Linköping University Medical Dissertation No. 1771

Atypical Femoral Fractures: Another Brick in the Wall.

Hans Peter Bögl

LINKÖPING UNIVERSITY

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Atypical femoral fractures: Another brick in the wall.

On aspects of healing, treatment strategies and surveillance.

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This work is dedicated to my family, in particular to my wife Karin for all her loving support, my children Lene and Finn, who are a great source of inspiration, and finally my beloved parents who, with their unconditional support and encouragement, enabled me to become the person I am today!

" Logic will get you from A to B;

your imagination will get you everywhere."

- Albert Einstein

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ABSTRACT

Atypical femoral fractures are stress fractures of the femoral subtrochanteric and diaphyseal region. It is a common notion that these fractures heal poorly, if at all. In this thesis we show that patients with atypical femoral fractures have a good capacity to generate bone and therefore heal fractures. In daily practice, these patients have a higher risk for reoperation when compared with patients with a normal femoral fracture. However, this risk is less likely to be dependent on the type of fracture than other factors such as age, gender, comorbidities and survival. Using an implant that protects the fragile proximal femur, the risk for reoperations can be attenuated dramatically. An intramedullary nail with fixation of the femoral neck protects the femur from subsequent hip fractures – the most common complication in elderly patients with any type of femoral shaft fracture.

Atypical femoral fractures are difficult to identify in the population. Erroneous diagnosis coding, poor reporting of adverse drug reactions and low accuracy of radiology reports make the identification and surveillance a difficult task. The Swedish Fracture Register has provided the option to register this special fracture since 2015. With its physician-based registration process, it enables researchers and treating physicians to identify and follow these rare fractures longitudinally.

SVENSK SAMMANFATTNING

Atypiska lårbensfrakturer är sällsynta utmattningsbrott i lårbensskaftet med en stark koppling till bisfosfonatbehandling. Bisfosfonater är en grupp av läkemedel som bland annat används mot benskörhet. Atypiska lårbensfrakturer beskrevs för första gången 2005 som frakturer som liknar stressfrakturer i lårbensskaftet hos patienter med långvarig bisfosfonatbehandling. Orsaken till dessa frakturer är fortfarande oklar. Stora epidemiologiska studier har beskrivit ett samband mellan behandlingsduration med bisfosfonater och risken för atypisk fraktur. Därför rekommenderas idag ett behandlingsuppehåll efter cirka 5 år. Risken för atypisk lårbensfraktur påverkas av många faktorer som exempelvis lårbenets form och genetiska faktorer.

Atypiska frakturer kännetecknas av ett enkelt frakturmönster med en tämligen tvärgående frakturlinje som börjar där dragkrafterna är som störst (yttre kortex i femur). Frakturen övergår till en snedgående frakturlinje mot insidan. Ofta går lårbenet av spontant eller vid minimalt trauma. Mer än hälften av patienterna beskriver föregående symtom som till exempel belastningsvärk i låret några veckor innan frakturen.

Atypiska lårbensfrakturer anses vara svåra att läka och den kirurgiska behandlingen förknippas ofta med en hög risk för komplikationer. Hur dessa frakturer ska behandlas på bästa sätt är fortfarande oklart.

Delarbetena i denna avhandling har bidragit med kunskapsdetaljer om dessa sällsynta frakturer och om hur lårbensfrakturer i allmänhet och atypiska frakturer i synnerhet ska opereras för att undvika framtida reoperationer.

I delarbete 1 beskrivs läkningsförmågan hos patienter med inkompletta atypiska lårbensfrakturer i en fallserie. Vi följde 8 patienter som tidigare hade genomgått en kirurgisk excision av frakturområdet med hjälp av en hålborr (diameter 11,5 mm) samtidigt som frakturen stabiliserades kirurgisk. Alla patienter hade behandlats med bisfosfonater i många år (i genomsnitt 8 år) och beskrev belastningssmärta i det drabbade benet innan frakturen. Efter operationen fick patienterna belasta på benet efter förmåga. Uppföljningen skedde med hjälp av röntgenbilder där vi bedömde kallusbildning över tid. Alla 8 patienter visade nybildat ben i defekterna under uppföljningen. Läkningen skedde inom tidsramar som man förväntar sig i samband med läkning av vanliga lårbensfrakturer. Vi noterade inga komplikationer kopplade till ingreppen och alla patienter

uppgav besvärsfrihet vid sista uppföljningen. Detta arbete visar att patienter med inkompletta atypiska lårbensfrakturer har en normal förmåga att regenerera benvävnad i kortikala defekter. De läkningssvårigheter som beskrivs i litteraturen beror alltså med stor sannolikhet inte på den atypiska frakturen i sig utan snarare på andra faktorer som till exempel de mekaniska förhållandena i fraktursspalten och andra patientrelaterade faktorer.

I delarbete 2 undersöks orsaker till den höga reoperationsfrekvensen hos patienter med atypiska lårbensfrakturer. Som ursprungskohort valde alla patienter äldre än 54 år i Sverige som hade fått en fraktur i lårbensskaftet under åren 2008–2010. Patienterna identifierades via utdrag från Patientregistret. Vi valde två sätt att identifiera reoperationer. Alla röntgenbilder granskades från första operationen fram till år 2015. I den granskningen noterade vi alla förändringar som antydde att en reoperation hade genomförts, men också om frakturerna var läkta eller ej. Sedan extraherades information över alla återinläggningar via ett förnyat utdrag från registret. Vi fann 1025 patienter med frakturer i lårbensskaftet, varav 862 vanliga lårbensfrakturer och 163 atypiska. Reoperationsfrekvensen var nästan dubbel så hög bland patienter med atypisk lårbensfraktur med totalt 28 (17,2%) reoperationer, varav 9 (5,5%) relaterade till läkningsstörningar. Bland normala lårbensfrakturer identifierade vi totalt 74 reoperationer (8,6%), varav 23 (2,7%) relaterade till läkningsstörningar. Det fanns dock skillnader i ålder, könsfördelning, läkemedelsanvändning och framförallt dödlighet som skulle kunna förklara skillnaderna i reoperationsfrekvens. Efter statistisk justering med regressionsmodeller fann man ingen skillnad mellan frakturtyperna. Den ökade risken för reoperation vid atypisk fraktur kan alltså förklaras av skillnader i ålder, kön, läkemedelsanvändning och dödlighet snarare än frakturtyp.

I delarbete 3 undersöker vi risken för reoperation beroende på vilken typ av märgspik som används för fixation av frakturer i lårbensskaftet. Vi delade in spikarna i 2 grupper: den ena gruppen var märgspikar där man hade låst spiken med 1 eller 2 skruvar upp i lårbenshuvudet, den andra gruppen var spikar där låsskruven hade fästs mot trochanter minor men lårbenshuvuvdet lämnats utan låsskruv. Vi använde samma kohort som i delarbete 2 men exkluderade patienter som var opererade med plattor. Reoperationer definierades inom 2 kategorier: Stora reoperationer (t.ex. höftfraktur på samma sida eller annan refraktur i anslutning till spiken) och mindre reoperationer (så som t.ex. skruvextraktion). Vi identifierade 897 patienter som hade opererats med märgspik. Av dessa hade 640 en spik med låsning i lårbenshalsen och 257 patienter utan. Vi identifierade inga sekundära höftfrakturer i gruppen med låsning i lårbenshalsen och 14 (5,4%) i gruppen utan låsning i lårbenshalsen. Risken för en senare fraktur

runt implantatet var 5 gånger högre och risken för en stor reoperation dubbel så stor om spiken inte var låst i lårbenshuvudet. Resultaten kvarstod även efter justering för ålder, kön, läkemedelsanvändning, samsjuklighet och dödlighet. En märgspik med skruvfixation i lårbenshuvudet minskar risken för reoperation utan att några nackdelar med denna typ av låsning kunnat identifieras. Vi rekommenderar därför att spikmodeller med en låsning i lårbenshalsen används vid fixation av frakturer i lårbensskaftet hos den äldre patienten.

I det fjärde delarbetet granskar vi kvalitén av data på atypiska lårbensfrakturer i Svenska Frakturregistret (SFR) och möjligheten att förbättra datakvalitén med en utbildningsinsats. Våra tidigare studier har visat att processen att identifiera atypiska lårbensfrakturer i ett nationellt perspektiv är svår. Granskningar av röntgenutlåtanden eller utdrag från Patientregistret har låg träffsäkerhet. Det är i stort sett omöjligt att identifiera dessa frakturer i befolkningen på ett enkelt sätt som till exempel via registerutdrag från Patientregistret. År 2015 infördes därför variabeln atypisk lårbensfraktur i SFR. Vi rekvirerade alla registreringar av atypiska lårbensfrakturer i SFR och inhämtade alla röntgenundersökningar för dessa patienter under 2015–2018. 178 fall med atypiska frakturer identifierades i SFR. En åldersmatchad kontrollgrupp av 176 fall av vanliga lårbensfrakturer valdes ut. Studiekohorten bestod således av 354 frakturer. Alla röntgenundersökningar granskades av 3 läkare, varav två var erfarna forskare i ämnet och en var en ST-läkare i ortopedi som erhöll en kort introduktion över atypiska lårbensfrakturer. Bedömningen av de två erfarna granskarna formade referensbedömningen. Bedömningen i SFR stämde i 58% överens med referensen, ST-läkarens i 80%. Resultatet indikerar att en riktad utbildning i bedömning av röntgenbilder leder till förbättrat träffsäkerhet i klassifikationen.

