barbiturates
Proton pump inhibitors (PPI)	Benzodiazepines
Thiazolidinediones	Hypnotics and sedatives
	Loop diuretics
	Nitrates
	Other antidepressants
	Selective serotonin reuptake inhibitors (SSRI)
	Thiazides
	Thiazide-like diuretics
	Tricyclic antidepressants (TCA)

Statistical Analysis

Results are presented as mean ± SD or percentages. Data were analyzed using the Chi-square tests and Fisher's exact tests. Subgroup analyses were performed for gender, age per decade, BMD (normal versus osteopenia versus osteoporosis), and fracture type (minor versus major versus hip). Logistic regression analyses were performed to adjust for age, gender, BMD (normal versus osteopenia versus osteoporosis), and fracture type (minor versus major versus hip). All analyses were performed using SPSS for Mac (version 21.0, IBM SPSS Statistics, USA). A p-value ≤0.05 was considered as statistically significant.

RESULTS

From January 2009 until June 2011, 3131 patients aged 50 years or older visited the emergency department with a recent clinical vertebral or non-vertebral fracture. Seventy-four patients were deceased before the invitation for fracture risk evaluation at the FLS was sent, resulting in 3057 patients being invited to the FLS (Figure 1). Of those, 1694 (55.4%) patients were willing and able to be evaluated. Included in this study were 1282 (41.9%) FLS patients (71.8% women and 28.2% men, mean age 65.0 ± 9.4 years) that were fully assessed. Characteristics of these patients are shown in Table 2. Osteoporosis was diagnosed in 30.3%, osteopenia in 47.4%, and 22.3% had a normal BMD. According to the classification by Center *et al.* [15], 8.4% sustained a hip fracture, 30.4% a major fracture, and 61.2% a minor fracture. According to BMI, 17% was obese (*i.e.,* BMI ≥ 30 kg/m^2). Previous fractures at 50+ years, previous falls in the last 12 months, and parental history of hip fractures were present in respectively 31.0%, 24.1% and 1.7% of patients.

Clinical risk factors

Previous fractures at or above the age of 50 years increased with increasing age (50-59 years: 21.6% vs. 60-69 years: 26.2% vs. 70-79 years: 40.0% vs. 80+ years: 56.9%, p=0.000) and decreasing BMD (normal BMD: 24.6% vs. osteopenia: 26.4% vs. osteoporosis 43.1%, p=0.000). Previous falls in the last 12 months also increased with increasing age (50-59 years: 25.5% vs. 60-69 years: 17.9% vs. 70-79 years: 24.6% vs. 80+ years: 41.1%, p=0.000) and decreasing BMD (normal BMD 22.7% vs. osteopenia 20.6% vs. osteoporosis 30.7%, p=0.004). A parental history of hip fractures was present in 1.7% of osteoporotic patients, 2.5% of osteopenic patients, and 0.0% of those with a normal BMD (p=0.043). There were no significant differences in prevalence rates of these risk factors by gender and fracture type.

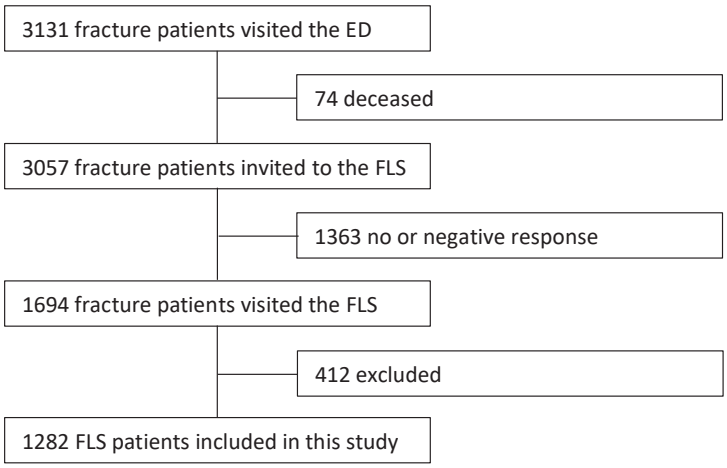


Figure 1. Selection procedure of patients with a fracture.

Abbreviations: ED, emergency department; FLS, Fracture Liaison Service.

ICD-10 comorbidities

As shown in Table 3, 81.0% of patients had at least one chronic ICD-10 comorbidity; 25.4% had 1, and 55.6% had multiple (up to 13). An overview of the proportion of patients with at least one chronic comorbidity per ICD-10 subgroups is presented in Supplemental table 1. The prevalence of at least one chronic ICD-10 comorbidity was similar for women and men, and among BMD categories, but increased with increasing BMI (obese: 89.6% vs. non-obese: 79.3%, p=0.001), increasing fracture severity (minor fractures: 78.4% vs. major fractures: 84.6% vs. hip fractures: 86.1%, p=0.015) and increasing age (72.8% of patients aged 50-59 years up to 89.5% of patients aged 80+ years, p<0.001) (Table 3). In multivariate regression analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI): 1.60 (1.35-1.90), p<0.001), and major fracture (OR (95% CI): 1.41 (1.02-1.96), p=0.040) were associated with at least one chronic ICD-10 comorbidity. After additional adjustments for BMI, age (1.46 (1.27-1.66), p<0.001) and BMI (1.09 (1.05-1.14), p<0.001) were associated with at least one chronic ICD-10 comorbidity, whereas fracture type was no longer associated.

ATC medication

The proportion of patients using medication was 68.1%. An overview of the proportion of patients using at least one medication per ATC medication subgroup is presented in Supplemental table 2. The proportion of patients using at least one medication was similar for women and men, and among BMD categories, but was higher in patients with major and hip fractures compared to those with minor fractures (74.4% vs. 74.1% vs. 64.2%, respectively, p=.001), and increased with increasing BMI (obese: 78.8% vs.

non-obese: 66.7, p=0.001) and increasing age (55.7% in patients aged 50-59 years up to 84.2% in patients aged 80+ years, p<0.001) (Table 3). In multivariate regression analysis adjusted for age, gender, fracture type and BMD status, using at least one medication was associated with age (OR (95% CI) 1.65 (1.44-1.90) per decade, p<0.001), and major fractures (OR (95% CI) 1.49 (1.13-1.97), p=0.004). Additional adjustments for BMI showed that in addition to age and fracture severity, BMI (OR (95% CI): 1.07 (1.04-1.11), p<0.001) was associates with using at least one medical drug.

Table 2. Characteristics of the study population.

	Total (n=1282)	**Men** (n=362)	**Women** (n=920)
Age (years), continuous	65 ± 9	64 ± 9	65 ± 9
Age (years), decades			
50-59	415 (32)	132 (37)	283 (31)
60-69	446 (35)	123 (34)	323 (35)
70-79	307 (24)	79 (22)	228 (25)
80+	114 (9)	28 (8)	86 (9)
Women	920 (72)		
Height (m)	1.67 ± 0.09	1.76 ± 0.08	1.64 ± 0.07
Weight (kg)	73.5 ± 14.5	82.5 ± 13.4	70.0 ± 13.5
BMI (kg/m^2), continuous	26.2 ± 4.4	26.6 ± 3.9	16.0 ± 4.6
BMI (kg/m^2), ≥30	193 (17.2)	52 (16.6)	141 (17.5)
Fracture type			
Minor	784 (61)	213 (59)	571 (62)
Major	390 (30)	109 (30)	281 (31)
Hip	108 (8)	40 (11)	68 (7)
BMD			
Normal BMD	286 (22)	110 (30)	176 (19)
Osteopenia	608 (47)	182 (50)	426 (46)
Osteoporosis	388 (30)	70 (19)	318 (5)
Previous fractures at 50+ year	222 (31.0)	50 (25.9)	172 (33.0)
Previous falls last 12 months	252 (24.1)	65 (21.6)	187 (25.1)
Parental history of hip fractures	16 (1.7)	4 (1.3)	12 (1.8)

Data presented as mean ± standard deviation or number (percentage). Abbreviations: BMI, body mass index; BMD, bone mineral density.

Comorbidities associated with an increased fracture risk

At least one comorbidity associated with an increased risk of fractures was found in 50.1% of patients. At least one bone-related risk comorbidity (BRC) was found in 42.4% of patients, with at least one BRC in medical history in 20.2% and at least one BRC in laboratory tests in 29.4% of patients. The proportion of patients with at least one BRC in medical history increased significantly with increasing age (50-59 years: 16.9% vs. 60-69 years: 19.1% vs. 70-79 years: 24.4% vs. 80+ years: 25.4%, p=0.036) and increasing BMI (obese: 25.9% vs. non-obese: 19.1%, p=0.031). Similarly, the proportion of patients with at least one BRC in laboratory tests increased significantly with increasing age (50-59 years: 20.7% vs. 60-69 years: 27.4% vs. 70-79 years: 36.5% vs. 80+ years: 50.0%, p<0.001) and increasing BMI (obese: 43% vs. non-obese: 25.6%, p<0.001). There were no significant differences in the prevalence rates of at least one BRC in medical history and at least one BRC in laboratory tests between men and women, fracture types and BMD categories. At least one fall-related risk comorbidity (FRC) was found in 26.0% of patients (Table 3). Only BRC were present in 24.1% of patients, only FRC in 7.6%, and a combination of both in 18.3%. A detailed overview of individual BRC and FRC is presented in Supplementary table 1. Individual BRC in laboratory tests according to age and fractures type are presented in Supplementary table 2.

Medications associated with increased fracture risk

At least one medication associated with an increased risk of fractures was used by 44.9% of patients, with 26.2% using at least one BRM, and 32.9% at least one FRM (Table 3). Only BRM was used by 11.9% of patients, only FRM by 18.6%, and a combination of both by 14.3%. A detailed overview of BRM and FRM is presented in Supplementary table 3.

Bone-related fracture risks

The proportion of patients with at least one BRC was similar for women and men, and BMD categories, but was significantly higher in obese than in non-obese patients (56% vs. 39%, p<0.001), in patients with major fractures (48.2%) and hip fractures (44.4%) compared to those with minor fractures (39.3%, p=0.013), and increased with increasing age (33.5% of patients aged 50-59 years up to 59.6% of patients aged 80+ years, p<0.001) (Table 3). In multivariate regression analysis adjusted for age, gender, fracture type and BMD status, at least one BRC was associated with age (OR (95% CI): 1.45 (1.28-1.64), p<0.001), and major fractures (OR (95% CI): 1.36 (1.06-1.75), p=0.016) (Table 4). Additional adjustments for BMI showed that besides age and fracture severity, BMI (OR (95% CI): 1.07 (1.04-1.10), p<0.001) was associated with at least one BRC (Supplementary table 4).

Table 3. The proportion of patients with comorbidities and medications by gender, BMD, fracture type, age decade, and obesity.

	Total (n=1282)	**Women** (n=920)	**Men** (n=362)	**Normal BMD** (n=286)	**Osteopenia** (n=608)	**Osteoporosis** (n=388)
≥ 1 ICD-10 comorbidity	1038 (81)	744 (81)	294 (81)	233 (812)	479 (79)	326 (84)
≥ 1 ATC medication	873 (68)	620 (67)	253 (70)	185 (65)	407 (67)	281 (72)
≥ 1 BRR	682 (53)	503 (55)	179 (49)	135 (47)	317 (52)	230 (59) **
≥ 1 BRC	544 (42)	404 (44)	140 (39)	115 (40)	250 (41)	179 (46)
≥ 1 BRM	336 (26)	255 (28)	81 (22)	60 (21)	151 (25)	125 (32) **
≥ 1 FRR	585 (46)	425 (46)	160 (44)	126 (44)	263 (43)	196 (51)
≥ 1 FRC	333 (26)	232 (25)	101 (28)	68 (24)	155 (26)	110 (28)
≥ 1 FRM	422 (33)	312 (34)	110 (30)	91 (32)	184 (30)	147 (38) *
Any fracture risk	841 (66)	612 (67)	229 (63)	172 (60)	399 (66)	270 (70) *
Only BRR	256 (20)	187 (20)	69 (19)	46 (16)	136 (22)	74 (19)
Only FRR	158 (12)	109 (12)	50 (14)	37 (13)	82 (14)	40 (10)
Both	426 (33)	316 (34)	110 (30)	89 (31)	181 (30)	156 (40) **
Polypharmacy	297 (23)	214 (23)	83 (23)	51 (18)	134 (22)	112 (29) **

Data presented as n (%). * P-value < 0.05. ** P-value < 0.01. Abbreviations: ICD-10, tenth revision of the International Classification of Disease; ATC, Anatomic Therapeutic Chemical;

Minor (n=784)	**Major** (n=390)	**Hip** (n=108)	**50-59 y.** (n=415)	**60-69 y.** (n=446)	**70-79 y.** (n=307)	**80+ y.** (n=114)	**Non-obese** (n=929)	**Obese** (n=193)
615 (78)	330 (85)	93 (86) *	302 (723)	359 (801)	275 (90)	102 (90) **	737 (79)	173 (90) **
503 (64)	290 (74)	80 (74) **	231 (56)	303 (68)	243 (79)	96 (84) **	620 (67)	152 (79) **
380 (49)	232 (60)	70 (65) **	180 (43)	229 (51)	195 (64)	78 (68) **	466 (50)	126 (65) **
308 (39)	188 (48)	48 (44) *	139 (34)	175 (39)	162 (53)	68 (60) **	365 (39)	108 (56) **
170 (22)	125 (32)	41 (38) **	85 (21)	116 (26)	99 (32)	36 (32) **	225 (24)	65 (34) **
325 (42)	201 (52)	59 (55) **	142 (34)	192 (43)	183 (60)	68 (60) **	400 (43)	115 (60) **
176 (22)	126 (32)	31 (29) **	70 (17)	115 (26)	105 (34)	43 (38) **	222 (24)	70 (36) **
228 (29)	148 (38)	46 (43) **	97 (23)	137 (31)	137 (45)	51 (45) **	282 (30)	86 (45) **
480 (61)	276 (71)	85 (79) **	226 (55)	284 (64)	239 (78)	92 (81) **	585 (63)	150 (78) **
155 (20)	75 (19)	26 (24)	84 (20)	92 (21)	56 (18)	24 (21)	185 (20)	35 (18)
100 (13)	44 (11)	15 (14)	46 (11)	55 (12)	44 (14)	14 (12)	119 (13)	24 (12)
225 (29)	157 (40)	44 (41) **	96 (23)	137 (31)	139 (45)	54 (47) **	281 (30)	91 (47) **
146 (19)	117 (30)	34 (32) **	53 (13)	86 (19)	110 (36)	48 (42) **	190 (21)	65 (34) **

BRR, bone-related fracture risk; BRC, bone-related risk comorbidity; BRM, bone-related risk medication; FRR, fall-related fracture risk; FRC, fall-related risk comorbidity; FRM, fall-related risk medication.

Table 4. Univariate and multivariate regression analysis adjusted for gender, age, fracture type and BMD status, for bone- and fall-related risk comorbidities and medications and their combinations.

	BRC	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
Age, per decade	1.47 (1.30-1.65) **	1.45 (1.28-1.64) **
Gender		
Male	*Reference*	*Reference*
Female	1.24 (0.97-1.59)	1.20 (0.93-1.55)
BMD		
Normal BMD	*Reference*	*Reference*
Osteopenia	1.04 (0.78-1.38)	0.93 (0.70-1.25)
Osteoporosis	1.27 (0.94-1.74)	0.97 (0.70-1.34)
Fracture type		
Minor	*Reference*	*Reference*
Major	1.44 (1.13-1.84) **	1.36 (1.06-1.75) *
Hip	1.24 (0.82-1.86)	1.05 (0.69-1.60)
	BRM	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
Age, per decade	1.27 (1.12-1.45) **	1.18 (1.03-1.35) *
Gender		
Male	*Reference*	*Reference*
Female	1.33 (0.99-1.77)	1.28 (0.96-1.73)
BMD		
Normal BMD	*Reference*	*Reference*
Osteopenia	1.25 (0.89-1.75)	1.12 (0.79-1.58)
Osteoporosis	1.79 (1.26-2.55) **	1.41 (0.97-2.05)
Fracture type		
Minor	*Reference*	*Reference*
Major	1.70 (1.30-2.24) **	1.63 (1.24-2.14) **
Hip	2.21 (1.45-3.38) **	1.98 (1.28-3.06) **
	BRR	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
Age, per decade	1.46 (1.30-1.65) **	1.39 (1.23-1.58) **
Gender		
Male	*Reference*	*Reference*
Female	1.23 (0.97-1.57)	1.18 (0.92-1.52)

FRC		Any risk comorbidity	
Univariate OR (95% CI)	**Multivariate** OR (95% CI)	**Univariate** OR (95% CI)	**Multivariate** OR (95% CI)
1.49 (1.30-1.69) **	1.47 (1.28-1.69) **	1.56 (1.38-1.75) **	1.52 (1.34-1.72) **
Reference	*Reference*	*Reference*	*Reference*
0.87 (0.66-1.15)	0.83 (0.62-1.10)	1.10 (0.86-1.41)	1.04 (0.81-1.35)
Reference	*Reference*	*Reference*	*Reference*
1.10 (0.79-1.52)	1.00 (0.72-1.41)	1.17 (0.88-1.55)	1.05 (0.98-1.41)
1.27 (0.89-1.80)	1.01 (0.70-1.47)	1.45 (1.06-1.96) *	1.09 (0.79-1.52)
Reference	*Reference*	*Reference*	*Reference*
1.65 (1.26-2.16) **	1.55 (1.17-2.04) **	1.55 (1.21-1.98) **	1.44 (1.12-1.85) **
1.39 (0.89-2.18)	1.12 (0.70-1.78)	1.41 (0.94-2.11)	1.14 (0.75-1.73)
FRM		**Any risk medication**	
Univariate OR (95% CI)	**Multivariate** OR (95% CI)	**Univariate** OR (95% CI)	**Multivariate** OR (95% CI)
1.49 (1.32-1.68) **	1.44 (1.27-1.64) **	1.51 (1.34-1.70) **	1.43 (1.27-1.62) **
Reference	*Reference*	*Reference*	*Reference*
1.18 (0.90-1.53)	1.15 (0.87-1.50)	1.21 (0.95-1.55)	1.17 (0.90-1.51)
Reference	*Reference*	*Reference*	*Reference*
0.93 (0.69-1.26)	0.82 (0.60-1.12)	1.08 (0.82-1.45)	0.96 (0.71-1.28)
1.31 (0.95-1.80)	0.96 (0.68-1.36)	1.63 (1.20-2.22) **	1.19 (0.86-1.66)
Reference	*Reference*	*Reference*	*Reference*
1.49 (1.15-1.93) **	1.41 (1.09-1.83) *	1.59 (1.24-2.02) **	1.49 (1.16-1.91) **
1.81 (1.20-2.73) **	1.54 (1.00-2.36) *	2.30 (1.52-3.47) **	1.92 (1.26-2.94) **
FRR		**Any risk**	
Univariate OR (95% CI)	**Multivariate** OR (95% CI)	**Univariate** OR (95% CI)	**Multivariate** OR (95% CI)
1.54 (1.37-1.74) **	1.50 (1.33-1.70) **	1.62 (1.42-1.84) **	1.56 (1.18-3.18) **
Reference	*Reference*	*Reference*	*Reference*
1.08 (0.85-1.38)	1.05 (0.81-1.35)	1.15 (0.90-1.49)	1.12 (0.86-1.46)

Table 4. Continued

	BRR	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
BMD		
Normal BMD	*Reference*	*Reference*
Osteopenia	1.22 (0.92-1.62)	1.09 (0.82-1.45)
Osteoporosis	1.63 (1.20-2.22) **	1.22 (0.88-1.70)
Fracture type		
Minor	*Reference*	*Reference*
Major	1.56 (1.22-2.00) **	1.47 (1.14-1.88) **
Hip	1.96 (1.29-2.98) **	1.65 (1.07-2.54) *

* P-value < 0.05. ** P-value <0.01. Abbreviations: BRR, bone-related fracture risk; BRC, bone-related risk comorbidity; BRM, bone-related risk medication;

The proportion of patients using at least one BRM were similar for women and men, but increased significantly with increasing BMI (obese: 34% vs. non-obese: 24%, p=0.006), decreasing BMD (normal BMD: 21.0% vs. osteopenia: 24.8% vs. osteoporosis: 32.2%, p=0.003), increasing fracture severity (minor fractures: 21.7% vs. major fractures 32.1% vs. hip fractures: 38.0%, p<0.001), and increasing age (50-59 years: 20.5% vs. 60-69 years: 26.0% vs. 70-79 years: 32.2% vs. 80+ years: 31.6%, p=0.002) (Table 3). In multivariate regression analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI): 1.18 (1.03-1.35), p=0.019), major fractures (OR (95% CI): 1.63 (1.24-2.14), p=0.001), and hip fractures (OR (95% CI): 1.98 (1.28-3.06), p=0.002) were associated with at least one BRM (Table 4). After an additional adjustment for BMI, female gender (OR (95% CI): 1.40 (1.01-1.94), p=0.041), increasing BMI (OR (95% CI): 1.04 (1.01-1.07), p=0.016) and osteoporosis (OR (95% CI): 1.62 (1.07-2.45), p=0.023) were also associated with at least one BRM (Supplementary table 4).

At least one BRR was present in 53.2% of patients (only BRC in 211.0%, only BRM in 10.8%, and both in 15.4%). The proportion of patients with at least one BRR was similar for women and men, but increased significantly with increasing BMI (obese: 65% vs. non-obese: 50%, p<0.001), decreasing BMD (normal BMD: 47.2% vs. osteopenia 52.1% vs. osteoporosis: 59.3%, p=0.006), increasing fracture severity (minor fractures 48.5% vs. major fractures 59.5% vs. hip fractures 64.8%, p<0.001), and increasing age (50-59 years: 43.4% vs. 60-69 years: 51.3% vs. 70-79 years: 63.5% vs. 80+ years: 68.4%, p<0.001) (Table 3). In multivariate analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI): 1.39 (1.23-1.58) per decade, p<0.001), major fractures (OR (95% CI): 1.47 (1.14-1.88), p=0.003), and hip

	FRR		Any risk	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Reference	*Reference*	*Reference*	*Reference*
	0.97 (0.73-1.29)	0.86 (0.64-1.15)	1.27 (0.95-1.69)	1.12 (0.83-1.51)
	1.30 (0.95-1.76)	0.96 (0.69-1.34)	1.51 (1.10-2.09) *	1.08 (0.77-1.52)
	Reference	*Reference*	*Reference*	*Reference*
	1.50 (1.18-1.92) **	1.41 (1.10-1.81) **	1.53 (1.18-1.99) **	1.43 (1.09-1.86) **
	1.70 (1.14-2.55) *	1.41 (0.93-2.15)	2.34 (1.45-3.79) **	1.93 (1.18-3.18) **

FRR, fall-related fracture risk; FRC, fall-related risk comorbidity; FRM, fall-related risk medication.

fractures (OR (95% CI): 1.65 (1.07-2.54), p=0.023) were associated with at least one BRR (Table 4). After additional adjustments for BMI, BMI (OR (95% CI): 1.06 (1.03-1.09), p<0.001) and osteoporosis (OR (95% CI): 1.45 (1.01-2.08), p=0.046) were also associated with at least one BRR (Supplemental table 4).

Fall-related fracture risks

The proportion of patients with at least one FRC was also similar for women and men, and BMD categories, but was significantly higher in major fractures (32.3%) and hip fractures (28.7%) compared to those with minor fractures (22.4%, p=0.001), and increased with increasing BMI (obese: 36% vs. non-obese: 24%, p<0.001), and increasing age (16.9% of patients aged 50-59 years up to 37.7% of patients aged 80+ years, p<0.001) (Table 3). In multivariate regression analysis adjusted for age, gender, fracture type and BMD status, at least one FRC was also associated with age (OR (95% CI): 1.55 (1.17-2.04), p=0.002), and major fractures (OR (95% CI): 1.47 (1.28-1.69), p<0.001) (Table 4). Additional adjustments for BMI showed that besides age and fracture severity, BMI (OR (95% CI): 1.06 (1.02-1.09), p<0.001) was associated with at least one FRC (Supplemental table 4).

The proportion of patients using at least one FRM was also similar for women and men, but was significantly higher in patients with osteoporosis (37.9%) compared to those with osteopenia (30.3%), and a normal BMD (31.8%, p=0.040), and increased with increasing BMI (obese: 45% vs. non-obese: 30%, p<0.001), increasing fracture severity (minor fractures: 29.1% vs. major fractures: 37.9% vs. hip fractures: 42.6%, p=0.001), and increasing age (50-59 years: 23.4% vs. 60-69 years: 30.7% vs. 70-79

years 44.6% vs. 80+ years 44.7%, p<0.001) (Table 3). In multivariate analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI): 1.44 (1.27-1.64), p<0.001), major fractures (OR (95% CI): 1.41 (1.09-1.83), p=0.010), and hip fractures (OR (95% CI): 1.54 (1.00-2.36), p=0.048) were associated with at least one FRM (Table 4). Additional adjustments for BMI showed that besides age and fracture severity, BMI (OR (95% CI): 1.08 (1.04-1.11), p<0.001) was associated with at least one FRM (Supplemental table 4).

At least one FRR was present in 45.6% of patients (only FRC in 12.7%, only FRM in 19.7%, and both in 13.3%). The proportion of patients with at least one FRR was similar for women and men, and among BMD categories, but increased significantly with increasing fracture severity (minor fractures: 41.5% vs. major fractures: 51.5% vs. hip fractures: 54.6%, p=0.001), increasing BMI (obese: 60% vs. non-obese 43%, p<0.001) and increasing age (50-59 years: 34.2% vs. 60-69 years: 43.0% vs. 70-79 years: 59.6% vs. 80+ years: 59.6%, p<0.001) (Table 3). In multivariate analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI): 1.50 (1.33-1.70) per decade, p<0.001), and major fractures (OR (95% CI): 1.41 (1.10-1.81), p=0.001) were significantly associated with FRR (Table 4). After additional adjustments for BMI, BMI (OR (95% CI): 1.08 (1.05-1.11), p<0.001) was also associated with at least one FRR (Supplemental table 4).

Any fracture risk

The proportion of patients having at least one risk (BRC, BRM, FRC, FRM or any combination) was 65.6% (only BRR in 20.0%, only FRR in 12.3%, and both in 33.3%). The prevalence of at least one risk was similar for women and men, but increased significantly with increasing BMI (obese: 78% vs. non-obese: 63%, p<0.001), decreasing BMD (normal BMD: 60.1% vs. osteopenia: 65.6% vs. osteoporosis: 69.6%, p=0.039), with increasing fracture severity (minor fractures: 61.2% vs. major fractures: 70.8% vs. hip fractures: 78.7%, p<0.001), and with increasing age (50-59 years: 54.5% vs. 60-69 years 63.7% vs. 70-79 years 77.9% vs. 80+ years: 80.7%, p<0.001) (Table 3). In multivariate analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI): 1.56 (1.18-3.18) per decade), p<0.001), major fracture (OR (95% CI): 1.43 (1.09-1.86), p<0.001), and hip fracture (OR (95% CI): 1.93 (1.18-3.18), p=0.009) (Table 4). Additional adjustment for BMI showed that besides age and fracture severity, BMI (OR (95% CI): 1.08 (1.05-1.12), p<0.001) was associated with at least one risk (Supplemental table 4).

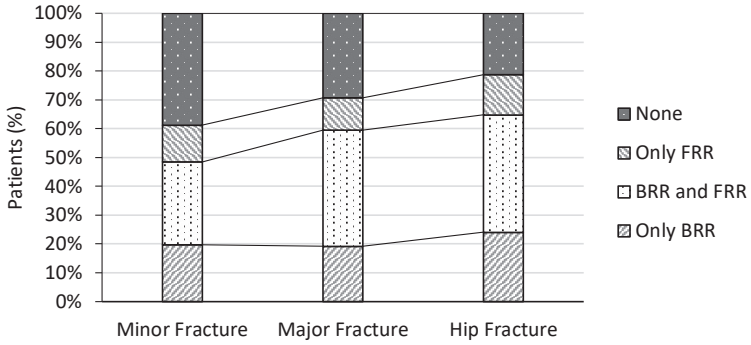
As shown in Table 3, the proportion of patients with only BRR as well as the proportion of patients with only FRR were similar among gender, BMI, BMD, fracture, and age subgroups. In contrast, the proportion of patients with a combination of BRR and FRR was similar for women and men, but significantly higher in obese compared

to non-obese patients (47% vs. 30%, p<0.001), in patients with osteoporosis (40.2%) compared to those with osteopenia (29.8%) and a normal BMD (31.1%, p=0.002), higher in patients with major fractures (40.3%) and hip fractures (40.7%) compared to minor fractures (28.7%, p<.001), and increased significantly with increasing age per decade (50-59 years: 23.1% vs. 60-69 years: 30.7% vs. 70-79 years: 45.3% vs. 80+ years: 47.4%, p<0.001) (Figure 2). In multivariate analysis adjusted for age, gender, fracture type and BMD status, the combination of BRR and FRR was significantly associated with age per decade (OR (95% CI): 1.47 (1.30-1.68), p<0.001) and major fracture (OR (95% CI): 1.58 (1.21-2.04), p=0.001). Additional adjustments for BMI showed that besides age and fracture severity, BMI (OR (95% CI): 1.08 (1.05-1.12), p<0.001) was associated with at least one risk.

Polypharmacy

Polypharmacy was present in 23.2% of patients (Table 3). The prevalence of polypharmacy was similar for women and men, and all fracture locations, but was significantly higher in patients with osteoporosis compared to those with osteopenia, and a normal BMD (28.9% vs. 22.0% vs. 17.8%, p=0.002) (Table 2), and increased with increasing BMI (obese 33.7% vs. 20.5%, p<0.001) and increasing age from 12.8% in patients aged 50-59 years to 42.1% in patients aged 80+ years (p<0.001). In multivariate analysis adjusted for age, gender, fracture type and BMD status, age (OR (95% CI) 1.06 (1.05-1.08), p<0.001), and major fracture (OR (95% CI) 1.65 (1.23-2.21), p=0.001) were associated with polypharmacy. After additional adjustments for BMI, osteoporosis (OR (95% CI): 1.66 (1.07-2.58), p=0.025) and BMI (OR (95% CI: 1.09 (1.05-1.13), p<0.001) were also associated with polypharmacy.

A



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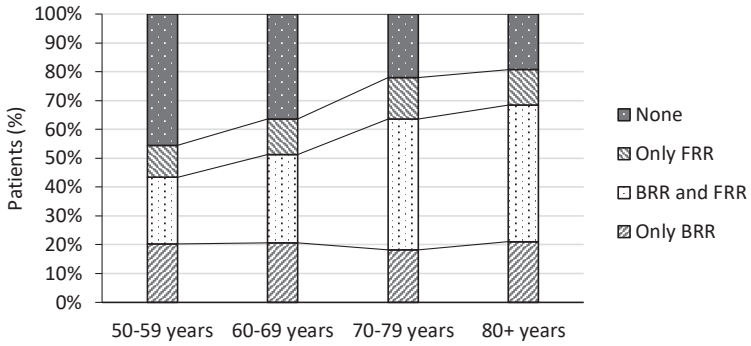

C

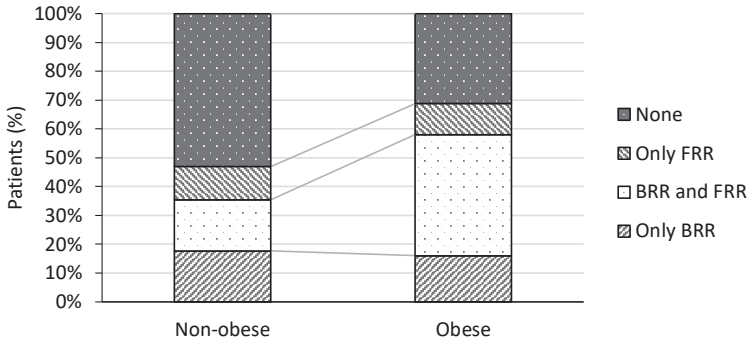

Figure 2. Proportion of patients with only bone-related fracture risks, only fall-related fracture risks, a combination of both, and none according to fracture type (**A**), age per decade (**B**), and obesity (**C**). The proportion of patients with only BRR (±20%) and the proportion of patients with only FRR (±10%) remained constant, whereas the proportion of patients with a combination of BRR and FRR increased significantly with fracture severity ($p<.001$), increasing age ($p<.001$) and obesity ($p<.001$).

Abbreviations: BRR, bone-related fracture risk; FRR, fall-related fracture risk.

DISCUSSION

In this study, we systematically evaluated the comorbidities and medications in patients aged 50 years or older with a recent clinical vertebral or non-vertebral fracture visiting the FLS. At least one chronic ICD-10 comorbidity was found in more than 80% of patients and at least one medication was used by almost 70% of patients. At least one BRR was present in more than 50% of patients, at least one FRR in almost 50%, and 65.6% of all FLS patients had at least one BRR and/or FRR. At least one BRR as well as at least one FRR were associated with older age, higher BMI and more severe fracture (major, and for BRR also hip fractures), but not with gender or BMD. Interestingly, the proportion of patients only having at least one BRR or at least one FRR was similar for gender, age, BMI, BMD and fracture type subgroups, whereas the proportion of patients having a combination of BRR and FRR increased significantly with increasing age, BMI and severity of the fracture. These findings imply that comorbidities and medications associated with a bone- or fall-related risk of fractures are often present in FLS patients, and that bone- and fall-related fracture risk often co-exist, especially in patients at older age, higher BMI and with more severe fractures.