LIST OF PAPERS

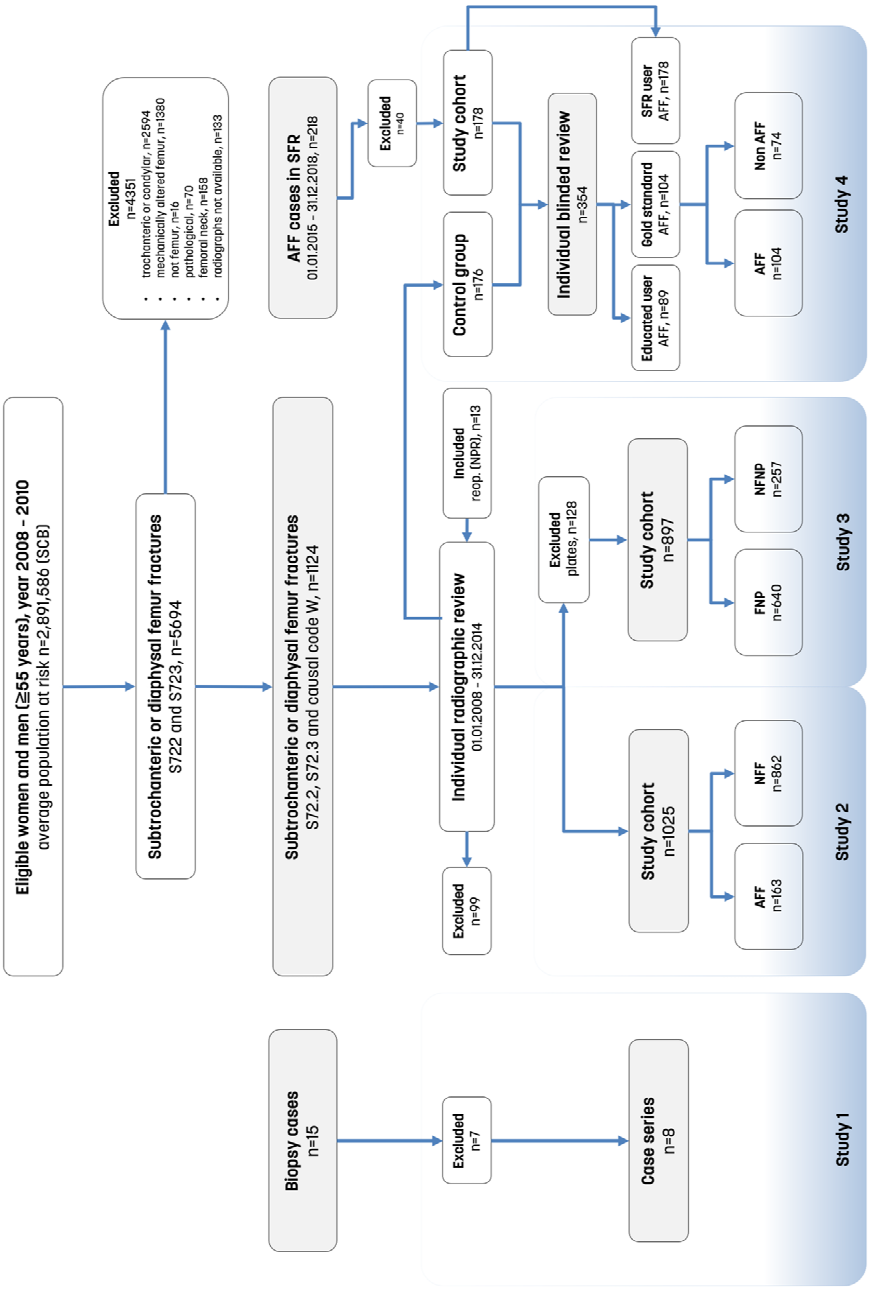
I. Bögl, H. P., Aspenberg, P. & Schilcher, J. (2017)
Undisturbed local bone formation capacity in patients with atypical femoral fractures: a case series.
Osteoporosis International 2017; 28(8): 2439-44

II. Bögl, H. P., Michaëlsson, K., Zdolsek, G., Höijer, J. & Schilcher, J. (2020). Increased rate of reoperation in atypical femoral fractures is related to patient characteristics and not fracture type. A nation-wide cohort study.
Osteoporosis International 2020; 31(5): 951-959

III. Bögl, H. P., Zdolsek, G., Michaëlsson, K., Höijer, J. & Schilcher, J. (2020). Reduced risk of reoperation using intramedullary nailing with femoral neck protection in low-energy femoral shaft fractures.
Journal of Bone and Joint Surgery American Volume. 2020; 102(17): 1486-94

IV. Bögl H.P., Barnisin L., Möller M., Schilcher J. (2021) Surveillance of atypical femoral fractures in a nationwide fracture register.
(submitted manuscript)

PATIENT FLOWCHART, STUDIES 1–4



OVERVIEW OF STUDIES

Study 1 – Healing capacity –

In this study we investigated eight patients who underwent excision of an incomplete atypical femoral fracture (AFF). During follow-up we examined bone formation with plain radiographs and found a good capacity to form new bone in the defect.

Published in Osteoporosis International, 2017.

Study 2 – Risk for reoperation –

Reoperation rates after osteosynthesis of AFF are reported to be very high. We studied the risk for reoperation in a nationwide cohort of patients with 163 AFF and 862 normal fractures (NFF). Reoperation rates in patients with AFF were twice as high compared to patients with NFF. This difference disappeared when calculations were adjusted for differences in background characteristics.

Published in Osteoporosis International, 2020.

Study 3 – Implant choice –

Implant choices may be crucial for the outcome after surgically treated femoral shaft fractures. We evaluated the risk for reoperation in a nationwide cohort of 640 patients treated with nails protecting the femoral neck, and 257 patients treated with nails without such protection. Femoral neck protecting nails reduced the risk for subsequent ipsilateral hip fractures, peri-implant fractures and the total number of major reoperations in elderly patients with femoral shaft fractures.

Published in the Journal of Bone and Joint Surgery, 2020.

Study 4 – Register validation –

Atypical femoral fractures are rare and difficult to capture in the population. We studied the Swedish Fracture Register (SFR) as a way to survey this type of a fracture in the population, validated the data on AFFs and studied the effect of a brief educational instruction on the quality of AFF registrations. Roughly half of the AFFs were correctly registered in the SFR. This proportion increased to 83% for an educated user. The SFR greatly outperforms traditional methods to identify AFFs and has the potential to contribute to the surveillance of AFFs in the population.

Manuscript under review at *Acta Orthopaedica*.

ABBREVIATIONS

AFF	Atypical femoral fracture
ASBMR	American Society for Bone and Mineral Research
BP	Bisphosphonate
csHR	Cause-specific hazard ratio
FEM	Finite element modelling
ICD-10	International Classification of Diseases, 10th Revision
NFF	Normal/common femoral fracture
NOMESCO	Nordic Medico-Statistical Committee
NPR	Swedish National Inpatient Register
OR	Odds ratio
RR	Relative risk
SCB	Statistics Sweden
sdHR	Subdistribution hazard ratio
SFR	Swedish Fracture Register

INTRODUCTION

No effect without side effects

Atypical femoral fractures (AFFs) are a specific type of insufficiency fracture. The first publication to report on spontaneous non-traumatic fractures of the femur in the 'atypical' diaphyseal localisation was an observational study published 15 years ago (Odvina et al., 2005). Already in this first report, the authors suggested an insufficiency type of fracture associated with the use of bisphosphonates. In the following years, intense research in the field laid the groundwork for a better understanding of the pathophysiology of this particular type of fracture. At present more than 900 publications are listed in PubMed under the term 'atypical femoral fracture' (February 2021).

Today, we know that AFFs have a strong association with the use of bisphosphonates that is both dose- and duration-dependent (Schilcher et al., 2015b, Schilcher et al., 2011). Despite this strong association, AFFs remain a rare complication, with an incidence rate of 2–10 per 10 000 patient-years. For the medical profession these fractures pose a challenge in terms of appropriate diagnostics and adequate treatment strategies. For patients and doctors in some countries with strong medico-legal aspects to healthcare, these fractures have emphasised treatment side effects to such an extent that prescription rates of bisphosphonates have declined dramatically.

Bisphosphonates

Bisphosphonates are a group of drugs with an interesting path through history. The chemical structure was first synthesised in the late 1800s (Menschutkin, 1865). Initially used in industrial applications as water softeners, their pharmacological effects started to be explored in the 1960s.

Chemically, bisphosphonates represent an analogue of inorganic pyrophosphates (Junankar and Rogers, 2015) and are characterised by a Phosphate-Carbon-Phosphonate bond. This bond is responsible for their high affinity to the calcium ions of hydroxyapatite, a natural calcium phosphate mineral in the human skeleton.

Etidronate and Clodronate were the first bisphosphonates introduced to clinical applications in the late 60s (Francis et al., 1969). The efficacy in inhibiting bone resorption of these first generation bisphosphonates was further improved by adding side chains containing nitrogen (Russell, 2011). This was the starting point for the second generation of bisphosphonates, the amino-bisphosphonates. Amino-bisphosphonates have become

the mainstay of the pharmaceutical treatment of osteoporosis since the mid-90s.

Due to their high affinity to hydroxyapatite, bisphosphonates bind to the hydroxyapatite whenever exposed, for example by cracks and fractures in the skeleton. Through phagocytosis, the osteoclast incorporates hydroxyapatite molecules with the adherent bisphosphonates. Once intracellular, the amino-bisphosphonates inhibit, among other things, the enzyme farnesyl pyrophosphate synthase that is critical for osteoclast function, thus inhibiting osteoclast function (La-Beck et al., 2021). This leads to a significant suppression of bone metabolism. Suppression of bone metabolism is desired in the treatment of osteoporosis and other conditions that alter bone metabolism (i.e. Paget´s disease, hypercalcaemia secondary to malignancy) or as a prophylaxis for drug-induced secondary osteoporosis (i.e. due to glucocorticosteroid therapy).

Today, the two most common amino-bisphosphonates in clinical use are alendronate and zoledronate. Alendronate is administered as an oral once-weekly tablet, zoledronate as an intravenous drug once a year.

What makes it break? Aspects of the pathogenesis of atypical femoral fractures

The precise aetiology of AFFs is still unknown. However, some possible predisposing risk factors have been identified.

Geometry matters

Femoral whole bone geometry may contribute to the development of AFFs in several ways. Increased lateral femoral bow, decreased femoral offset and a varus hip configuration all contribute to increase tensile forces on the lateral aspect of the femur (Oh et al., 2017, Haider et al., 2019) (Figure A).

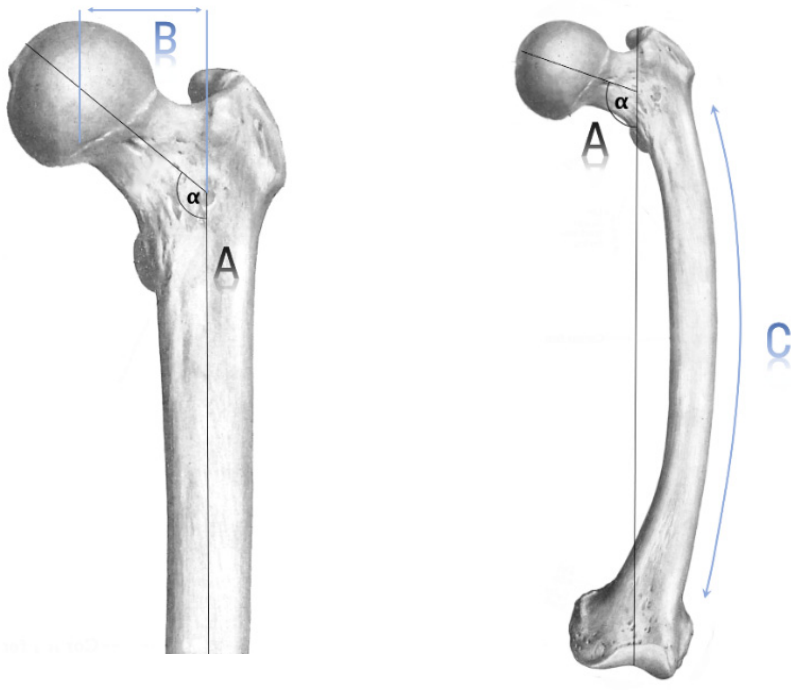


Figure A: Normal hip alignment and mechanical axis in the middle of the femoral canal (left). Femur with coxa vara and pronounced lateral bow, medialisation of the mechanical axis of the femur (right). (A) neck-shaft / CCD angle, (B) hip offset, (C) tensile forces along the lateral bow.