Several but not all fracture risk calculators include comorbidities and medications in their models. They are implemented separately in the QFracture risk calculator [28], indicating that the risk for fractures increases with the number of mentioned comorbidities and medications. Apart from rheumatoid arthritis and glucocorticoid use, other comorbidities and medications are included as a combined risk factor (secondary osteoporosis, regardless of the number of comorbidities), not taking into account the number and severity, in the fracture risk assessment tool (FRAX).[29] Comorbidities and medications are not included in the Garvan fracture risk calculator.[30,31] One study [32] investigated the number of comorbidities in relation to subsequent fracture risk, and reported hazard ratio of 2.0 for subsequent fracture over seven years in the presence of >3 comorbidities, independent of the use of glucocorticoids (hazard ratio 1.75). Therefore, documenting the comorbidities and medications in patients attending the FLS contributes to a more profound assessment of subsequent fracture risk, but more prospective studies will be needed to evaluate the additive or synergistic effects of multiple risk factors on fracture risk.

This study provides a detailed overview of comorbidities and medications in patients able and willing to visit the FLS, but these findings may not be generalized to all other patients with a recent fracture. In this study, 42% of all invited patients with a recent fracture attended the FLS. From previous studies, we know that patients who were not willing or able to have their fracture risk evaluated at the FLS were older and more frequently had a hip fracture.[33-36] Consequently, in the non-attenders, the proportion of patients with BRR and FRR may be even higher.

In conclusion, comorbidities and medications associated with an increased bone- or fall-related fracture risk are present in two-thirds of patients attending the FLS after a recent fracture. Additionally, the proportion of patients only having at least one BRR or at least one FRR was similar for gender, age, BMI, BMD and fracture type subgroups, whereas the proportion of patients having a combination of BRR and FRR increased significantly with increasing age, BMI and severity of the fracture. This indicates that systematic evaluation of these factors is important for a more profound assessment of subsequent fracture risk in FLS care.

SUPPLEMENTARY TABLES AND FIGURES

Supplementary table 1. Detailed overview of ICD-10, and bone- and fall-related risk comorbidities

	Total cohort n=1282
Chronic ICD-10 comorbidity subgroups	
Endocrine, nutritional and metabolic diseases	467 (36.4)
Circulatory system	419 (32.7)
Musculoskeletal system and connective tissue	389 (30.3)
Genitourinary system	223 (17.4)
Digestive system	164 (12.8)
Respiratory system	140 (10.9)
Nervous system	127 (9.9)
Neoplasms	95 (7.4)
Eye and adnexa	90 (7.0)
Ear and mastoid process	60 (4.7)
Mental and behavioral disorders	54 (4.2)
Blood and blood-forming organs	34 (2.7)
Skin and subcutaneous tissue	28 (2.2)
Bone-related risk comorbidities	
Medical history	
Hyperparathyroidism	1 (0.1)
Chronic kidney disease stage 3 or 4	10 (0.8)
Diabetes mellitus	95 (7.4)
Hyperthyroidism	55 (4.3)
Chronic obstructive pulmonary disease	63 (4.9)
Rheumatoid arthritis	30 (2.3)
Hypogonadism (in males)	1 (0.1)

Supplementary table 1. Continued

	Total cohort n=1282
Inflammatory bowel diseas3	11 (0.9)
MGUS/multiple myeloma	1 (0.1)
Malabsorption	5 (0.4)
Liver cirrhosis	3 (0.2)
Leukemia	2 (0.2)
Anorexia nervosa	2 (0.2)
Celiac disease	1 (0.1)
Systemic lupus erythematosus	1 (0.1)
Hemophilia	1 (0.1)
Lymphoma	1 (0.1)
Sarcoidosis	1 (0.1)
Laboratory tests	
Hyperparathyroidism (primary and secondary)	239 (18.6)
Primary hyperparathyroidism	64 (5.0)
Secondary hyperparathyroidism	158 (12.3)
Chronic kidney disease	133 (10.4)
Hyperthyroidism	33 (2.6)
Hypogonadism (in males)	28 (2.2)
Monoclonal gammopathy of unknown significance (MGUS)	6 (0.5)
Multiple myeloma	0 (0.0)
Fall-related risk comorbidities	
Diabetes mellitus	95 (7.4)
Arrhythmia	71 (5.5)
Osteoarthritis	52 (4.1)
Stroke	41 (3.2)
Rheumatoid arthritis	30 (2.3)
Visual impairment	29 (2.3)
Peripheral neuropathy	28 (2.2)
Depression	24 (1.9)
Epilepsy	17 (1.3)
Dizziness	13 (1.0)
Chronic heart failure	11 (0.9)
Cognitive impairment	9 (0.7)
Parkinson's disease	8 (0.6)
Incontinence	4 (0.3)

Data presented as n (%).

Supplementary table 2. Bone-related comorbidities in laboratory tests according to age (</≥ 75 years) and fracture type (minor/major/hip)

	Age		**Fracture type**		
	< 75 year (n=1028)	**≥ 75 year** (n=254)	**Minor** (n=784)	**Major** (n=390)	**Hip** (n=108)
Hyperparathyroidism	167 (16.2)	72 (28.3) **	130 (16.6)	86 (22.1)	23 (21.3)
Primary hyperparathyroidism	52 (5.1)	12 (4.7)	37 (4.7)	18 (4.6)	9 (8.3)
Secondary hyperparathyroidism	96 (9.3)	62 (24.4) **	78 (9.9)	66 (16.9)	14 (13.0) **
Chronic kidney disease	69 (6.7)	64 (25.2) **	70 (8.9)	49 (12.6)	14 (13.0)
Hyperthyroidism	20 (1.9)	13 (5.1) **	18 (2.3)	8 (2.1)	7 (6.5) *
Hypogonadism (in males)	28 (2.7)	-	16 (2.0)	10 (2.6)	2 (1.9)
MGUS	6 (0.6)	0 (0.0)	5 (0.6)	1 (0.3)	0 (0.0)
Multiple myeloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data presented as n (%). * P-value < 0.05. ** P-value < 0.01. Abbreviations: MGUS, Monoclonal gammopathy of unknown significance

Supplementary table 3. Detailed overview of ATC, and bone- and fall-related risk medications.

	Total cohort (n=1282)
ATC medications	
Cardiovascular system	559 (43.6)
Alimentary tract and metabolism	400 (31.2)
Nervous system	319 (24.9)
Blood and blood forming organs	313 (24.4)
Musculo-skeletal system	172 (13.4)
Respiratory system	156 (12.2)
Systemic hormonal preparations	79 (6.2)
Genito-urinary system and sex hormones	63 (4.9)
Sensory organs	47 (3.7)
Anti-neoplastic and immune-modulating agents	19 (1.5)
Bone-related risk medication	
Proton pump inhibitors	226 (17.6)
Inhaled glucocorticoids	87 (6.8)
Anticonvulsants	49 (3.8)
Oral glucocorticoids	16 (1.2)
Thiazolidinediones	9 (0.7)
H2-receptor inhibitor	6 (0.5)
Fall-related risk medication	
Thiazide diuretics	153 (11.9)
Benzodiazepines	99 (7.7)
Loop diuretics	60 (4.7)
Selective serotonin reuptake inhibitors	54 (4.2)
Nitrates	48 (3.7)
Thiazide-like	32 (2.5)
Tricyclic antidepressants	26 (2.0)
Other Anti-depressants	23 (1.8)
Anti-arrhythmic drugs	19 (1.5)
Hypnotics	18 (1.4)
Antipsychotics	17 (1.3)
Anti-Parkinson	17 (1.3)
Barbiturates	1 (0.1)

Data presented as n (%).

Supplementary table 4. Univariate and multivariate regression analysis adjusted for gender, age, BMI, fracture type and BMD status, for bone- and fall-related risk comorbidities and medications and all combinations.

	BRC	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
Age, per decade	1.41 (1.28-1.55) **	1.41 (1.27-1.55) **
Gender		
Male	*Reference*	*Reference*
Female	1.21 (0.93-1.58)	1.18 (0.89-1.55)
BMD		
Normal BMD	*Reference*	*Reference*
Osteopenia	1.08 (0.79-1.46)	1.06 (0.77-1.46)
Osteoporosis	1.23 (0.88-1.71)	1.13 (0.79-1.63)
Fracture type		
Minor	*Reference*	*Reference*
Major	1.46 (1.12-1.90) **	1.38 (1.06-1.81) *
Hip	0.99 (0.63-1.54)	0.93 (0.78-1.48)
BMI	1.06 (1.03-1.09) **	1.07 (1.04-1.10) **
	BRM	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
Age, per decade	1.30 (1.15-1.44) **	1.21 (1.06-1.04) **
Gender		
Male	*Reference*	*Reference*
Female	1.48 (1.08-2.02) *	1.40 (1.01-1.94) *
BMD		
Normal BMD	*Reference*	*Reference*
Osteopenia	1.34 (0.93-1.92)	1.26 (0.87-1.84)
Osteoporosis	1.87 (1.28-2.74) **	1.62 (1.07-2.45) *
Fracture type		
Minor	*Reference*	*Reference*
Major	1.67 (1.25-2.24) **	1.60 (1.19-2.15) **
Hip	1.91 (1.20-3.05) **	1.81 (1.12-2.94) *
BMI	1.02 (0.99-1.05)	1.04 (1.01-1.07) *

FRC		Any risk comorbidity	
Univariate OR (95% CI)	**Multivariate** OR (95% CI)	**Univariate** OR (95% CI)	**Multivariate** OR (95% CI)
1.46 (1.31-1.61) **	1.44 (1.28-1.60) **	1.47 (1.33-1.61) **	1.45 (1.31-1.60) **
Reference	*Reference*	*Reference*	*Reference*
0.85 (0.63-1.14)	0.78 (0.58-1.07)	1.07 (0.83-1.39)	1.02 (0.77-1.34)
Reference	*Reference*	*Reference*	*Reference*
1.06 (0.75-1.51)	1.04 (0.72-1.50)	1.21 (0.90-1.64)	1.21 (0.89-1.66)
1.33 (0.92-1.93)	1.24 (0.82-1.87)	1.39 (1.00-1.93) *	1.31 (0.91-1.88)
Reference	*Reference*	*Reference*	*Reference*
1.78 (1.33-2.38) **	1.67 (1.24-1.25) **	1.57 (1.21-2.04) **	1.48 (1.13-1.94) **
1.39 (0.85-2.27)	1.20 (0.72-2.00)	1.12 (0.73-1.74)	1.01 (0.64-1.61)
1.04 (1.01-1.07) **	1.06 (1.02-1.09) **	1.06 (1.03-1.09) **	1.07 (1.04-1.10) **
FRM		**Any risk medication**	
Univariate OR (95% CI)	**Multivariate** OR (95% CI)	**Univariate** OR (95% CI)	**Multivariate** OR (95% CI)
1.42 (1.28-1.56) **	1.39 (1.24-1.54) **	1.45 (1.31-1.59) **	1.39 (1.24-1.53) **
Reference	*Reference*	*Reference*	*Reference*
1.18 (0.89-1.56)	1.15 (0.85-1.54)	1.29 (0.99-1.69)	1.24 (0.94-1.64)
Reference	*Reference*	*Reference*	*Reference*
0.89 (0.64-1.22)	0.86 (0.62-1.21)	1.10 (0.81-1.49)	1.05 (0.76-1.44)
1.26 (0.90-1.78)	1.16 (0.79-1.70)	1.64 (1.18-2.28) **	1.44 (1.00-2.08) *
Reference	*Reference*	*Reference*	*Reference*
1.45 (1.10-1.91) **	1.39 (1.04-1.84) *	1.58 (1.22-2.06) **	1.50 (1.15-1.97) **
1.61 (1.03-2.52) *	1.58 (0.98-2.54)	1.93 (1.24-2.99) **	1.82 (1.15-2.89) *
1.06 (1.03-1.09) **	1.08 (1.04-1.11) **	1.04 (1.02-1.07) **	1.07 (1.03-1.10) **

Supplementary table 4. Continued

	BRR	
	Univariate OR (95% CI)	**Multivariate** OR (95% CI)
Age, per decade	1.42 (1.28-1.56) **	1.37 (1.23-1.05) **
Gender		
Male	*Reference*	*Reference*
Female	1.23 (0.95-1.60)	1.19 (0.90-1.56)
BMD		
Normal BMD	*Reference*	*Reference*
Osteopenia	1.29 (0.95-1.73)	1.27 (0.93-1.74)
Osteoporosis	1.56 (1.13-2.17) **	1.45 (1.01-2.08) *
Fracture type		
Minor	*Reference*	*Reference*
Major	1.53 (1.18-2.00) **	1.45 (1.11-1.91) **
Hip	1.49 (0.96-2.32)	1.41 (0.89-2.25)
BMI	1.05 (1.02-1.08) **	1.07 (1.04-1.10) **

* P-value < 0.05. ** P-value <0.01. Abbreviations: BRR, bone-related fracture risk; BRC, bone-related risk comorbidity; BRM, bone-related risk medication; FRR, fall-related fracture risk; FRC, fall-related risk comorbidity; FRM, fall-related risk medication; BMI, body mass index.

	FRR		Any risk	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	1.47 (1.33-1.61) **	1.44 (1.30-1.58) **	1.52 (1.37-1.67) **	1.48 (1.32-1.64) **
	Reference	*Reference*	*Reference*	*Reference*
	1.10 (0.84-1.42)	1.06 (0.81-1.40)	1.12 (0.85-1.47)	1.09 (0.82-1.46)
	Reference	*Reference*	*Reference*	*Reference*
	0.94 (0.70-1.27)	0.92 (0.67-1.26)	1.36 (1.00-1.85)	1.35 (0.97-1.86)
	1.31 (0.95-1.82)	1.21 (0.84-1.73)	1.49 (1.06-2.09) **	1.35 (0.92-1.97)
	Reference	*Reference*	*Reference*	*Reference*
	1.52 (1.17-1.97) **	1.44 (1.10-1.89) **	1.52 (1.15-2.01) **	1.42 (1.06-1.90) *
	1.58 (1.02-2.45) *	1.50 (0.95-2.39)	1.87 (1.14-3.07) *	1.78 (1.05-3.00) *
	1.06 (1.03-1.09) **	1.08 (1.05-1.11) **	1.06 (1.03-1.10) **	1.08 (1.05-1.12) **

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CHAPTER 4

THE PREVALENCE OF CELIAC DISEASE IN A FRACTURE LIAISON SERVICE POPULATION

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Calcif Tissue Int. 2020;107(4):327-334

ABSTRACT

Celiac disease (CD) is a known risk factor for osteoporosis and fractures. The prevalence of CD in patients with a recent fracture is unknown. We therefore systematically screened patients at a fracture liaison service (FLS) to study the prevalence of CD. Patients with a recent fracture aged ≥50 years were invited to VieCuri Medical Center's FLS. In FLS attendees, bone mineral density (BMD) and laboratory evaluation for metabolic bone disorders and serological screening for CD was systematically evaluated. If serologic testing for CD was positive, duodenal biopsies were performed to confirm the diagnosis CD. Data were collected in 1042 consecutive FLS attendees. Median age was 66 years (Interquartile range (IQR) 15), 27.6% had a major and 6.9% a hip fracture, 26.4% had osteoporosis and 50.8% osteopenia. Prevalent vertebral fractures were found in 29.1%. CD was already diagnosed in two patients (0.19%), one still had a positive serology. Three other patients (0.29%) had a positive serology for CD (one with gastrointestinal complaints). In two of them, CD was confirmed by duodenal histology (0.19%) and one refused further evaluation. The prevalence of biopsy-proven CD was therefore 0.38% (4/1042) of which 0.19% (2/1042) was newly diagnosed. The prevalence of CD in patients with a recent fracture at the FLS was 0.38% and within the range of reported prevalences in the Western-European population (0.33-1.5%). Newly diagnosed CD was only found in 0.19%. Therefore, standard screening for CD in FLS patients is not recommended.

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy induced by dietary proteins in wheat, rye and barley. The presentation of symptoms widely varies. In 2012 the following Oslo definitions for CD were stated: 'classical CD presents with signs and symptoms of malabsorption. Besides malabsorption, other symptoms of diarrhea, steatorrhea, weight loss or growth failure are required. Non-classical CD presents with gastro-intestinal symptoms and extra intestinal manifestations, but without signs and symptoms of malabsorption and diarrhea. Subclinical CD is disease below the threshold of clinical detection without signs or symptoms sufficient to trigger CD testing in routine practice'.[1] It was demonstrated that in a period of 15 years (1998-2012) an increasing part of the CD patients had a subclinical CD or a non-classical phenotype instead of the classical CD phenotype.[2]

CD is a known risk factor for osteoporosis and fractures, with a RR of 1.3-1.9 for fractures.[3-6] Malabsorption of calcium and vitamin D deficiency leads to secondary hyperparathyroidism. General malnutrition and underweight also result in a reduced bone mineral density (BMD).[3,7] Further, hypogonadism associated with CD might also affect bone metabolism.[7,8] Chronic inflammation and release of proinflammatory cytokines leads to an increase in osteoclastic bone resorption.[9] Appropriate treatment of CD relieves symptoms and can improve BMD.[10-12] However, after diagnosis of CD the increased risk of fractures persists.[6] It was demonstrated that the increased fracture risk remained 20 years after diagnosis of CD.[13]

The worldwide prevalence of CD based on serologic tests is reported to be 1.4% and of biopsy-proven CD 0.7%.[14] In the general unselected Northern American and Western European populations the prevalence of CD is close to 1% and in Northern European countries it is slightly higher, around 1-1.5%.[15] Rostami *et al.* reported a prevalence of biopsy-proven CD of 3 per 1000 persons in a Dutch population of healthy blood donors.[16] In high risk populations, such as in in type 1 diabetes patients and first-degree relatives of patients with CD, the prevalence of CD is estimated to be higher than in the general population: 3-6% in patients with type 1 diabetes and up to 20 % in first-degree relatives of CD patients.[15] Based on a clinical review the prevalence of CD was estimated between 2-3% in low-BMD populations.[17] A recent meta-analysis showed a prevalence of biopsy-proven CD of 1.6% in patients with osteoporosis.[18]

From 1999 onwards, fracture liaison services (FLSs) were initiated aiming at reduction of subsequent fracture risk in high-risk patients, namely those who sustained a recent fracture.[19,20] Besides screening for osteoporosis, screening for metabolic bone disorders is recommended in FLS patients.[21-24] In general, laboratory evaluation of secondary causes of osteoporosis and metabolic bone disorders does not include screening for CD. Rios *et al.* concluded that there is no evidence for routine screening for CD in all patients with low BMD.[17]

To our knowledge, the prevalence of CD in an FLS population has not been studied so far. This might be important, given the fact that CD is associated with increased fracture risk.[6, 13] Therefore, our aim was to study the prevalence of CD in an FLS population. In view of the increased risk of fractures in CD, we hypothesized that CD would be more frequent in the FLS population than the reported prevalence in the total population.

METHODS

Fracture liaison service

We conducted a retrospective cohort study in patients with a recent clinical fracture, aged 50-90 years, visiting the FLS of a regional teaching hospital for fracture risk evaluation (VieCuri Medical Center, Venlo, The Netherlands). Patients with a skull fracture, patients older than 90 years and patients with an active malignancy were excluded.

FLS attendees received a detailed questionnaire for evaluation of clinical risk factors for fractures, medical history, medication, previous fractures, and calcium intake and were scheduled for dual x-ray absorptiometry (DXA) measurement and a blood test. A visit at the outpatient clinic was scheduled after completion of these tests. At this visit height and weight were assessed, the questionnaire was evaluated and additional questions were asked. If laboratory results were abnormal, additional investigations were performed for detailed evaluation of newly diagnosed disorders when necessary. Depending on the BMD results, calcium intake and serum 25-hydroxyvitamin D [25(OH)D] levels, patients were treated with calcium and vitamin D supplements, and anti-osteoporosis medication according to the Dutch guidelines for treatment of osteoporosis.[25]

Index fractures were classified according to the Center classification: hip, major (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and proximal humerus), minor (all others except major and finger & toe fractures), and finger & toe fractures.[26]

DXA and VFA

BMD in the left or right hip and the lumbar spine was determined using dual-energy X-ray absorptiometry (DXA) with the Hologic QDR 4500 (Hologic, Bedford, MA, USA). Diagnosis of osteoporosis was based on the World Health Organization criteria for BMD [27], as provided by the manufacturer for women and men and which are based on the National Health and Nutrition Examination Survey III database. T-score calculations were done for women with a female and for men with a male reference population, as provided by the manufacturer. Patients were classified according to

the lowest value of T-score in total hip, femoral neck, or lumbar spine: osteoporosis as a T-score of -2.5 or less, osteopenia as a T-score between -2.5 and -1.0, and normal BMD as a T- score of -1.0 or higher.

Assessment of vertebral fractures was performed via vertebral fracture assessment (VFA). Vertebral fractures were graded according to the grading of Genant *et al*. as grade 1, 20–24% reduction in vertebral body height at the anterior, mid, or posterior location; grade 2, 25–39%; or grade 3, ≥40% reduction, respectively.[28]

Screening and diagnosis of celiac disease

In accordance with the Dutch and American guidelines of CD, as first-line test the serological screening for CD was performed in this low risk cohort.[29,30] Serological screening consisted of measurement of serum IgA and IgA tissue transglutaminase antibodies (tTG). Serum IgA tTG values were measured using the ELiA Celikey IgA kit (Phadia AB, Uppsala, Sweden). The sensitivity and specificity for this test are 96% and 99%, respectively. Anti-tTG IgA can only be assessed accurately if an IgA deficiency is excluded. Since IgA deficiency is more prevalent in patients with CD than in the general population, IgA was evaluated in all patients in addition to anti-tTG IgA.[31] If the IgA titer was less than 0.2 g/l, IgG tTG antibodies were measured. An anti-tTG IgA titer of 8 U/ml or more was considered as a positive test result suspicious for CD. In patients with a positive anti-tTG IgA test, without a history of positive CD serology, an additional anti-endomysial IgA (EMA) (SciMedX IFA, Libra Diagnostica) test was performed as confirmation test. The sensitivity and specificity for this test vary between 95-99% and 97-98%, respectively.

In the case of positive anti-tTG and anti-EMA test result, patients were referred to the gastroenterologist for a duodenoscopy with duodenal biopsies. Histopathological examination was performed according to the Modified Marsh criteria.[32,33] This classification describes the histopathology of CD, based on 3 aspects: microscopic enteritis (increased intraepithelial lymphocyte (IEL) count), crypt hyperplasia and villus atrophy.

CD was diagnosed in case of a positive anti-tTG IgA and anti-endomysial IgA serology in combination with a duodenal biopsy with characteristics of CD conform the Modified Marsh classification.

Since the positive serology for CD can normalize with a gluten-free diet, CD cannot be excluded with negative serology. In addition to the serology, we verified the past medical history. In the case of a positive medical history for celiac disease, the medical record of the patient was checked for positive serology and duodenal biopsies in the past.

Statistics

Data were analyzed using descriptive statistics (mean, median) by IBM SPSS statistics 24. This retrospective cohort study was approved by the medical research ethics committee of the Academic Hospital Maastricht/University Maastricht (METC 2020-1508).

RESULTS

From a total of 2376 consecutive patients with a recent fracture who were invited at the FLS, 1042 patients (43.9%) actually attended the FLS. All FLS attendees were screened for CD. As shown in Table 1, median age of the study population was 66.0 years (Interquartile range (IQR) 15) and 719 (69.0%) were women. The majority (54.4%) had a minor fracture, 27.6% a major fracture, 6.9% a hip fracture and 11% a finger or toe fracture. Osteoporosis was diagnosed in 26.4%, osteopenia in 50.8% and 22.8% had a normal BMD. VFA analysis showed at least one prevalent vertebral fracture (at least one grade 1, 2 or 3) in 303 patients (29.1%) and at least one grade 2 or 3 vertebral fracture in 190 patients (18.2%). Vitamin D deficiency (serum 25(OH) D < 50 nmol/l) was present in 40%. The median serum calcium (corrected for serum albumin) was 2.42 mmol/l (IQR 0.10). None of the patients had hypocalcemia (serum calcium corrected for albumin < 2.10 mmol/l) and 69 patients had hypercalcemia with a corrected serum calcium of > 2.55 mmol/l. The median parathyroid hormone (PTH) was 5.3 pmol/l (IQR 3.5) (reference range: 2.2-10.0 pmol/l). The median hemoglobin was 8.5 mmol/l (IQR 0.9). In total 75 patients had anemia; of which 35 men with a hemoglobin of < 8.0 mmol/l, and 40 women with a hemoglobin of < 7.2 mol/l. The self-reported calcium intake was 780.0 mg per day (IQR 387.0).

Serologic testing and histopathological testing for CD

Two out of 1042 patients had IgA deficiency (0.19%) and were further tested with anti-tTG IgG which was negative in both. Anti-tTG IgA serology was positive in 4 (0.38%) patients (patient A-D, table 2). In one patient with previously positive CD serology and biopsy-proven CD, current anti-tTG IgA serology was negative (patient E, table 2). Of the four patients with positive anti-tTG IgA serology, one patient was already diagnosed with biopsy-proven CD (patient D). The tTG titers varied between 1.6 U/ml and 91.4 U/ml (normal range < 8.0 U/ml). The three new patients with positive serology all had a positive IgA anti-EMA.

Table 1. Baseline characteristics FLS population (n=1042)

Age (years)	66.0 (15)
Women	69.0
Length (cm)[a]	165.5 (12)
Weight (kg)[a]	75.0 (19.7)
BMI (kg/m^2)[a]	26.8 (6.2)
Fracture type	
Finger or toe	11.0
Minor	54.4
Major	27.6
Hip	6.9
BMD[b]	
Normal BMD	22.8
Osteopenia	50.8
Osteoporosis	26.4
Vertebral fractures[c]	
At least one grade 1-3	29.1
At least one grade 2-3	18.2
Grade 1	15.1
Grade 2	13.8
Grade 3	6.5
Self-reported calcium intake (mg/day)[d]	780.0 (387.0)
Calcium (mmol/l)	2.42 (0.10)
Phosphate (mmol/l)	1.13 (0.22)
Albumin (g/l)	40 (4)
PTH (pmol/l)	5.3 (3.5)
Hemoglobin (mmol/l)	8.5 (0.9)
IgA (g/l), <0.2	0.19
Anti-tTG IgA (U/ml), >8	0.38
Vitamin D (nmol/l), <50	40.0

Data presented as median (IQR) or percentages. [a] Data missing of 6 patients. [b] Data missing of 2 patients. [c] Data missing of 3 patients. [d] Data missing of 22 patients. Abbreviations: BMI, body mass index; BMD, bone mineral density; PTH, parathyroid hormone; anti-tTG, anti-tissue transglutaminase.

Table 2. Characteristics of the FLS patients with positive tTG serology or known celiac disease

	Patient A	**Patient B**
Age (years)	64	50
Gender	Female	Female
Length (cm)	163.3	162
Weight (kg)	81.9	62.2
BMI (kg/m^2)	30.71	23.70
Fracture type (Center)	Minor	Minor
Fracture location	Radial head	Distal radius
BMD (T-scores)		
Lumbar spine	-2.6	-2.9
Femoral neck	-2.4	-2.2
Total hip	-2.2	-0.8
BMD, categorical	Osteoporosis	Osteoporosis
VFA	No VF	No VF
Self-reported calcium intake (mg/day)	711	369
Calcium (mmol/l)	2.35	2.46
Phosphate (mmol/l)	1.30	1.25
Albumin (g/l)	39	41
25-OH vitamin D (nmol/l)	75	101
PTH (pmol/l)	4.4	4.0
Hemoglobin (mmol/l)	7.4	8.0
IgA (g/l)	6.38	2.72
IgA anti-tTG (U/ml)	91.4	36.5
IgA anti-EMA	Positive	positive
Duodenal biopsy	-	Marsh 3c
	Uncertain celiac disease	Proven celiac disease (new)
Osteoporosis treatment	Refused treatment	Start alendronic acid

Abbreviations: FLS, fracture liaison service; BMI, body mass index; BMD, bone mineral density; VFA, vertebral fracture assessment; VF, vertebral fracture;

Patient C	Patient D	Patient E
68	76	60
Female	Male	Male
164.6	178	183.5
69.7	85	86
25.73	26.83	25.54
Major	Minor	Minor
Tibial plateau	Tarsal bone	Midshaft ulnar
-0.2	-1.7	-0.7
-1.2	-2.3	-0.2
-0.4	-1.8	0
Osteopenia	Osteopenia	Normal BMD
Th11 grade 1	Th12 grade 3	No VF
1169	1028	1020
2.43	2.42	2.34
1.17	1.03	1.00
38	34.0	41.0
29	83	60
7.8	18.0	5.0
8.3	8.2	8.8
2.14	4.03	4.43
24.6	37.4	1.6
positive	not performed	not performed
Marsh 3a	Marsh 3b	Marsh 3b
Proven celiac disease (new)	Proven celiac disease (known)	Proven celiac disease (known)
No indication for treatment	Treated with risedronic acid	No indication for treatment

PTH, parathyroid hormone; IgA, Immunoglobulin A; anti-tTG, anti-tissue transglutaminase antibodies; anti-EMA anti-endomysial antibodies.

Based on the positive serology with an anti-tTG IgA of 91.4 U/ml and positive anti-EMA IgA, patient A was suspected for having CD, but she refused further examination and treatment. The two other new patients with positive serology were further evaluated by the gastroenterologist. Duodenal biopsies confirmed the diagnosis of CD in both patients (patient B and C) with biopsy results of Marsh 3c and 3a histology, respectively. Patients D and E with known CD had both previous biopsy results with Marsh 3b histology. The prevalence of biopsy-proven CD in our FLS cohort was therefore 0.38% (4/1042), with newly diagnosed, biopsy-proven CD in 0.19% (2/1042).

Symptoms and signs in CD patients at the FLS

At the outpatient clinic, only one patient (B) had gastro-intestinal complaints, namely loose stools. In two patients CD was diagnosed three and nine years before the visit at the FLS, based on iron deficiency anemia in patient D and gastro-intestinal complaints in patient E. One patient (C) had a low vitamin D, the others had a normal vitamin D level (reference range: 50-140 nmol/l). In patient D the PTH was 18 pmol/l with normal calcium and vitamin D levels, which points at a secondary hyperparathyroidism possibly due to malabsorption. BMD was normal in one patient (Patient E), two patients had osteopenia (C and D) and two had osteoporosis (A and B). Prevalent VFs were found in two patients (one grade 1 vertebral fracture in patient C and one grade 3 vertebral fracture in patient D).

Treatment of CD and osteoporosis

Patient A refused treatment for CD and osteoporosis. Patients B and C started a gluten free diet and patients D and E already had a gluten free diet. All four patients (B-E) had regular visits at the outpatient clinic of the gastroenterologist. Treatment with oral bisphosphonates was started in patient B because of the diagnosis of osteoporosis after a recent major osteoporotic fracture at the distal radius, patient D already received treatment with risedronic acid. Patient C and E did not receive anti-osteoporosis treatment according to the Dutch guidelines (indication for treatment: T-score ≤ -2.5 and/or a moderate or severe vertebral fracture).

DISCUSSION

In this cohort of 1042 consecutive FLS patients, four patients had biopsy-proven CD. In two patients CD was already known (0.19%) and in two patients CD was newly detected (0.19%) by systematic serologic testing. One patient was suspected of having CD but refused further analysis. Since we based the diagnosis of CD on well-established criteria of positive CD serology and abnormal duodenal histology [34,35], the diagnosis of CD could not be confirmed in the fifth patient.

The prevalence of CD in general unselected Western populations is close to 1% and in the general unselected Northern European populations it is approximately 1-1.5%.[15] In a Dutch population of healthy blood donors the reported prevalence of biopsy-proven CD was 0.33%.[16] The prevalence of 0.38% in our Dutch FLS cohort was somewhat lower than reported in the general Western population and in the same range as in the Dutch healthy blood donors, but it was lower than most of the reported prevalences of CD in osteoporosis patients.[15,16] Studies of the prevalence of CD in populations with osteoporosis showed varying prevalences. Legroux-Gérot *et al.* did not demonstrate positive CD serology (anti-tTG) in a cohort of 140 patients with osteoporosis.[36] Nuti *et al.* found a positive CD serology in 24 (9.4%) patients with osteoporosis, but only in 10 patients a biopsy was done to prove CD.[37] Gonzalez *et al.* reported a prevalence of biopsy-proven CD of 0.8% in osteoporosis patients which was demonstrated to be equal to the prevalence in the healthy population.[38] A recent meta-analysis reported a prevalence of biopsy-proven CD of 1.6% among 3188 individuals with osteoporosis.[18] These results of varying prevalences might be explained by the different populations and importantly also by the different screening tests which were used for the diagnosis of CD. Hill *et al.* described differences in sensitivity and specificity of the serological tests.[39]

The prevalence of CD in patients with a recent fracture at the FLS has not been studied before. This might be important, given the fact that CD is associated with increased fracture risk.[6,13] Hjelle *et al.* studied the prevalence of CD in 400 patients aged 40 years or older with a distal radius or ankle fracture compared to community-based controls.[40] The diagnosis of CD was based on serological screening of anti-tTG IgA in combination with histology from duodenal biopsy or a previous diagnosis of CD. Three patients with a fracture had known CD and among all patients with a fracture, 10 had positive serological screening and nine of them underwent duodenal biopsies. Six patients with a fracture were newly diagnosed with biopsy-proven CD (a prevalence of 1.5%) and in total nine patients had CD, a prevalence of 2.25%. In the control group of 197 patients four had biopsy-proven CD (2.0%) and in one patient with positive serology no biopsy was performed. Serology was only positive in two controls because of the use of a gluten free diet in three known CD patients.[40] In this study, in patients with a fracture a positive anti-tTG IgA was more prevalent than in controls, but the prevalence of biopsy-proven CD in the fracture cohort was comparable to the control cohort. Compared to our study, the prevalence of CD was higher, although it was only studied in patients with a distal radius and ankle fracture. In addition, the prevalence in the control group was higher than in the general Western population. The prevalence of CD in our Dutch FLS cohort was comparable to the reported prevalence of CD in healthy Dutch blood donors. Hence, based on the study of Hjelle *et al.* and our findings, the prevalence of CD is not higher compared to healthy subjects without fractures. Therefore, we do not recommend standard screening for CD in all patients with a recent fracture.

The two patients with known CD of our cohort had signs or symptoms of CD, namely iron deficiency anemia and gastro-intestinal complaints at the time of the CD diagnosis years ago. The three patients with new positive serology were not clinically suspected and therefore did not present as the classical phenotype, but seemed to have a subclinical or non-classical CD. It has been demonstrated that in the past years an increasing part of the CD patients has a subclinical CD or a non-classical phenotype instead of the classical CD phenotype.[2]

Larussa *et al.* reported that a low BMD was found in 38-72% of patients at time of diagnosis of CD and in 9-47% of patients on a gluten-free diet.[41] In small a cohort patients aged > 65 years with a new diagnosis of CD, osteoporosis was found in 67% of men and 70% of the women.[42] Appropriate treatment of CD relieved symptoms and can improve BMD.[10-12] Improvement of BMD with a gluten-free diet could also be achieved in patients aged > 65 years.[42]

In our cohort, of the five with positive serology or biopsy-proven CD, two had osteoporosis (40%), two had osteopenia (40%) and one had a normal BMD. One patient had a major fracture at the tibia (patient C). On the other hand, only 0.73% (2/275) of all patients with osteoporosis and only 0.35% (1/288) of all patients with a major fracture and 0.66% (2/303) of all patients with a prevalent vertebral fracture had CD. Therefore, fracture or BMD characteristics cannot be used to distinguish patients with possible CD from patients without CD.

The costs of serologic CD screening (IgA and anti-tTG IgA) at our hospital were €22,42 per patient and for the confirmation test (anti-endomysial IgA) €32,41. Given the low prevalence of CD in our FLS cohort, the number needed to screen in order to diagnose one patient with CD is 261. In FLS patients with osteoporosis the number needed to screen was 138 and in patients with a major osteoporotic fracture or a prevalent VF it was 288 and 152, respectively. Based on these findings, we believe screening for CD in FLS patients is not recommended, which is in line with Laszkowska *et al.* who also reported that routinely screening for CD in osteoporosis is not recommended because of the low prevalence of CD.[18] Nevertheless, it will be still indicated to analyze the presence of CD in FLS patients with laboratory results, comorbidity or symptoms suggestive of CD. This is in line with the recommendation of Rios *et al.* of a targeted case finding approach.[17] Further, in younger patients with osteoporosis (aged < 50 years) it is indicated to perform serological screening for CD because underlying causes of osteoporosis or metabolic bone diseases are more prevalent in these patients.[43]

This study has several limitations. Approximately 50 % of invited patients with a recent fracture actually attended the FLS. It is therefore unknown whether the prevalence of CD in the attenders is comparable of those of the non-attenders. There might be a selection bias since patients with known CD will have standard DXA

evaluations in the Netherlands according to the guidelines [29], which could have led to a higher proportion of CD patients in FLS non-attenders. Furthermore, one patient with positive serology refused further analysis for CD. Therefore, it was not possible to confirm the positive serology with biopsies to diagnose CD properly. Thirdly, we did not check if patients were eating a gluten-free diet. The use of a gluten-free diet can normalize serology for CD. Over the past years there is an increase in people consuming a gluten-free diet. This increase can be explained partially because of people without CD avoiding gluten, for example as 'healthy' lifestyle.[44, 45] Fourthly, at our FLS there was no systematic evaluation of gastro-intestinal symptoms and no standard evaluation of the family history of CD. Therefore, we could not calculate the number needed to screen in FLS patients with gastro-intestinal complaints, nor could we calculate the number needed to screen in the high-risk patients with a first-degree relative with CD. One of the strengths of this study was that serological screening consisted of measurement of serum IgA and IgA tissue transglutaminase antibodies (tTG) with a sensitivity and specificity for this test of 96% and 99%, respectively. Further, this was the first study for CD screening in a general FLS population.

In conclusion, the prevalence of CD in patients with a recent fracture at the FLS was 0.38% and within the range of reported prevalences in the Western-European population (0.33% to 1.5%). Newly diagnosed CD was only found in 0.19%. We therefore believe that standard screening for CD in FLS patients is not recommended.

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CHAPTER 5

CARDIOVASCULAR RISK FACTOR ANALYSIS IN PATIENTS WITH A RECENT CLINICAL FRACTURE AT THE FRACTURE LIAISON SERVICE

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Biomed Res Int. 2014;2014:710945

ABSTRACT

Patients with a low bone mineral density have an increased risk of cardiovascular diseases (CVD) and venous thromboembolic events (VTE). The aim of our retrospective chart review was to investigate the prevalence of CVD, VTE, hypertension (HT), and diabetes mellitus type 2 (DM2) in patients with a recent clinical fracture visiting the Fracture Liaison Service (FLS). Out of 3057 patients aged 50–90 years, 1359 consecutive patients, who agreed and were able to visit the FLS for fracture risk evaluation, were included (71.7% women; mean age 65.2 year). Based on medical history, 29.9% had a history of CVD (13.7%), VTE (1.7%), HT (14.9%), and DM2 (7.1%) or a combination. Their prevalence increased with age (21% in patients aged 50–59 years to 48% in patients aged >80 years) and was higher in men than in women (36% versus 27%), but independent of bone mineral density and fracture type. Careful evaluation of medical history with respect to these risk factors should be performed in patients with a recent clinical fracture before starting treatment with medications that increase the risk of VTE or cardiovascular events, such as raloxifene, strontium ranelate, or NSAIDs.

INTRODUCTION

Osteoporosis and cardiovascular diseases (CVD) are two health care problems with a major impact on mortality and morbidity. In addition, the prevalence of both conditions increases as the population ages, and it is expected that the number of patients suffering from these conditions will rise in the future due to the increased life expectancy. Patients with a recent clinical fracture are screened and treated for osteoporosis, if necessary, at the Fracture Liaison Service (FLS) according to guidelines on osteoporosis and fracture prevention.[1-6]

Patients with a low bone mineral density (BMD) have an increased risk for new cardiovascular events [7,8] and low BMD is associated with more severe or advanced vascular calcification [9-16]. Postmenopausal women were reported to have an increased risk of cardiovascular events [17], with higher mortality [18], although in other studies these associations were not observed.[19]. On the other hand, in patients diagnosed with a CVD, bone loss and fracture risk were increased.[20-25]

The association between CVD and low BMD has clinical consequences for several therapies. Raloxifene is contraindicated in postmenopausal patients with a history of or an increased risk for venous thromboembolic events (VTE).[26,27] Nonsteroidal anti-inflammatory drugs (NSAIDs), prescribed for pain management, are contraindicated in patients with CVD or at risk of CVD including hypertension (HT), heart failure, and diabetes mellitus type 2 (DM2).[27,28]. Strontium ranelate is contraindicated in patients with a history of cardiovascular diseases.[29]

The aim of our retrospective chart review was therefore to investigate the prevalence of cardiovascular risk factors such as CVD, VTE, HT, and DM2 in medical history in patients at highest risk for a subsequent fracture, namely, those with a recent clinical fracture visiting the FLS.

METHODS

Study design and population

This study was designed as a retrospective chart review to examine the prevalence of cardiovascular risk factors in postmenopausal women and men aged between 50 and 90 years with a recent clinical vertebral or nonvertebral fracture who were evaluated at FLS of VieCuri Medical Center Noord-Limburg located in Venlo (The Netherlands). Patients with metastatic cancer in bone, fracture due to high energy trauma, or failure of prosthesis were excluded.

After primary fracture care, a specialized nurse in osteoporosis invited all patients with a recent clinical fracture to the FLS for screening for osteoporosis according to the Dutch guidelines.[1] Patients who agreed to be evaluated at the FLS received a detailed questionnaire for evaluation of risk factors for fractures, falls, detailed medical history including previous fractures and medication use, and daily dietary calcium intake. During the visit at the FLS, a trained nurse measured height and weight and evaluated the questionnaire with special attention to medical history and daily dietary calcium intake. In addition a BMD measurement with dual-energy X-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck was performed and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease.[30] Depending on the results of BMD measurement, calcium intake, and serum 25-hydroxyvitamin D [25(OH)D] levels, patients were treated with adequate calcium intake, vitamin D supplements, and antiosteoporosis medication according to the Dutch guidelines for treatment of osteoporosis.[1]

Fractures were classified according to Center *et al.* into hip fractures, major fractures (vertebra, multiple rib, humerus, pelvis, distal femur, and proximal tibia), minor fractures (all remaining fractures except fingers and toes), and finger and toe fractures.[31]

Bone densitometry

BMD in the hip and lumbar spine was measured using DXA with the Hologic QDR 4500 (Hologic, Bedford, MA, USA). Osteoporosis was diagnosed according to the WHO criteria for BMD.[31] Patients were classified according to the lowest value of *T*-score femoral neck, total hip, or lumbar spine. *T*-scores of ≤−2.5 standard deviations (SD) below the reference mean were classified as osteoporosis; *T*-scores between −1.0 and −2.5 SD were classified as osteopenia; and *T*-scores ≥−1.0 SD were classified as normal.

Cardiovascular Risk Factors

Medical history of all patients was systematically screened and cardiovascular risk factors were classified into CVD, VTE, HT, and DM2. CVD comprised ischemic heart disease, myocardial infarction, angina pectoris, percutaneous coronary intervention, coronary bypass, cerebrovascular accident, transient ischemic attack, and peripheral artery disease. VTE comprised venous thromboembolism and pulmonary embolism. In addition, patients were classified as having at least one cardiovascular risk factor if CVD or VTE or HT was present in medical history.

Statistical Analysis

Results are presented as means ± SD or percentages. Chi-square tests and Fisher's exact tests were used to test whether the variables are independent. Subgroup analyses were performed for gender, age per decade, BMD (normal versus osteopenia versus osteoporosis), and fracture type according to the Center classification (finger and toe versus minor versus major versus hip). Logistic regression analyses were performed to adjust for age, sex, BMD (normal versus osteopenia versus osteoporosis), and fracture type according to the Center classification (finger and toe versus minor versus major versus hip). All analyses were performed using SPSS for Mac (version 21.0, IBM SPSS Statistics, USA). A *P* value ≤ 0.05 was considered as statistically significant.

RESULTS

Study population

From January 2009 until June 2011, 3131 patients aged between 50 and 90 years visited the emergency department with a recent clinical fracture. Seventy-four patients deceased before the invitation for fracture risk evaluation was sent, resulting in 3057 patients being invited. Of those, 1694 patients (55.4%) visited the FLS of whom 1359 (44.5%) had a fracture risk evaluation including BMD measurement. A total of 1359 patients (71.7% women and 28.3% men) with a mean age of 65.2 ± 9.5 years were evaluated at the FLS (Table 1). Osteoporosis was diagnosed in 29.6%, osteopenia was diagnosed in 47.7%, and 22.7% had a normal BMD. According to the Center classification [31], 7.9% sustained a hip fracture, 28.7% a major fracture, 57.7% a minor fracture, and 5.7% a fracture of finger or toe. Based on medical history, 29.9% of the patients had a diagnosis of either CVD and/or VTE and/or hypertension and/or DM2. CVD was present in 13.7%, VTE in 1.7%, hypertension in 14.9%, and DM2 in 7.1% of patients visiting the FLS with a recent clinical fracture (Table 2).

Table. 1 Characteristics of the study population.

	Total (n=1359)	**Women** (n=974)	**Men** (n=385)
Age (years)	65.2 ± 9.5	65.6 ± 9.5	64.2 ± 9.4
Women	974 (71.7)		
Weight (kg)[a]	73.7 ± 14.6	70.3 ± 13.5	82.6 ± 13.4
Height (m)[b]	1.68 ± 0.09	1.64 ± 0.07	1.76 ± 0.08
BMI (kg/m^2)[c]	26.3 ± 4.5	26.1 ± 4.7	26.7 ± 3.8
Fracture type			
Hip	108 (7.9)	68 (7.0)	40 (10.4)
Major	390 (28.7)	281 (28.9)	109 (28.3)
Minor	784 (57.7)	571 (58.6)	213 (55.3)
Finger and toe	77 (5.7)	54 (5.5)	23 (6.0)
BMD			
Osteoporosis	402 (29.6)	329 (33.8)	73 (19.0)
Osteopenia	648 (47.7)	457 (46.9)	191 (49.6)
Normal BMD	309 (22.7)	188 (19.3)	121 (31.4)

Data presented as mean ± SD or number (percentage). [a] Measured in 1194 patients (855 women, 339 men). [b] Measured in 1237 patients (995 women, 352 men). [c] Calculated for 1150 patients (824 women, 326 men). Abbreviations: BMI, body mass index, BMD, bone mineral density.

Cardiovascular Risk Factors and Gender

The prevalence of CVD and/or VTE and/or hypertension and/or DM2 was significantly higher in men than in women (36.3% versus 27.3%; p=0.001) (Table 2). CVD was more frequently diagnosed in men (p<0.001), whereas the prevalence of VTE, HT, and DM2 was comparable for men and women. For the subcategories of CVD, myocardial infarction (p=0.001), percutaneous coronary intervention (p<0.001), and peripheral arterial disease (p=0.001) were more frequently diagnosed in men. For other subcategories of CVD and for subcategories of VTE, HT, and DM2, the prevalence of those diseases was comparable between men and women.

Cardiovascular Risk Factors and Bone Mineral Density

There was no significant difference in the prevalence of CVD and/or VTE and/or HT and/or DM2 between patients with osteoporosis, osteopenia, and normal BMD (28.6%, 31.2%, and 29.1%, resp.; p=NS). Further, there was no significant difference in the prevalence of CVD, VTE, HT, DM2, and the subcategories of CVD and VTE (data not shown).

Table 2. Prevalence of cardiovascular risk factors and diabetes mellitus type 2 in patients presenting with a fracture after age 50

	Total (n=1359) N (%)	Women (n=974) N (%)	Men (n=385) N (%)	Value	df	P value
Cardiovascular disease (CVD)[a]	186 (13.7)	102 (10.5)	84 (21.8)	30.068	1	<0.001
Ischemic heart disease	3 (0.2)	2 (0.2)	1 (0.3)			NS[b]
Myocardial infarction	39 (2.9)	19 (2.0)	20 (5.2)	10.418	1	0.001
Angina pectoris	27 (2.0)	18 (1.8)	9 (2.3)	0.340	1	NS
Percutaneous coronary intervention	33 (2.4)	12 (1.2)	21 (5.5)	20.765	1	<0.001
Coronary bypass	22 (1.6)	12 (1.2)	10 (2.6)	3.230	1	NS
Cerebrovascular accident	44 (3.2)	26 (2.7)	18 (4.7)	3.544	1	NS
Transient ischemic attack	35 (2.6)	24 (2.5)	11 (2.9)	0.170	1	NS
Peripheral artery disease	40 (2.9)	19 (2.0)	21 (5.5)	11.858	1	0.001
Venous thromboembolic events (VTE)[c]	23 (1.7)	18 (1.8)	5 (1.3)	0.500	1	NS
Venous thromboembolism	15 (1.1)	13 (1.3)	2 (0.5)			NS
Pulmonary embolism	10 (0.7)	7 (0.7)	3 (0.8)			NS
Hypertension (HT)	202 (14.9)	145 (14.9)	57 (14.8)	0.001	1	NS
Diabetes mellitus type 2 (DM2)	96 (7.1)	68 (7.0)	28 (7.3)	0.036	1	NS
CVD or VTE	202 (14.7)	112 (11.5)	88 (22.9)	28.362	1	<0.001
CVD or VTE or HT	360 (26.5)	233 (23.9)	127 (33.0)	11.644	1	0.001
CVD or VTE or HT or DM2	407 (29.9)	266 (27.3)	141 (36.3)	11.408	1	0.001

[a] Cardiovascular disease: having ischemic heart disease or myocardial infarction or angina pectoris or percutaneous coronary intervention or bypass or cerebrovascular accident or transient ischemic attack or peripheral artery disease in medical history. [b] Fisher's exact test. [c] Venous thromboembolic events: having venous thromboembolism or pulmonary thromboembolism in medical history.

Cardiovascular Risk Factors and Fracture Type

As shown in Figure 1, in 34.4% of patients with a major fracture at least one cardiovascular risk factor or DM2 was present in medical history, as compared to 28.6% of patients with a minor fracture, 25.9% with a hip fracture, and 27.3% with a fracture of finger or toe (p=NS). In addition, there was no significant difference in the prevalence of CVD including its subcategories, VTE, HT, and DM2, if patients are classified according to fracture type. Only the prevalence of venous thromboembolism was significantly different (1.9% hip versus 0.5% major versus 2.3% minor versus 1.3% finger and toe; p=0.029) (data not shown).

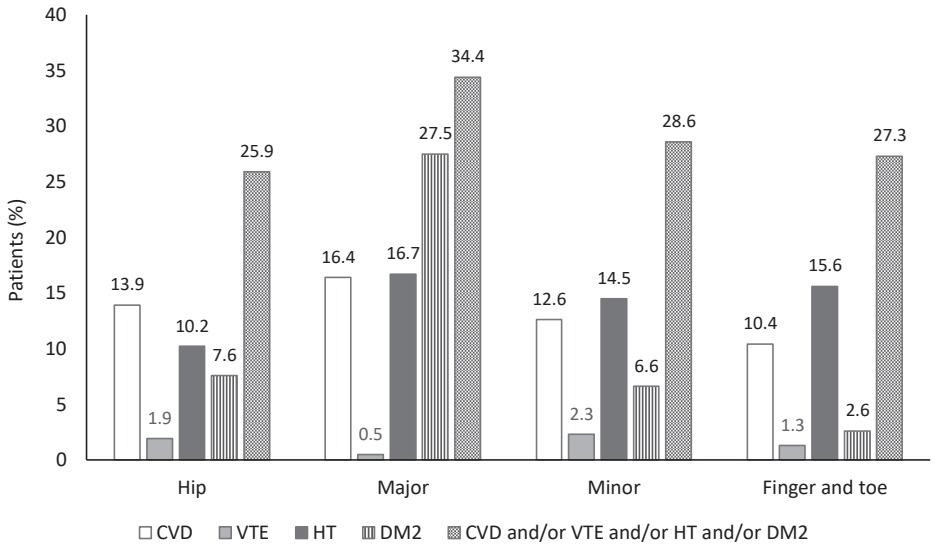

Figure 1. Prevalence of cardiovascular risk factors and diabetes mellitus type 2 according to the center classification. Abbreviations: CVD, cardiovascular disease; VTE, venous thromboembolic event; HT, hypertension; DM2, diabetes mellitus type 2.

Cardiovascular Disease and Age

As presented in Table 3 and in Figure 2, it is shown that the prevalence of CVD and/or VTE and/or HT and/or DM2 in medical history increased significantly with age, rising from 20.8% in patients aged 50–59 years to 48.3% in patients aged 80–89 years ($p<0.001$). From the subgroups, CVD, HT, and DM2 increased significantly with age; CVD was present in 7.6% of patients aged 50–59 years up to 25.8% in patients aged 80–89 years ($p=0.006$); HT 11.0% up to 23.3% ($p=0.001$); and DM2 3.6% up to 23.3% ($p=0.006$). For all subcategories of CVD except percutaneous coronary intervention, the prevalence increased significantly with age (Table 3). For VTE, only a significant increase was found for the presence of pulmonary embolism in medical history ($p=0.009$).

In Table 4, it is shown that, for each decade except for the decade 80–89 years, the prevalence of cardiovascular risk factors is significantly higher in men as compared to women. Only in women and men aged between 60 and 69 years, the prevalence of having at least one cardiovascular risk factor and the prevalence of having at least one cardiovascular risk factor or DM2 is comparable between women and men (Table 4).

In addition, at least one of these conditions was present in medical history in 25.6% of patients aged 50–69 years and in 39.3% patients aged 70 years and older ($p<0.001$). CVD, VTE, HT, or DM2 increased with age and was more frequently present in men

as compared to women: 23.1% of women aged 50–69 years versus 35.6% of women aged 70 years and older (p<0.001 within women) as compared to 31.2% of men aged 50–69 years versus 50.5% men aged 70 years and older (p<0.001 within men) (data not shown).

Table 3. *P*revalence of cardiovascular risk factors and diabetes mellitus type 2 according to age per decade in patients with a recent fracture after age 50.

	50–59 y. (n=447) N (%)	**60–69 y.** (n=474) N (%)	**70–79 y.** (n=318) N (%)	**80–89 y.** (n=120) N (%)	***P*-value**[a]
Cardiovascular disease (CVD)[b]	34 (7.6)	57 (12.0)	64 (20.1)	31 (25.8)	0.006
Ischemic heart disease	0 (0.0)	0 (0.0)	1 (0.3)	2 (1.7)	0.013
Myocardial infarction	5 (1.1)	17 (3.6)	12 (3.8)	5 (4.2)	0.030
Angina pectoris	1 (0.2)	5 (1.1)	14 (4.4)	7 (5.8)	<0.001
Percutaneous coronary intervention	6 (1.3)	14 (3.0)	9 (2.8)	4 (3.3)	NS
Coronary bypass	3 (0.7)	6 (1.3)	10 (3.1)	3 (2.5)	0.038
Cerebrovascular accident	10 (2.2)	6 (1.3)	17 (5.3)	11 (9.2)	<0.001
Transient ischemic attack	7 (1.6)	10 (2.1)	10 (3.1)	8 (6.7)	0.024
Peripheral artery disease	7 (1.6)	13 (2.7)	13 (4.1)	7 (5.8)	0.040
Venous thromboembolic events (VTE)[c]	4 (0.9)	7 (1.5)	7 (2.2)	5 (4.2)	NS
Venous thromboembolism	3 (0.7)	6 (1.3)	4 (1.3)	2 (1.7)	NS
Pulmonary embolism	2 (0.4)	1 (0.2)	3 (0.9)	4 (3.3)	0.009
Hypertension (HT)	49 (11.0)	65 (13.7)	60 (18.9)	28 (23.3)	0.001
Diabetes mellitus type 2 (DM2)	16 (3.6)	42 (8.9)	27 (8.9)	11 (9.2)	0.006
CVD or VTE	37 (8.3)	62 (13.1)	67 (21.1)	34 (28.3)	<0.001
CVD or VTE or HT	81 (18.1)	120 (25.3)	105 (33.0)	54 (45.0)	<0.001
CVD or VTE or HT or DM2	93 (20.8)	142 (30.0	114 (35.8)	58 (48.3)	<0.001

[a] Fisher's exact test. [b] Cardiovascular disease: having ischemic heart disease or myocardial infarction or angina pectoris or percutaneous coronary intervention or bypass or cerebrovascular accident or transient ischemic attack or peripheral artery disease in medical history. [c] Venous thromboembolic events: having venous thromboembolism or pulmonary thromboembolism in medical history.

Adjusted Analyses

After adjustments for age, sex, BMD, and fracture type, age and sex remained significant predictors for CVD (p<0.001 for age; p<0.001 for sex), age for VTE (p=0.012), age and osteoporosis for HT (p<0.001; p=0.048 resp.), and age and osteoporosis for DM2 (p<0.001 for age; p=0.008 for osteoporosis).

Table 4. Prevalence of cardiovascular risk factors and diabetes mellitus type 2 according to age per decade and sex in patients with a recent fracture after age 50.

	50-59 y.			60-69 y.	
	Women (n=302) N (%)	**Men** (n=145) N (%)	**P value**	**Women** (n=343) N (%)	**Men** (n=131) N (%)
Cardiovascular disease (CVD)[a]	12 (4.0)	22 (15.2)	<0.001	22 (4.0)	25 (19.1)
Venous thromboembolic events (VTE)[b]	3 (1.0)	1 (0.7)	NS[c]	6 (1.7)	1 (0.8)
Hypertension (HT)	31 (10.3)	18 (12.4)	NS	49 (14.3)	16 (21.2)
Diabetes mellitus type 2 (DM2)	11 (3.6)	5 (3.4	NS	30 (8.7)	12 (9.2)
CVD or VTE	14 (4.6)	23 (15.9)	<0.001	36 (10.5)	26 (19.8)
CVD or VTE or HT	42 (13.9)	39 (26.9)	0.001	82 (23.9)	38 (29.0)
CVD or VTE or HT or DM2	50 (16.6)	43 (29.7)	0.001	99 (28.9)	43 (32.8)

[a] Cardiovascular disease: having ischemic heart disease or myocardial infarction or angina pectoris or percutaneous coronary intervention or bypass or cerebrovascular accident or transient ischemic attack or peripheral artery disease in medical history.

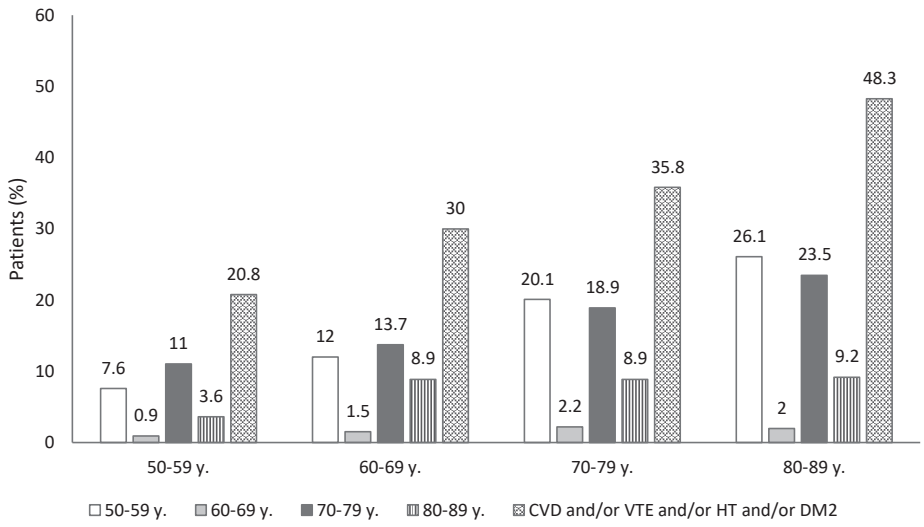

Figure 2. Prevalence of cardiovascular risk factors and diabetes mellitus type 2 according to age per decade.

In adjusted analyses only age and sex were significant predictors for the presence of at least one cardiovascular risk factor (CVD, VTE, or HT), ($p<0.001$ for age; $p<0.001$ for sex) and for the presence of at least one cardiovascular risk factor including DM2 ($p<0.001$ for age; $p<0.001$ for sex).

		70–79 y.			80–89 y.	
P value	**Women** (n=237) N (%)	**Men** (n=81) N (%)	**P value**	**Women** (n=92) N (%)	**Men** (n=28) N (%)	**P value**
0.004	38 (16.0)	26 (32.1)	0.002	20 (21.7)	11 (39.3)	NS
NS[c]	4 (1.7)	3 (3.7)	NS[c]	5 (5.4)	0 (0.0)	NS[c]
NS	40 (16.9)	20 (24.7)	NS	25 (27.2)	3 (10.7)	NS
NS	18 (7.6)	9 (11.1)	NS	9 (9.8)	2 (7.1)	NS[c]
0.007	39 (16.5)	28 (34.6)	0.001	23 (25.0)	11 (39.3)	NS
NS	67 (28.3)	38 (46.9)	0.002	42 (46.7)	12 (42.9)	NS
NS	72 (30.4)	42 (51.9)	0.001	45 (48.9)	13 (46.4)	NS

[b] Venous thromboembolic events: having venous thromboembolism or pulmonary thromboembolism in medical history.

[c] Fisher's exact test.

DISCUSSION

The aim of our retrospective review was to investigate the prevalence of cardiovascular risk factors including CVD, VTE, HT, and DM2 in medical history in patients with a recent clinical fracture visiting the FLS. Based on medical history, nearly one out of three patients had a medical history of CVD, VTE, HT, or DM2. CVD was more frequently present in men, whereas the prevalence of VTE, HT, and DM2 was similar in men and women. With increasing age, the prevalence of CVD, VTE, HT, and DM2 increased as well, up to half of men older than 70 years and of women older than 80 years.

There was no significant increase in the prevalence of these risk factors with decreasing BMD and increasing severity of fracture, except for BMD and HT and DM2. Adjusted analyses showed that age and sex remained significant predictors for the presence of CVD, VTE, HT, DM2, or at least one of these conditions, independent of BMD and fracture type according to the center classification and age and BMD for HT and DM2, independent of other risks.

The presence of cardiovascular risk factors in patients with a recent clinical fracture has important implications with regard to treatment and prevention of osteoporosis. Raloxifene is contraindicated in women with a history of VTE (including venous thromboembolism and pulmonary embolism) or women at risk of VTE [6,33,34], resulting in a contraindication in the prescription of raloxifene in 1.8% of women in

our study. NSAIDs are contraindicated in patients with a history of CVD, heart failure, myocardial infarction, cerebrovascular accident, or transient ischemic attack and in patients with an increased risk of ischemic heart disease such as angina pectoris and percutaneous coronary disease and should be prescribed with caution in patients with HT and DM2 [28,35], resulting in a contraindication for prescription of NSAIDs in 29.9% of patients (27.3% women versus 36.3% men). Recently, the EMA has advised to restrict the prescription of strontium ranelate in patients with a history of VTE, in patients at risk of VTE, and in patients with a CVD or HT in medical history [29], resulting in a contraindication for prescription of strontium ranelate in 26.5% of all patients (23.9% women versus 33.0% men).

Previous research has recommended that the treatment of cardiovascular disease should not only prevent new cardiovascular events, but also prevent fractures by evaluation and treatment of osteoporosis and vice versa.[6]

This study has several limitations. First, the study is designed as a retrospective chart review. Therefore, we were not able to investigate the occurrence of new cardiovascular events after treatment with the antiosteoporosis medications was initiated. Second, only 55.4% of patients who visited the emergency department visited the FLS for fracture risk evaluation. Patients not visiting the FLS might be older, might have more severe fractures such as hip or humerus fractures for which surgical intervention was performed, might have postoperative complications, and might be living in a nursing home and are not able to visit the FLS. In combination with VTE often occurring after a major orthopedic operation such as hip fracture surgery, the prevalence of cardiovascular risk factors might be underestimated.

In conclusion, CVD, VTE, HT, or DM2 was present in medical history of 29.9% of patients with a recent clinical fracture after age 50. The prevalence of these diseases increased with age and was higher in men than in women. These results emphasize that careful evaluation of medical history with respect to cardiovascular risk factors such as CVD, VTE, HT, and DM2 should be performed since medications such as raloxifene, strontium ranelate, and NSAIDs may increase cardiovascular risk or even may be contraindicated in a substantial number of patients with a recent clinical fracture.

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CHAPTER 6

THE ASSOCIATION BETWEEN PREVALENT VERTEBRAL FRACTURES AND BONE QUALITY OF THE DISTAL RADIUS AND DISTAL TIBIA AS MEASURED WITH HR-PQCT IN POSTMENOPAUSAL WOMEN WITH A RECENT NON-VERTEBRAL FRACTURE AT THE FRACTURE LIAISON SERVICE

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Osteoporos Int. 2019 Sep;30(9):1789-1797

ABSTRACT

We evaluated the association between prevalent vertebral fractures and bone micro-architecture and strength measured using HR-pQCT in postmenopausal women with a recent non-vertebral fracture visiting the Fracture Liaison Service. The presence and severity of prevalent vertebral fractures reflect generalized bone deterioration.

Introduction: We evaluated the association between prevalent vertebral fractures (VFs) and bone micro-architecture and strength measured using HR-pQCT in postmenopausal women visiting the Fracture Liaison Service.

Methods: In this cross-sectional study in women aged 50-90 with a recent non-vertebral fracture (NVF), VFs were identified on lateral spine images by Dual-energy X-ray Absorptiometry. Bone micro-architecture and strength was measured at non-dominant distal radius and distal tibia using HR-pQCT. Linear regression analyses were used to estimate the association between prevalent VFs and HR-pQCT parameters.

Results: We included 338 women of whom 74 (21.9%) women had at least one prevalent VF. After adjustment for femoral neck aBMD (FN-aBMD) and other parameters, women with at least one prevalent vertebral fracture had significantly lower total and trabecular vBMD and trabecular number (b: -16.7, -11.8 and -7.8 in radius and -21.4, -16.6 and -7.2 in tibia, respectively), higher trabecular separation at the radius and tibia (b: 9.0 and 9.3, respectively), and lower cortical thickness and calculated ultimate failure load and compressive bone strength at the tibia (b: -5.9, -0.6 and -10.9, respectively) as compared to those without prevalent VFs. Furthermore, more severe prevalent VFs were associated with even lower total and trabecular vBMD and lower ultimate failure load and compressive stiffness at the radius and tibia, and lower trabecular number and higher trabecular separation at the radius.

Conclusion: This study indicates that the presence and severity of prevalent VFs reflect generalized bone deterioration in women with a recent NVF, independently of FN-aBMD.

INTRODUCTION

Vertebral fractures (VFs) are the most frequently occurring osteoporotic fractures.[1-3] Because only one third of patients with VFs present with an acute, symptomatic episode [4], VFs are underdiagnosed.[5,6] The Dutch guideline on osteoporosis and fracture prevention recommends Vertebral Fracture Assessment (VFA) in all patients aged 50 years and older with a recent non-vertebral fracture (NVF).[7] In patients with a recent NVF at the Fracture Liaison Service (FLS), prevalent VFs have been reported in 20-26% of patients [8-10] and moderate or severe prevalent VFs in 15-17%.[8,10]

Prevalent VFs have been positively associated with subsequent VFs and NVFs, independent of age and bone mineral density (BMD).[11-15] Increased fracture risk may be caused by other factors not captured by BMD measurements, such as bone micro-architecture and bone strength. Indeed, previous cross-sectional studies have shown that, compared to subjects without a VF, patients with prevalent VFs have significantly impaired bone micro-architecture of trabecular and cortical bone in the distal radius and tibia after adjustment for BMD in spine or hip.[16-19] Furthermore, in previous prospective studies, deterioration of HR-pQCT indices of trabecular and cortical bone, and lower calculated bone strength improve prediction of fracture beyond femoral neck areal BMD or FRAX scores alone.[20-24]

The above mentioned cross-sectional studies compared patients with prevalent VFs to fracture-free controls [16-19]. Additionally, Stein *et al*. [18] compared women with a prevalent VF to women with a NVF, and reported significantly greater deterioration of bone micro-architecture at the tibia in those with VFs. Currently, there are no studies evaluating whether the presence of a prevalent VF is associated with impaired bone micro-architecture in the presence of a recent NVF. We therefore evaluated the association between prevalent VFs and bone micro-architecture and strength in the distal radius and distal tibia measured using HR-pQCT in postmenopausal women visiting the FLS after a recent NVF.