An increased lateral femoral bow in incomplete AFFs appears to shift the localisation of AFF into the femoral diaphysis, while lower bowing is associated with a subtrochanteric fracture location (Chen et al., 2014). This finding was verified in a cohort of AFF patients from Singapore but could not be found in a Swedish cohort (Schilcher et al., 2015a).

Other factors associated with AFFs are the neck-shaft angle and hip-axis length. In a comparative study, AFFs had significantly lower angles (more varus) and shorter femoral necks (less offset) when compared with normal femoral shaft fractures (Taormina et al., 2014).

Skeletal geometry might, at least partially, explain why AFFs often occur bilaterally. A review of the literature from 2011 to 2013 performed by the task force of the American Society for Bone and Mineral Research (ASBMR) showed that 28% of AFFs occurred bilaterally (Shane et al., 2014). Consequently, bilateralism is included as a minor feature in the current ASBMR case definitions for AFFs. Interestingly, in cases of bilateral AFFs, the

localisation of the fractures appears identical on both sides (Saita et al., 2014, Capeci and Tejwani, 2009).

In summary, it appears that geometric factors of the femur play an important role in the pathogenesis of AFFs. Both a varus hip alignment and an increased lateral femoral bow may act as predisposing factors for the development of atypical femoral fractures and may influence the localisation of the fracture along the femoral shaft.

Genetic predisposition? When genes go wild…

Millions of patients are treated with bisphosphonates every year. But why do some develop atypical fractures while others do not? One explanation might be a genetic predisposition for AFF in some individuals. Such an explanation is supported by findings showing that some individuals sustain AFFs without ever having used bisphosphonates. The proportion of patients with AFFs unrelated to bisphosphonate use varies widely in the literature, from 6%-25%. In our own patient cohort (studies 2 and 3) we found about 22% of patients without reported use of bisphosphonates. Furthermore, ethnic differences might influence the risk of AFFs. For example, patients of Asiatic ethnicity have a five- to eight-fold increased risk of developing AFFs compared to Caucasians (Black et al., 2020, Lo et al., 2016).

Monogenetic bone diseases have been described in certain individuals with AFFs. In some of the reported cases, the monogenetic bone disease was previously unknown and only became apparent and diagnosed after the AFF had been diagnosed. Currently, seven variations of genes, coupled to known monogenetic bone diseases, have been linked to AFFs in both patients with reported bisphosphonate use and without. Examples of these variations are ALPL (hypophophatasia, four cases), COL1A1 (osteogenesis imperfecta, five cases) and CTSK (pycnodysostosis, seven cases, all bisphosphonates-naïve). These and other reported cases led to the proposition that mild forms of these monogenetic bone diseases may act as predisposing factors in the pathogenesis of AFFs (Nguyen et al., 2018). However, such a genetic predisposition has been questioned.

Kharazmi et al. studied 51 cases of AFFs and 4891 controls in an attempt to verify the association with single-nucleotide polymorphisms and candidate genes and AFFs in a large case-control genome-wide array. They were unable to prove a significant association between common genetic traits and atypical femoral fractures (Kharazmi et al., 2019).

To date, it remains unclear if, and to what extent genetic factors contribute as predisposing risk factors. It is therefore a matter of ongoing research to elucidate the role of a genetic predisposition in the development of AFFs.

Aspects of bisphosphonates and fracture union

Bone is a fascinating tissue. Unlike any other tissue (except for liver tissue), bone can regenerate itself through the reactivation of embryonal processes. While other tissues heal with scar formation resulting in inferior tissue quality, regenerated bone does not. Bone tissue is exposed to continuous loading in daily living leading to fatigue damage. This damage can occur as micro-cracks or diffuse micro-damage, and triggers a unique healing mechanism called targeted remodelling. Another mechanism, leading to the replacement of old bone with new bone, is stochastic remodelling (Burr, 2003, Burr, 2002). Together, the two types of remodelling will replace the entire bone mass of an adult human within roughly 10 years. The remodelling process is driven by osteoclasts, which resorb the bone, and osteoblasts, which build new bone. The balance between resorption and new bone formation is critical and is regulated through several control processes.

In osteoporosis, coupling mechanisms between osteoclasts and osteoblasts are altered, leading to an imbalance in the bone's homeostasis with increased resorption and decreased bone formation. Over time, this results in net bone loss and deteriorations in the microarchitecture of the bone. Bisphosphonates inhibit osteoclast function. This effect is used in the treatment of osteoporosis with the aim of correcting the imbalance between bone resorption and formation. However, this means that the natural healing process of the bone tissue is inhibited and accumulation of micro-damage will occur (Hirano et al., 2000, Burr et al., 1998). Depending on the degree of inhibition, indirect signs of remodelling measurable by biomarkers indicate that remodelling processes might be decreased up to 90%, a condition called *severely suppressed bone turnover* (Odvina et al., 2005). In this situation micro-damage can coalesce into a stress fracture. Stress fractures typically heal by the resorption of the fracture surfaces through osteoclasts. This resorption is necessary to create a mechanical environment that allows osteoblasts to form new bone without exceeding tissue deformation thresholds that lead to the formation of scar tissue with inferior mechanical properties (Gustafsson et al., 2016).

Stress fractures weaken the bone's strength, leading to completion of the fracture after no or only minimal trauma. Once the bone is broken completely, osteoblast-driven bone formation in the callus is no longer coupled to osteoclastic bone resorption and therefore not influenced by bisphosphonates. Successful healing rates of metaphyseal and diaphyseal fractures in animal experiments (Peter et al., 1996) and in clinical studies are therefore not surprising (Egol et al., 2014). However, bisphosphonate treatment influences fracture healing at later stages, leading to larger persistent callus formations in the remodelling phase of the fracture healing process (Li et

al., 1999). Given this well-studied biological and pharmacological background, it is reasonable that incomplete fractures heal poorly; however, it appears unreasonable that complete AFFs should heal with delay or not at all.

Nevertheless, there is a common notion among orthopaedic surgeons that AFFs in general heal poorly (Weil et al., 2011, Prasarn et al., 2012). This may partly be explained by the fact that incomplete AFFs are burdened by poor spontaneous healing. Another possible explanation is that the research field of atypical femoral fractures has been dominated by osteoporosis researchers, shifting the focus away from research related to fracture treatment. As a result, the notion that complete AFFs heal poorly might have become a self-fulfilling prophecy because surgeons use more proactive treatment strategies when compared to common fractures. This misconception is addressed in studies 1 and 2.

In summary, there is no good evidence indicating that bisphosphonates impact negatively on fracture healing with regard to time to union and union strength (Wilkinson, 2020, Kates and Ackert-Bicknell, 2016, Duckworth et al., 2019).

Atypical femoral fractures and healing

Considering the reasoning above, it seems reasonable to expect reliable fracture healing in bisphosphonate users with complete AFFs. Unfortunately, this appears not to be the case when reviewing the literature, since there are numerous reports of complicated healing courses in this patient group. The notion of problematic healing is reinforced by the reports of the task force of the ASBMR, which defined delayed healing as a minor feature of their case definitions for AFFs (Shane et al., 2010, Shane et al., 2014). It has been postulated that the severely suppressed bone metabolism in patients with long-term bisphosphonate use may be a contributing factor to complicated healing of AFFs (Armamento-Villareal et al., 2009, Odvina et al., 2005).

In line with the abovementioned, recent research from South Korea reports a significantly higher proportion of delayed unions or non-unions in a group of patients with AFFs and known bisphosphonate use when compared with NFFs without bisphosphonate use. In a multicentre case-control study of 196 atypical femoral fractures and 94 normal femoral fractures in women 50 years of age and older, they found a three-fold increased OR for complicated healing for patients with AFFs (Lim et al., 2018).

In a retrospective case series on 33 patients with 41 complete AFFs, all but one united at a mean of 8.4 months (Egol et al., 2014). Interestingly,

there were differences in healing times dependent on the success of reduction. The group of anatomically reduced fractures united at a mean of 7.1 months, whereas the non-anatomically reduced group united at 10.8 months, highlighting the importance of anatomical alignment in the treatment of these fractures. Despite the overall good union rate, the authors conclude that healing was delayed (Egol et al., 2014). However, it is questionable whether healing times in the patient category of AFFs should be compared with those of normal femoral fractures. These often-cited references are based on healing times of three to six months in younger patients with traumatic injuries (Yoon et al., 2021). In summary, it appears that complete AFFs show reliable healing when treated adequately with good alignment and stable fixation with intramedullary, reamed nails (Egol et al., 2014, Githens et al., 2018).

In analogy to complete AFFs, the early incomplete stages of AFFs generally heal well when the fracture is stabilised, and bisphosphonate treatment stopped. As a subtype of stress fractures, incomplete AFFs do not spontaneously heal reliably (Lee et al., 2021). Case series on incomplete AFFs confirm unfavourable results when these fractures are managed non-operatively, indicating poor spontaneous healing (Lee et al., 2021, Banffy et al., 2011, Saleh et al., 2012). Unfortunately, the numbers of patients with incomplete AFFs studied are very small, highlighting the difficulties in diagnosing patients with atypical femoral fractures in the early stages.

Rationale behind study 1

The discrepancy between the unaffected acute fracture healing during bisphosphonate treatment on the one hand and the poor track record of spontaneous healing of incomplete AFFs on the other hand, raises the question of whether bone formation is impaired in patients with bisphosphonate treatment and incomplete AFFs. In order to achieve a better understanding of the healing capacities of this special patient group we performed study 1.

STUDY 1
– HEALING CAPACITY –

Aims

We aimed to study the healing capacity of patients with bisphosphonate treatment and incomplete atypical femoral fractures in a case series of eight patients.

We hypothesised that these patients would have a normal capacity to generate bone in a surgical bone defect. Furthermore, we hypothesised that healing would occur within timeframes comparable with those of fracture healing in healthy individuals.

Methods and Results

We selected a cohort of 15 patients that previously had undergone excisional biopsies of AFFs to describe histological features in and surrounding the fracture gap (Schilcher et al., 2014). We included eight patients with incomplete AFFs with confirmed long-term bisphosphonate use. Seven patients were excluded because of pre-existing conditions affecting the ipsilateral femur (i.e. Paget's disease, previous fracture), previous operation with implants other than intramedullary femoral nails, and patients without a confirmed history of bisphosphonate use or insufficient follow-up (Figure 1-1).

Our study cohort consisted predominantly of women (N = 7) with a history of oral bisphosphonate use. The mean duration of bisphosphonate use was eight years prior to surgery (range four to 15 years). All patients reported on prodromal symptoms such as pain or discomfort on weight bearing prior to surgery.

Surgical intervention

All patients underwent surgical excision of the AFF using an 11.5 mm cylindrical core drill through a minimal open transvastus approach, followed by surgical stabilisation of the femur with an antegrade reamed intramedullary nail (figure 1-2).