METHODS

Subject and study procedures

Data from the FX MoVie study, an ongoing prospective observational study, were used. The primary objective of this study is to assess bone structure parameters and bone strength by HR-pQCT and physical activity in relation to falls, fractures and mortality in patients with a recent clinical fracture. Included were 500 patients aged between 50 and 90 years with a recent, radiologically confirmed clinical vertebral or non-vertebral

fracture, who visited the FLS of VieCuri Medical Center in The Netherlands, and who were willing and able to participate. Excluded were non-Caucasian patients, patients with a fracture due to high energy trauma, bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment.

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

The present cross-sectional study includes baseline data of postmenopausal women with a recent NVF. Patients who presented with a symptomatic VF were excluded. Mean time between NVF and baseline assessment was 4.2 ± 1.1 months. Baseline assessment included a detailed questionnaire for evaluation of risk factors for osteoporosis, falls and fractures, laboratory tests to detect contributors to secondary osteoporosis and metabolic bone disease, BMD measurement and lateral imaging of the spine by dual-energy X-ray absorptiometry (DXA), and HR-pQCT scans of the distal radius and tibia. Fractures were categorized according to FRAX into major osteoporotic fractures (except clinical vertebral fractures which were excluded from this study) or all other fractures.[25]

Areal bone mineral density

Areal bone mineral density (aBMD) was measured at the hip and lumbar spine by DXA using the Hologic QDR 4500 (Hologic, Bedford, MA, USA). Lumbar spine evaluation was performed according to the International Society of Clinical Densitometry (ISCD) criteria (https://www.iscd.org/official-positions/6th-iscd-position-development-conference-adult). Vertebrae with grade 2 or 3 deformities according to Genant [26] were excluded and lumbar spine aBMD was determined based on the remaining vertebrae. Lumbar spine evaluation was based on at least two vertebrae.

Osteoporosis was diagnosed according to the World Health Organization (WHO) criteria for BMD.[27] Patients were classified according to the lowest value of T-score in femoral neck, total hip, or lumbar spine. T-scores of ≤ −2.5 standard deviations (SD) below the reference mean were classified as osteoporosis, T-scores between −1.0 and −2.5 SD were classified as osteopenia, and T-scores ≥ −1.0 SD were classified as normal.

Vertebral fracture assessment

Prevalent vertebral fractures were identified on lateral spine images made with DXA. According to the semi-quantitative method of Genant [26], VFs were graded as mild (grade 1, height loss between 20% and 25%), moderate (grade 2, height loss between 25% and 40%), or severe (grade 3, height loss >40%). Patients were

classified according to the most severe VF as those without VFs, those with at least one mild VF, or those with at least one moderate or severe VF. Vertebral deformities related to other conditions such as Scheuermann's disease, degenerative disease and Schmorl's nodes, were not classified as prevalent VF.

HR-pQCT imaging

The non-dominant radius was scanned using the second-generation HR-pQCT scanner (XtremeCT II; Scanco Medical AG, Brüttisellen, Switzerland) using the standard in vivo protocol as provided by the manufacturer (effective energy of 68 kVp, tube current of 1470 μA and 43 ms integration time) unless the patient had previously sustained a distal radius fracture at the non-dominant site, then the dominant site was scanned. The distal tibia was scanned at the same site as the distal radius unless that site was previously fractured, then the other site was scanned. The forearm and lower leg were placed into a carbon fiber cast. The region of interest was determined based on an anteroposterior scout projection of the scan site. A reference line was placed on the distal radius and distal tibia joint surface. The scan started 9.0 mm from the reference line in the proximal direction and spanned 10.2 mm in length. Images were reconstructed using an isotropic voxel size of 61 μm, resulting in 168 consecutive slices. Each scan was graded for motion-induced image artifacts by the operator according to the manufacturer's guideline and as described by Pialat *et al.*.[28] In case the images were of insufficient quality, *i.e.*, grade 4 or 5, the scan was repeated with a maximum up to two times. Only scans with quality 1 to 3 were used for analyses in this study.

Image analysis of HR-pQCT scans

All scans were evaluated using the standard patient evaluation protocol as provided by the manufacturer. We used a fully automated segmentation method, which uses two thresholds and a series of morphological dilatation and erosions to extract the endosteal and periosteal surface of the cortex.[29] This is based on the assumption that trabecular region is enclosed by the cortical region. The periosteal contour was automatically derived and manually modified by a single operator when contours visually deviated from the periosteal boundary. The following bone parameters were measured: volumetric bone mineral density [mgHA/cm3] was assessed for the total region (Dtot) and trabecular (Dtrab) and cortical region (Dcort) separately. For the trabecular region, the micro-architectural parameters trabecular bone volume fraction (Tb.BVTV) [%], trabecular number (Tb.N) [mm-1], trabecular thickness (Tb.Th) [mm], and trabecular separation (Tb.Sp) [mm] were measured. For the cortical region, cortical perimeter (Ct.Pm) [mm], cortical thickness (Ct.Th) [mm], cortical porosity (Ct.Po) [%] and cortical pore diameter (Ct.Po.Dm) [mm] were measured.

Micro-finite element models were generated directly from the segmented HR-pQCT images [30,31] by converting voxels representing bone tissue into brick elements of the same size. A Young's modulus of 10 GPa and a Poisson's ratio of 0.3 were assigned to every element. Compression stiffness and estimated failure load were determined by simulating a "high-friction" compression test in the axial direction.[30]

Statistical analysis

General characteristics and mean HR-pQCT parameters were compared between women with and without prevalent VFs using the independent student's t-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Further, mean HR-pQCT parameters were compared between women according and to prevalent VF severity (none vs. mild (grade 1) vs. moderate or severe (grade 2-3)) using one-way ANOVA with Bonferroni correction. Descriptives are provided as mean ± SD for continuous variables and number (%) for categorical variables. Log-transformation was performed if variables showed a skewed distribution. Multiple linear regression analysis was used to estimate the association between VF and HR-pQCT parameters, yielding unstandardized beta (b) and 95% confidence interval (CI). Potential confounders were included in the analyses if they independently changed the beta-coefficient for VF by at least 5%. All regression analyses were adjusted for age, height, weight, type of recent NVF (major osteoporotic fracture, *i.e.,* hip, proximal humerus and distal radius fracture), previous fractures at or above the age of 50 years, self-reported use of anti-osteoporosis treatment (never vs. history vs. current), and femoral neck aBMD. A P-value ≤ 0.05 was considered statistically significant for general characteristics, and a P-value ≤ 0.002 for HR-pQCT parameters. Analyses were conducted using SPSS for Mac (version 24.0, IBM SPSS statistics, USA).

RESULTS

In total, 338 postmenopausal women with a NVF were included in this study (Figure 1). HR-pQCT scans were not performed in 11 women at the radius, and in 5 women at the tibia because of bilateral fractures. Additionally, 20 radius and 5 tibia scans were excluded because of insufficient scan quality due to motion artifacts, resulting in 307 radius and 328 tibia scans that were included in the analyses.

Of the 338 women, 74 (21.9%) had at least one prevalent VF and 264 had no prevalent VF. General characteristics of women according to their prevalent VF status are shown in Table 1. Compared to women without a prevalent VF, women with at least one prevalent VF were older, had lower femoral neck (FN) and total hip (TH) aBMD, were more likely to have had a previous fracture at or above the age of 50 years and were more likely to have ever used anti-osteoporosis treatment.

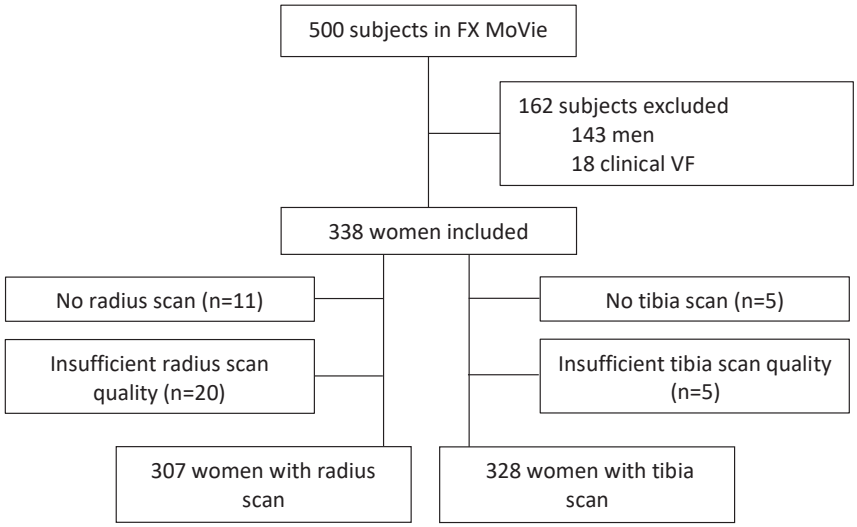

Figure 1. Flowchart of patient inclusion.

HR-pQCT parameters according to prevalent VF status

The mean unadjusted HR-pQCT parameters at the radius and tibia for women according to presence, and severity of prevalent VFs are shown in Table 2. Compared to women without a prevalent VF, those with at least one prevalent VF had lower total and trabecular vBMD, trabecular number, ultimate failure load and compression stiffness, and higher trabecular separation at both the radius and tibia, and lower cortical thickness at the tibia.

Results of linear regression analyses examining the association between prevalent VF status and HR-pQCT parameters at the radius and tibia are shown in Table 3. In the adjusted analyses, at least one prevalent VF was associated with lower total and trabecular vBMD and trabecular number (b: -1.6, -11.8 and -7.8 in the radius and -21.4, -16.6 and -7.2 in the tibia, respectively), and higher trabecular separation at the radius and tibia (b: 9.0 and 9.3, respectively), and lower cortical thickness, ultimate failure load and compression stiffness at the tibia (b: -5.9, -0.6 and -10.9, respectively).

Table 1. General characteristics of e patients with a recent NVF at the FLS according to the presence of prevalent vertebral fracture (n=338).

	No VF (n=264)	**≥ 1 VF Gr. ≥ 1** (n=74)	***p* value**
Age (years)	62.9 ± 7.8	67.7 ± 8.4	0.000
Height (cm)	1.6 ± 0.1	1.6 ± 0.1	0.295
Weight (kg)	74.6 ± 14.3	72.7 ± 12.1	0.296
BMI (kg/m^2)	27.6 ± 5.0	27.1 ± 4.0	0.474
FRAX major osteoporotic fractures	82 (31.1)	30 (40.5)	0.126
LS aBMD (g/cm^2)	0.93 ± 0.14	0.91 ± 0.17	0.388
FN aBMD (g/cm^2)	0.70 ± 0.11	0.67 ± 0.10	0.032
TH aBMD (g/cm^2)	0.85 ± 0.13	0.81 ± 0.12	0.028
BMD, categorical			
Normal BMD	72 (27.3)	13 (17.6)	0.113
Osteopenia	135 (51.1)	38 (51.4)	
Osteoporosis	57 (21.6)	23 (31.1)	
Previous fracture after age 50 years	48 (18.2)	36 (48.6)	0.000
Parent fractured hip	17 (6.4)	4 (5.4)	0.999
Current smoking	36 (13.6)	9 (12.2)	0.741
Glucocorticoids	12 (4.5)	3 (4.1)	0.999
Rheumatoid arthritis	10 (3.8)	4 (5.4)	0.516
Secondary osteoporosis	70 (26.5)	21 (28.4)	0.749
Alcohol ≥ 3 units/day	4 (1.5)	1 (1.4)	0.999
History or current use of anti-osteoporosis drugs	21 (8.0)	19 (26.0)	0.000
Self-reported use of anti-osteoporosis medication	18 (6.9)	18 (24.7)	0.000
Type[a]			
Alendronic acid	11 (61.1)	9 (50.0)	0.887
Risedronic acid	5 (27.8)	6 (33.3)	
Zoledronic acid	0 (0.0)	1 (5.6)	
Unknown	2 (11.1)	2 (11.1)	
Duration (year)[a]	4.5 ± 2.7	5.2 ± 4.1	0.577
Current[a]	3 (16.7)	10 (55.6)	0.015
History[a]	15 (83.3)	8 (44.4)	
Time since cessation of treatment (year)[a]	2.6 ± 2.6	1.1 ± 2.3	0.109
Falls past year	79 (30.0)	21 (28.8)	0.834

Data presented as mean ± standard deviation or number (percentage). [a] Percentage of patients who have ever used anti-osteoporosis medication. Abbreviations: VF, vertebral fracture; BMI, body mass index; LS, lumbar spine; FN, femoral neck, TH, total hip; aBMD, areal bone mineral density.

Table 2. HR-pQCT parameters at the distal tibia and radius according to presence, and severity of prevalent VFs in women with a recent NVF at the FLS.

		Presence of prevalent VFs	Severity of prevalent VFs		
Radius (n=307)	**No VF** (n=240)	**≥1 VF Gr. ≥1** (n=67)	**≥1 VF Gr. 1** (n=35)	**≥1 VF Gr. 2-3** (n=32)	**P-value for trend**
vBMD					
Dtot (mgHA/cm3)	270 ± 62	233 ± 55 *	236 ± 56 *	230 ± 55 *	0.000
Dtrab (mgHA/cm3)	121 ± 39	96 ± 37 *	101 ± 33 *	91 ± 41 *	0.000
Dcort (mgHA/cm3)	892 ± 62	872 ± 69	870 ± 64	875 ± 75	0.068
Micro-architecture					
Tb.N (1/mm)	1.20 ± 0.26	1.02 ± 0.31 *	1.06 ± 0.28 *	0.97 ± 0.34 *	0.000
Tb.Th (mm)	0.22 ± 0.02	0.23 ± 0.02	0.23 ± 0.02	0.23 ± 0.02	0.362
Tb.Sp (mm)	0.86 ± 0.27	1.15 ± 0.68 *	1.04 ± 0.46 *	1.28 ± 0.86 *	0.000
Ct.Po (%)	0.86 ± 0.56	0.88 ± 0.49	0.86 ± 0.43	0.90 ± 0.56	0.899
Ct.Th (mm)	0.92 ± 0.18	0.85 ± 0.15	0.85 ± 0.15	0.84 ± 0.15	0.012
Ct.Po.Dm (mm)	0.19 ± 0.03	0.20 ± 0.03	0.20 ± 0.04	0.20 ± 0.03	0.359
Biomechanical					
F.Ult (kN)	2.81 ± 0.72	2.49 ± 0.55 *	2.58 ± 0.51	2.40 ± 0.59 *	0.002
Scomp (kN/mm)	52 ± 13	47 ± 10 *	49 ± 9	45 ± 10 *	0.002
Tibia (n=328)	**No VF** (n=256)	**≥1 VF Gr. ≥1** (n=72)	**≥1 VF Gr. 1** (n=37)	**≥1 VF Gr. 2-3** (n=35)	**P-value for trend**
vBMD					
Dtot (mgHA/cm3)	243 ± 54	209 ± 46 *	211 ± 42 *	207 ± 52 *	0.000
Dtrab (mgHA/cm3)	140 ± 38	119 ± 34 *	121 ± 31 *	117 ± 37 *	0.000
Dcort (mgHA/cm3)	837 ± 73	813 ± 72	820 ± 66	806 ± 77	0.035
Micro-architecture					
Tb.N (1/mm)	1.19 ± 0.23	1.08 ± 0.29 *	1.10 ± 0.28	1.06 ± 0.30 *	0.004
Tb.Th (mm)	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.02	0.405
Tb.Sp (mm)	0.87 ± 0.33	1.02 ± 0.45 *	0.99 ± 0.44	1.05 ± 0.46 *	0.004
Ct.Po (%)	3.22 ± 1.32	3.22 ± 1.37	3.04 ± 1.12	3.41 ± 1.59	0.505
Ct.Th (mm)	1.21 ± 0.25	1.10 ± 0.21 *	1.10 ± 0.19 *	1.11 ± 0.22	0.005
Ct.Po.Dm (mm)	0.23 ± 0.03	0.23 ± 0.04	0.23 ± 0.03	0.24 ± 0.04	0.426
Biomechanical					
F.Ult (kN)	8.00 ± 1.62	7.14 ± 1.49 *	7.27 ± 1.35 *	7.00 ± 1.63 *	0.000
Scomp (kN/mm)	147 ± 32	131 ± 28 *	133 ± 26 *	128 ± 31 *	0.000

Data presented as mean ± SD. P-value < 0.05 is considered significant. * p < 0.05 compared to patients without a prevalent VF (with Bonferroni correction for multiple testing). Abbreviations: VF, vertebral fracture; vBMD, volumetric bone mineral density; Dtot, total density; Dtrab, trabecular density; Dcort, cortical density; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Ct.Th, cortical thickness; Ct.Po, cortical porosity; Ct.Po.Dm, cortical pore diameter; F.Ult, ultimate failure load; Scomp, compression stiffness.

Table 3. Associations between the presence, severity and number of prevalent vertebral fractures and HR-pQCT parameters in women with a recent NVF at the FLS

	Presence of prevalent VFs	
Radius	**No VF**	**VF,** β (95% CI)
vBMD		
Dtot (mgHA/cm3)	Reference	-16.66 (-31.93, -1.39) *
Dtrab (mgHA/cm3)	Reference	-11.75 (-21.91, -1.58) *
Dcort (mgHA/cm3)	Reference	-9.88 (-26.38, 6.62)
Micro-architecture		
Tb.N (1/mm)	Reference	-7.83 (-15.19, -0.46) *
Tb.Th (mm)	Reference	0.20 (-0.27, 0.67)
Tb.Sp (mm)	Reference	8.98 (0.68, 17.29) *
Ct.Po (%)	Reference	3.26 (-16.09, 22.61)
Ct.Th (mm)	Reference	-3.10 (-7.70, 1.51)
Ct.Po.Dm (mm)	Reference	3.41 (-1.59, 8.41)
Biomechanical		
F.Ult (kN)	Reference	-0.15 (-0.32, 0.02)
Scomp (kN/mm)	Reference	-2.47 (-5.49, 0.55)
Tibia	**No VF**	**VF,** β (95% CI)
vBMD		
Dtot (mgHA/cm3)	Reference	-21.35 (-33.04, -9.66) *
Dtrab (mgHA/cm3)	Reference	-16.55 (-25.22, -7.66) *
Dcort (mgHA/cm3)	Reference	-1.65 (-19.28, 15.97)
Micro-architecture		
Tb.N (1/mm)	Reference	-7.18 (-13.69, -0.67) *
Tb.Th (mm)	Reference	-0.28 (-0.84, 0.27)
Tb.Sp (mm)	Reference	9.31 (1.92, 16.70) *
Ct.Po (%)	Reference	-8.90 (-21.20, 3.39)
Ct.Th (mm)	Reference	-5.90 (-11.69, -0.11) *
Ct.Po.Dm (mm)	Reference	0.95 (-2.71, 4.62)
Biomechanical		
F.Ult (kN)	Reference	-0.55 (-0.90, -0.21) *
Scomp (kN/mm)	Reference	-10.88 (-17.56, -4.21) *

All analyses are adjusted for age, weight, height, type of recent non-vertebral fracture type (major osteoporotic fracture vs. other fractures), previous fractures at or above the age of 50 years, anti-osteoporosis medication (never vs. history vs. current) and femoral neck areal BMD. No prevalent VF is used as the reference group. *, significant.

	Severity of prevalent VFs		
	Gr. 1 VF, β (95% CI)	**Gr. 2-3 VF,** β (95% CI)	**P-value for trend**
	-10.05 (-28.65, 8.56)	-26.10 (-47.65, -4.56) *	0.015 *
	-7.66 (-20.06, 4.73)	-17.57 (-31.92, -3.22) *	0.012 *
	-7.58 (-27.74, 12.58)	-13.16 (-36.50, 10.18)	0.216
	-5.50 (-14.49, 3.49)	-11.15 (-21.56, -0.75) *	0.024 *
	0.16 (-0.41, 0.74)	0.25 (-0.42, 0.91)	0.400
	5.21 (-4.91, 15.33)	14.37 (2.66, 26.08) *	0.014 *
	0.07 (-23.57, 23.70)	7.82 (-19.55, 35.19)	0.628
	-1.62 (-7.24, 4.00)	-5.21 (-11.71, 1.30)	0.117
	2.24 (-3.86, 8.34)	5.08 (-1.99, 12.14)	0.136
	-0.08 (-0.28, 0.13)	-0.26 (-0.49, -0.02) *	0.038 *
	-1.02 (-4.69, 2.66)	-4.55 (-8.80, -0.29) *	0.045 *
	Gr. 1 VF, β (95% CI)	**Gr. 2-3 VF,** β (95% CI)	**P-value for trend**
	-16.83 (-31.23, -2.42) *	-27.58 (-44.02, -11.13) *	0.000 *
	-13.88 (-24.70, -3.05) *	-19.96 (-32.32, -7.61) *	0.000 *
	3.7 (-18.26, 25.20)	-8.69 (-33.50, 16.12)	0.637
	-6.81 (-14.85, 1.22)	-7.68 (-16.85, 1.49)	0.040 *
	-0.40 (-1.09, 0.28)	-0.12 (-0.90, 0.66)	0.479
	8.74 (-0.38, 17.86)	10.09 (-0.32, 20.50)	0.018 *
	-8.10 (-23.28, 7.07)	-10.00 (-27.32, 7.33)	0.167
	-4.49 (-11.63, 2.65)	-7.83 (-15.99, 0.32)	0.036 *
	0.20 (-4.32, 4.72)	1.99 (-3.17, 7.15)	0.492
	-0.47 (-0.89, -0.04) *	-0.67 (-1.15, -0.18) *	0.002 *
	-9.20 (-17.43, -0.97) *	-13.20 (-22.59, -3.80) *	0.001 *

Abbreviations: VF, vertebral fracture; vBMD, volumetric bone mineral density; Dtot, total density; Dtrab, trabecular density; Dcort, cortical density; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Ct.Th, cortical thickness; Ct.Po, cortical porosity; Ct.Po. Dm, cortical pore diameter; F.Ult, ultimate failure load; Scomp, compression stiffness.

HR-pQCT parameters according to prevalent VF severity

Compared to women without prevalent VFs, those with at least one moderate or severe prevalent VF had lower total and trabecular vBMD, trabecular number, ultimate failure load and compression stiffness, and higher trabecular separation at both the radius and tibia (Table 2). Further, a similar pattern was found when patients with at least one mild prevalent VF were compared to those without prevalent VF, with the exception that ultimate failure load and compression stiffness at the radius, and trabecular number and separation at the tibia were not significantly different for these two groups (Table 2).

Adjusted regression analyses showed that total and trabecular vBMD, ultimate failure load and compression stiffness were lower at the radius and tibia (b: -26.10, -17.6, -0.3 and -4.6 in the radius and -27.6, -20.0, -0.7 and -13.2 in the tibia, respectively), trabecular number was lower (b: -10.9), and trabecular separation was higher (b: 14.4) at the radius in women with moderate or severe prevalent VF as compared to those without prevalent VF (Table 3). Further, in women with at least one mild prevalent VF, total and trabecular vBMD and calculated ultimate failure load and compressive bone strength were lower at the tibia (b: -16.4, -13.1, -0.5 an -9.1, respectively) than in those without prevalent VF.

In addition, there was a significant trend analysis for lower total and trabecular vBMD, trabecular number, ultimate failure load and compression stiffness, and higher trabecular separation at the radius and tibia, and lower cortical thickness at the tibia with increasing prevalent VF severity (Table 3).

DISCUSSION

In this study, in postmenopausal women attending the FLS with a recent NVF, the presence of at least one prevalent VFs was independently associated with lower total and trabecular vBMD, lower trabecular number, higher trabecular separation at the radius and tibia and with lower cortical thickness, ultimate failure load and compressive stiffness at the tibia. Furthermore, moderate or severe prevalent VFs were associated with even lower total and trabecular vBMD and lower ultimate failure load and compressive stiffness at the radius and tibia, and lower trabecular number and higher trabecular separation at the radius.

To the best of our knowledge, there are no studies evaluation the association between prevalent VFs and bone micro-architecture and bone strength in patients with a recent NVF. Previous cross-sectional studies have shown that, compared to fracture-free controls, patients with VFs have significantly impaired bone micro-architecture of trabecular and cortical bone in the distal radius and tibia after adjustment for

BMD in spine or hip.[16-19] Furthermore, Stein *et al*. [18] reported a significantly greater deterioration of bone micro-architecture in the tibia, but not the radius in women with a VF compared to those with a NVF. However, in this study by Stein *et al*. [18], only 12 out of 30 women with a VF had a history of a NVF, whereas in our study all patients had a recent NVF.

In line with our findings, two previous studies reported more bone micro-architectural deterioration with increasing severity of prevalent VFs in women [16,17], whereas one study found no association between severity of prevalent VFs and HR-pQCT parameters.[18] In contrast to our study, all three studies compared women with prevalent VFs to fracture-free controls.

The short time since the NVF is important, because patients with a fracture have an increased risk of subsequent fractures, which is highest immediately after the fracture. This imminent subsequent fracture risk emphasizes the need for immediate and accurate secondary fracture prevention. The fact that the presence of a vertebral fracture in postmenopausal women with a NVF at the FLS is associated with impaired bone quality compared to not having a VF may indicate that patients with a prevalent VF are even at higher subsequent fracture risk.

Interestingly, we found no difference in LS aBMD between women with at least one prevalent VF in addition to a NVF and those without VF, whereas previous studies reported lower LS aBMD in (asymptomatic and/or symptomatic) VF patients than in fracture-free controls. Similarly to our results, Stein *et al*. [18] reported that there was no difference in LS aBMD when vertebral subjects were compared to NVF subjects. One explanation could be that in NVF patients, the presence of prevalent VFs is not associated with lower LS aBMD. Another explanation could be the impact of degenerative changes in the lumber spine on the LS aBMD. This should be confirmed and evaluated in future research.

This study has important implications. In women with a recent NVF, the presence of morphometric VF can be used as a marker for generalized bone micro-architecture deterioration, independent of areal BMD and prior fracture. Our results extend previous observations towards women with a NVF, in whom the presence of at least one prevalent VF was associated with impaired trabecular micro-architecture in the radius and tibia, and cortical micro-architecture and bone strength in the tibia.

This study has several limitations. First, this is a cross-sectional study. Hence the interpretation of our findings in the context of subsequent fracture risk in FLS patients cannot be addressed. In previous prospective studies, deterioration of HR-pQCT indices of trabecular and cortical bone and lower bone strength improved prediction of fracture beyond femoral neck areal BMD or FRAX scores alone.[20-24] Future studies are needed to determine the relevance of prevalent VF in addition to a NVF, in terms of subsequent VF and NVF risk. Second, prevalent VFs were identified

on lateral spine images by DXA instead of X-ray. The reproducibility of vertebral fracture assessment by DXA is limited, especially for mild (*i.e.*, grade 1) VFs. The inter-rater reliability of absorptiometry was better when only grade 2 or 3 deformities were considered fractured (kappa (95% CI): 0.640 (0.621-0.659)), as compared to when grade 1 deformities were also considered fractures (kappa (95% CI): 0.560 (0.54100.580)).[32] Additionally, sensitivity was reported to be 62.5% and specificity was 93.1% for grade 2-3 vertebral deformities, and 51.8% and 88.7%, respectively, when grade 1 vertebral deformities were also considered fractured.[32] This implies that patients could have been incorrectly classified as (mild, *i.e.*, grade 1) VF cases.[33] However, a false-positive VF classification would probably only reduce the HR-pQCT differences between patients with at least one (mild) VF and patients without VFs. Fourth, the reference line for the HR-pQCT scans was placed at a fixed reference point, which resulted in scanning the same region in all patients. However, bone morphology at that region differs between individual patients, where a higher amount of cortical bone will be present in patients with relatively short extremities.[34,35] A recent study suggests scanning at a percentage distance of the total length of the bone.[36] Since we this information was not available, as an alternative, we have adjusted all the analyses for height. Finally, our results cannot be generalized to the total fracture population, since probably only the most fit and mobile patients were willing and able to visit the FLS and participate in our study, with a healthy complier bias as a consequence.

In conclusion, in this cross-sectional study in postmenopausal women with a recent NVF, the presence and severity of prevalent VF were associated with impaired bone micro-architecture and strength in the radius and tibia. Therefore, in postmenopausal women with a recent NVF, evaluation of morphometric VF can be used as a marker of generalized micro-architecture deterioration, independent of BMD. Future studies are needed to confirm our results and to determine the relevance of prevalent VF in addition to a NVF, in terms of subsequent VF and NVF risk.

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PART II

OUTCOME OF PATIENTS AT THE FLS

CHAPTER 7

DECREASED MORTALITY AND SUBSEQUENT FRACTURE RISK IN PATIENTS WITH A MAJOR AND HIP FRACTURE AFTER THE INTRODUCTION OF A FRACTURE LIAISON SERVICE: A 3-YEAR FOLLOW-UP SURVEY

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J Bone Miner Res. 2022 Oct;37(10):2025-2032

ABSTRACT

Fracture Liaison Services (FLS) are considered to be the most effective organizational approach for secondary fracture prevention. In this study, we evaluated whether FLS care was associated with reduced subsequent fracture and mortality risk over 3 years of follow-up. In total, 8,682 consecutive patients aged 50-90 years with a recent fracture were included. Before FLS introduction, regular fracture treatment procedures were followed (pre-FLS). After FLS introduction, patients were invited to the FLS and FLS attenders were assessed for osteoporosis, prevalent vertebral fractures, metabolic bone disorders, medication use, fall risk and treatment for fracture prevention was initiated according to Dutch guidelines. All fractures were radiographically confirmed and categorized into major/hip (pelvis, proximal humerus or tibia, vertebral, multiple rib, distal femur) and non-major/non-hip (all other fractures). Mortality risk was examined using age and sex adjusted Cox proportional hazard models. For subsequent fracture risk, Cox proportional hazard models were adjusted for age, sex and competing mortality risk (subdistribution hazard (SHR) approach). The pre-FLS group consisted of 2,530 patients (72% women), of whom 1,188 (46.9%) had major/hip index fractures, the post-FLS group consisted of 6,152 patients (69% women), of whom 2,973 (48.3%) had major/hip index fractures. In patients with a non-major/non-hip fracture there was no difference in subsequent non-major/non-hip fracture risk or mortality between pre- and post-FLS. In patients with a major/hip index fracture, mortality risk was lower post-FLS (hazard ratio [HR]: 0.84; 95% confidence interval [CI] 0.73-0.96) and subsequent major/hip fracture risk was lower in the first 360 days after index fracture post-FLS compared to pre-FLS (SHR 0.67; 95% CI 0.52-0.87). In conclusion, FLS care was associated with a lower mortality risk in the first 3 years and a lower subsequent major/hip fracture risk in the first year in patients with a major/hip index fracture but not in patients with a non-major/non-hip fracture.

INTRODUCTION

Patients with a recent fracture have an increased risk of subsequent fractures and mortality.[1-3] Subsequent fracture risk changes over time and is the highest immediately after an initial fracture.[4] Besides the increased subsequent fracture risk, mortality risk is also increased during the first five years after a fracture, even after a non-hip fracture.[2] Despite the proven effectiveness of anti-osteoporosis treatment in reducing subsequent fractures, only a minority of patients with a recent fracture receive appropriate fracture risk evaluation and treatment.[5] Therefore, Fracture Liaison Services (FLS) have been developed and implemented to identify, evaluate and treat patients with an increased risk of subsequent fractures, namely those with a recent fracture. The overall aim of the FLS is increase to the number of patients receiving appropriate fracture risk evaluation and treatment to reduce subsequent fracture risk.[6-8]

The effectiveness of FLS in terms of subsequent fracture reduction and reduction of mortality has been summarized in several reviews [9-11], suggesting variable impacts on mortality and subsequent fracture risk. In a recently published meta-analysis, Li *et al*. [12] concluded that FLS care was associated with a lower probability of subsequent fractures (OR:0.70, 95% CI: 0.52-0.93) in the overall comparison, as well as in the post- versus pre-FLS comparison (OR: 0.62, 95% CI: 0:42-0.91). With respect to the outcome mortality, they concluded that FLS care was not associated with reduced mortality in the overall comparison (OR: 0.73, 95% CI: 0.40-1.09%), while in the post-FLS vs. pre-FLS studies mortality risk was reduced by 35% (OR:0.65, 95% CI: 0.44-0.95%). The systematic review by Li *et al*. [12] was based on a limited number of heterogeneous studies, limited lengths of follow-up, mixed groups (*i.e.*, before and after the introduction of an FLS in the same hospital (post-FLS vs. pre-FLS) or between hospitals with and without FLS) and most studies did not apply a competing mortality risk analysis when analyzing subsequent fracture risk.

Our aim was to evaluate whether FLS care was associated with a reduced subsequent fracture and mortality risk within 3 years after a major/hip or non-major/non-hip index fracture.

METHODS

Study design and population

This study was designed as a retrospective cohort study and conducted among all consecutive patients aged 50 to 90 years presenting with an index fracture at the Emergency Department (ED) of VieCuri Medical Center (Venlo, the Netherlands)

from January 2005 until December 2013. Only patients with radiographically confirmed fractures living in the referral area of this hospital were included. The study was approved by the institutional review board of VieCuri Medical Center (CEM 14-011).