Figure 1-1: Recruitment and patient characteristics

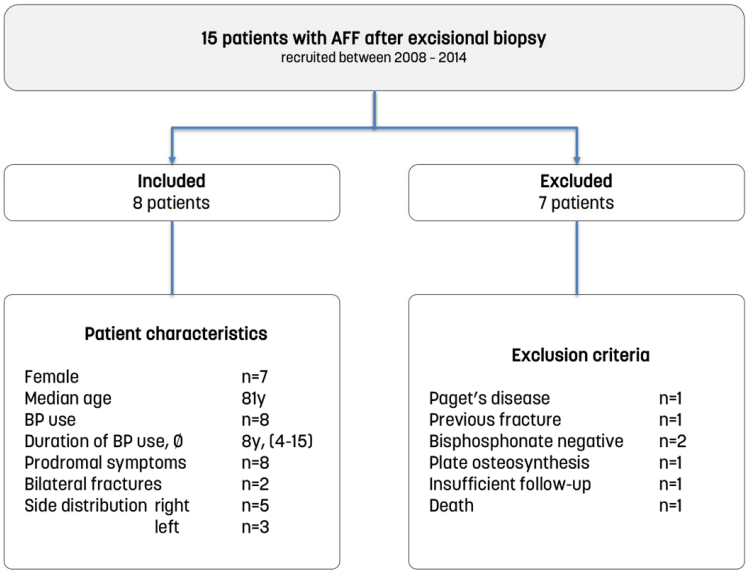
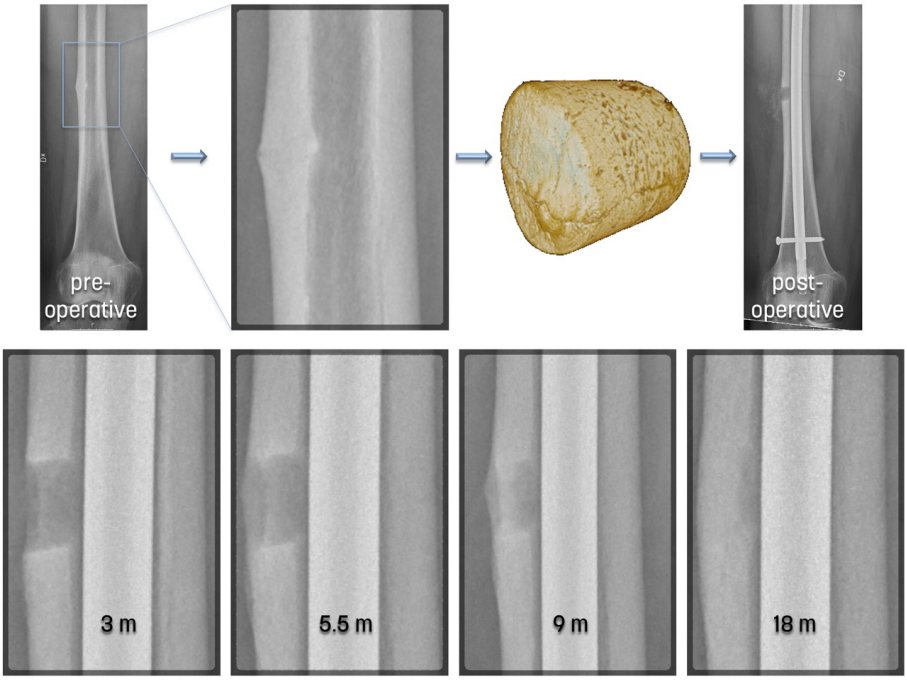
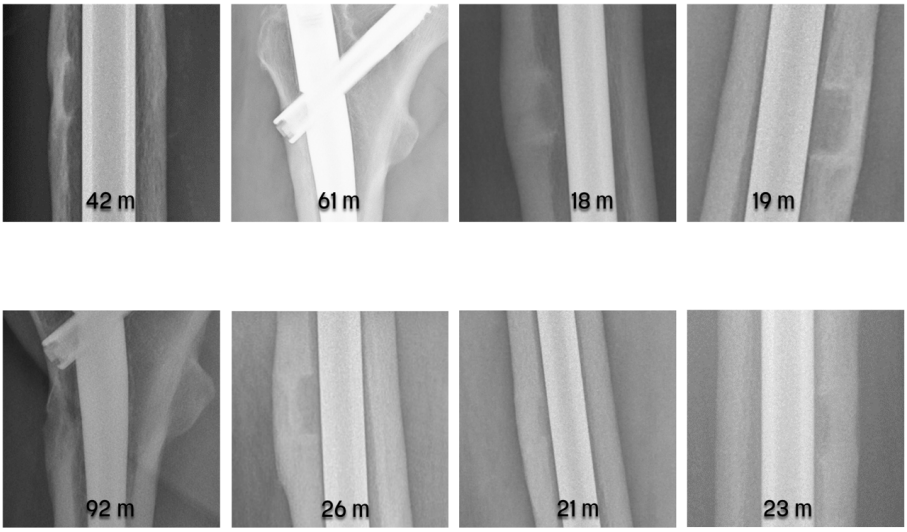


Figure 1-2: First row from left to right: incomplete diaphyseal AFF, fracture area enlarged, 3D reconstruction of a micro-CT of the biopsy including the fracture and day one postoperative radiograph. Second row: healing of the defect over time on plain radiographs.



We followed the patients radiographically until complete healing of the surgical defect in the femoral cortex was confirmed (as defined by continuous calcified callus). Radiographs were available from different time points and all but one patient had radiographs available three months postoperatively. All patients with available radiographs at three months showed callus development in the defect. A bridging callus was seen in all patients between three and seven months. All patients had healed uneventfully with continuous calcified callus by 18 months (median, range 13-26 months). Healing occurred within the surgical defect in the cortical bone. We did not observe any bulging periosteal callus beyond the cortical limits (figure 1-3). At the final follow-up, all patients reported complete regression of their initial symptoms and we did not identify any complications and related reoperations.

Figure 1-3: Radiographs at final follow-up for all eight cases. Continuous bridging callus not exceeding the limits of the biopsy site.



Discussion and Conclusions

Our results show that patients with incomplete AFFs appear to have a good capacity to form callus and generate bone despite their long-term use of bisphosphonates prior to surgery. This is in line with preclinical findings in animal fracture models on the effects of bisphosphonates on fracture healing that showed normal callus formation but delayed callus remodelling (Amanat et al., 2005, Hao et al., 2015).

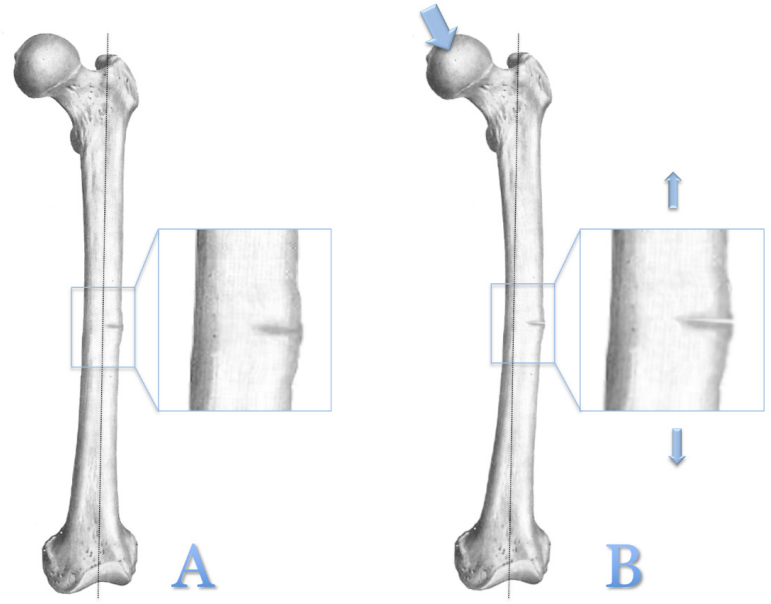
The unfavourable results in the non-operative management of incomplete AFFs and generally good results with operative treatment suggest that mechanical factors may contribute to both the development of AFFs and the poor spontaneous healing of incomplete AFFs. A relevant mechanical contribution to the poor spontaneous healing capacity is supported by the histological studies on biopsies of AFFs, among those, some of the cases included in this series (Schilcher et al., 2014). Upon microscopic examination of these biopsies, the thin fracture gap (mean width 180 μm) was filled with amorphous material without living cells despite signs of remodelling in the surrounding bone. The signs of remodelling are suggestive of an intact physiological response in the bone surrounding the fracture and the near periosteum in terms of attempts to heal the fracture. The amorphous material within the fracture gap was interpreted as necrotic material probably related to the disadvantageous mechanical environment. The minimal width of the fracture gap, causes strains incompatible with cell survival, thus leading to cell death (Schilcher et al., 2014, Gustafsson et al., 2016) (Figure 1-4). Strain levels within the incomplete fracture gap exceed those strain thresholds required for bone formation when simulated by finite element modelling on clinical CT and micro-CT images (Gustafsson et al., 2016). Another possible explanation of the poor healing observed in non-surgically treated incomplete AFFs is selection bias. The progression of incomplete lesions is significantly higher in those where bisphosphonate treatment was not stopped (Lee et al., 2021). Patients selected to undergo surgical fixation might have a higher chance of discontinuing bisphosphonate treatment because of the higher degree of alertness in the medical team surrounding them. Also, bisphosphonate cessation decreases the risk of AFF in the following year by roughly 70%, independent of the duration of bisphosphonate treatment (Schilcher 2011).

The physiologic response to micro cracks is the repair mechanism called targeted remodelling. This process involves a limited resorption of the damaged area followed by new bone formation through osteoblasts. In this manner, the resorption diminishes strains within the fracture gap and enables osteoblasts to invade the fracture gap and initiate healing (Foster et al., 2021, Perren, 2002). This natural healing mechanism appears to be inhibited in patients with ongoing bisphosphonate therapy, as adherent

bisphosphonates on the surfaces of the fracture gap will impact the osteoclast function with the detrimental result of accumulation and propagation of cortical cracks.

In this study, we surgically altered the biomechanical environment by excising the fracture in this case series, thus reducing strains within the fracture gap. In addition, the excision also removed the bisphosphonates bound within the fracture gap, leaving freshened surfaces behind that would not alter osteoclast function locally. The results of this case series support the theory that patients with AFFs have a normal capacity to form callus tissue. The poor healing of incomplete AFFs is probably related to the special mechanical environment within the fracture gap and the inability of executing a physiologic osteoclast response by resorbing the fracture ends.

Figure 1-4: Illustration of a femur with an incomplete diaphyseal atypical femoral fracture in (A) an unloaded condition, and (B) with simulated loading condition resulting in distraction in the fracture gap.



Rationale leading to study 2

The patients in study 1 showed a rather uncomplicated healing of the fracture and the cortical defect despite wide excisions of the bone around the fracture. This contrasts with the literature, which reports on strikingly high rates of complications such as delayed healing, non-union and reoperations (Edwards et al., 2013, Bogdan et al., 2016). Some case series report reoperation rates as high as 46% in patients with complete AFFs (Weil et al., 2011) and implant failure in roughly 30% of cases treated with plates (Prasarn et al., 2012). In our own experience, these remarkably high complication rates are unexpected, particularly as femoral fractures in general show reliable union rates and low complication rates (Lodde et al., 2021, Winquist et al., 1984) if evidence-based treatment is applied (COTS, 2003).