Outline of the FLS

The FLS was initiated at the end of 2007 at the outpatient clinic at the department of Internal Medicine in close collaboration with the departments of trauma surgery and orthopedic surgery of VieCuri Medical Center. Our staff consisted of a fulltime nurse and two endocrinologists. Patients visiting the ED between January 2005 until December 2007 received regular fracture treatment by trauma surgeons or orthopedic trauma surgeons and were grouped into the "*pre-FLS*" group.

The "*post-FLS*" group consisted of patients who visited the ED between January 2008 and December 2013. In this period, a trained nurse systematically selected all patients with a clinical fracture based on diagnostic codes on a monthly basis. Patients were invited to the FLS if they were aged 50-90 years, had a radiographically confirmed fracture, and lived in the referral area of VieCuri Medical Center. Patients were not invited to the FLS if they had a fracture of the skull, fractures due to failure of a prosthesis, osteomyelitis, metastasis, an active malignancy, or Paget's disease. If patients were admitted to the hospital, *i.e.*, because of hip fracture, screening and invitation was repeated during the next month's screening.

All patients received an invitation letter. If the patient didn't respond to the invitation letter, a reminder letter was sent the next month. All patients who responded positively and visited the FLS completed a detailed questionnaire on demographics, calcium and vitamin D intake (including supplements), comorbidities, medication use and clinical risk factors for falls and fractures according to the Dutch national guideline.[13] Further, in all patients bone mineral density (BMD) was assessed by Dual Energy X-Ray Absorptiometry (DXA) (Hologic QDR 4500, Bedford, MA, USA) at the lumbar spine, total hip and femoral neck, and categorized according to the WHO guideline as normal BMD (T-score ≥ -1.0), osteopenia (T-score < -1.0 and > -2.5) and osteoporosis (T-score ≤ -2.5). In addition, a standard blood sample was collected and analyzed to diagnose underlying contributors to secondary osteoporosis and metabolic bone disorders as previously reported by Bours *et al.*.[14] From 2011 onwards, after the implementation of the Dutch national guideline on osteoporosis and fracture prevention, vertebral fracture assessment was performed at the same time as the BMD measurements.[13]

An appointment at the FLS consisted of a consultation with a specialized nurse and an endocrinologist. Based on the medical history, comorbidities, BMD and VFA results, calcium intake and serum 25(OH)D levels, patients were counselled on lifestyle,

including nutrition, exercise, alcohol, smoking, fall risks, and treatment was initiated with anti-osteoporosis medication, calcium and vitamin D supplements according to the national guideline for treatment of osteoporosis and fracture prevention.[13] If contributors for secondary osteoporosis and metabolic bone disorders were diagnosed, treatment was initiated according to the specific guidelines for those disorders.

Data collection and outcome measures

For all patients, data were collected retrospectively by yearly anonymized exports of the electronic patient records. The following baseline data were collected: gender, age, index fracture location and date. All index and subsequent fractures were grouped into hip and major fractures (pelvis, proximal humerus or tibia, vertebral, multiple rib, distal femur) and non-major/non-hip according to Center *et al.*.[15] Patients were followed from their index fracture date until death, first subsequent fracture (same groupings as index fractures, *i.e.*, major/hip or non-major/non-hip) or end of follow-up, which ever came first. All patients were followed for a maximum of 3 years. The data regarding the outcome of subsequent fractures were obtained by diagnostic codes and additional verification of the radiology reports; only radiographically confirmed fractures were included in the analyses. Subsequent fractures due to failure of a prosthesis, osteomyelitis, malignancy and Paget's diseases and fractures of the skull were excluded. In case a fracture in the post-FLS period was a subsequent fracture from the pre-FLS period, this was counted as index fracture for the post-FLS period as well. Data regarding the outcome mortality were obtained by the National death registration database providing only the date of death. For this study, data of patients who emigrated were excluded. Data on the yearly FLS attendance rate and the proportion of patients that received prescription for AOM were retrieved on a group level.

Statistical analyses

Data were analyzed using Cox proportional hazard models with mortality or subsequent fracture as event. The proportional hazards assumption was tested using time-dependent Cox regression analyses with interaction with time tested for each baseline variable separately. In case of violation, the analyses were separated in two time-intervals and the -2LogLikelihood were compared between models with different cut-off point to identify the best cut-off (*i.e.*, the model with the lowest -2LogLikelihood). All analyses were performed with adjustments for age (decades) and gender. To adjust for the competing risk of mortality, the subdistribution hazard approach (SHR) by Fine and Gray was applied [16,17] for the analyses with subsequent fracture as outcome. Explorative subgroup analyses with mortality and subsequent

fractures as outcomes were performed for gender, age decades and index fracture type. Sensitivity analyses for both mortality and subsequent fractures were performed with classification of index fracture location as major osteoporotic fractures (MOF, including wrist, humerus, spine, hip fractures) and non-MOF (all other fracture types) according to the IOF classification.[18] Further, as a consequence of the formal tracking of individuals, their invitation and attendance to the FLS introduced a median lag time of 125 days between index fracture and FLS visit. Therefore, sensitivity analyses were performed for mortality and subsequent fractures with follow-up initiated at day 126 to minimize immortal time bias [19] for the total post-FLS group, as well for FLS attenders and non-attenders separately. All statistical analyses were performed using SAS version 9.4.

RESULTS

A total of 8,682 consecutive patients aged 50-90 years with a clinical index fracture was included. The pre-FLS group consisted of 2,530 patients with a recent fracture (1,832 (72.4%) women) with a mean age of 68.2 (± 11.7) years of whom 365 (14.4%) had a hip fracture, 704 (27.8%) a major fracture and 1,460 (57.7%) a non-major/non-hip fracture (Table 1). Of all patients in the pre-FLS group, 131 sustained a subsequent fracture in the post-FLS period. The post-FLS group consisted of 6,152 patients (4244 (69.0%) women), with a mean age of 68.2 (± 11.0) years. In this group, 763 (14.1%) patients had a hip fracture, 1,944 (31.7%) a major fracture and, 3,445 (54.2%) a non-major/non-hip fracture (Table 1). In the post-FLS group, 53% attended the FLS of whom 40% had an indication for treatment with anti-osteoporosis medication (AOM). The median follow-up for both mortality and subsequent fractures was 1,095 days.

Mortality

In patients presenting with a major/hip index fracture, the cumulative mortality during the three-year follow-up period was significantly lower in the post-FLS group (n= 668, 22.5%) compared to the pre-FLS group (n=308, 25.9%; p=0.019), while in patients presenting with a non-major/non-hip index fracture mortality pre-FLS and post-FLS was comparable, 9.3% pre-FLS vs. 8.0% post-FLS respectively (p=0.122).
In patients with a major/hip index fracture, the adjusted mortality risk was significantly lower in the post-FLS group (HR: 0.84, 95% CI: 0.73-0.96). In patients with a non-major/non-hip index fracture, there was no difference in mortality risk between pre- and post-FLS (Table 2).

Table 1. Baseline characteristics of all patients with a major or hip index fracture and non-major/non-hip index fracture before (Pre-FLS) and after (Post-FLS) the introduction of the FLS

	Major/hip index fracture		Non-major/non-hip index fracture	
Characteristic	**Pre-FLS** (n=1188)	**Post-FLS** (n=2973)	**Pre-FLS** (n=1557)	**Post-FLS** (n=3607)
Gender, Female	72.8	68.4	71.3	68.8
Age (years)	72.6 ± 10.4	72.2 ± 11.0	65.9 ± 10.4	65.9 ± 10.4
Age, decades				
50–59 years	15.8	17.4	34.2	33.3
60–69 years	18.0	21.4	27.7	30.7
70–79 years	33.7	28.8	24.9	22.5
80–90 years	32.5	32.5	13.2	13.5

Data are presented as mean ± standard deviation or percentage.

Table 2. Multivariable Cox regression model for mortality risk during 3 years of follow-up in patients with a major/hip index fracture and patients with a non-major/non-hip index fracture

	Major/hip index fracture *		Non-major/non-hip index fracture **	
Parameter	**Number of deaths**	**Hazard ratio (95% CI)**	**Number of deaths**	**Hazard ratio (95% CI)**
FLS				
Pre-FLS	308	Reference	145	Reference
Post-FLS	668	0.84 (0.73–0.96)	290	0.86 (0.70–1.04)
Gender				
Men	345	Reference	135	Reference
Women	631	0.56 (0.49–0.64)	300	0.61 (0.50–0.75)
Age at fracture (years)				
50–59	23	Reference	38	Reference
60–69	81	3.20 (2.01–5.09)	56	1.81 (1.20–2.74)
70–79	261	7.61 (4.97–11.66)	122	5.44 (3.76–7.86)
80 and older	611	20.90 (13.76–31.73)	219	19.91 (14.03–28.26)

* Major/hip: fractures of hip, pelvis, proximal humerus or tibia, vertebral, multiple rib, distal femur.
** Non-major/non-hip: all other fractures.

In subgroup analyses, mortality risk post-FLS was significantly lower in patients with a major index fracture, in patients aged 80+ and in women (fig 1). In men and the age group 70-79 years, the analyses were separated in two time-intervals due to violation of the proportional hazard assumption. In men, mortality risk was significantly lower in the first 330 days after a major/hip index fracture in the post-FLS group and in patients aged 70-79 mortality risk was significantly lower in the first 480 days after a major/hip index fracture (Figure 1).

Subsequent fractures

The cumulative incidence of a subsequent major/hip fracture after major/hip index fracture during the three-year follow-up period was comparable between pre-FLS and post-FLS, 6.0% and 5.6% respectively (p=0.616). Further, the cumulative incidence of subsequent non-major/non-hip fracture after non-major/non-hip index fracture was 3.3% pre-FLS and 3.2% post-FLS (p=0.852).

The risk of a subsequent major/hip fracture after a major/hip index fracture was significantly lower in the first 360 days after index fracture post-FLS compared to pre-FLS, taking the competing risk of death into account (SHR: 0.67 95% CI: 0.52-0.87), but there was no difference in the second period (SHR: 1.29 (0.97-1.73) (Table 3). There was no difference in the risk of subsequent non-major/non-hip fracture risk after a non-major/non-hip index fracture between pre- and post-FLS.

In subgroup analyses, women and patients with a major index fracture had a significantly lower risk of subsequent major/hip fractures within the first 360 days and 210 days after index fracture, respectively (Figure 2).

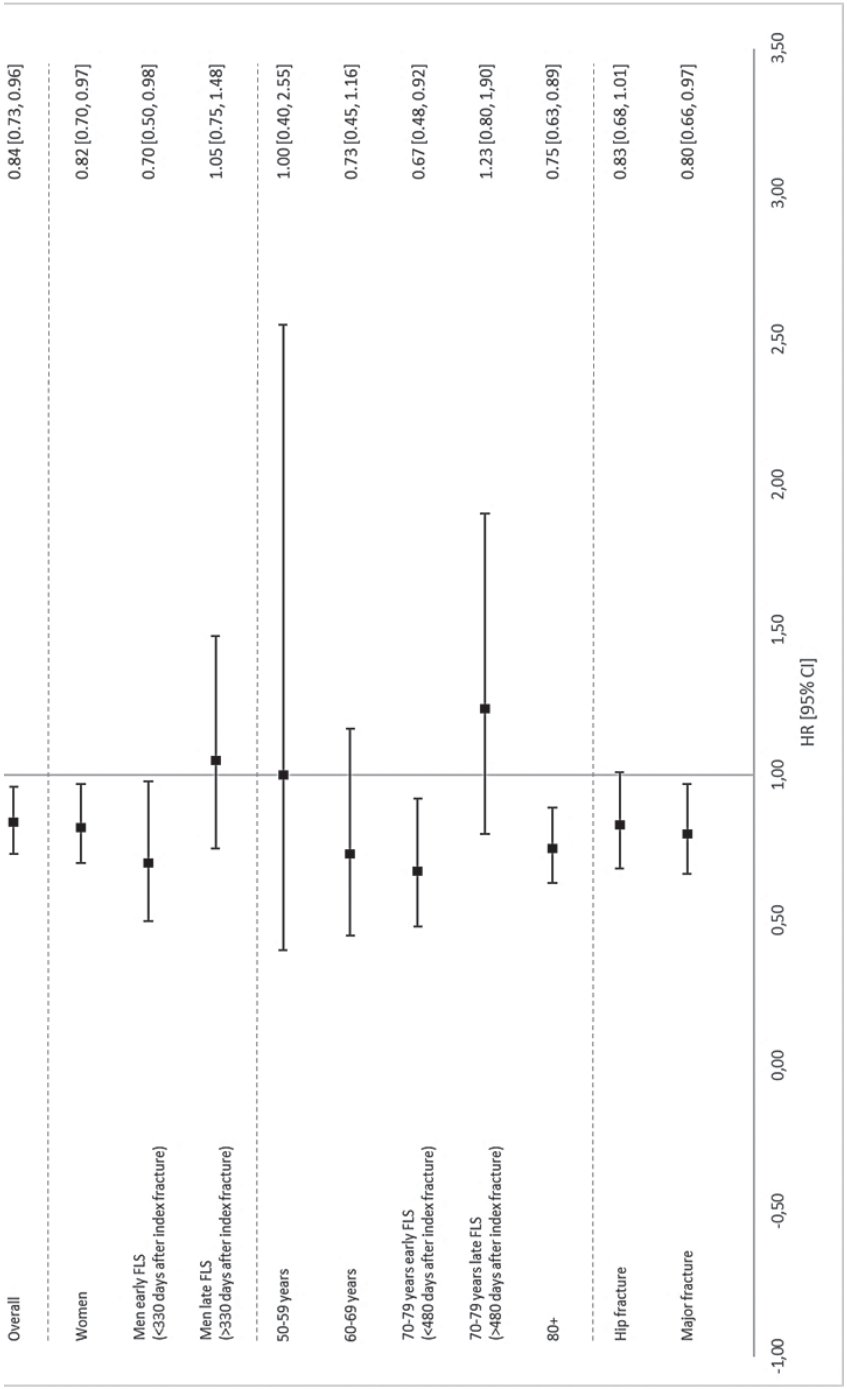


Figure 1. Mortality risk after a major or hip index fracture during 3 years of follow-up, starting from date of index fracture.

Table 3. Multivariable Cox regression model for subsequent major/hip fracture risk after major/hip index fracture, and subsequent non-major/non-hip fracture after non-major/non-hip index fracture for 3 years follow-up, starting from date of index fracture

		Major/hip index fracture *	
Parameter	**Number of events**	**Hazard ratio (95% CI)**	**SHR (95% CI)**
FLS			
Pre-FLS	153	Reference	Reference
Post-FLS			
Post-FLS ≤ 360 days	153	0.66 (0.51–0.85)	0.67 (0.52–0.87)
Post-FLS > 360 days	192	1.25 (0.94–1.68)	1.29 (0.97–1.73)
Gender			
Men	112	Reference	Reference
Women	386	1.26 (1.02–1.56)	1.41 (1.14–1.74)
Age at fracture (years)			
50–59	52	Reference	Reference
60–69	73	1.19 (0.83–1.70)	1.14 (0.80–1.63)
70–79	160	1.93 (1.41–2.64)	1.71 (1.26–2.34)
80 and older	213	2.91 (2.15–3.96)	2.12 (1.57–2.87)

*** Major/hip: fractures of hip, pelvis, proximal humerus or tibia, vertebral, multiple rib, distal femur. ** Non-major/non-hip: all other fractures. SHR, subdistribution hazard ratio.**

Sensitivity analyses in patients with MOF

The adjusted mortality risk in patients with an index MOF (wrist, humerus, spine, hip fracture) was significantly lower in the post-FLS group (HR: 0.79 95% CI: 0.70-0.91). There was no difference in subsequent MOF fracture risk after an index MOF fracture between pre- and post-FLS.

In subgroup analyses, mortality risk was lower in women post-FLS (Supplementary figure 1). In men, mortality risk was lower in the first 330 days after an index MOF fracture (HR: 0.63 95% CI: 0.46-0.86), but there was no difference in the second period. Mortality risk was lower in post-FLS patients aged 70-79 years, in patients aged 80 years and in patients with an index clinical vertebral fracture.

In subgroup analyses, there was no difference in subsequent MOF fracture risk after an index MOF fracture between pre- and post-FLS (Supplementary figure 2).

Non-major/non-hip index fracture **		
Number of events	**Hazard ratio (95% CI)**	**SHR (95% CI)**
83	Reference	Reference
199	1.03 (0.80–1.33)	1.04 (0.81–1.35)
62	Reference	Reference
220	1.49 (1.12–1.99)	1.52 (1.14–2.02)
81		Reference
86	1.14 (0.84–1.55)	1.13 (0.84–1.53)
66	1.13 (0.81–1.57)	1.09 (0.79–1.51)
49	1.65 (1.15–2.37)	1.39 (0.97–2.00)

Sensitivity analyses with follow-up initiated at 126 days after fracture

In the analyses where day 126 after the index fracture was used as the first day of follow-up, the adjusted mortality risk was significantly lower in the post-FLS group in patients with a major/hip index fracture (HR: 0.79 95%CI: 0.67-0.93) and in patients with an index MOF (HR: 0.75 95%CI: 0.64-0.88). There was no difference in subsequent major/hip fracture risk after a major/hip index fracture, or subsequent MOF risk after an index MOF between pre- and post-FLS (HR: 1.00 95% CI: 0.79-1.27, HR: 0.93 95% CI: 0.55-1.14, respectively).

In FLS attenders with a major/hip index fracture, the adjusted mortality risk was significantly lower (HR: 0.43, 95% CI: 0.34-0.56) compared to the pre-FLS group, while the adjusted mortality risk was not different in FLS non-attenders (HR: 1.05, 95% CI: 0.88-1.25). The subsequent major/hip risk after a major/index fracture, both in attenders and non-attenders, was not significantly different as compared to the pre-FLS group (SHR: 0.80 (95% CI: 0.60-1.07) in attenders; SHR: 1.18 (95% CI: 0.93-1.53) in non-attenders, respectively).

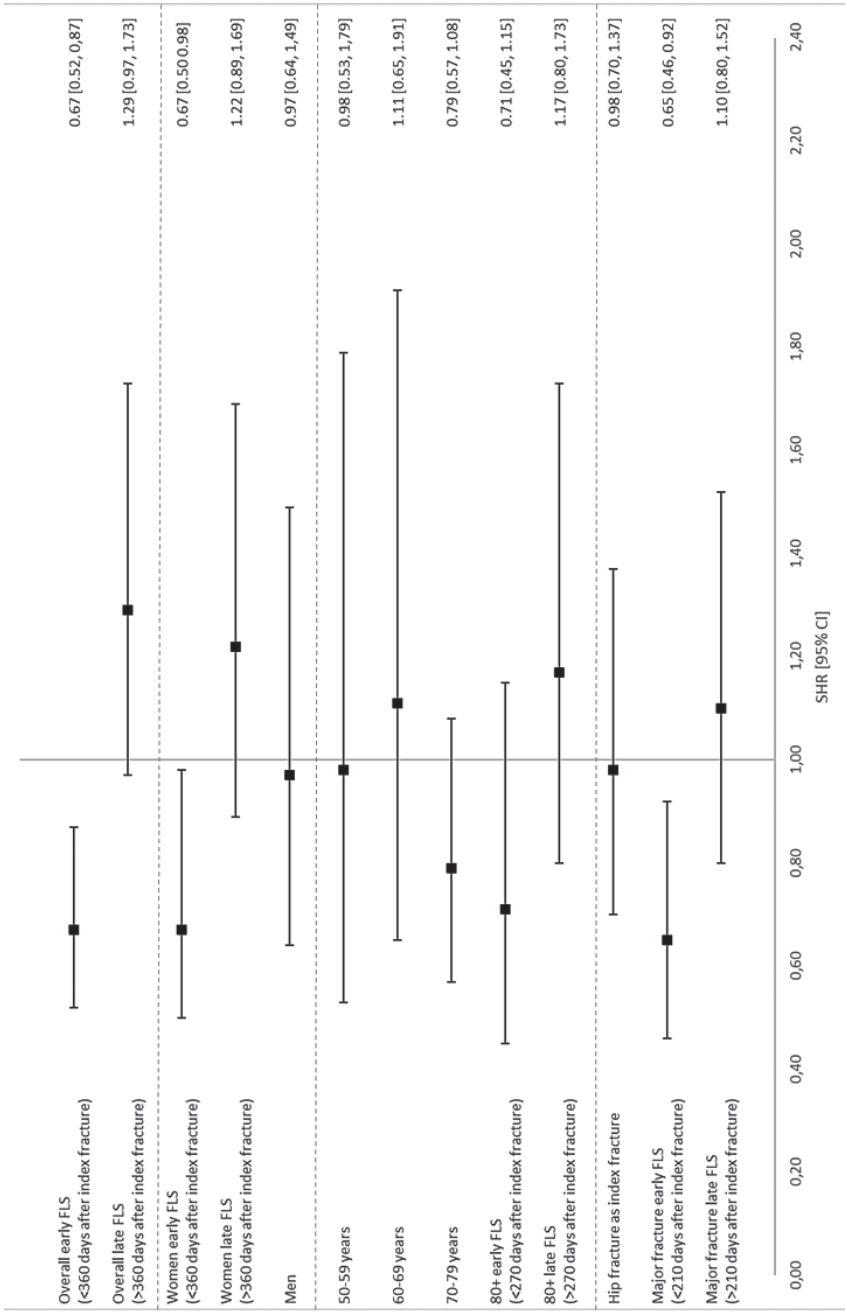


Figure 2. Subsequent major or hip fracture risk after a major or hip index fracture during 3 years of follow-up, starting from date of index fracture.

In accordance with the main analyses, the major/hip subsequent fracture risk after a major/hip index fracture was lower in the FLS attenders in the first 360 days after index fracture compared to the pre-FLS group (SHR: 0.62; 95% CI: 0.40-0.95), while in non-attenders there was no difference (SHR: 0.99; 95% CI: 0.70-1.38). In the late post-FLS period (from 360 days onwards), subsequent major/hip fracture risk was not different in FLS attenders (SHR: 1.00; 95% CI: 0.67-1.50), but higher in non-attenders (SHR: 1.42; 95% CI: 1.00-1.99) presenting with a major/hip index fracture.

DISCUSSION

In the present study, we found that the adjusted mortality risk in patients with a major/hip index fracture was 16% lower in the post-FLS group as compared to the pre-FLS group. Further, subsequent major/hip fracture after a major/hip index fracture was 33% lower in the first 360 days after index fracture post-FLS compared to pre-FLS, taking the competing risk of death into account. However, in patients with a non-major/non-hip index fracture, there was no difference in mortality or subsequent fracture risk between post- and pre-FLS.

Studies on the effectiveness of the implementation of an FLS in terms of subsequent fracture risk reduction and mortality are heterogeneous, with respect to the length of follow-up (most often 2 years or less), the design of the study (*i.e.*, post-FLS vs. pre-FLS comparison, or comparison of hospitals with and without FLS), the included study population (age, index fracture types), the classifications of groups of fractures and most previous studies did not apply a competing mortality risk analysis when analyzing subsequent fracture risk.[12]

The finding of a lower 3-year mortality risk in our study is in line with the recent published meta-analysis of Li *et al.*.[12] Since five out of the six studies included in the meta-analysis had a follow-up duration of 2 years or less, and the only study with a median pre-post FLS follow-up period > 2 years in that meta-analysis had a post-FLS follow-up period of 1.5-1.7 year [20], our study is the first that indicates a longer-term mortality reduction 3 years after implementation of FLS care.

We found a 33% lower subsequent major/hip fracture risk post FLS, in the first year after a major/hip index fracture, taking the competing risk of death into account. Due to violation of the proportional hazards, we did not analyze the risk of subsequent fractures during the complete follow-up period of three years, rather the analyses were separated into two time-intervals. However, the finding of a lower subsequent fracture risk in the first period followed by a non-significant difference in the second period suggests that FLS care is associated with a longer-term subsequent fracture risk reduction. Regarding the risk of subsequent fractures, there are four

published FLS studies that used the competing risk analysis method described by Fine and Gray.[16, 20-23] Hawley *et al.* [21] reported a lower mortality risk, but no difference in the risk of subsequent hip fractures in the first year after an index hip fracture, after implementation of orthogeriatric and nurse led FLS models. By using the subdistribution hazard approach by Fine and gray, patients who died before sustaining a subsequent fracture (event of interest) are not censored, but these patients retain in the risk set for sustaining a subsequent fracture. If the competing risk of mortality is ignored, the incidence of subsequent fractures is overestimated. By taking the competing risk of death into account, a true estimate of the subsequent fracture risk is presented. Axelsson *et al.* [20] reported a SHR of 0.73 (95%CI: 0.66–0.82) for subsequent MOFs after an index MOF, including pelvis fractures as MOFs, with a median FLS follow-up of 1.7 years, which is in line with our study. Nakayama *et al.* [22] reported a SHR of 0.67 (95%CI: 0.47-0.95) for subsequent fractures over 3 years when comparing an FLS hospital with no-FLS hospital. Compared to our study, the study of Nakayama *et al.* [22] did not compare a pre-post FLS period but showed a comparison of a FLS hospital versus a non-FLS hospital, had a smaller sample size and the 3-year incidence of fractures (11% post-FLS and 6% pre-FLS) was substantially higher than in our study. Furthermore, in that study there was no violation of the proportional hazard assumption. Davidson *et al.* [23] reported a SHR of 0.58 (95%CI: 0.35-0.95) for subsequent fractures over 3 years when comparing the effectiveness of a nurse-led FLS vs. pre-FLS in patients with a minimal trauma fracture (MTF). MTF were defined fractures from femur, tibia, fibula, ankle, pelvis, humerus and wrist resulting from a standing height or less. The 3-year incidence of fractures in this small study of 140 patients aged 45 years and older was markedly higher as compared to our study (10.5% post-FLS vs. 19.1% pre FLS).[23] Overall, the findings of our study and the four other studies on subsequent fracture risk, indicate that FLS care is associated with a lower risk of subsequent fractures in the first two years after FLS implementation, when taking the competing risk of death into account. Studies reporting longer-term benefits in subsequent fracture risk reduction, especially when taking competing mortality risk into account, are currently lacking in FLS literature.

We found no difference in mortality and non-major/non-hip subsequent fracture risk in patients presenting with a non-major/non-hip fracture. Only Huntjens *et al.* [24], Nakayama *et al.* [22] and Shin *et al.* [25] evaluated the outcomes of FLS-care in patients with a non-major/non-hip index fracture and distal radius fractures, respectively. Huntjens *et al.* [24] reported that subsequent fracture and mortality risk in patients with a minor fracture between a non-FLS and FLS hospital was not reduced, but the competing risk of death was not taken into account. In line with our study, Nakayama *et al.* [22] reported that the reduction of minor refractures was not as pronounced as the reduction in major refractures between the FLS-hospital and non-FLS hospital, but due to small

the number of events, the authors did not perform a separate subgroup analysis for patients with a minor fracture. Shin *et al.* [25] evaluated the effect of osteoporosis care after a distal radius fracture and reported a risk reduction of 65% for subsequent fractures, but the competing risk of death was not taken into account.

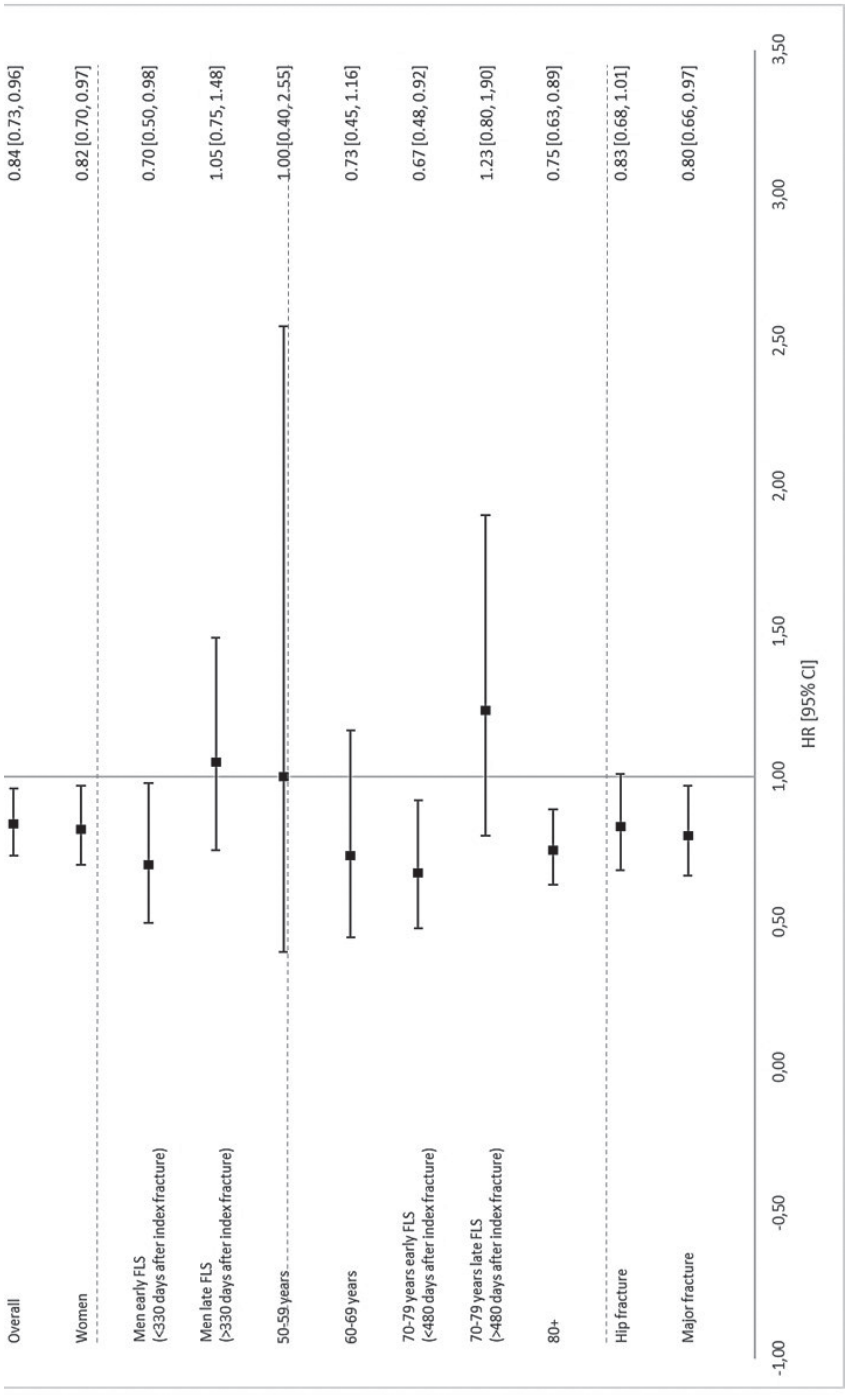
The early benefits in terms of subsequent fracture risk reduction, in the first year after index fracture combined with the lower 3-year mortality risk in this study can only partially be explained by the use of AOM since only 40% of the FLS attenders was treated with AOM. It is likely that improvements of fracture related procedures in combination with the integrated approach after implementation of FLS care resulted in favorable outcomes in the post-FLS period. FLS attenders were extensively evaluated, not only by BMD measurement and VFA, but also for the presence of underlying metabolic bone disorders (including calcium and vitamin D deficiencies). Furthermore, next to initiation of AOM, co-morbidities were treated, medication was reviewed and optimized, and patients were followed up to a year post fracture.

The outcome of FLS care as presented in this study could potentially be further improved by reaching higher FLS attendance rates, since only 53% of patients with a fracture visited our FLS. Furthermore, at the time of FLS care in this study, alendronic acid was the first choice AOM in the Dutch guideline, zoledronic acid was hardly used, denosumab was not available in the first years of the post-FLS period (introduced in the Netherlands in 2011) and teriparatide treatment could only be prescribed in patients who had a third fracture during treatment with an oral bisphosphonate.[13] Although oral bisphosphates have proven their effect in fracture risk reduction in clinical trials in patients with an increased fracture risk *i.e.*, osteoporosis, real-life persistence with this type of medication is often poor which might in turn dilute the fracture risk reduction. Klop *et al.* [26] evaluated persistence with bisphosphonates in newly treated fracture patients in the Netherlands and concluded that persistence was 75% one year after treatment initiation and only 45 % 5 years after initiation, respectively. More recently, the treatment options for fracture prevention have been enlarged with teriparatide and romosozumab, bone forming agents, which have early and superior fracture risk reductions as compared to oral bisphosphonates. Therefore, it has to be advocated those future studies evaluating the FLS should include all treatment options for osteoporosis including treatment persistence rates. Further, these future studies should have a longer follow-up period *i.e.,* 5 years and, as advised by Li *et al.*[12], the competing risk of mortality should be taken into account while exploring the FLS effect on subsequent fracture risk.

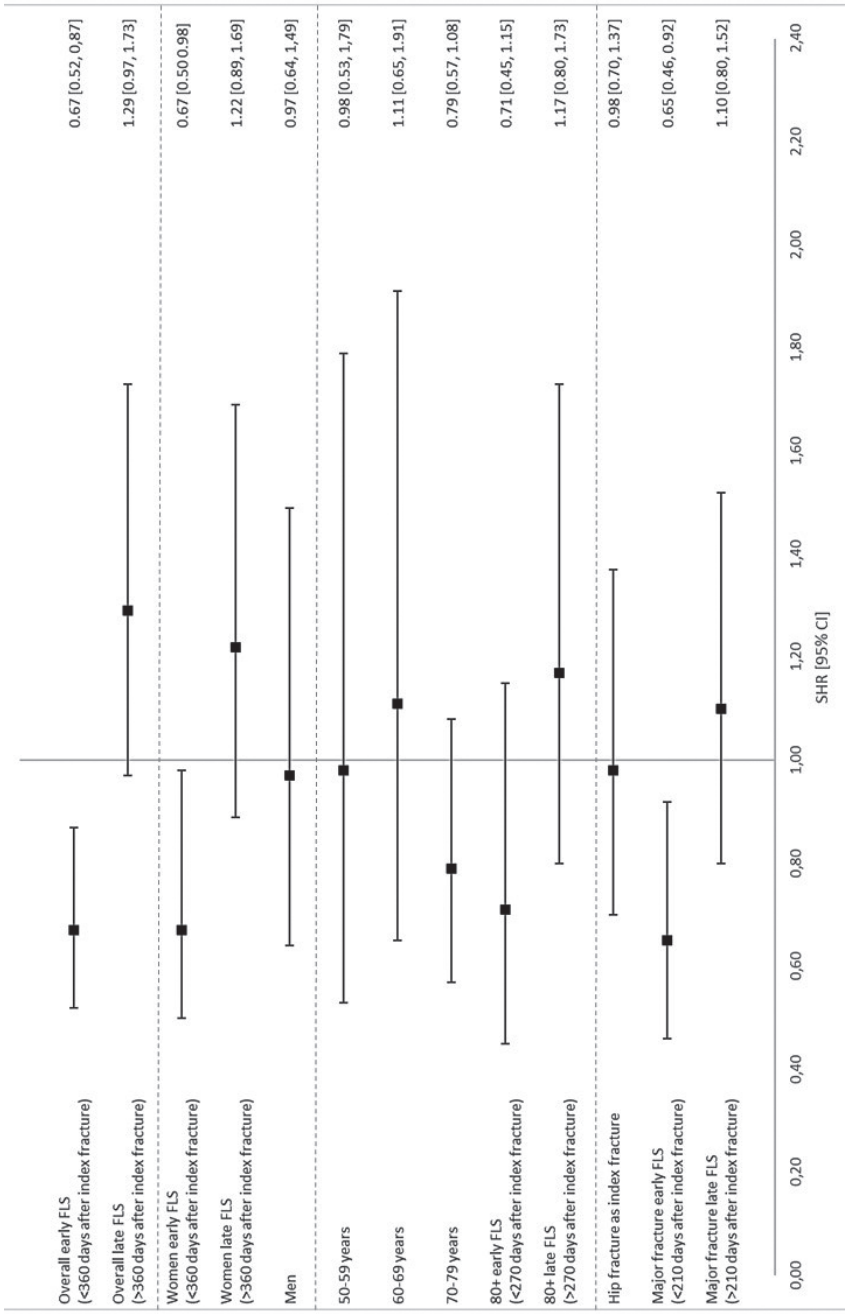
This study has strengths and limitations. A strength of this study is that we were able to evaluate all patients with radiographically confirmed index fracture and subsequent fractures. Further, we included all consecutive patients, including those who did not attend the FLS. Although this approach might result in a dilution of the

FLS effect, especially in subsequent fracture risk, we consider this as the proper method to evaluate the real-life outcome of FLS-care and to minimize selection bias. Our analyses were performed including the competing risk of mortality. Ignoring this competing risk could introduce bias in the estimation of fracture risk. An important limitation of this study is that we were not able to identify the FLS attenders on an individual level, in whom treatment was initiated either with AOM or underlying causes and we have no data on treatment persistence during follow-up.

In conclusion, FLS care was associated with a lower mortality risk in the first three years and a lower subsequent major/hip fracture risk in the first year in patients with a major/hip index fracture but not in patients with a non-major/non-hip fracture. Although the early benefits suggests that the multidisciplinary approach at the FLS could improve the outcomes of patients with a recent fracture, there is still a window of opportunity by increasing FLS attendance and treatment rates, the use of anabolic medication and long-term follow-up with attention to treatment adherence.



Supplementary figure 1. Subgroup analyses mortality risk after a MOF index fracture during 3-years follow-up



Supplementary figure 2. Subgroup analyses subsequent MOF risk after a MOF index fracture during 3 years follow-up (competing risk models).

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CHAPTER 8

ASSOCIATION BETWEEN INCIDENT FALLS AND SUBSEQUENT FRACTURES IN PATIENTS ATTENDING THE FRACTURE LIAISON SERVICE AFTER AN INDEX FRACTURE: A 3-YEAR PROSPECTIVE OBSERVATIONAL COHORT STUDY.

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BMJ Open. 2022 Jul 27;12(7):e058983

ABSTRACT

Objectives: To evaluate the risk of subsequent fractures in patients who attended the Fracture Liaison Service (FLS), with and without incident falls after the index fracture.

Design: A 3-year prospective observational cohort study.

Setting: An outpatient FLS in The Netherlands.

Participants: Patients aged 50+ years with a recent clinical fracture.

Outcome measures: Incident falls and subsequent fractures.

Results: The study included 488 patients (71.9% women, mean age 64.6 ± 8.6 years). During the 3-year follow-up, 959 falls had been ascertained in 296 (60.7%) patients (*i.e.,* fallers), and 60 subsequent fractures were ascertained in 53 (10.9%) patients. Of the fractures, 47 (78.3%) were fall-related, of which 25 (53.2%) were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold (hazard ratio 8.6, 95% confidence interval 3.1 to 23.8) increase in the risk of subsequent fractures.

Conclusion: These data suggest that subsequent fractures among patients on treatment prescribed in a FLS setting are common, and that an incident fall is a strong predictor of subsequent fracture risk. Immediate attention for fall risk could be beneficial in an FLS model of care.

INTRODUCTION

Patients with a recent fracture have a high imminent risk of subsequent fractures as shown after most fractures [1-6], and a high risk of subsequent falls, as shown after a recent hip fracture.[7-11] The Fracture Liaison Service (FLS) is considered the most effective organizational approach for secondary fracture prevention in patients after the age of 50 years with a recent fracture.

Most fractures are caused by a fall, but most falls do not result in a fracture.[12,13] Falls are a major contributing factor to the occurrence of fractures, independent and additive to the risk attributable to age and bone mineral density (BMD).[14-17] Guidelines on the FLS therefore recommend fall prevention and prescription of anti-osteoporosis medication (AOM) in high-risk patients.[18-22] However, it is not well known to what extent the imminent risk of subsequent fractures after an index fracture can be attributed to incident falls. We hypothesized that the risk of subsequent fractures would be substantially higher in patients with falls after a recent fracture than in those without falls. The aim of this study was therefore to evaluate the incidence of falls and subsequent fractures, and the risk of subsequent fractures in those with and without falls after a recent index fracture in patients who attend the FLS.

METHODS

Study population and design

A 3-year prospective observational cohort study was conducted including 500 consecutive patients aged between 50 and 90 years with a recent, radiologically confirmed clinical vertebral or non-vertebral low-trauma fracture, and who were willing and able to participate. Patients were recruited at the FLS in VieCuri Medical Center, Venlo, The Netherlands. Low-trauma fractures were defined as fractures that resulted from a fall from standing height or less. Excluded were non-Caucasian patients, patients with bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment.

According to standard care, a nurse specialized in osteoporosis invited all patients aged 50 year and older, who visited the emergency department because of a recent clinical vertebral or non-vertebral fracture, to the FLS. All patients who responded and agreed to be evaluated were scheduled an appointment for fracture risk evaluation. Fracture risk evaluation included a detailed questionnaire for evaluation of risk factors for fractures and falls, including medical history and medication use. This questionnaire was based on the Dutch guidelines on osteoporosis and fracture prevention, and prevention of falls in the elderly.[23,24] Also, height and weight were

measured, a bone mineral density (BMD) measurement with dual-energy X-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck, with vertebral fracture assessment (VFA) was performed, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease.[25] According to the Dutch osteoporosis guideline [23], AOM was started in patients with osteoporosis or having at least one moderate to severe prevalent vertebral fracture according to Genant *et al.* [26] Bisphosphonates and denosumab were first-choice treatments. Teriparatide was restricted to patients already on another AOM with at least 3 fractures, of which 2 were vertebral fractures.

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

Falls and subsequent fractures

During the 3-year follow-up, patients were requested to record falls weekly in a fall diary. Fall registration started at the beginning of the study, mean 3.5 ± 1.0 months after the index fracture. A fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower level.[27] Patients were asked to return their fall diaries by mail at 3 and 6 months, and during the study visit at 1, 2 and 3 year of follow-up. They were contacted by telephone if the fall diary was not received or incomplete. Patients were categorized as those with at least one incident fall (*i.e.,* faller) or without an incident fall (*i.e.,* non-faller) during follow-up.

When patients recorded a fall in their diary, they were also asked to record whether or not they sustained a subsequent clinical fracture as a direct result of the fall. Additionally, at 1-, 2-, and 3-year follow-up, patients had to complete a detailed questionnaire, including a question on whether they sustained a fracture due to another trauma than a fall or without an overt trauma. All subsequent fractures were radiologically confirmed according to radiology reports in the electronic patient records. Since no imaging of the spine was performed at the end of the study, all reported vertebral fractures were symptomatic, clinical vertebral fractures. A distinction was made between subsequent fractures that were directly caused by a fall (*i.e.,* fall-related fractures), and those that occurred without an overt trauma or were the result of another trauma than a fall (*i.e.,* non-fall-related fractures).

Data analysis

Baseline characteristics were compared between fallers and non-fallers, and between patients with and without subsequent fractures using the Student's t test or Wilcoxon test for continuous variables, and Chi-squared or Fisher's exact test for categorical variables where appropriate. The incidence rate of falls and subsequent fractures

per 100 person-years was estimated at 3 and 6 months and 1, 2 and 3 year follow-up, assuming a Poisson distribution. Kaplan Meier curves were made for incident falls and subsequent fractures, in which patients were included once, and only the first incident fall or subsequent fracture was included. Cox proportional hazards regression was used to determine the association between incident falls and subsequent fractures, yielding hazard ratios (HR) and 95% confidence intervals (CI). Proportional hazard assumptions were not violated. Follow-up time was determined by the first subsequent fracture, lost-to-follow-up or the end of the study, whatever occurred first. All analyses were adjusted for the predefined covariates, including age, gender, index fracture type (major or hip versus any other fracture), BMD (lowest measured at lumbar spine, total hip, femoral neck), prevalent vertebral fractures (moderate or severe versus mild or no prevalent vertebral fractures). A p-value < 0.05 was considered statistically significant.

Two sensitivity analyses were planned; (i) excluding patients with index and subsequent finger or toe fractures, and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller, even if they fell at another time during follow-up.

Patient and public involvement

Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

RESULTS

Study population

Among 1220 patients approached from the FLS, 1011 patients met the study criteria. Of the 1011 patients, 511 were not willing or able to participate in the study, and after excluding 12 patients with missing fall data, ultimately 488 patients were available for analysis (Supplementary figure 1) of whom 34 (7.0%) patients had incomplete follow-up data on incident falls (5 patients died, 8 withdrew consent, 21 had incomplete fall registration).

The mean time between the index fracture and FLS visit at which patients were included for this study was 3.9 ± 1.1 months for patients with a hip fracture and 3.5 ± 1.0 months for patients with other fractures. Baseline characteristics of the 488 study participants are presented in Table 1. Mean age was 64.6 ± 8.6 year and 71.9% of the patients were women. In 86.5% of patients, the index fracture was caused by a fall, and 28.5% of patients had at least one other fall in the year before the start of the study. At baseline, 21.9% of patients were diagnosed with osteoporosis, 51.1% with osteopenia,

and 27.1% had a normal BMD. Lowest BMD was measured at the femoral neck in 470 participants, at the total hip in 3 participants, and at the lumber spine in 15 participants. Moderate to severe (*i.e.*, grade 2-3) prevalent vertebral fractures were present in 14.3% of patients. AOM was prescribed in 34.2% of patients (8 (1.6%) were already using AOM, and 159 (32.6%) started using AOM at baseline visit).

Compared to eligible FLS attenders, who were not willing or able to participate in our study, patients included in our study were younger, had fewer major or hip fractures, had a higher BMD, and a lower proportion had prevalent vertebral fractures (Supplementary table 1).

Falls

During a median follow-up of 3 years (range 0.1 to 3.0), 296 (60.7%) patients recorded 959 falls, corresponding to 68.6 falls per 100 person-years. The cumulative fall incidences and incidence rates per 100 person-years at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in Figure 1. Of the 296 patients with at least one fall, 115 (38.9%) had one fall and 181 (61.1%) had two or more falls (up to 39 falls in one patient).

A first fall was recorded by 189/488 (38.7%) patients during the first year of follow-up, by 56/299 (18.7%) during the second, and by 51/243 (21.0%) during the third year of follow-up. The median time to the first fall was 34 (range 1-156) weeks. Of the 959 falls, 47 (4.9%) resulted in a subsequent fall-related fracture.

There were no significant differences in baseline characteristics between patients with and without a fall during the 3-year follow-up, except for that a higher proportion of patients with incident falls reported at least one fall in the year before the start of the study (34.5% vs. 19.3%, $p<0.001$) (Table 1). There were no significant differences in baseline characteristics between patients with one fall and those with multiple falls (data not shown).

Subsequent fractures

In total, 53 (10.9%) patients recorded 60 subsequent fractures, corresponding to 4.29 subsequent fractures per 100 person-years. The cumulative subsequent fracture incidences and incidence rates (per 100-person years) at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in Figure 2. Of all subsequent fractures, 47 (78.3%) were fall-related, and 13 (21.7%) were non-fall-related. Fall-related subsequent fracture sites were: radius and ulna (n=9), tibia and fibula (n=8), proximal femur (n=4), metatarsal (n=4), hand phalanx (n=4), symptomatic vertebra (n=3), proximal humerus (n=3), clavicula (n=3), costal bones (n=2), scapula (n=2), pelvic bone (n=1), metacarpal (n=1), tarsal (n=1), patella (n=1), and foot phalanx (n=1), whereas subsequent non-fall-related fractures sites were: symptomatic vertebral (n=5), metatarsal (n=2), foot phalanx (n=5), and hand phalanx (n=1). Half (53.2%) of all fall-related subsequent fractures were sustained at the first fall.

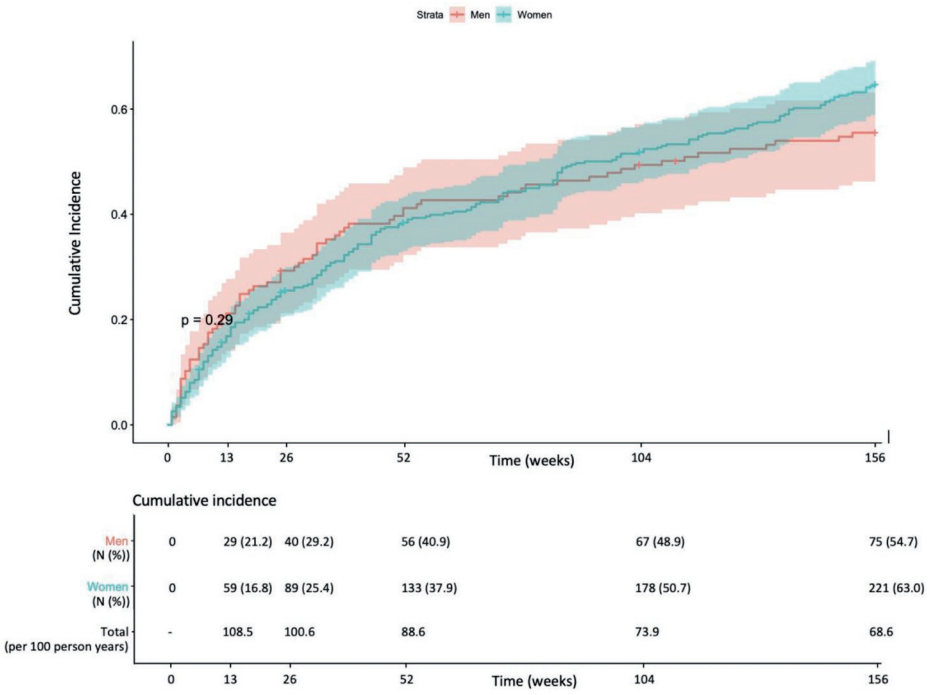


Figure 1. Cumulative incidence of falls stratified by gender.

Baseline characteristics for patients with and without subsequent fractures are presented in Table 1.

Of the 296 patients with at least one fall, 41 (13.9%) had 46 fall-related subsequent fractures, 7 (2.4%) had 7 non-fall-related subsequent fractures, and 1 (0.3%) had 1 fall- and 1 non-fall-related subsequent fracture. Of the 192 patients without a fall, 4 (2.1%) had 5 non-fall-related subsequent fractures. Of note, the risk of subsequent fractures was higher in patients with at least one fall than in those without a fall (adjusted HR (95% CI): 8.6 (3.1-23.8); cumulative incidence: 16.6%% versus 2.1%) (Figure 3 and Table 2). Results were similar when femoral neck BMD instead of the lowest BMD was used for adjustments (adjusted HR (95% CI): 8.3 (3.0-23.0)). Additionally, subsequent fracture risk was higher in patients with moderate or severe prevalent vertebral fractures than in those with no or mild prevalent vertebral fractures (adjusted HR (95% CI): 3.9 (2.1-7.3); cumulative incidence: 24.3% versus 8.6%) (Table 2).

The association between falls and subsequent fractures remained significant in sensitivity analyses (i) excluding patients with index and subsequent finger and toe fractures (adjusted HR (95% CI): 8.2 (2.5-26.6)), and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller (adjusted HR (95% CI): 2.9 (1.5-5.6)).

Table 1. Baseline characteristics of 488 participants stratified by incident fall and subsequent fracture status.

	Total population (n=488)	**Non-fallers** (n=192)	**Fallers** (n=296)
Age (years)	64.6 ± 8.6	64.4 ± 8.0	64.8 ± 9.0
Women	351 (71.9)	130 (67.7)	221 (74.7)
Baseline fracture			
Finger or toe	55 (11.3)	30 (15.6)	25 (8.4)
Minor	303 (62.1)	109 (56.8)	194 (65.5)
Major	104 (21.3)	44 (22.9)	60 (20.3)
Hip	26 (5.3)	9 (4.7)	17 (5.7)
Fall-related[a]	422 (86.5)	164 (85.4)	258 (87.2)
Fall previous year[b]			
0	349 (71.5)	155 (80.7)	194 (65.5)
≥ 1	139 (28.5)	37 (19.3)	102 (34.5)
BMI (kg/m^2)	27.7 ± 4.4	27.7 ± 4.4	27.7 ± 4.4
BMD			
Normal BMD	132 (27.1)	54 (28.1)	78 (26.4)
Osteopenia	249 (51.0)	97 (50.5)	152 (51.4)
Osteoporosis	107 (21.9)	41 (21.4)	66 (22.3)
Prevalent vertebral fracture[cd]			
None	356 (73.0)	139 (72.4)	217 (73.3)
Grade 1	62 (12.7)	22 (11.5)	40 (13.5)
Grade 2-3	70 (14.3)	31 (16.1)	39 (13.2)
Anti-osteoporosis treatment	167 (34.2)	70 (36.5)	97 (32.8)

Continuous variables are shown in mean ± SD (standard deviation), categorical variables are shown as number of patients (%). [a] Signifying that fracture was caused by a fall. [b] Fall resulting in baseline fracture not included.

	P-value	No subsequent fracture (n=435)	Subsequent fracture (n=53)	P-value
	0.608	64.5 ± 8.8	65.3 ± 7.1	0.488
	0.095	308 (70.8)	43 (81.1)	0.114
	0.060	49 (11.3)	6 (11.3)	0.460
		270 (62.1)	33 (62.3)	
		95 (21.8)	9 (17.0)	
		21 (4.8)	5 (9.4)	
	0.582	378 (86.9)	44 (83.0)	0.436
	<0.001	315 (72.4)	34 (64.2)	0.208
		120 (27.6)	19 (35.8)	
	0.961	27.8 ± 4.4	26.9 ± 4.8	0.154
	0.906	123 (28.3)	9 (17.0)	0.081
		222 (51.0)	27 (50.9)	
		90 (20.7)	17 (32.1)	
	0.572	328 (75.4)	28 (52.8)	<0.001
		54 (12.4)	8 (15.1)	
		53 (12.2)	17 (32.1)	
	0.402	142 (32.6)	25 (47.2)	0.035

[c] According to Genant *et al.* [d] According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density.

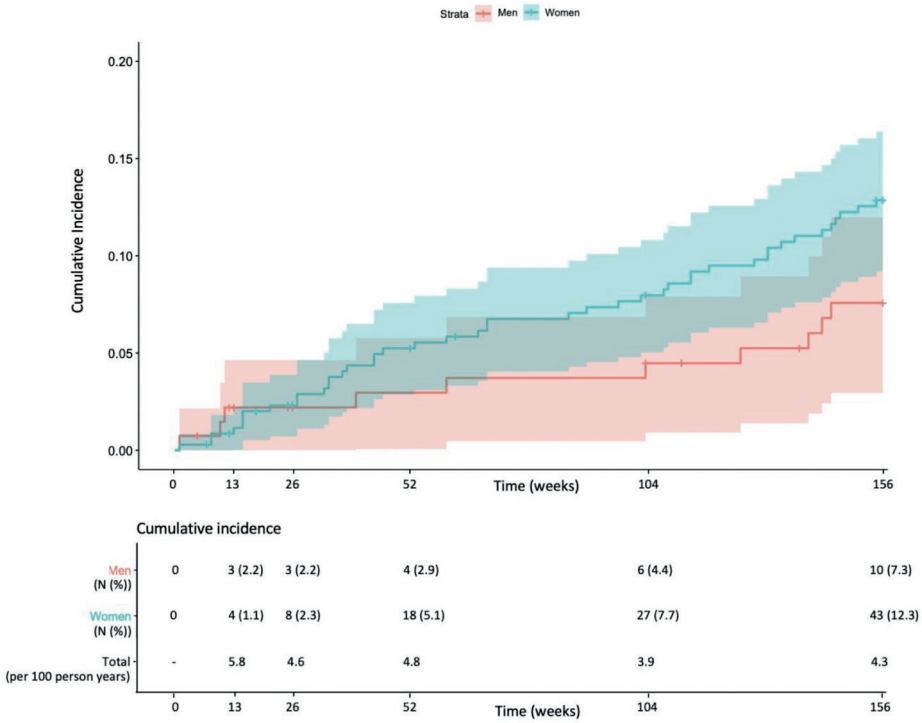


Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

Table 2. Predictors of refracture: results of the Cox's proportional hazard model

Predictor	Unit of comparison	Hazard ratio (95% CI)	P-value
Gender	Women versus men	1.39 (0.68-2.83)	0.362
Age	+5 years	0.97 (0.82-1.13)	0.662
Index fracture	Major or hip versus all other	0.68 (0.35-1.33)	0.263
BMD	-0.12 g/cm^2	1.30 (0.95-1.78)	0.101
Prevalent vertebral fracture	Yes versus no	3.88 (2.07-7.27)	<0.0001
Fall	Yes versus no	8.58 (3.09-23.8)	<0.0001

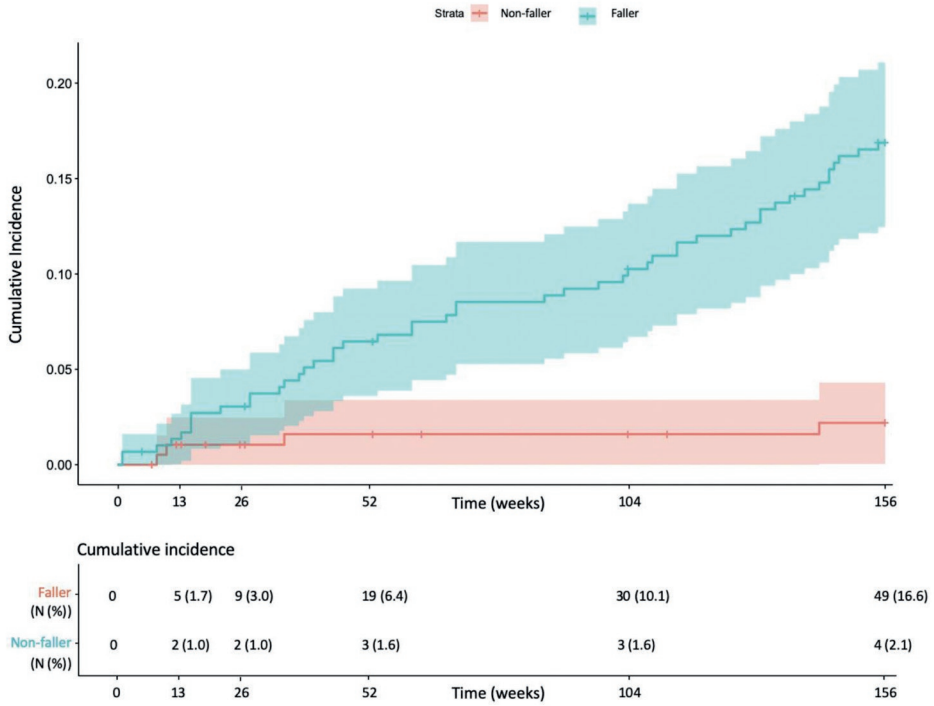


Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.

DISCUSSION

In this 3-year prospective observational cohort study in patients aged 50+ years with a recent clinical fracture, treated according to current Dutch osteoporosis guidelines at a FLS, 60.7% of patients had at least one fall, and 10.9% had at least one subsequent fracture. The majority (78.3%) of subsequent fractures was caused by a fall, and of all fall-related subsequent fractures, 53.2% occurred at the first fall. Subsequent fracture risk was nine-fold higher in fallers than in non-fallers.

Literature reporting fall incidence in fracture patients is limited. Comparable to our results, Van Helden *et al.* [28] reported a 3-month fall incidence of 15% in patients with a recent fracture at a FLS, and Matsumoto *et al.* [29] reported a 1-year fall incidence of 40% in ambulatory patients with a recent fracture. Various other studies included older, hip fracture patients and reported higher one year fall incidences up to 55% [7-11], except for the study from Yeh *et al.* that reported a lower 1-year fall incidence (31%).[30] Higher fall incidences in hip fracture studies can partially be explained by

the older study population. Unfortunately, other fall risk factors cannot be compared. An explanation for the lower fall incidence in the study by Yeh *et al*. may be that information on the occurrence of falls was provided by patients and family caregivers, which may have resulted in under registration of falls.

A comparison between the fall incidence in our study and that in the general population is difficult to make, because population-based studies were conducted in a 65+ aged, community-dwelling population, whereas approximately 50% of our study population was <65 years old. The proportion of community-dwelling people aged 65+ years sustaining at least one fall over a 1-year period ranged from 28 to 35% [31-33], with an increasing incidence with increasing age [34]. The 1-year fall incidence reported is our study is comparable to that in an older (65+ aged) population, and therefore relatively high. However, in contrast to what has been reported in literature, we found no higher 3-year fall incidence with increasing age. An explanation for this could be that, especially in the older age group, relatively more healthy patients participated in our study, resulting in a lower fall incidence in older age group. Another explanation could be that patients aged 50-65 years are more physically active, and therefore fall more often.

Compared to our results, previously published FLS studies reported lower [34,35], similar [28,37,38], and higher [39,40] subsequent fracture rates. Differences can be explained by differences in patient selection. Studies that included older patients [39] and patients with more severe fractures [40] reported higher subsequent fracture rates, whereas studies that excluded hand and foot index and subsequent fractures [35] or frail patients reported lower rates [36].

In 2010, the Dutch population consisted of approximately 6,000,000 people aged 50+ years, of whom 119,419 sustained a fracture that year [41], corresponding to a calculated annual fracture incidence of 2.0% in the general Dutch 50+ population. Compared to the general Dutch 50+ population, the fracture incidence was more than 2 times higher in our study, even in the 3rd year of follow-up. In our study, fracture incidence remained high despite treatment according to the current osteoporosis guideline, raising the question of what more can be done to prevent subsequent fractures. Even though conflicting results have been published about the effect of fall prevention strategies on subsequent fracture [42], we hypothesize that fall interventions could be effective in patients at highest risk, namely those with a recent fracture at risk of falling. Furthermore, according to literature, recurrent fallers have an almost fourfold increased odds of sustaining a fall-related fracture compared to individuals with a single fall.[43] However, we found that the majority of subsequent fall-related fractures occur at the first fall after the index fracture, with a median time to the first fall of 34 weeks. Interestingly, fall incidence was higher in the first year of follow-up compared to the second and third year. This may indicate an imminent fall risk, which may attribute to the imminent subsequent fracture risk after an index fracture.[1-6] This

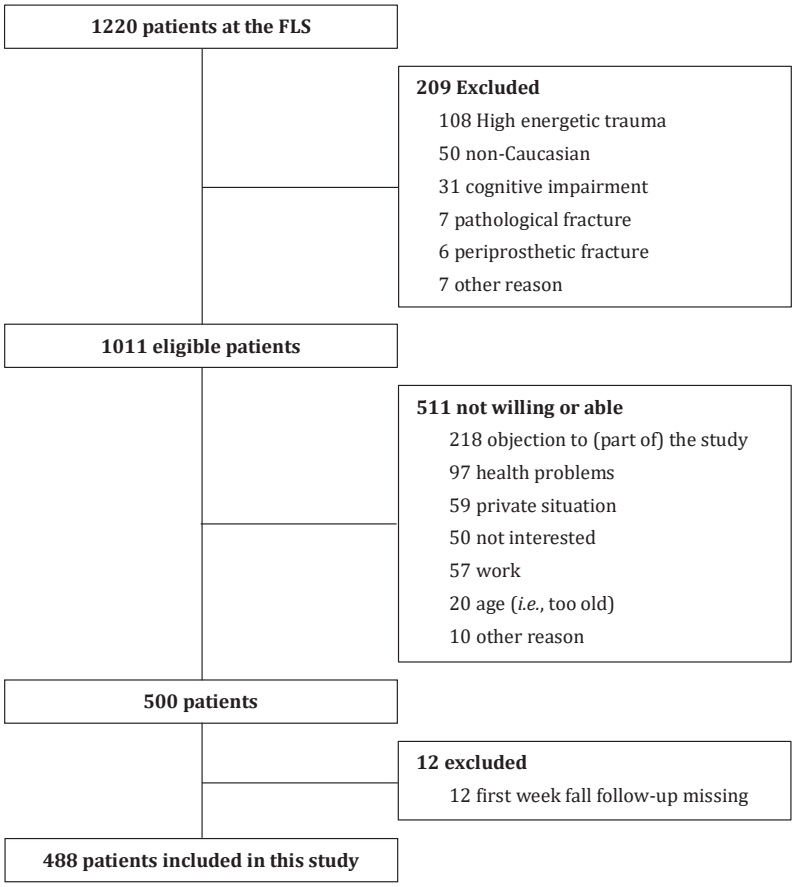
implies that the FLS patients with a high fall risk should be identified immediately, because there is a small window of opportunity to prevent falls and fall-related subsequent fractures.

Remarkably, in contrast to previous studies indicating that imminent fracture risk that was highest in the first year after an index fracture [44,45], there was a linear subsequent fracture incidence during 3-year follow-up in this study. An explanation for the linear subsequent fracture incidence may be the relatively healthy patients who agreed to participate in our study. Compared to non-attenders, they were younger, and a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis, and if indicated, were more likely to receive AOM. Importantly, in addition to falls, moderate to severe prevalent vertebral fractures at baseline were associated with subsequent fractures, even though anti-osteoporosis medication had been prescribed to these patients according to the current Dutch osteoporosis guideline.

This study has several limitations. Although, this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively low. Therefore, the association between falls and fall-related, and non-fall-related subsequent fractures could not be analyzed separately. A fall 'not-resulting-in-a-subsequent-fracture' might indicate frailty of patients, and might be different from those falls that directly resulted in a subsequent fracture. Future studies are needed to investigate this difference. Finally, because of small numbers, subgroup analyses should not be performed. Furthermore, data on falls were collected prospectively using fall diaries that had to be returned at 3 and 6 months, and 1, 2, and 3 year. However, no procedures were in place to validate self-reported falls, and it is possible that recall bias, could have led to underregistration of falls. Moreover, no information was available on falls between the index fracture and enrollment in the study. Finally, relatively healthy patients participated in the study. Compared to non-attenders, they were younger, a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis. The proportion of patients with a fall and subsequent fractures could be expected to be even higher in the total FLS population.

In conclusion, in this 3-year prospective observational cohort study in FLS patients, subsequent fracture incidence was high despite being prescribed anti-osteoporosis medications according to the current Dutch osteoporosis guideline. Subsequent fracture risk was nine-fold higher in fallers than in non-fallers, and the majority of fall-related subsequent fractures occurred at the first fall at a median time of 34 weeks. These findings emphasize that immediate attention for fall risk reduction could be beneficial in FLS care. Various risk factors, including comorbidities, medication use, polypharmacy and alcohol use among others, contribute to patient's fall risk and further research is needed to determine predictors for falls to identify patients at highest risk of falling.

SUPPLEMENTATRY TABLES AND FIGURES



Supplementary figure 1. Patient selection.

Supplementary table 1. Characteristics of 1011 FLS patients that participated and not-participated in this study.