The discrepancy between the overall good healing capacity of patients with incomplete AFFs and the reports on unexpected high rates of reoperations posed the question of whether there are other factors that influence the risk for reoperation apart from the fracture itself. The risk for reoperation in AFFs in direct comparison to NFFs and corrected for patient background characteristics was previously unknown. To fill this knowledge gap we investigated a nationwide Swedish patient cohort that had previously been studied to establish the association between bisphosphonates and AFFs (Schilcher et al., 2015b).

STUDY 2
– RISK FOR REOPERATION –

Aims

With this study we aimed to investigate the risk for reoperation in patients with atypical femoral fractures (AFF) compared to patients with normal femoral fractures (NFF) in a nationwide cohort study in Sweden. Furthermore, we aimed to elucidate potential risk factors that might lead to an increased risk for reoperation.

We hypothesised that the risk for reoperation would be higher in the group of patients with AFFs, but that the risk would be attenuated when adjusting for confounding risk factors.

Method and Results

We chose to study a Swedish nationwide patient cohort that had previously been studied to estimate the risk for AFFs in relation to bisphosphonate use. This cohort consisted of all men and women, 55 years or older with a femoral shaft fracture (ICD-10 codes S722 or S723 (International Classification of Diseases, 10th Revision)) registered in the Swedish National Inpatient Register between 01.01.2008 and 31.12.2010. All diagnostic radiographs had been reviewed previously and patients with pre-existing implants, previous ipsilateral fractures, pathological fractures and apparent diseases altering bone homeostasis were excluded from further analysis, resulting in a cohort of 1124 patients (Schilcher et al., 2015b).

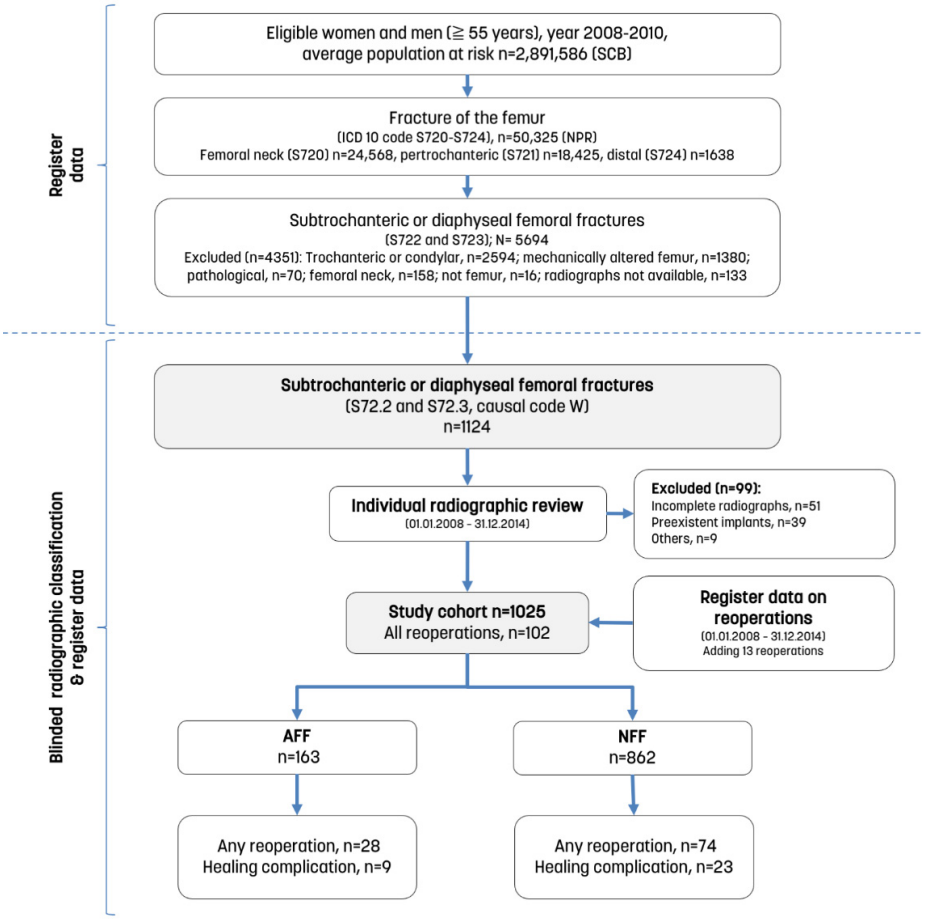
We identified reoperations in two complementary approaches: a review of follow-up imaging and a study of data on hospital readmissions according to the Swedish National Inpatient Register. We analysed the total of reoperations and a subgroup of reoperations related to a healing complication (eg. implant failure, non and delayed union) separately. To account for possible confounding risk factors for reoperations, adjustments with register data on comorbidities (Swedish National Inpatient Register), death (Swedish Tax Agency) and drug use (Swedish Prescribed Drug Register) were made. The fractures were categorised into AFFs and NFFs. Descriptive data on the study cohort are presented in table 2-1.

Table 2-1: Patient background characteristics

		AFF	NFF
N		163	862
Age, mean (SD)		76.6 (8.19)	82.2 (9.58)
Sex	M	11 (6.7%)	169 (19.6%)
	F	152 (93.3%)	693 (80.4%)
Charlson's Comorbidity Index, median (IQR)		3 (1–5)	3 (1–6)
Time to complication (years)[1], median (IQR)		0.74 (0.46–1.2)	0.64 (0.19–1.3)
Outcome	No event	104 (63.8%)	290 (33.6%)
	Reoperation	28 (17.2%)	74 (8.6%)
	Death	31 (19.0%)	498 (57.8%)
Time to death [years][2], median (IQR)		2.8 (1.9–4.2)	1.9 (0.4–3.4)
Follow-up time [years], median (IQR)		4.5 (2.7–5.5)	3.2 (0.9–4.9)
Bisphosphonate use before fracture		127 (77.9%)	102 (11.8%)
Bisphosphonate use after fracture [first year]		110 (67.5%)	127 (14.7%)
Bisphosphonate use before fracture. Duration [years], mean (SD)		3.64 (1.1)	2.34 (1.65)
Corticosteroid use		49 (30.1%)	140 (16.2%)
Fracture location	Subtrochanteric	25 (15.3%)	559 (64.8%)
	Diaphyseal	138 (84.7%)	303 (35.2%)

[1]for those with complication, [2]for those who died during observation interval

Figure 2-1: Flowchart of recruitment and fracture classification



Patients with AFFs were more often reoperated than patients with NFF with an age-adjusted relative risk of 1.61 (95% CI, 1.07 to 2.43) for any reoperation and 1.69 (95% CI, 0.78 to 3.68) for reoperations related to healing complications. When adjusting for the variables age, sex, Charlson's comorbidity index and Cortisone use the relative risk was reduced to 1.41, both for any reoperation (95% CI, 0.92 to 2.17) and for reoperations related to healing complications (95% CI, 0.63 to 3.17).

There was a marked difference in survival and follow-up time between the two groups. Patients with normal femoral fractures were older (82.2 years vs. 76.6 years), were more likely to die during follow-up (58% vs. 19%) and died within a shorter period of time (1.9 years vs. 2.8 years). This resulted in shorter follow-up time in patients with NFFs (3.2 versus 4.5 years). When adjusting for these differences in a time-to-event multivariable adjusted analysis, cause-specific hazard ratios were further reduced to

1.34 (0.85–2.13) for any reoperation and 1.32 (0.58–3.0) for reoperations related to healing complications (Table 2-2).

In a stratified multivariable adjusted analysis, factors with significantly increased cause-specific hazard ratios were male gender and no bisphosphonate use before the index fracture (Figure 2-2).

Figure 2-2: Forest plot of stratified, multivariable adjusted cause-specific hazard ratios (x-axis) for any reoperation

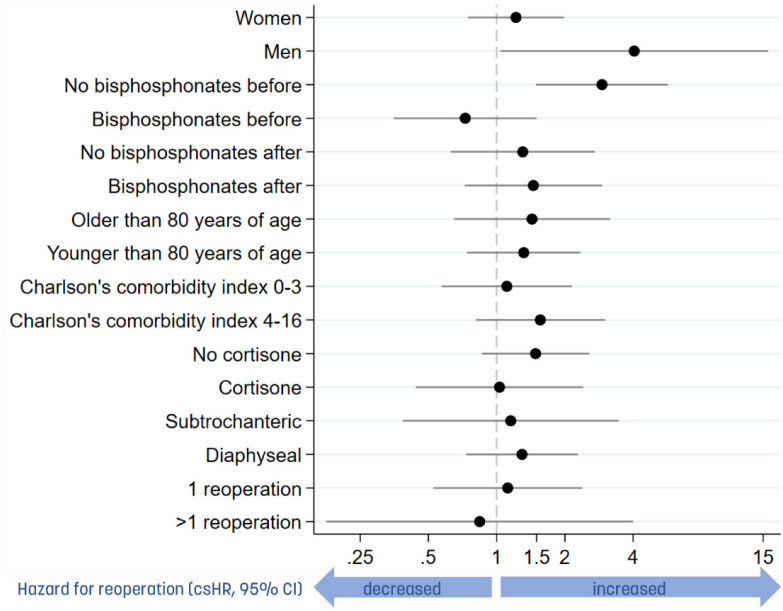


Table 2-2: Differences in reoperation rates between AFFs and NFFs based on different statistical methods. Odds ratios (ORs) calculated with binominal logistic regression. Cause-specific hazard ratios (csHRs) taking differences in follow-up time into account, using cox regression. Sub-distribution hazard ratios (sdHRs) using the Fine and Gray proportional sub-distribution hazard regression (sdHR) model to control for differences in death rates between the groups. All with 95% confidence intervals (95% CIs)

Event as binary	**Fracture type**	**No. events (N)**	**Risk**	**Age-adjusted OR (95% CI)**	**Multivariable-adjusted* OR (95% CI)**	**Age-adjusted RR (95% CI)**	**Multivariable-adjusted* RR (95% CI)**
Reoperation	NFF	74	8.6%	Ref.	Ref.	Ref.	Ref.
	AFF	28	17.2%	1.76 (1.08 - 2.86)	1.54 (0.93 - 2.56)	1.61 (1.07 - 2.43)	1.41 (0.92 - 2.17)
Reoperation -healing complication	NFF	23	2.7%	Ref.	Ref.	Ref.	Ref.
	AFF	9	5.5%	1.73 (0.76 - 3.92)	1.46 (0.62 - 3.41)	1.69 (0.78 - 3.68)	1.41 (0.63 - 3.17)
Time to event		**Time at risk (years)**	**Age-standardized rate (events per 1000 person-year)**	**Age-adjusted csHR (95% CI)**	**Multivariable-adjusted* csHR (95% CI)**	**Age-adjusted sdHR (95% CI)**	**Multivariable-adjusted* sdHR (95% CI)**
Reoperation	NFF	2657	27.9	Ref.	Ref.	Ref.	Ref.
	AFF	669	35.0	1.49 (0.95 - 2.33)	1.34 (0.85 - 2.13)	1.69 (1.09 - 2.64)	1.49 (0.92 - 2.42)
Reoperation -healing complication	NFF	2826	8.1	Ref.	Ref.	Ref.	Ref.
	AFF	740	15.0	1.55 (0.7 - 3.42)	1.32 (0.58 - 3.0)	1.71 (0.76 - 3.85)	1.43 (0.57- 3.58)