	Participants (n=500)	**Non-participants** (n=511)	**P-value**
Age (years)	64.6 ± 8.6	68.3 ± 9.8	<0.001
Women	357 (71.4)	396 (77.5)	0.026
Baseline fracture			
Finger or toe	58 (11.6)	53 (10.4)	<0.001
Minor	311 (62.2)	259 (50.7)	
Major	105 (21.0)	157 (30.7)	
Hip	26 (5.2)	42 (8.2)	
Fall-related	431 (86.2)	441 (86.3)	0.963
Fall previous year[a]			
0	356 (71.2)	359 (70.3)	0.741
≥ 1	144 (28.8)	152 (29.7)	
≥ 2	72 (14.4)	87 (17.0)	0.252
BMD			
Normal BMD	135 (27.0)	90 (17.6)	<0.001
Osteopenia	255 (51.0)	258 (50.5)	
Osteoporosis	110 (22.0)	163 (31.9)	
Prevalent vertebral fracture[b]			
None	366 (73.2)	349 (68.3)	0.010
Grade 1	63 (12.6)	53 (10.4)	
Grade 2-3	71 (14.2)	109 (21.3)	
At least one fall past year	143 (29.3)	152 (29.9)	0.704

Data presented as mean ± SD or number (percentage) of patients. [a] Fall resulting in baseline fracture not included. [b] According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density

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CHAPTER 9

GENERAL DISCUSSION

GENERAL DISCUSSION

In this thesis we focused on the bone- and fall-related phenotype and the outcomes of patients aged 50+ years with a recent clinical fracture attending the Fracture Liaison Service (FLS) for fracture risk evaluation and secondary fracture prevention. In the first part (**Chapter 2-6**), we focused on the phenotype of FLS patients. We performed a literature survey to identify the phenotype of patients with a recent fracture attending the FLS. Subsequently, we evaluated comorbidities, specifically celiac disease and cardiovascular disease, and medications associated with an increased risk of osteoporosis, falls and fractures. Finally, we studied the association between prevalent vertebral fractures and bone quality of the distal radius and distal tibia as measured with high-resolution peripheral quantitative computed tomography (HR-pQCT) in postmenopausal women with a recent non-vertebral fracture at the FLS. In the second part (**Chapter 7 and 8**), we focused on outcomes of fracture patients at the FLS. We evaluated the impact of FLS care on the 3-year subsequent fracture and mortality risk of patients with a recent fracture and we studied the association between incident falls and subsequent fracture risk in patients attending the FLS.

PART I – PHENOTYPE OF PATIENTS AT THE FLS

Literature review

During the last two decades, the perspectives on secondary fracture prevention have considerably been changed. Whereas secondary fracture evaluation traditionally implied to perform a bone mineral density (BMD) measurement and to start treatment in patients with osteoporosis, it is now known that many more risk factors may contribute to an increased secondary fracture risk. Therefore, the approach for secondary fracture prevention is becoming more complex. In order to be able to improve FLS care, this thesis focused on the FLS patients' characteristics and outcomes.

In **Chapter 2**, we have conducted a literature survey to describe components of the bone- and fall-related phenotype of patients attending the FLS. This survey indicated that there was a high variability in terms of patient identification (case finding), selection, and FLS attendance among the different studies. Consequently, there was a high variability in patient characteristics, such as mean age, proportion of men and fracture locations. Furthermore, the studies varied in the risk evaluation that was performed, resulting in substantial variability in the percentage of patients with osteoporosis, prevalent vertebral fractures, newly diagnosed contributors to secondary osteoporosis and metabolic bone disorders, and fall-related risk factors.

The heterogeneity of the reported phenotypes of FLS patients in literature could be explained by the different approaches of FLS care. The method used to identify patients was not described in any of the studies. Subsequently, whereas fracture risk evaluation is recommended in all patients aged 50+ years with a recent fracture, various selection criteria were used. Additionally, the patients' response to the FLS invitation (*i.e.,* FLS attendance rates) varied considerably among studies. Finally, heterogeneity in published data on FLS populations can be further explained by the use of a selection or subgroup of FLS attenders included as study populations.

Although, dual-energy X-ray assessment (DXA) was performed and reported in all studies according to the traditional approach for secondary fracture prevention, there was a high variability regarding vertebral fracture assessment (VFA), laboratory testing to diagnose contributors to secondary osteoporosis and metabolic bone disease (SECOB) and fall risk assessment. Consequently, the execution of fracture risk evaluation varied considerably among studies.

It is therefore important to improve the implementation and effectiveness of FLS care. Future research should focus on the evaluation of patient characteristics associated with an increased risk of osteoporosis, falls and fractures, especially in relation to outcome measures, such as subsequent fractures and mortality, as well as quality of life and fracture-related costs.

The phenotype of patients at the FLS in VieCuri Medical Center

The studies described in **Chapter 3-8** of these thesis have been performed by using data of the FLS in the VieCuri Medical Center. In general, this FLS invites all men and women aged 50+ years with a recent fracture at any location, except patients with facial and skull fractures, high-energy trauma fractures and patients with fractures due to failure of prothesis, (metastatic) cancer, osteomyelitis and Paget's disease.

Comorbidities and medication use associated with bone- and fall-related risk

In **Chapter 3**, comorbidities in medical history and medication use associated with an increased bone- and/or fall-related risk of fractures (*i.e.,* known contributors to SECOB) were studied in patients attending the FLS. We found a high prevalence of patients with bone-related risk factors (BRR, 53.2%), fall-related risk factors (FRR, 45.6%) and the combination of BRR and/or FRR (65.6%).

Interestingly, the proportion of patients only having at least one BRR or at least one FRR was similar for women and men, age, BMI, BMD, and fracture type subgroups, whereas the proportion of patients having a combination of BRR and FRR increased significantly with increasing age, BMI, and severity of the fracture. These findings imply that comorbidities and medications associated with a bone- or fall-related risk of fractures are often present in FLS attenders and that bone- and

fall-related fracture risk often co-exist, especially in patients at older age, higher BMI, and with more severe fractures. However, the impact of combinations and total number of contributors to bone- and fall-related risk factors on the risk of incident falls and subsequent fractures is currently unknown and could not be evaluated in our study because longitudinal data were not available. Further research is needed to investigate the impact of unique and combinations of risk factors on subsequent fall and fracture risk in FLS patients in order to identify and treat patients with an increased risk of falls and subsequent fractures.

Celiac disease

In **Chapter 4**, we evaluated the prevalence of celiac disease (CD), one of the comorbidities associated with an increased risk of fractures, in FLS patients. We found a prevalence of biopsy-proven CD of 0.38% of which 0.19% was newly diagnosed. Unexpectedly, this was within the range of the prevalence in the general West-European population [1] and in Dutch healthy blood donors [2], and lower than in most studies in osteoporosis patients.[3,4] Furthermore, in our cohort, fracture and BMD characteristics could not be used to distinguish between patients with or without possible CD, although the number of patients with CD was low.

Since CD is a risk factor for fractures [5–8], we expected to find a higher prevalence of CD in our FLS cohort. Since it is recommended in the guidelines to perform DXA in patients diagnosed with CD, which may lead to earlier intervention and better management of fracture risk, these patients might be less likely to fracture or to attend the FLS.

The cost of serologic CD screening (IgA and anti-tissue transglutaminase IgA) at our hospital was €22,42 per patient and for the confirmation test (anti-endomysial IgA) €32,41. Given the low prevalence of CD in our FLS cohort, the number needed to screen in order to diagnose one patient with CD is 261. Even in patients with osteoporosis, the number needed to screen was 138 and in patients with major osteoporotic fractures or a prevalent vertebral fracture, it was 288 and 152, respectively. Although serological screening for CD is minimally invasive and of low burden for the patient, based on our results, we believe that standard screening for CD is not recommended. Nevertheless, it remains indicated to evaluate the presence of CD in FLS patients with symptoms, comorbidities and laboratory results suggestive of CD.

Cardiovascular risk factors

In **Chapter 5**, we evaluated the prevalence of cardiovascular risk factors in patients attending our FLS and found that 29.9% of patients had a medical history of: cardiovascular disease (CVD, 13.7%), venous thromboembolic event (VTE, 1.7%), hypertension (HT, 14.9%)

and/or diabetes mellitus type 2 (DM2, 7.1%). The prevalence of cardiovascular risk factors increased with age (21% in patients aged 50-59 years to 48% in patients aged >80 years) and was higher in men than in women (36% versus 27%), but independent of BMD and fracture type. Apparently, the previously reported association between osteoporosis and CVD in epidemiological studies, with an increased risk of cardiovascular events in patients with osteoporosis [9,10], was not found in patients with a recent fracture.

The presence of CVD has implications for osteoporosis treatment. Strontium ranelate is contra-indicated in patients with a history of ischemic heart disease, peripheral artery disease, cerebrovascular disease and uncontrolled hypertension.[11,12] Raloxifene is contra-indicated in post-menopausal women with a history of, or an increased risk for VTE.[11,13,14] Also, the new available osteo-anabolic drug Romosozumab has been associated with an increased risk of cardiovascular events. A numeral increase in serious cardiovascular events were reported in the phase III randomized ARCH trial [15], but not in the FRAME trial.[16] Consequently, Romosozumab should not be initiated in post-menopausal women who have experienced a myocardial infarction or cerebrovascular accident and used cautiously in patients with a high CVD risk.[17,18]

In conclusion, 30% of FLS patients had a medical history of CVD, VTE, HT and/or DM2. Therefore, we recommend careful evaluation of the medical history with respect to cardiovascular risk factors in all FLS patients, since this may have implications for treatment with anti-osteoporosis medication.

Bone quality in patients with vertebral fracture

Prevalent vertebral fractures have been associated with an increased subsequent vertebral and non-vertebral fracture risk independent of BMD [19-22], and bone micro-architecture has been shown to be impaired in patients with prevalent vertebral fractures compared to fracture free controls.[23-26] However, the association between prevalent vertebral fractures and bone micro-architecture and bone strength has not been evaluated in patients with a recent non-vertebral fracture at the FLS. Therefore, in **Chapter 6**, we studied the association between prevalent vertebral fractures and bone quality of the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture at the FLS.

We provide novel evidence that in an FLS cohort the presence and severity of prevalent vertebral fractures reflects a generalized bone deterioration, independent of femoral neck areal BMD. Compared to women with a NVF but without a prevalent vertebral fracture, those with at least one prevalent vertebral fracture had a lower total and trabecular vBMD and a lower trabecular number with higher trabecular separation at the radius and tibia, and lower cortical thickness and calculated ultimate failure load and compressive bone strength at the tibia.

The findings in **Chapter 6** suggest that despite a normal BMD, prevalent vertebral fractures are associated with an impaired bone micro-architecture and are a potential indicator for increased subsequent fracture risk, thus, emphasizing the importance of performing VFA. Detection of prevalent vertebral fractures does not only have implications for proper fracture risk assessment, but it also affects anti-osteoporosis treatment initiation both in terms of the number of patients eligible for treatment as well as type of preferred anti-osteoporosis medication.[27,28] This has been shown by van der Velde *et al*. [29], who reported a 25% prevalence of grade 1-3 vertebral fractures and a 15% prevalence of grade 2-3 vertebral fractures based on routine VFA in patients with a recent non-vertebral fracture. They also reported that the proportion of patients with an indication for anti-osteoporosis treatment increased by 25%. In addition, knowledge of baseline vertebral fractures allows a reliable identification of incident vertebral fractures during treatment, which may result in the adjustment of treatment. Further, in the recently updated Dutch osteoporosis and fracture prevention guideline [28], the bone forming agents Romosozumab and Teriparatide are recommended as first line therapy in post-menopausal based on a combination of low T-scores and the presence of one or more Grade 2-3 vertebral fractures.

Currently, Grade 1 prevalent vertebral fractures have no therapeutic implications for secondary fracture prevention in The Netherlands. Interestingly, in our study (**Chapter 6**), we found that patients with a Grade 1 prevalent vertebral fracture also had a deteriorated bone micro-architecture and calculated bone strength, which indicates the importance of these VFs. Furthermore, in a recently published study [30], grade 1 vertebral fractures were associated with increased incident fracture risk, independent of age, clinical risk factors and FN-aBMD. Also, in the CaMos study, grade 1 vertebral fractures were associated with incident vertebral, but not with non-vertebral fractures.[31] Our results combined with the results of these studies, suggest that a reconsideration of therapeutic implications of Grade 1 prevalent vertebral fractures, especially in case of multiple grade 1 vertebral fractures, should be considered.

A limitation of the DXA-VFA method is that it has a lower sensitivity for the detection of grade 1-3 as well as grade 2-3 vertebral fractures compared to X-ray and computed tomography (CT) [32-34], which may have resulted in misclassification of patients and thereby in a dilution of differences in bone microarchitecture between patients with and without vertebral fractures.[32,33] It remains to be studied whether the deterioration in bone micro-architecture as observed in our study in patients with a vertebral fracture is more pronounced when using more sensitive assessment methods. Further, multiple classification methods for vertebral fractures exist such as the modified algorithm-based qualitative (mABQ) method, which differs in the

classification Genant's method resulting in lower prevalence rates according to mABQ.[31,35] It would be interesting to determine the impact of this classification method on the association between vertebral fractures, bone micro-architecture and subsequent fracture risk.

PART II – OUTCOME OF PATIENTS AT THE FLS

Subsequent fractures and mortality

In **Chapter 7**, we evaluated whether FLS care was associated with reduced subsequent fracture and mortality risk over 3 years of follow-up and concluded that in patients with a major/hip index fracture, the implementation of an FLS was associated with a lower mortality risk (-16%) in the first 3 years after a fracture and a lower subsequent major/hip fracture risk in the first year after fracture (-33%). In patients with a non-major/non-hip index fracture there was no difference in subsequent non-major/non-hip fracture risk or mortality before and after FLS implementation.

Although it is advocated that the FLS is the most effective approach for secondary fracture prevention, the number of studies on this topic is quite scarce and several methodological challenges have to be taken into account while studying FLS related outcomes such as subsequent fractures and mortality.

As recently published by Li *et al.*, previous studies on the impact of FLS care on subsequent fracture and mortality risk are heterogeneous with respect to the design of the study, the included study population, the classification of the fractures, the length of follow-up (which is limited to 2 years or less in most studies) and most previous studies did not apply a competing mortality risk analysis when analyzing subsequent fracture risk.[36]

One of the main limitations regarding the evaluation of outcomes of FLS care is that it is not ethical to perform a randomized controlled trial where patients with the highest risk of a subsequent fracture (*i.e.,* those with a recent fracture) are randomized to FLS care or no FLS care, which would imply that patients allocated to the no FLS care group would not receive adequate risk assessment and treatment. As a consequence, we have to use real world data with observational study designs.[37] In **Chapter 7**, we have compared a pre-FLS group with a post-FLS group including both attenders and non-attenders, which we consider to be the most appropriate approach to evaluate the real-life effect of the implementation of an FLS. Further, by this approach selection bias is minimized, even though this might have resulted in the dilution of the FLS effect. Comparing attenders to non-attenders or attenders with a pre-FLS group would introduce selection bias,

since non-attending has been associated with male gender, frailty, living alone, low education, not being interested in bone health and being unaware of an increased subsequent fracture risk.[38]

Studies reporting long-term benefits in mortality and subsequent fracture risk reduction related to FLS care are still lacking in literature. Since five out of the six studies included in the meta-analysis by Li *et al.* [36] had a follow-up duration of 2 years or less, and the only study with a median follow-up period of >2 years had a post-FLS follow-up of 1.5-1.7 year [39], our study is the first that indicates a longer-term mortality risk reduction up to 3 years after fracture.

In literature, several fracture classifications have been used in the assessment of FLS outcomes (*e.g.* minor, major and hip fractures according to Center *et al.* [40], major osteoporotic fractures (MOF) as defined by the International Osteoporosis Foundation). To the best of our knowledge, our study was the first to have used multiple fracture classifications. While, in major/hip fracture patients, the implementation of an FLS resulted in a lower mortality and subsequent fracture risk, we found no association in patients presenting with a non-major/non-hip fracture. Similarly, in sensitivity analysis, there was no difference in subsequent MOF risk after an index MOF between pre-FLS and post-FLS. Although our study population was one of the largest as compared to previous studies, we were not able to perform detailed fracture specific analyses. Recently, the Dutch guideline on osteoporosis and fracture prevention was updated and recommended that patients with a finger or toe fracture should not be invited for secondary fracture prevention at the FLS, because of their low subsequent fracture and mortality risk, while in our study, these patients were still included in the minor index and subsequent fracture group.

Another methodological consideration which needs to be addressed analyzing subsequent fracture risk is the competing risk of mortality. In traditional Cox proportional hazard analyses, subjects who have not experienced the outcome of interest (*i.e.,* subsequent fracture), and who cannot be followed to the end of follow-up for any reason (*i.e.,* lost to follow-up or death), are censored. If mortality is not taken into account, the fracture risk is expected to be overestimated, especially in populations with a higher mortality rate, which is the case especially in older patients and in hip fracture patients. In our study, we have used the subdistribution Hazard approach as described by Fine and Gray.[41] According to this approach, patients who died, defined as competing event, before sustaining a subsequent fracture, defined as our outcome of interest, are not censored, but these patients retain in the risk set for sustaining a subsequent fracture. By taking the competing risk of mortality into account, a true estimate of the subsequent fracture risk is presented. In previous studies, competing risk of mortality was taken into account in only 4 out of 16 FLS studies.[36]

With respect to FLS studies, immortal time bias also needs to be considered. Immortal time bias occurs when there is a period of time during follow-up where an event or death cannot occur. With respect to FLS attendance, patients must survive until they can attend the FLS for fracture risk evaluation. In our hospital, the median time between fracture and FLS attendance was 125 days. Hence, from a study perspective, patients have to be 'immortal' in the time between fracture and FLS visit in order to be a FLS attender. To take this bias into account, we have performed sensitivity analyses for mortality and subsequent fractures with follow-up initiated at day 126.[42] In these sensitivity analyses, similar to the main analyses, the adjusted mortality risk was significantly lower in post-FLS group in patients with a major/hip index fracture (HR 0.79 (95% CI): 0.67-0.93)) and in patients with an index MOF (HR 0.75 (95% CI: 0.64-0.88)), whereas there was no difference in subsequent major/hip fracture risk after a major/hip index fracture, or subsequent MOF risk after an index MOF.

In our study, a 33% lower subsequent major/hip fracture risk was found in post-FLS patients with a major/hip index fracture in the first 360 days, taking the competing risk of death into account. Due to the violation of the proportional hazard assumption, the analyses were separated into two time-intervals. Therefore, we could not report the subsequent fracture risk during the complete follow-up period of 3 years, although the finding of a lower subsequent fracture risk in the first period followed by a non-significant difference in the second period suggests that FLS care may be associated with a longer-term subsequent fracture risk reduction.

Early FLS benefits in terms of subsequent fracture risk reduction, in the first 360 days after a major/hip index fracture as well as the lower 3-year mortality risk in our study can only partially be explained by the use of anti-osteoporosis medication (AOM), since post-FLS approximately half of patients attended the FLS and only 40% of the FLS attenders was treated with AOM. We speculate that favorable outcomes in the post-FLS group were likely due to parallel changes in fracture related procedures combined with the integrated approach at the FLS. Although guidelines for treatment and rehabilitation for hip fracture patients were updated during the post-FLS study period, our subgroup-analyses did not show a significant reduction in mortality (HR: 0.83 (95% CI: 0.68-1.10)) nor in subsequent fracture risk (SHR: 0.98 (95% CI: 0.70-1.37)) in patients presenting with a hip fracture. Furthermore, FLS attenders were extensively evaluated, not only by BMD measurement and VFA, but also for the presence of underlying metabolic bone disorders (including calcium and vitamin D deficiencies) and in addition to the initiation of AOM according to the national guidelines, co-morbidities were treated, medication use was reviewed and optimized, and patients who started AOM were followed up to a year post fracture. It is likely that the integrated approach at the FLS, and not only AOM treatment, may result in a more favorable (short term) outcome in the post FLS group.

The lack of the long-term subsequent fracture risk reduction might be explained by poor adherence to oral bisphosphonates, which were the preferred treatment option during our post-FLS period. Although oral bisphosphates have proven their effect in fracture risk reduction in clinical trials in patients with an increased fracture risk, i.e., osteoporosis, real-life persistence with this type of medication is often poor which might in turn dilute the fracture risk reduction. Klop *et al.* [43] evaluated persistence with bisphosphonates in newly treated fracture patients in the Netherlands and concluded that persistence was 75% one year after treatment initiation and only 45% 5 years after initiation, respectively. Unfortunately, we have no data on treatment persistence of patients prescribed AOM due to privacy restrictions. If non-persistence could be identified based on pharmacy data or by using a medication adherence scoring tool, interventions could be initiated to improve treatment adherence, such as the educational and motivational support program which was used to improve the persistence with teriparatide.[44]

Incident fall and subsequent fracture incidence

In **Chapter 8**, we prospectively evaluated incident falls and their association with subsequent fracture. We found that incident falls are common in FLS patients and that subsequent fractures in these patients still occur despite AOM treatment. As shown in our study, incident falls were associated with subsequent fracture risk and the majority of subsequent fall-related fractures occurred at the first fall after the index fracture, with a median time to the first fall of 34 weeks. This implies that FLS patients at high risk of falling should be identified at the time of FLS attendance, because there is a small window of opportunity to potentially prevent falls and fall-related subsequent fractures.

In the general population, one in three individuals aged 65+ years sustain a fall at least once a year [45,46] and approximately 5% of these falls result in fractures.[47,48] In 2020 in the VieCuri reference area (Venlo), where our study was conducted, the estimated number of citizens aged 65+ with an increased risk of falling was 6,300, corresponding to estimated total healthcare costs due to falls of 6.9 million euros, which is expected to increase by 17.9% by 2035.[49] In our 3-year observational cohort study, 3-year fall incidence was 60.7% and incident falls were associated with subsequent falls. In addition, the 3-year incidence of subsequent fractures was 10.6% despite treatment according to the Dutch osteoporosis guideline [27] and subsequent fracture risk was nine-fold higher in fallers than in non-fallers.

According to literature, recurrent fallers have an almost fourfold increased odds of sustaining a fall-related subsequent fracture compared to individuals with a single fall.[50] A novel finding in our study was that the majority of subsequent fall-related fractures

occur at the first fall after de index fracture, with a median time to the first fall of 34 weeks. Further, fall incidence was higher in the first year of follow-up compared to the second and third. This may indicate an imminent fall risk, which may attribute to the well-known imminent subsequent fracture risk after an index fracture.[51] This implies that FLS patients with a high fall risk should be identified immediately, since there is a small window of opportunity to prevent falls and fall-related fractures. We can only speculate on the potential causes of this imminent fall risk, which could be caused by pain due to the fracture, walking with crutches or another walking aid, conditional decline due to decreased mobility after the fracture or fear of falling or the presence of risk factors for fractures that also increase risk of falls.

Since various fall risk factors are potentially modifiable, optimizing strategies for early fall prevention in FLS patients is important. Several studies on the effect of exercise training focusing on muscle strength, balance and weight-bearing and fall prevention intervention programs in patients with osteoporosis or a fracture have been published. Wilson *et al.* [52] published a comprehensive systematic review on the prevention and management of osteoporotic fractures by paramedics, and concluded that structured exercise reduced fall risk in hip fracture patients, whereas there was insufficient evidence to determine the effect of this intervention in vertebral fracture patients. In a RCT in women with a recent osteoporotic fracture showed that balance training resulted in a decrease in the number of falls and improved balance compared to a control group that received physical therapy.[53] Two meta-analyses showed that in patients with a hip fracture structured exercise intervention and in particular progressive resistance training gave a significant improvement (compared to usual care or no intervention) of mobility, better balance, increased strength and less care dependence in activities of daily living (ADL).[54,55] In another meta-analysis on exercise interventions in vertebral fracture patients, there was a small reduction of pain and improvement of quality of life in the exercise group, whereas function tests and mobility did not improve.[56] However, not evaluated in all these studies was the effect of fall prevention interventions on subsequent fractures. The RESPOND-trial demonstrated that providing a telephone-based patient-centered fall prevention program to community-dwelling elderly aged 60-90 years presenting to the emergency department after a fall reduced falls and fractures.[57]

In a Cochrane review [58] on multifactorial and multiple component interventions to prevent falls in community-dwelling elderly, interventions focused on the specific risk profile of individual patients were more effective in comparison to usual care (RR 0.77 (95% CI 0.67-0.87)). As discussed above, risk factors for falls are prevalent in an FLS population, and should be systematically evaluated for a more profound assessment of the risk of subsequent fractures. However, literature on risk factors

for falls in patients with a recent fracture is limited, and currently, no prospectively validated tool for fall prediction is available. Future research should focus on how best to identify patients at risk of falling and who might benefit from a fall intervention program.

Another interesting finding in our study was that in addition to falls, the presence of prevalent vertebral fractures at baseline was associated with subsequent fracture risk (HR 3.88 (95% CI: 2.07-7.27)), independent of incident falls. Prevalent vertebral fractures are a well-known independent risk factor for fractures and an indication for anti-osteoporosis treatment. In our study, according to the guidelines in place at the time, most patients with prevalent vertebral fractures were treated with oral bisphosphonates. Teriparatide treatment was reserved for patients who had a third fracture during treatment with an anti-resorptive agent.[27] Recent evidence indicates that anabolic agents reduce non-vertebral and vertebral fractures to a greater extent and faster than potent oral anti-resorptive treatments.[15,16,59] Accordingly, guidelines recommend initial treatment with an anabolic agent in patients at very high fracture risk and in the new Dutch guideline on osteoporosis and fracture risk it is advocated to initiate treatment with osteoanabolic agents in patients who have a low T-score in combination with one or more grade 2 or 3 vertebral fractures. It is likely that this approach will further reduce subsequent fracture risk in the very high-risk patients at the FLS presenting with a non-vertebral fracture who also have one or more prevalent vertebral fractures.

An important point to address is that the frailest patients did not attend our FLS and did not participate in our study, which could have resulted in an underestimation of the incident fall and subsequent fracture incidence. On the other hand, since it has been hypothesized that the association between physical activity and falls is U-shaped [60], implying that both inactive and highly active older adults have higher fall rates, a relative healthy population could also have a higher risk of falls and fracture because of a more active lifestyle.

Altogether the findings in **Chapter 8** indicate a high imminent fall risk in the first three years after a recent fracture, which results in a substantial subsequent fracture risk despite adequate treatment with AOM. FLS care should therefore include adequate fall risk evaluation [61,62], as recommended in the new Dutch guideline on osteoporosis and fracture prevention.[28] However, a recent studied showed that only half of the Dutch FLSs adhere to current standards of fall guidelines.[63] Adequate implementation of fall risk assessment next to the evaluation of clinical risk factors, DXA, VFA ad laboratory testing care is therefore still an important and challenging issue in Dutch FLS.

FUTURE PERSPECTIVES

Understanding the impact of the various risk factors in patients attending the FLS for fracture risk evaluation is important for an optimal approach to reduce subsequent fracture and mortality risk. Based on the work presented in this thesis it is clear that fracture risk assessment in FLS patients comprises an integrated approach including a thorough assessment of medical history, medication, DXA, VFA, laboratory testing and fall risk. FLS attendance rates however, are still quite low in Dutch FLSs and future research should focus on how to improve FLS attendance rates.

Next, data on important FLS related outcomes such as subsequent fractures, mortality and quality of life are still sparse and studies with a follow-up longer than three years are not available.

Despite effective treatment for osteoporosis, many patients still do not receive appropriate fracture risk evaluation and treatment. In fact, the number of patients initiating anti-osteoporosis treatment after a fracture has been decreasing in the past years. Whereas, in order to improve secondary fracture prevention, focus on performing DXA and VFA remains important, future research should focus other outcomes measures, such as subsequent fractures and mortality, as well as quality of life and fracture-related costs. These future studies should have a longer follow-up period (*i.e.,* 5 years), and as advised by Li *et al.* [36] the competing risk of mortality should be taken into account while exploring the FLS effect on subsequent fracture risk. Further, it has to be advocated that future studies evaluating the FLS should include all treatment options for fracture prevention, including teriparatide and romosozumab, together with treatment persistence rates and the patients' history of anti-osteoporosis treatment.

Future research should also focus on fall risk assessment and prevention in patients at the FLS since we found that incident falls are common in FLS patients and strongly associated with subsequent fractures. Further, most fall-related subsequent factures occurred at the first incident fall which indicates a small window of opportunity to potentially prevent falls and fall-related subsequent fractures. Despite guideline recommendations for fall risk evaluation and prevention at the FLS, the implementation is clinical practice is limited. Although evidence for the effect of fall prevention interventions on subsequent fractures is scarce, we speculate that in addition to anti-osteoporosis treatment, multifactorial fall prevention interventions in those at highest risk of falls and fractures may have a positive effect on subsequent. Future research should focus on how to identify the patients that would have the most benefit of fall prevention programs. In addition to the well-known risk factor falls in the past year, physical activity and performance measures could be of special interest in the prediction of future falls and could help to identify the FLS patients at highest risk for fall related fractures.

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ADDENDUM

ADDENDUM

SUMMARY

SUMMARY

Fractures constitute a major health care problem worldwide, and are expected to increase due to aging of the population. Fractures are associated with increased morbidity and mortality, have an impact on patients' quality of life, and result in major health care costs. They indicate an increased risk of subsequent fractures, which in highest immediately after the fracture. This means there is a window of opportunity for immediate recognition of this imminent subsequent fracture risk and start interventions to reduce the risk. Despite the well-known importance of secondary fracture prevention and various effective treatments being available, such as anti-resorptive drugs (*i.e.*, bisphosphonates, denosumab, raloxifene) and osteo-anabolic drugs (*i.e.*, teriparatide and romosozumab), only a minority of patients receive appropriate evaluation and treatment. To close this treatment gap, Fracture Liaison Services (FLS) have been designed and implemented in post fracture care, since the first initiative reported in 1999, to facilitate case finding of patients aged 50 years and older with a recent fracture to provide routine assessment, and treatment in high-risk patients.

To further improve secondary fracture prevention, knowledge about risk factors in and outcomes of FLS patients is important. Potential risk factors are numerous and diverse and include both bone- and fall-related factors.

The overall aim of this thesis was to examine the bone- and fall-related phenotype of patients with a recent clinical fracture attending the FLS. Additionally, we aimed to examine the incidence of falls and subsequent fractures prospectively in a FLS population, and to study the impact of FLS care on subsequent fracture and mortality risk by comparing these outcomes before and after the implementation of a FLS.

For all chapters in this thesis, except Chapter 2, we used data from the FLS in the VieCuri Medical Center (Venlo, The Netherlands). This FLS was initiated at the end of 2007 at the outpatient clinic of the department of Internal medicine in close collaboration with the department of Trauma surgery and Orthopedic surgery. Procedures at the FLS were as follows. A trained nurse systematically selected all patients aged 50-90 years who visited the emergency department because of a clinical fracture using diagnostic codes. Patients with a radiologically confirmed fracture were invited at the FLS. Those who responded positively, visited the FLS approximately 3 to 4 months after the fracture event. Patients received a detailed questionnaire for the evaluation of clinical risk factors for falls and fractures, including medical history and medication use. Further, bone mineral density (BMD) was assessed by Dual Energy X-Ray Absorptiometry (DXA) at the lumbar spine, total

hip, and femoral neck, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease (SECOB). In addition, from 2011 onwards, vertebral fracture assessment was performed using the DXA device. Based on the BMD and VFA results, calcium intake and serum 25(OH)D levels, treatment was initiated with anti-osteoporosis medication and calcium and vitamin D supplements according to the Dutch osteoporosis and fracture prevention guideline of 2011. Regular FLS care data were used in **Chapter 3-5 and 7**.

Additionally, we conducted a prospective observational cohort study in 500 consecutive patients who visited the FLS, and who were willing and able to participate (called the FX MoVie study). Excluded were non-Caucasian patients, patients with a fracture due to high energy trauma (*i.e.*, another trauma than a fall from standing height or less (*e.g.*, a fall from higher height than standing height and motor vehicle accident)), bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment (*i.e.*, patients who were not compos mentis and could not understand the patient information). The primary objective of this study is to assess bone structure parameters and bone strength by HR-pQCT and physical activity in relation to falls, fractures and mortality in patients with a recent clinical fracture. Data from the FX MoVie study were used in Chapter 6 and 8.

PART I – PHENOTYPE OF PATIENTS AT THE FRACTURE LIAISON SERVICE

In the first part of this thesis, we focused on several characteristics of the phenotype of patients at the FLS. In **Chapter 2**, we performed a literature survey to describe components of the bone- and fall-related phenotype of patients attending the FLS that had been reported in 33 FLS papers. The reported patient selection varied widely in terms of patient identification, selection for invitation and the proportion of patients that attended the FLS. Consequently, the reported phenotypic characteristics varied widely among the publications in terms of mean age (64-80 years), proportion of men (13-30%), and fracture location (2-51% hip, <1-41% vertebral, and 9-95% non-hip/non-vertebral fractures). Furthermore, the studies varied in performance of fracture risk evaluation. This high variability in patient selection and risk evaluation resulted in a highly variable phenotype. When reported, there was a high variability in the proportion of patients with osteoporosis (12-54%), prevalent vertebral fractures (20-57%), newly diagnosed contributors to secondary osteoporosis and metabolic bone disorders (3-70%) and fall-related risk factors (60-84%). We concluded that systematic studies on the presence and combinations of these risks are needed, to specify the bone- and fall-related phenotypes of patients attending the FLS.

In **Chapter 3**, we systematically evaluated the prevalence of comorbidities and medication use associated with increase bone- or fall-related fracture risk in patients attending our FLS clinic. In total, 66% of FLS patients had at least one bone- or fall-related risk factor, with at least one bone-related risk factor in 53%, and at least one fall-related risk factor in 46%. At least one bone-related risk factor and/or at least one fall-related risk factor was associated with age, BMI and major fractures, but not with gender and BMD. Nevertheless, comorbidities and medication associated with an increased bone- or fall-related risk were found across all subgroups (age, gender, fracture type, BMD and BMI). This indicates that systematic evaluation of these factors is important for a more profound assessment of subsequent fracture risk in FLS care.

In **Chapter 4**, we specifically evaluated the prevalence of celiac disease (CD) in FLS patients. CD was already diagnosed in 2 patients (0.19%), of whom 1 still had positive serology. Three other patients (0.29%) had positive serology for CD (one with gastro-intestinal complaints). In 2 of them, CD was confirmed by duodenal histology, resulting in a newly diagnosed biopsy-proven CD prevalence of 0.19%. The other patient refused further evaluation.

The total prevalence of CD at our FLS was 0.38% and within the range of reported prevalence in the Western-European population (0.33-1.5%). Based on these results, we concluded that standard screening for CD is not recommended in FLS care.

In **Chapter 5**, we specifically focused on the prevalence of cardiovascular risk factors in patients at the FLS. Based on medical history, 29.9% had at least one cardiovascular risk factor. Cardiovascular disease (CVD), venous thromboembolic events (VTE), hypertension (HT), and diabetes mellitus (DM2) were found in 13.7%, 1.7%, 14.9%, and 7.1%, respectively. CVD were more frequently present in men, whereas the prevalence of VTE, HT, and DM2 were similar in men and women. The prevalence of all cardiovascular risk factors increased with increasing age, with a prevalence up to 50% of men 70 years and older, and women 80 years and older. Myocardial infarction was found in 2.9% (2.0% in women, and 5.2% in men) and a stroke in 3.2% of patients (2.7% in women, and 4.7% in men). These results indicate that careful evaluation of medical history with respect to these risk factors should be performed in FLS patients before starting treatment with medications that are associated with an increased risk of cardiovascular events, such as Raloxifene, the recently new available osteo-anabolic drug romosozumab, and nonsteroidal anti-inflammatory drugs for fracture pain management (NSAIDs).

Many patients with a non-vertebral fracture (NVF) at the FLS also have a prevalent vertebral fracture (VF). The prevalence of prevalent VFs has been reported to be similar among BMD subgroups. No studies were available that evaluated whether the presence of a prevalent VF is associated with impaired bone micro-architecture in patients with a recent NVF.

In **Chapter 6**, we therefore evaluated the association between prevalent vertebral fractures (VF) and bone quality in terms of micro-architecture and calculated bone strength at the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture (NVF) at the FLS. Compared to postmenopausal women with a recent NVF without a prevalent VF, those with a recent NVF and at least one prevalent VF had lower total and trabecular volumetric BMD (vBMD) and trabecular number, and higher trabecular separation at the radius and tibia, and lower cortical thickness and calculated ultimate failure load and compressive bone strength at the tibia. Further, more severe prevalent VFs were associated with even lower total and trabecular vBMD and lower ultimate failure load and compressive stiffness at the radius and tibia, and lower trabecular number and higher trabecular separation at the radius. These results indicate that the presence and severity of prevalent VFs reflect generalized bone deterioration in postmenopausal women with a recent NVF, independent of femoral neck aBMD.

PART II – OUTCOME OF PATIENTS AT THE FRACTURE LIAISON SERVICE

The second part of this thesis focused on outcomes of patients with a recent fracture at the FLS. Patients with a recent fracture have an increased risk of subsequent fractures and mortality. Subsequent fracture risk changes over time and is the highest immediately after a fracture. In **Chapter 7**, we evaluated whether FLS care was associated with reduced subsequent fracture and mortality risk over 3 years of follow-up by using data before FLS introduction (pre-FLS) and after FLS introduction (post-FLS). We found that the adjusted mortality risk in patients with a major/hip fracture as index fracture was 16% lower in the post-FLS group as compared to the pre-FLS group. Further, the subsequent major/hip fracture risk after a major/hip index fracture was 33% lower in the first 360 days after index fracture post-FLS compared to pre-FLS, taking the competing risk of death into account. In patients presenting with a non-major/non-hip fracture, there was no difference in mortality or subsequent fracture risk between post- and pre-FLS. Based on these results, we concluded that FLS care was associated with a lower mortality risk in the first 3 years and a lower subsequent major/hip fracture risk in the first year in patients with a

major/hip index fracture but not in patients with a non-major/non-hip fracture. The early impact on subsequent fractures may suggest that more focus on long-term adherence to treatment could further improve outcomes.

Finally, **Chapter 8** described the 3-year incidence of incident falls and subsequent fractures, and their association in patients at the FLS. During the 3-year follow- up, 959 falls had been ascertained in 296 patients (60.7%) (*i.e.*, fallers), and 60 subsequent fractures were ascertained in 53 patients (10.9%). Of all subsequent fractures, 78.3% were fall-related, of which 53.2% were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold increase in the risk of subsequent fractures. These data indicate that subsequent fractures among patients on adequate treatment prescribed in a FLS setting are common and an incident fall is a strong predictor of subsequent fracture risk. Immediate attention for fall risk could be beneficial in an FLS model of care.

In conclusion, this thesis showed that the phenotype of FLS patients is heterogenic and that risk factors for osteoporosis, fractures and falls are common in a FLS population. Systematic evaluation of comorbidities and medication associated with an increased bone- and fall-related fracture risk, including cardiovascular risk is necessary for a profound fracture risk evaluation and adequate treatment recommendation. On the other hand, the prevalence of CD is low and comparable to that in the general population, hence systematic screening of CD is not recommended. Further, the presence and severity of prevalent vertebral fractures can be used as a marker for generalized bone deterioration, independent of BMD.

Implementation of the FLS has an important positive impact on subsequent fractures and mortality in patients aged 50-90 years with a recent fracture. However, despite treatment according to the current Dutch osteoporosis and fracture prevention guideline at the FLS, subsequent fractures are still common and an incident fall is a strong predictor for subsequent fractures, suggesting that immediate attention to fall risk could be beneficial in FLS care.

ADDENDUM

SAMENVATTING

SAMENVATTING

Fracturen vormen wereldwijd een groot probleem in de gezondheidszorg en de incidentie zal naar verwachting enkel maar toenemen door de vergrijzing van de bevolking. Fracturen gaan gepaard met een verhoogde morbiditeit en mortaliteit, hebben een impact op de kwaliteit van leven van patiënten en leiden tot hoge kosten voor de gezondheidszorg. Het doorgemaakt hebben van een fractuur betekend een verhoogd risico op het opnieuw doormaken van een fractuur. Dit risico is het grootste in de periode direct na de fractuur. Het is van belang dit potentiële risico op refracturen te onderkennen en interventies te starten om het risico te verkleinen. Ondanks de reeds bestaande kennis over secundaire fractuurpreventie en de beschikbaarheid van diverse effectieve behandelingen, zoals anti-resorptieve geneesmiddelen (bisfosfonaten, denosumab en raloxifeen) en osteo-anabole geneesmiddelen (teriparatide en romosozumab), krijgt slechts een minderheid van de patiënten de juiste evaluatie en behandeling. Om deze behandelingskloof te dichten zijn er sinds 1999 Fracture Liaison Services (FLS) opgezet en ingevoerd. De FLS heeft als doel om het opsporen van patiënten van 50 jaar en ouder met een recente fractuur te vergemakkelijken en hen te voorzien van een routinebeoordeling en eventuele behandeling.

Om de secundaire fractuurpreventie verder te verbeteren, is kennis over risicofactoren bij en uitkomsten van FLS-patiënten belangrijk. De potentiële risicofactoren zijn talrijk en divers en omvatten zowel bot- als val-gerelateerde kenmerken.

Het algemene doel van dit proefschrift was het in kaart brengen van het bot- en val-gerelateerde fenotype van patiënten met een recente klinische fractuur die de FLS bezochten. Daarnaast wilden we de incidentie van vallen en refracturen prospectief onderzoeken in een FLS-populatie en het effect van FLS-zorg op het refractuurrisico en het sterfterisico bestuderen door deze uitkomsten te vergelijken voor en na de implementatie van een FLS.

Voor alle hoofdstukken in dit proefschrift, behalve hoofdstuk 2, hebben we gegevens gebruikt van de FLS in het VieCuri Medisch Centrum (Venlo, Nederland). Deze FLS werd eind 2007 geïmplementeerd op de polikliniek van de afdeling Interne geneeskunde, in nauwe samenwerking met de afdeling Traumachirurgie en Orthopedische chirurgie. De procedures bij het FLS waren als volgt: een getrainde verpleegkundige selecteerde systematisch alle patiënten van 50-90 jaar die de spoedeisende hulp bezochten vanwege een klinische fractuur aan de hand van diagnose-behandelcombinatie (DBC) codes. Patiënten met een radiologisch bevestigde fractuur werden uitgenodigd

op de FLS. Degenen die positief reageerden, bezochten het FLS ongeveer 3 tot 4 maanden na de fractuur. De patiënten kregen een gedetailleerde vragenlijst voor de evaluatie van klinische risicofactoren voor vallen en fracturen, waaronder medische voorgeschiedenis en medicijngebruik. Verder werd met Dual Energy X-Ray Absorptiometry (DXA) de botmineraaldichtheid (BMD) beoordeeld van de lumbale wervelkolom, totale heup en femurhals, en werd een bloedmonster afgenomen om secundaire osteoporose en metabole botziekte (SECOB) te onderzoeken. Bovendien werd vanaf 2011 vertebral fracture assessment (VFA) gedaan met het DXA-apparaat. Op basis van de BMD- en VFA-resultaten, calciuminname en serum 25(OH) D-spiegels werd behandeling gestart met anti-osteoporosemedicatie en calcium- en vitamine D-supplementen volgens de Nederlandse richtlijn voor osteoporose en fractuurpreventie van 2011. De reguliere FLS-zorggegevens werden gebruikt in **hoofdstuk 3-5 en 7**.

Daarnaast voerden wij een prospectief observationeel cohortonderzoek uit bij 500 opeenvolgende patiënten die het FLS bezochten en die bereid en in staat waren deel te nemen (de FX MoVie-studie genoemd). Uitgesloten waren niet-Kaukasische patiënten, patiënten met een fractuur als gevolg van een hoog-energetisch trauma (d.w.z. een ander trauma dan een val van stahoogte of minder (bijv. een val van grotere hoogte dan stahoogte en een motorvoertuigongeval)), botmetastase, falen van de prothese of osteomyelitis, en patiënten die niet in staat waren informed consent te verlenen. Het primaire doel van deze studie was de beoordeling van botstructuurparameters en botsterkte middels high resolution peripheral quantitative computed tomography (HR-pQCT) en het in kaart brengen van de fysieke activiteit in relatie tot vallen, fracturen en mortaliteit bij patiënten met een recente klinische fractuur. Gegevens van de FX MoVie-studie werden gebruikt in **hoofdstuk 6 en 8**.

DEEL I - FENOTYPE VAN PATIËNTEN OP DE FRACTURE LIAISON SERVISE

In het eerste deel van dit proefschrift hebben we ons gericht op verschillende kenmerken van het fenotype van FLS-patiënten. In **hoofdstuk 2** hebben we een literatuuronderzoek uitgevoerd om componenten te beschrijven van het bot- en val-gerelateerde fenotype van FLS-patiënten, die in 33 FLS-papers waren gerapporteerd. De gerapporteerde patiënten selectie liep sterk uiteen in termen van identificatie, selectie voor uitnodiging en het percentage van de patiënten dat de FLS bezocht. Daardoor liepen de gerapporteerde fenotypische kenmerken tussen de publicaties sterk uiteen wat betreft gemiddelde leeftijd (64-80 jaar), percentage mannen (13-30%) en fractuurlocatie (2-51% heup, <1-41% wervel, en 9-95% niet-heup/niet-vertebraal).

Voorts verschilden de studies in de uitvoering van de evaluatie van het fractuurrisico. Deze grote variabiliteit in patiëntselectie en fractuurrisico evaluatiestrategie resulteerde in een zeer uiteenlopend fenotype. Indien gerapporteerd, was er een grote variabiliteit in het aandeel patiënten met osteoporose (12-54%), prevalente wervelfracturen (20-57%), nieuw gediagnosticeerde secundaire osteoporose en metabole botaandoeningen (3-70%) en val-gerelateerde risicofactoren (60-84%). Wij concluderen dat systematisch onderzoek naar de aanwezigheid en combinaties van deze risicofactoren nodig is, om de bot- en val-gerelateerde fenotypes van FLS-patiënten te specificeren.

In **hoofdstuk 3** evalueerden we systematisch de prevalentie van comorbiditeiten en medicatie geassocieerd met een verhoogd bot- of val-gerelateerd risico op fracturen bij patiënten die de FLS bezochten. In totaal had 66% van de FLS-patiënten tenminste één risicofactor, waarvan 53% tenminste één bot-gerelateerde risicofactor en 46% tenminste één val-gerelateerde risicofactor. Het hebben van een bot- en/of val-gerelateerde risicofactor was significant geassocieerd met leeftijd, BMI en fractuurtype, maar niet met geslacht en leeftijd. Desalniettemin werden comorbiditeiten en medicatie met een bot- of val-gerelateerd risico gevonden in alle subgroepen (leeftijd, geslacht, fractuurtype, BMD en BMI). Dit wijst erop dat een systematische evaluatie van deze factoren belangrijk is voor een grondiger beoordeling van het refractuurrisico binnen de FLS-zorg.

In **hoofdstuk 4** hebben we de prevalentie van coeliakie bij FLS-patiënten bestudeerd. Bij 2 patiënten (0,19%) was coeliakie reeds gediagnosticeerd, van wie 1 nog positieve serologie had. Drie andere patiënten (0,29%) hadden positieve serologie voor coeliakie (één met gastro-intestinale klachten). Bij 2 van hen werd coeliakie bevestigd door duodenale histologie, wat resulteerde in een nieuw gediagnosticeerde biopsie-bewezen coeliakie-prevalentie van 0,19%. De andere patiënt weigerde verdere evaluatie.

De totale prevalentie van coeliakie op onze FLS was 0,38% en binnen het bereik van de gerapporteerde prevalentie in de West-Europese bevolking (0,33-1,5%). Op basis van deze resultaten concluderen wij dat standaard screening op coeliakie niet wordt aanbevolen in de FLS-zorg.

In **hoofdstuk 5** hebben we ons gericht op de prevalentie van cardiovasculaire risicofactoren bij FLS-patiënten. Op basis van de medische voorgeschiedenis had 29,9% ten minste één cardiovasculaire risicofactor. Hart- en vaatziekten (HVZ), veneuze trombo-embolieën (VTE), hypertensie (HT) en diabetes mellitus type 2 (DM2) werden aangetroffen bij respectievelijk 13,7%, 1,7%, 14,9% en 7,1% van de patiënten.

HVZ kwamen vaker voor bij mannen, terwijl de prevalentie van VTE, HT en DM2 vergelijkbaar was bij mannen en vrouwen. De prevalentie van alle cardiovasculaire risicofactoren nam toe met toenemende leeftijd, met een prevalentie tot 50% bij mannen van 70 jaar en ouder, en bij vrouwen van 80 jaar en ouder. Myocardinfarct werd vastgesteld bij 2,9% (2,0% bij vrouwen en 5,2% bij mannen) en een beroerte bij 3,2% van de patiënten (2,7% bij vrouwen en 4,7% bij mannen). Deze resultaten wijzen erop dat een zorgvuldige evaluatie van de medische voorgeschiedenis met betrekking tot deze risicofactoren moet worden uitgevoerd bij FLS-patiënten alvorens een behandeling te starten met geneesmiddelen die in verband worden gebracht met een verhoogd risico op cardiovasculaire gebeurtenissen (raloxifeen, het recentelijk beschikbaar geworden osteo-anabole geneesmiddel romosozumab, en niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's)).

Uit de literatuur blijkt dat veel FLS-patiënten welke gezien worden vanwege een niet-vertebrale fractuur (NVF), ook een prevalente vertebrale fractuur (VF) hebben. Opvallend genoeg wordt beschreven dat de prevalentie van prevalente VF's vergelijkbaar is tussen BMD-subgroepen (normale BMD, osteopenie en osteoporose). Er waren geen studies beschikbaar die evalueerden of de aanwezigheid van een prevalente VF geassocieerd is met een verminderde microarchitectuur van het bot bij patiënten met een recente NVF.

In **hoofdstuk 6** onderzochten wij daarom het verband tussen prevalente vertebrale fracturen (VF) en botkwaliteit in termen van micro-architectuur en berekende botsterkte van de distale radius en distale tibia zoals bepaald met de HR-pQCT bij postmenopauzale vrouwen met een recente NVF op de FLS. Vergeleken met postmenopauzale vrouwen met een recente NVF zonder prevalente VF, hadden degenen met tenminste één prevalente VF, onafhankelijk van de areal BMD van de femurhals, een lagere total and trabecular volumetric BMD (vBMD) en trabecular number en een hogere trabecular separation van de distale radius en distale tibia. Ook hadden zij een lagere cortical thickness en calculated ultimate failure load en compression stiffness van de distale tibia. Verder werden ernstige prevalente VF's in verband gebracht met nog lagere total and trabeculaire vBMD en lagere ultimate failure load en compression stiffness van de distale radius en distale tibia, en een lager trabecular number en een hogere trabecular separation van de distale radius. Deze resultaten wijzen erop dat de aanwezigheid en de ernst van prevalente VF's een algemene verslechtering van bot weerspiegelen bij postmenopauzale vrouwen met een recente NVF, onafhankelijk van de areal BMD van de femurhals.

DEEL II - RESULTATEN VAN PATIËNTEN OP DE FRACTURE LIAISON SERVICE

In het tweede deel van dit proefschrift wordt het effect van het bezoeken van de FLS door patiënten met een recente fractuur beschreven. In **hoofdstuk 7** hebben we onderzocht of FLS-zorg geassocieerd was met een lager refractuur- en sterfterisico gedurende 3 jaar follow-up door gebruik te maken van gegevens vóór (pre-FLS) en na de invoering van FLS (post-FLS). We vonden dat het gecorrigeerde sterfterisico bij patiënten met een majeure/heupfractuur als indexfractuur 16% lager was in de post-FLS-groep dan in de pre-FLS-groep. Voorts was het risico op een majeure/heup refractuur na een majeure/heup index fractuur 33% lager in de eerste 360 dagen na de index fractuur in de post-FLS-groep dan in de pre-FLS-groep, rekening houdend met competing mortality risk. Bij patiënten met een niet-majeure/niet-heup fractuur was er geen verschil in mortaliteit- of refractuurrisico tussen post- en pre-FLS. Op basis van deze resultaten concludeerden wij dat FLS-zorg geassocieerd was met een lager sterfterisico in de eerste 3 jaar en een lager majeure/heup refractuurrisico in het eerste jaar bij patiënten met een majeure/heup index fractuur, maar niet bij patiënten met een niet-majeure/niet-heupfractuur. Het reeds vroeg aanwezige positieve effect op refracturen zou kunnen betekenen dat meer aandacht voor therapietrouw op de langere termijn de resultaten verder zou kunnen verbeteren.

Tenslotte werd in **hoofdstuk 8** de 3-jaars incidentie van valincidenten,refracturen en hun associatie beschreven bij patiënten die de FLS bezochten. Tijdens de 3 jaar follow-up werden 959 valincidenten door 296 patiënten (60,7%) en 60 refracturen door 53 patiënten (10,9%) gerapporteerd. Van alle refracturen was 78,3% valgerelateerd, waarvan 53,2% ontstond bij het eerste valincident op een mediane tijd van 34 weken na de index fractuur. Een valincident is geassocieerd met een ongeveer 9 keer verhoogd risico op refracturen. Deze resultaten wijzen erop dat refracturen vaak voorkomen bij patiënten ondanks adequate behandeling in een FLS-setting en dat een valincident sterk geassocieerd is met een refractuur. Onmiddellijke aandacht voor het verkleinen van het valrisico zou een positief effect kunnen hebben in een FLS-zorgmodel.

Kortom, dit proefschrift toont aan dat het fenotype van FLS-patiënten heterogeen is en dat risicofactoren voor osteoporose, fracturen en vallen veel voorkomen. Systematische beoordeling van comorbiditeiten in de medische voorgeschiedenis en medicatie ten aanzien van het cardiovasculair risico en risicofactoren voor osteoporose, vallen en fracturen, is belangrijk voor een grondige evaluatie van het fractuurrisico en bij het starten van een behandeling. Anderzijds is de prevalentie van

coeliakie laag en vergelijkbaar met die in de algemene bevolking, zodat systematische screening op coeliakie niet wordt aanbevolen. Voorts kunnen de aanwezigheid en de ernst van prevalente wervelfracturen worden gebruikt als marker voor algemene verslechtering van bot, onafhankelijk van de BMD.

Implementatie van de FLS heeft een belangrijk positief effect op refracturen en mortaliteit bij patiënten van 50-90 jaar met een recente fractuur. Echter, ondanks behandeling volgens de huidige Nederlandse osteoporose- en fractuurpreventierichtlijn, komen refracturen nog steeds vaak voor. Dat refracturen sterk zijn geassocieerd met valincidenten suggereert dat onmiddellijke aandacht voor het verkleinen van het valrisico een gunstige aanvulling zou kunnen zijn op de bestaande de FLS-zorg.

ADDENDUM

IMPACT PARAGRAPH

SOCIAL AND SCIENTIFIC IMPACT

In this thesis we focused on the phenotype and the outcomes of patients aged 50+ years with a recent fracture attending the Fracture Liaison Service (FLS) for fracture risk evaluation and secondary fracture prevention. In the first part (**Chapter 2-6**), we focused on the phenotype of FLS patients and in the second part (**Chapter 7 and 8**), we focused on outcomes of patients with fracture at the FLS.

In **Chapter 2**, a literature survey was performed to describe components of the bone- and fall-related phenotype of patients attending the FLS and we found that there was a high variability in terms of patient identification (case finding), selection, and FLS attendance among the different studies. This resulted in a high variability in patient characteristics, such as mean age, proportion of men and fracture locations. Based on this survey it can be concluded that there is not a uniform phenotype of FLS patients in literature. This has the implication that many concepts, findings and reported outcomes of FLS patients cannot be compared and this limits the implementation of FLS care. It is therefore needed that the FLS care pathway has to be described in a clear manner, including at least a minimum set of key performance indicators and that we need a more standardized approach for reporting outcomes of FLS care.

We have translated the findings of **Chapter 2** in **Chapter 3**, where we systematically evaluated patients' medical history and medication overview to identify comorbidities and medications associated with an increased bone- or fall-related fracture risk in FLS patients. We found a high prevalence of patients with bone-related risk factors (53.2%), fall-related risk factors (45.6%) and a combination of both was present in 65.6% of patients. In line with the findings of chapter 2, these findings indicate that a systematic evaluation of medical history and medication use is important for a more profound assessment of subsequent fracture risk in FLS patients.

These findings have important implications for health care professionals in FLS care, but also for health care professionals in general since they should be aware of the impact the diseases they treat and the medication they prescribe have on fall and fracture risk. These findings also indicate that FLS care should not only be focused on performing a DXA, which is the case in many FLS facilities, but should also pay attention to specific fall and bone related risk factors, which was further addressed in detail in **Chapter 4 to 6**.

Based on previous work, where we have showed that ± 25% of FLS patients has an underlying disorder that attributes to fracture risk and that can be detected by laboratory evaluation, we specifically focused on the prevalence of celiac disease (CD) in **Chapter 4**. We found that the prevalence of CD was low and within the range of the general West-European population. Therefore, based on this study, standard

screening for CD as a part of the standard laboratory evaluation of FLS patients is not recommended. Nevertheless, it is still indicated to analyze the presence of CD in FLS patients with laboratory results, comorbidities or symptoms suggestive of CD. This finding is also important for efficient use of health care resources which are constantly increasing both in terms of health care costs as well as the number of patients in need of FLS care.

In **Chapter 5**, we specifically focused on the prevalence of cardiovascular risk factors in FLS patients and found that 30% of patients had a medical history of cardiovascular disease, venous thromboembolic event, hypertension and/or diabetes mellitus type 2. The prevalence of cardiovascular risk factors increased with age, was higher in men than in women but independent of BMD and fracture type. These findings indicate that, in line with the findings of chapter 2 and 3, FLS patients often have several fall and bone related comorbidities and that a substantial proportion of patients (also) has cardiovascular risk factors. In addition, the presence of cardiovascular disease has implications for osteoporosis medication such as the selective estrogen receptor modulator raloxifene, the recently approved osteo-anabolic drug romosozumab and non-steroidal anti-inflammatory drugs frequently used for pain management.

The association between prevalent vertebral fractures and decreased bone micro-architecture and strength of the distal radius and distal tibia assessed with high resolution peripheral computed tomography (HR-pQCT) in postmenopausal women with a recent non-vertebral fracture at the FLS as presented in **Chapter 6**, is relevant to patients and health care professionals as well as health care policy makers and health insurance providers. These findings underline the importance of detecting subclinical, prevalent, vertebral fractures in patients that present with a non-vertebral fracture since it is known that the risk of subsequent fracturs is substantially higher in patients with a prevalent vertebral fracture compared to not having a prevalent vertebral fracture, independent of BMD, and emphasize the importance of performing systematic vertebral fracture assessment, which is now also implemented in the recently updated new Dutch guideline on osteoporosis and fracture prevention . In addition, the presence of a vertebral fracture has impact on the choice of treatment, since the Dutch guideline recommends treatment with osteoanabolic medication as first line therapy in high-risk patients with a low BMD in combination with one or more moderate or severe vertebral fractures. Furthermore, information on baseline vertebral fracture status allows reliable identification of incident vertebral fractures during treatment, which may change treatment. Besides on lateral DXA images, prevalent vertebral fractures can be identified with other imaging modalities such as chest X-ray, thoracal and abdominal CT and magnetic resonance imaging (MRI).

Thus, improvement in patient care can also be achieved by increasing awareness for the presence of vertebral fractures as opportunistic finding among radiologists and other health care professionals. The use of software tools can help identify and classify prevalent vertebral fractures accurately and efficiently. Also, the application of artificial intelligence to detect vertebral fractures is emerging.

In **Chapter 7 and 8**, we focused on outcomes of patients with a recent fracture. In **Chapter 7**, we evaluated the impact of FLS care on subsequent fracture and mortality and concluded that the implementation of the FLS resulted in a lower mortality risk and a lower subsequent major or hip fracture risk in patients presenting with a recent major or hip fracture at the emergency department. Good quality studies reporting the impact of FLS care on subsequent fractures and mortality are urgently needed to demonstrate value to patients, health and social care systems and ultimately justify sustainable support by health insurers and health care policy makers. Currently, secondary fracture prevention management is assigned low priority by primary care physicians, specialists, health administrators, policy makers, and the general public. Fractures are still perceived as a problem related to aging or the result of an unfortunate trauma and consequently, secondary fracture risk evaluation and prevention is considered unnecessary. Even though health initiatives, such as the international Capture the fracture program and the Dutch 'verbetersignalement osteoporose, Zorginstituut Nederland', were started to improve awareness and quality of care, the proportion of fracture patients receiving adequate diagnostic evaluation for fracture risk and treatment or fracture prevention is still low and may be even declining. There is an urgent need for recognition of the impact of fractures on quality of live, subsequent fractures and mortality by the general public, health care professionals and policy makers. More research on the impact of FLS care on subsequent fractures and mortality, as well as quality of life and health care and social costs may help further improvement of FLS care implementation.

The prospective evaluation of incident falls in relation to subsequent fractures in patients who visited the FLS due to a recent fracture as presented in **Chapter 8**, provides novel information regarding the imminent fall risk that may contribute to the well-known imminent subsequent fracture risk in patients with a recent fracture. The finding that 10% of FLS patients sustained a subsequent fracture within three years after an index fracture, despite adequate evaluation and treatment directly after their index fracture, and that 90% of all subsequent fractures were fall-related, suggests that immediate attention to fall risk could be beneficial in FLS care. Despite conflicting results that have been published about the effect of fall prevention strategies on subsequent fractures, we hypothesize that fall interventions could be effective in

patients at highest risk, namely those with a recent fracture at risk of falling. Future research should focus on how to identify patients at highest risk of falling and to evaluate multifactorial fall prevention interventions in these patients.

The findings in this thesis have been widely distributed to and recognized by the scientific society. The work of all chapters has been presented at international and national conferences and published in peer reviewed international journals, including the highest ranked journals in the field of bone research. The work presented in **Chapter 3** was awarded with an allied health professional award by the European Calcified Tissue Society in 2015.

ADDENDUM

DANKWOORD

DANKWOORD

"Met dankbaarheid zul je merken dat kleine dingen groot worden."

Allereerst wil ik mijn promotieteam bedanken voor het vertrouwen en de kans die jullie me gegeven hebben om te promoveren.

Prof. dr. Van den Bergh, beste Joop, mijn dankbaarheid is niet in een paar eenvoudige woorden uit te drukken. Je kennis en ideeën, motivatie en vertrouwen zijn onmisbaar geweest voor het voltooien van dit proefschrift. Je bent een groot voorbeeld voor mij en ik ben dankbaar met je te hebben mogen samenwerken!

Prof. dr. Geusens, beste Piet, uw enthousiasme en creativiteit zijn werkelijk ongeëvenaard. Tijdens ieder overleg wist u me hiermee te inspireren en motiveren. Hartelijk dank voor de goede begeleiding en uw oprechte interesse! Graag wil ik u ook bedanken voor uw steun bij mijn keuze voor de reumatologie.

Dr. Wyers, lieve Caroline, we begonnen als twee collega's, maar al snel werden we ook goede vriendinnen. Lief en leed hebben we de afgelopen jaren met elkaar gedeeld. Bedankt voor je hulp bij het onderzoek, je vriendschap en alle gezelligheid! Ik hoop dat we nog vaak samen zullen afspreken.

De leden van de beoordelingscommissie, prof. dr. Poeze, prof. dr. Lems, dr. Willems en dr. Bours wil ik bedanken voor het lezen en beoordelen van dit proefschrift.

Verder wil ik alle co-auteurs van de artikelen gepubliceerd in dit proefschrift bedanken. Dank voor de fijne samenwerking en jullie waardevolle input.

Natuurlijk wil ik graag iedereen van de osteoporose poli in het VieCuri Medisch Centrum bedanken. Ik ben ontzettend dankbaar en trots dat ik deel heb mogen zijn van zo'n fantastisch team. Joop, Robert, Caroline, Astrid, Marsha, Ingrid, Nel, Nicole, Bo en alle andere secretaresses van de interne geneeskunde, dank voor alles wat jullie me geleerd hebben en de vele mooie herinneringen, waar ik nog steeds met heel veel plezier aan terugdenk.

Alle collega's van de interne geneeskunde in het VieCuri Medisch Centrum en de reumatologie in het Zuyderland Medisch Centrum en Maastricht Universitair Medisch Centrum + wil ik hartelijk bedanken voor alle kansen die ze me hebben geboden. Het combineren van een promotieonderzoek en opleiding tot specialist is een uitdaging. Dank voor jullie geduld, luisterend oor en de wijze raad, die ik heb mogen krijgen.

Dank aan alle mede promovendi, Frans, Ellis, Michiel, Joost, Mayke, Irma, Marsha, Andrea, Ivette, Casper en Cindy voor hun hulp en alle gezelligheid. Mede door jullie is mijn promotietijd een onvergetelijke tijd geworden!

Lieve familie en vrienden, ome Frans en tante Tiny, Guus, Jolanda en Peter, tante Anny, tante Annemie en ome Albert, Rob, Emmy en Jan, Linda en Ralph, tante Nelly, Jack en Erika, Sanne, tante Corry en ome Thei, tante Riny en ome Lei, Pieter-Jan en Vera, Monique en Mike, Fabiënne, Suzanne, Mirna, Anke en Jeroen, Fleur, Jill en Lara, bedankt voor jullie warme vriendschap en steun, jullie luisterend oor en alle gezelligheid.

Mijn paranimfen:
Lieve Ellis, ondanks dat we een andere werkplek hadden, jij in Maastricht en ik in Venlo, werden we in no-time ontzettend goede vriendinnen. Je bent één van de liefste en loyaalste mensen die ik ken. Samen met Elton, Marit en Hugo hebben we al veel mooie herinneringen gemaakt. Ik weet 100% zeker dat, ook wanneer jullie terug naar Noord-Holland verhuizen, we altijd vriendinnen zullen blijven.

Lieve Constance, al vanaf groep 1 van de basisschool zijn we beste vriendinnen. Samen hebben we veel mooie en soms ook moeilijke momenten gedeeld. Ik weet dat ik altijd op jouw steun kan rekenen. Dankjewel daarvoor en natuurlijk ook voor alle gezelligheid! Ik weet zeker dat we altijd vriendinnen zullen blijven en wens je heel veel geluk en liefde toe.

Lieve mama en papa, uiteraard gaat mijn grootste dank uit naar jullie. Jullie hebben me onbezorgd laten opgroeien en me alle mogelijkheden gegeven om me te ontwikkelen tot de persoon die ik geworden ben. Jullie geloof in mijn kunnen, jullie onvoorwaardelijke steun en liefde betekenen alles voor mij. Ik houd ontzettend veel van jullie!

Lisanne

ADDENDUM

CURRICULUM VITAE

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Lisanne Vranken was born on November 22th in 1988 in Echt, The Netherlands.

After graduation from the Bisschoppelijk College Echt in 2007, she started medical school at the Maastricht University, Faculty of Health, Medicine and Life Sciences. During medical school, she worked as student assistant on scientific research for the department of thoracic surgery of the Maastricht University Medical Center + (MUMC +).

After obtaining her medical degree in 2013, Lisanne started working as a PhD-student at the division of Internal Medicine in the VieCuri Medical Center and MUMC + under the supervision of prof. dr. J.P.W. van den Bergh, prof. dr. Geusens and dr. Wyers. The research was performed within the School of Nutrition and Translational Research in Metabolism (NUTRIM).

In 2017, she started her residency Internal Medicine at the VieCuri Medical Center under the supervision of prof. dr. Koopmans and dr. Hermans. In 2020, she continued her training at the department of Rheumatology at the Zuyderland Medical Center under the supervision of dr. Starmans-Kool and dr. Magro Checa. Currently, Lisanne is working at the department of Rheumatology at the MUMC + under the supervision of dr. Vosse.

ADDENDUM

LIST OF PUBLICATIONS

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Published articles:

Vranken L.*, de Bruin I.J.A.*, Driessen A.H.M., Geusens P.P.M., Eisman J.A., Center J.R., van der Velde R.Y., Janzing H.M.J., Kaarsemaker S., van den Bergh J.P., Wyers C.E. *Decreased mortality and subsequent fracture risk in patients with a major and hip fracture after the introduction of a fracture liaison service: a 3-year follow-up survey.* J. Bone Miner. Res. 2022;37(10):2025-2023. (* Both authors contributed equally to the manuscript).

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