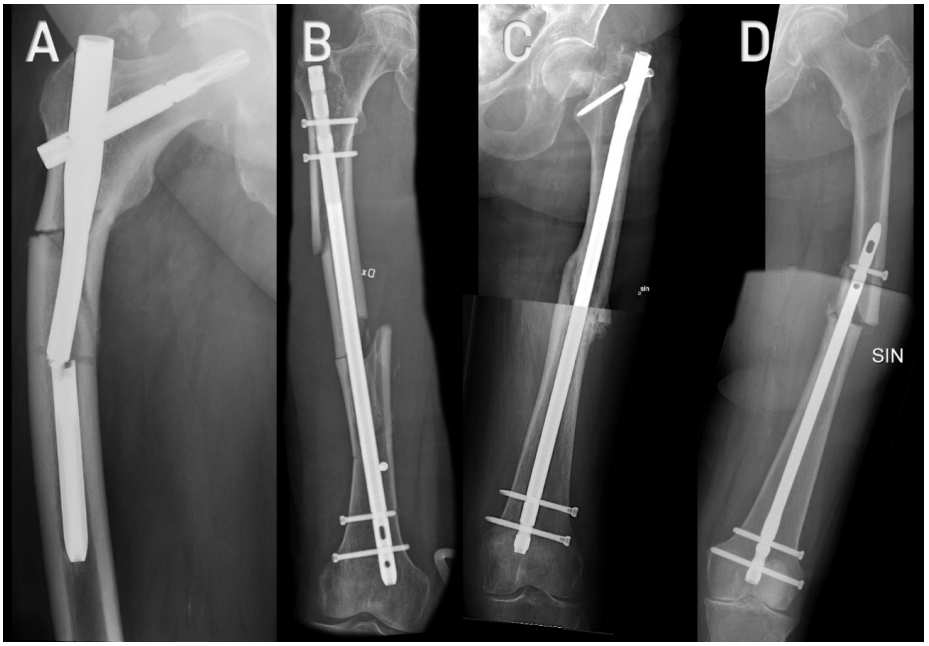
* Adjusted by age (continuous), sex, cortisone use (yes/no), and Charlson's comorbidity index (continuous).

Bisphosphonate use prior to the index fracture reduced the multivariable adjusted csHR to 0.34 (95% CI, 0.14 to 0.81) for any reoperation and csHR to 0.13 (95% CI, 0.03 to 0.54) for reoperations related to healing complications in the group of patients with AFFs. In contrast, it increased the multivariable adjusted csHR in patients with NFFs to 2.62 (95% CI, 1.03 to 6.68) for any reoperation and 1.65 (95% CI, 0.92 to 2.98) for reoperations related to healing complications.

Discussion and Conclusions

The results of this study confirm that patients with AFFs have a higher risk for reoperation even when compared with age-matched normal femoral fractures. This finding is in line with numerous previous publications, though the rate of reoperations varies widely from 4.6 to 46% (Weil et al., 2011, Lee et al., 2017). In our cohort the rate of reoperations was 17.2% (N=28/163). Comparison of reoperation rates is difficult as most publications present a series of patients without control groups and a wide variety of implants and operative techniques are used. One of the major advantages of our findings is the generalizability of our results due to the study design, at least with respect to a Caucasian population and surgical traditions as represented in our cohort.

Figure 2-3: Examples of complications identified upon radiographic review in the group of patients with AFFs. (A) Hardware failure (the distal locking screw is lacking after a previous dynamisation procedure), (B) complex multiple intraoperative fractures and mal-alignment, (C) the most common complication leading to major reoperation, a hip fracture above the implant and (D) proximal peri-implant due to insufficient working length of the retrograde nail.



An interesting finding in our study was the higher risk for reoperation in patients with AFFs without known bisphosphonate use. In contrast to that, bisphosphonate users showed a tendency towards a lower risk for reoperation. Very little is known about this subgroup of patients with AFFs without known bisphosphonate use. Nevertheless, it appears important to further elucidate the pathogenesis of this subgroup as it represented 22% of the cases in our cohort of AFFs. One can only speculate on whether this special subgroup represents a group of patients suffering from yet undetected conditions affecting the bone metabolism.

With our calculations, we were able to show that the increased risk for reoperation in AFFs is not solely explained by the atypical nature of the fracture. Other factors such as gender, ongoing medications, pre-existing comorbidities and the survival rates have a strong impact on the reoperation rates. Another factor that might affect the risk for reoperation is the implant that is chosen to stabilise the fracture. The majority of publications on the topic of reoperations and complications in the treatment of atypical fractures describe a variety of implants used and there are indications that

the choice of implant might have an impact on the risk for reoperation (Prasarn et al., 2012, Lee et al., 2017).

Rationale leading to study 3

In a pilot study on patients from Region Östergötland in Sweden, the concern about ipsilateral hip fractures being a serious, but unfortunately not uncommon complication after standard femoral nailing was raised (Schilcher, 2015). On conducting a literature review, we noticed that this was not a new finding. The first report on ipsilateral hip fractures as a complication after intramedullary nailing in a case series of 24 elderly patients was published more than 30 years ago (Moran et al., 1990). Unfortunately, this issue was, to our knowledge, not further studied until the Östergötland study. This issue became even more apparent during a review of the imaging in study 2, when we noticed numerous reoperations performed because the affected patients sustained an ipsilateral hip fracture during follow-up.

This raised the question of the optimal implant choice for femoral shaft fractures in the elderly. There is consensus that femoral shaft fractures are best treated with intramedullary nails (Memarzadeh et al., 2017, Trompeter and Newman, 2013), but it remains unclear which specific type of implant provides the best outcomes and with the fewest reoperations. There is a wide range of nails available and the main differences between them are the mode of insertion and locking. While nails to treat proximal fractures in the femur have been studied extensively, there is no guidance in the literature as to which type of nail should be used to avoid certain types of reoperations in femoral shaft fractures. The question becomes even more interesting when considering the elderly population with high incidences of osteoporosis and fragility and in the light of the significant background risk for hip fractures in the elderly population (Lofman, 2006). Particularly in this patient group, it appears both intuitive and common sense to use devices that include the femoral neck in the fixation, both to achieve a more stable fixation, but also to possibly protect the femoral neck from further injuries. We therefore aimed to study the risks for reoperation for intramedullary nails that either include the femoral neck in the fixation or exclude it when used in the fixation of femoral shaft fractures in elderly patients.

STUDY 3
– IMPLANT CHOICE –

Aims

In study 2 we reviewed thousands of radiographs to identify reoperations. During that work, the question of implant choice to prevent complications after femoral shaft fractures in general and atypical femoral fractures in particular, became a growing subject of interest. In the current study we aimed to elucidate the specific risks for reoperation after femoral shaft fractures treated with intramedullary nails and, in particular, the risk for subsequent ipsilateral hip fractures in a nationwide cohort of elderly patients.

We hypothesised that the risk for reoperation, particularly due to a subsequent ipsilateral hip fracture, would be reduced when nails with proximal locking into the femoral neck were used compared with nails with standard locking.

Methods and Results

For this study we selected the same baseline cohort as in study 2. The observation interval for reoperations was from 01.01.2008 – 31.12.2014. The previously retrieved radiographs were re-reviewed to define the types of implants used and reoperations performed. In cases of multiple reoperations, only the most complex one was included in our statistical analyses. We excluded from further analysis a further 128 patients that had been operated with any type of plate construct. The remaining 897 patients, all operated with intramedullary nails, were then categorised into two groups by radiographic review. The first group was named the 'femoral neck protection' group (FNP) and comprised all patients with intramedullary nails that locked proximally into the femoral neck (Figure 3-1). This group consisted of patients with cephalomedullary and reconstruction nails. The second group was named the 'no femoral neck protection' group (NFNP), and included all patients with intramedullary nails that locked distal to the femoral neck, such as standard antegrade femoral nails and retrograde femoral nails (Figure 3-1). Reoperations were then classified by the complexity of the surgical procedure as major or minor. From the group of major reoperations, two subgroups were analysed separately as reoperations due to proximal peri-implant fractures (mainly hip fractures) and those due to any peri-implant fractures (Figure 3-2). Table 3-1 specifies the different types of reoperations performed.

Table 3-1: Types and frequencies of reoperations

Surgical procedure	**No femoral neck protection** (N = 257)	**Femoral neck protection** (N = 640)
Major		
Complete implant removal	4 (1.6%)	1 (0.2%)
Revision with plate osteosynthesis	1 (0.4%)	6 (0.9%)
Revision with intramedullary nail osteosynthesis	5 (1.9%)	10 (1.6%)
Total hip replacement due to non-union	0 (0%)	3 (0.5%)
Proximal peri-implant fracture	14 (5.4%)	0 (0%)
Distal peri-implant fracture	0 (0%)	7 (1.1%)
Minor		
Partial implant removal	6 (2.3%)	6 (0.9%)
Dynamising procedures	4 (1.6%)	5 (0.8%)
Total hip replacement due to osteoarthritis	0 (0%)	2 (0.3%)
Other (arthroscopy, soft tissue procedures, ...)	2 (0.8%)	6 (0.9%)
None	221 (86.0%)	594 (92.8%)

Figure 3-1: The two study groups: The FNP group consisted of (A) cephalomedullary and (B) reconstruction nails. The NFNP group included (C) standard antegrade nails and (D) retrograde nails.

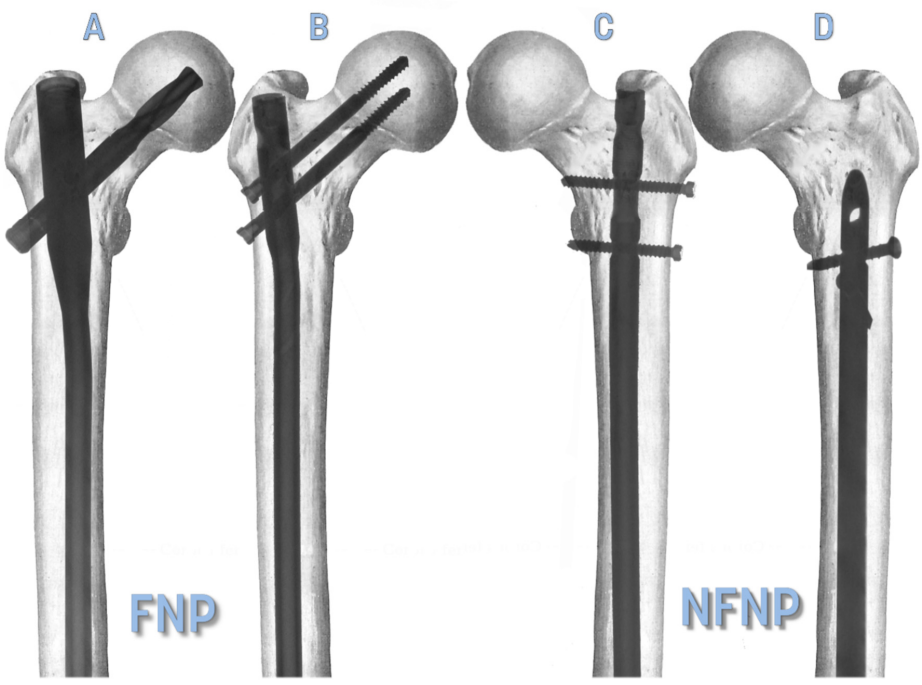
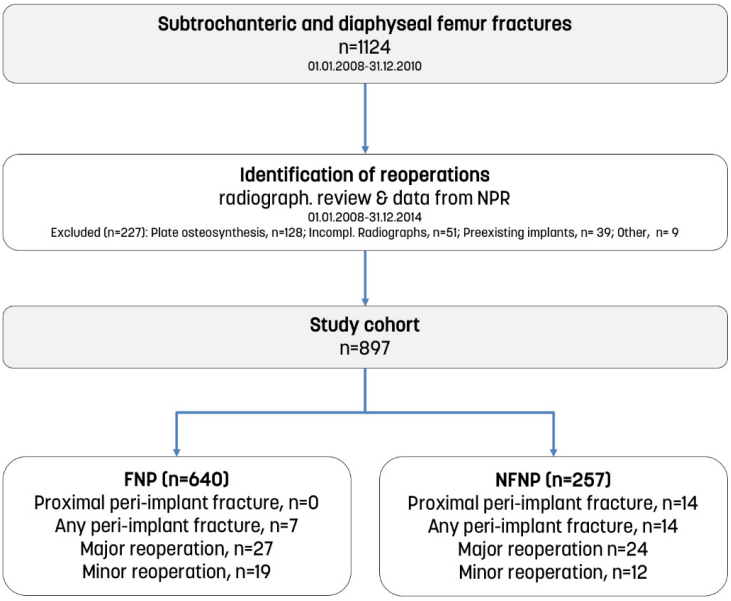


Figure 3-2: Flowchart



We observed a total of 82 reoperations of which 46 (7.2%) occurred in the FNP group and 36 (14.0%) in the NFNP group. No proximal peri-implant fracture occurred in the 640 patients of the FNP group but 14 (of 257) occurred in the NFNP group. Any peri-implant fractures were identified in seven cases in the FNP group and in 14 cases in the NFNP group, resulting in a five-fold risk reduction (sex and age-adjusted OR 0.18, 95% CI 0.07 to 0.46). The number needed to treat to avoid one proximal peri-implant fracture was 19. We even found a significant risk reduction for all major reoperations with a sex and age-adjusted odds ratio of 0.44 (95% CI 0.24 to 0.79), corresponding with a number needed to treat of 23. There was even a tendency for lower reoperation risks with regard to minor reoperations (3.0% versus 4.7%) though this was not statistically significant (sex and age-adjusted OR 0.77, 95%, CI 0.36 to 1.7).

As the two groups differed in their background characteristics, death and follow-up time (table 3-2), we calculated both multivariable adjusted cause-specific (csHR) and subdistribution hazard ratios (sdHR). Despite these adjustments our hazard estimates remained stable (Table 3-3).

In a separate analysis, we even calculated risks for reoperation for two subgroups of interest that were thought to possibly bias the overall risk for reoperation. The first was the fracture location along the shaft of the femur. We analysed subtrochanteric and diaphyseal fractures separately. Of the

515 patients with subtrochanteric fractures, 506 were treated with FNP nails. The multivariable adjusted cause-specific hazard ratio for reoperation due to any peri-implant fracture was 0.07 (95% CI, 0.01 to 0.7). For the diaphyseal localisation the multivariable adjusted cause-specific hazard ratio was 0.27 (95% CI, 0.06 to 1.22).

The other subgroup analysis was calculated for the group of patients with AFFs (N=160). In this group we noticed an almost even distribution of implants (45.6% FNP nails). In this group, 4.1% (N=3) were operated for any peri-implant fracture and 9.6% (N=7) had major reoperations, while in the group of normal fractures the reoperation frequencies were 6.9% (N=6) and 16.1% (N=14) respectively.

Table 3-2: Patients' characteristics at baseline.

		NFNP n=257	**FNP n=640**
Type of nail		114 (AMN) 143 (RMN)	570 (CMN) 70 (Recon)
Age in years, median (IQR)		80.4 (70.8, 87.4)	84.3 (77.5, 88.8)
Sex	M	31 (12.1%)	136 (21.3%)
	F	226 (87.9%)	504 (78.8%)
Atypical femoral fracture		87 (33.9%)	73 (11.4%)
Common femoral shaft		170 (66.1%)	567 (88.6%)
Fracture location	Subtrochanteric	9	506
	Shaft	248	134
Charlson Comorbidity Index, median score (IQR)		3 (1, 5)	4 (1, 6)
Corticosteroids	Never use	217 (84.4%)	512 (80.0%)
	Ever use	40 (15.6%)	128 (20.0%)
Bisphosphonates	Never use	176 (68.5%)	508 (79.4%)
	Ever use	81 (31.5%)	132 (20.6%)

AMN, antegrade intramedullary nail; CMN, cephalomedullary nail; RMN, retrograde intramedullary nail; Recon, reconstruction nail; IQR, interquartile range.

Table 3-3. Frequencies of and risks for reoperations

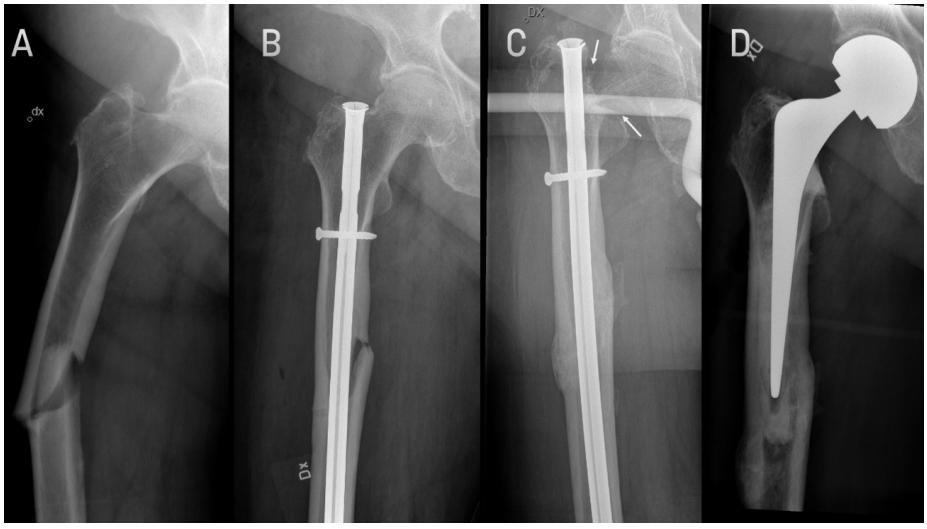
	FNP* n=640	NFNP* n=257	OR† (95% CI)	csHR§ (95% CI)	sdHR# (95% CI)
Proximal peri-implant fracture	0 (0.0%)	4 (5.4%)	-	-	-
Any peri-implant fracture	7 (1.1%)	14 (5.4%)	0.18	0.19	0.2
Time to any peri-implant fracture (years), median [IQR]	1.9 [0.58, 2.7]	0.28 [0.08, 0.53]	[0.07, 0.46]	[0.07, 0.5]	[0.07, 0.54]
Major reoperation	27 (4.2%)	24 (9.3%)	0.44	0.51	0.51
Time to major reoperation (years), median [IQR]	1.14 [0.37, 2.5]	0.53 [0.08, 1.0]	[0.24, 0.79]	[0.28, 0.92]	[0.28, 0.93]
Minor reoperation	19 (3.0%)	12 (4.7%)	0.77	0.81	0.81
Time to minor reoperation (years), median [IQR]	0.56 [0.07, 0.85]	0.70 [0.21, 1.2]	[0.36, 1.7]	[0.38, 1.7]	[0.34, 2.0]
Death	359 (56.1%)	101 (39.3%)	-	-	-
Time to death (years), for those who died, median [IQR]	1.9 [0.46, 3.5]	2.0 [0.46, 3.5]			

*The values are given as the number of patients, with the percentage in parentheses, or as the median, with the interquartile range (IQR) in parentheses (for time values). †The values are given as the age and sex-adjusted OR. §The values are given as the multivariable-adjusted cause-specific HR (adjusted for age, sex, glucocorticoid use [yes or no], and Charlson Comorbidity Index score), with the 95% CI in parentheses. #The values are given as the multivariable-adjusted subdistribution HR, with the 95% CI in parentheses; they were calculated using the Fine and Gray proportional subdistribution hazard regression model.

Discussion and Conclusions

Our results matched our expectations well and confirmed the significant impact of implant choice on the reoperation rates in this particular patient group. As expected, we did not observe any proximal peri-implant fractures in the FNP group, whereas this represented the most frequent indication for reoperation (14 of 24 major reoperations) in the NFNP group. As no such reoperation occurred in the FNP group, we were unable to calculate a risk reduction. The risk for any peri-implant fractures was decreased five-fold and the risk for major reoperations was reduced by half. These risk reductions remained stable even when we corrected for baseline characteristics such as age, gender, drug use, comorbidities and even for differences in survival and follow-up time (figure 3-3).

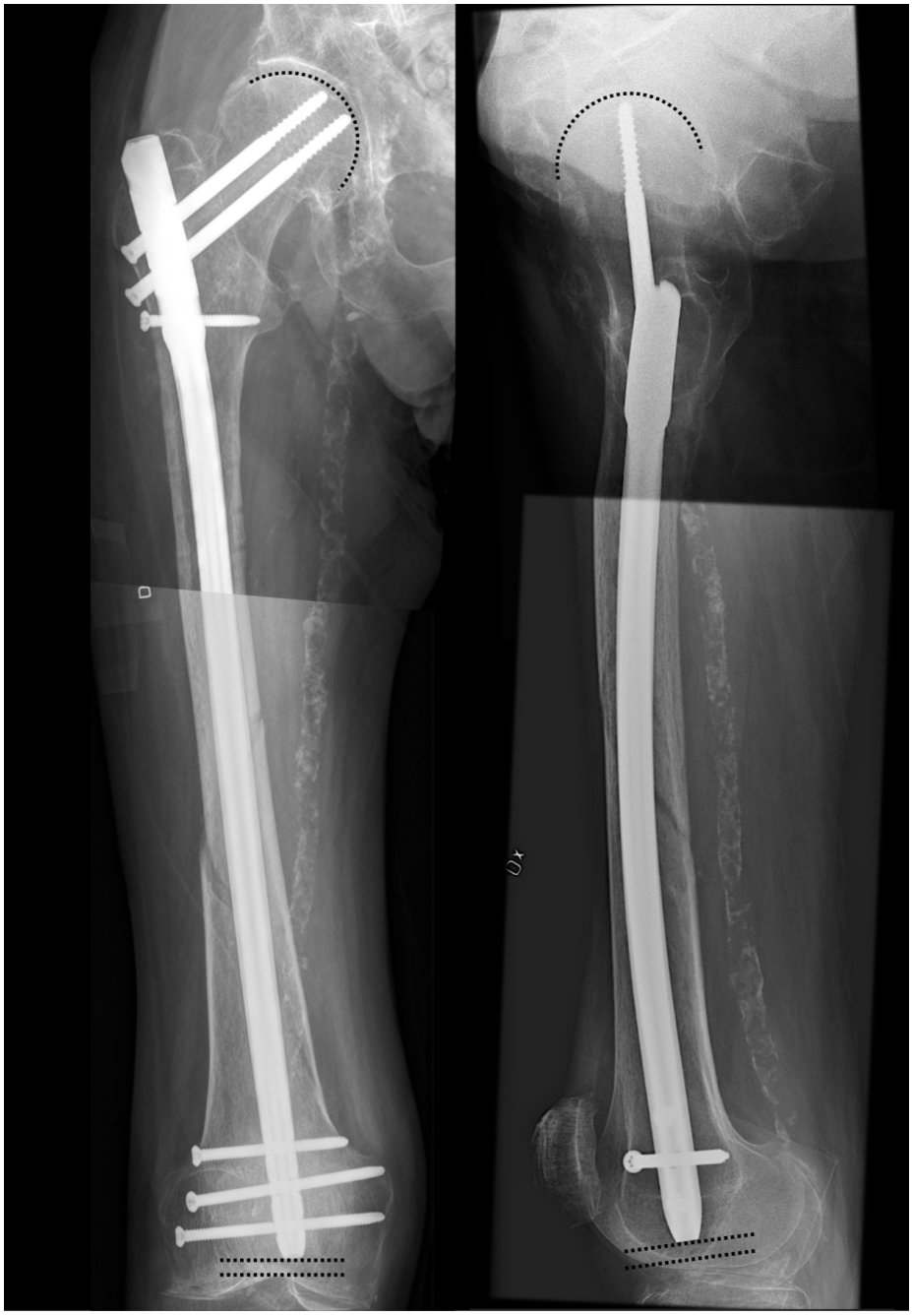
Figure 3-3: An avoidable complication? (A) Patient with an atypical femoral fracture operated with a NFNP nail (B). The subsequent peri-implant hip fracture (C) required major revision surgery with hardware removal and a cemented hemiarthroplasty (D).



Interestingly, we observed seven cases of reoperations for distal peri-implant fractures in the FNP group, whereas no such fractures occurred in the NFNP group. All seven cases were operated with cephalomedullary nails, of which two were operated with short nails that did not lock distally to the femoral isthmus, thereby leaving the distal femur unprotected. The remaining five cases were operated with long cephalomedullary nails

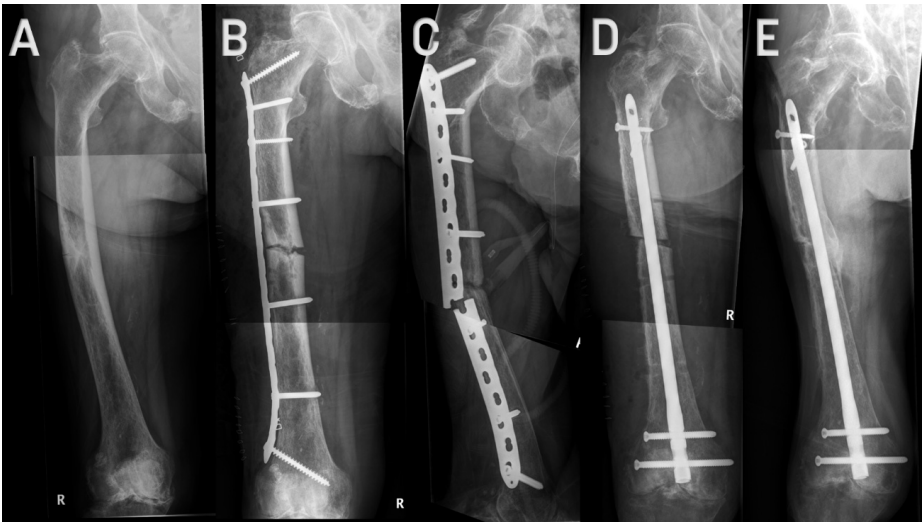
reaching well beyond the femoral isthmus with an average distance of 82 mm between the tip of the nail and the Blumensaat line (IQR, 35-95 mm). All nails were distally locked, and we observed one anterior penetration of the distal tip of the nail. The risk for distal anterior penetration of the nail tip is a well-known and documented problem in femoral nailing. The radius of curvature of the nail mismatches frequently with the antecurvation of the patient's femur. The most commonly used femoral nails have a radius of curvature of 1500-2500 mm, whereas newer CT studies on human femurs show that the average anatomic radius of curvature is lower than 1000 mm, particularly in women and Asians (Thiesen et al., 2018). This mismatch may be a reason to choose a slightly shorter nail to avoid the complication of anterior penetration (Fantry et al., 2015, Shetty et al., 2019). More recently, newer nail designs with a lower radius of curvature have become available to account for this surgical dilemma. None of the patients in our cohort were operated with such a newer nail design as these models were not available in Sweden during the recruitment phase of 2008-2010. We believe that an optimised working length of the chosen implant, ideally with a short distance between the tip of the nail and the Blumensaat line, might reduce the risk for distal peri-implant fractures (figure 3-4 and figure 5-1, p. 51). However, this question was beyond the scope of this study to evaluate.

Figure 3-4: Patient with a peri-implant femur fracture (below a dynamic hip screw plate; note the screw holes in the femoral cortex) operated with a long reconstruction nail with optimised working length (note the minimal distances between the tip of the nail and the Blumensaat line distally and the subchondral cortex in the femoral head).



Our primary aim was to investigate reoperation rates for intramedullary nails - the gold standard fixation device for femoral shaft fractures (Gosling and Krettek, 2019). However, in our review we also included cases that were operated with a plate construct (figure 3-5). Of the 128 cases operated with a plate, 69 cases had a subtrochanteric and 59 a diaphyseal fracture at a mean age of 81.1 years. The majority, 89% (115 of 128) were women. Reoperations were performed in 16% (20 of 128) of the cases at a median of 284 days from index surgery (range 11-2357 days). The majority were major reoperations (17 of 20). Six of these cases were reoperated for a subsequent ipsilateral hip fracture and an additional two cases for a diaphyseal proximal peri-implant fracture. The rate of proximal peri-implant fractures was higher (6.3 %, eight of 128) than in the NFNP group of intramedullary nails (5.4%, 14 of 257). Furthermore, 25% (five of 20) of the reoperated cases underwent more than one revision surgery.

Figure 3-5: An elderly woman suffering from dementia operated with a plate for an incomplete atypical femoral fracture that propagated to a complete fracture (note the marked lateral bow) (A). The fracture was treated with a long locking compression plate (B) that failed after only 9 weeks (C) and was revised with a retrograde intramedullary nail (D) showing the bony union after roughly 4 years (E).



Currently, the optimal fixation device for femoral shaft fractures in elderly comorbid patients remains unknown. The literature is restricted to case reports and there is no consensus regarding implant choices (Schilcher, 2015, Moran et al., 1990). Our results show a clear and significant advantage for the use of femoral neck protecting nails in this particular

patient group, with robust risk estimates even after adjustments for multiple variables. Unfortunately, our findings are not reflected in daily clinical practice as illustrated by multiple publications. In a single-centre case series of 109 atypical fractures in patients with known bisphosphonate treatment, all patients were treated with standard antegrade interlocking femoral nails, even including those with a subtrochanteric fracture location (Lim et al., 2016). In our cohort, 71% (640 of 897) of the cases were operated with FNP nails, which is a higher proportion than in most of the currently published articles.

As a result of this study, a further variable was introduced in the SFR in 2019. During the registration process of intramedullary femoral nails, surgeons are prompted to register the type of proximal locking in analogy to the grouping in this study. This new variable enables interested researchers and users to follow and analyse trends in treatment strategies over time.

One of the major strengths of our study is the generalizability of its results. The combination of nationwide high quality register data and two complementary approaches to identifying reoperations optimised the capture of reoperations in our cohort. The generalizability accounts at least for similar, mainly Caucasian populations as they differ in their geometric femoral features (hip offset and varus angle, etc.) from other populations such as Asian. The major drawback is the retrospective design, with the possibility for undetected selection and expertise biases. Furthermore, our cohort represents treatment strategies that are more than 10 years old and may not represent current treatment strategies. To confirm that no significant shifting in proximal locking practice has occurred, we reviewed the registrations in the Swedish Fracture Register for the year 2020. This revealed 1165 registrations of diaphyseal and subtrochanteric femoral fractures aged 55 and older. In that cohort 74% (840 of 1165) were operated with femoral neck protecting nails, thus confirming a very similar distribution with a slight shift towards femoral neck protecting nails, when compared to our study cohort (71%, 640 of 897). This is a very promising development on the first glance, which will need longitudinal follow-up to be confirmed.

Rationale leading to study 4

AFFs are very rare. Incidence rates are low (< 10 per 10000 person years) and depend on multiple risk factors (length of bisphosphonate use and others such as age, sex, ethnicity, etc.) (Schilcher et al., 2015b, Black et al., 2020). Our experiences in identifying and recruiting patients with AFFs in studies 1-3 clarified the lack of reliable register data on this particular fracture type. The difficulty is the absence of a unified ICD 10 code for AFFs. In women, who represent the vast majority of patients with AFFs the ICD 10 code M80.0F (postmenopausal osteoporosis with pathological fracture, femur) appears the best alternative, but it is hardly ever applied in Sweden. The majority of AFFs were and are coded with a traumatic fracture code, either S72.2 (subtrochanteric fracture) or S72.3 (diaphyseal femoral fracture), dependent on the localisation of the fracture.

This makes the identification of AFFs in the Swedish National Inpatient Register difficult as they disappear in the blur of the much more common normal femoral fractures. The approach in studies 1-3 was to retrieve data on any femoral fracture from the Swedish National Inpatient Register and in a second step retrieve all radiographic imaging on these patients to enable identification of AFFs via radiographic review. This was a very cumbersome and time-consuming process. Furthermore, the data from the Swedish National Inpatient Register contain no information on laterality which complicates the identification process even further.

The Swedish Fracture Register, a physician-based register, could be used as a surveillance tool for AFFs in the population. In 2015 a variable was introduced allowing for specific registration of AFFs as a subgroup of subtrochanteric and diaphyseal femoral fractures. To improve the quality of the data a short information window appears during the registration process, stating the classification criteria according to the task force of the American Society of Bone and Mineral Research.

In order to use the Swedish Fracture Register as a surveillance tool for AFFs, register data have to be validated.

STUDY 4
– REGISTER VALIDATION –

Aims

With this study we aimed to investigate the Swedish Fracture Register (SFR) as a surveillance tool for atypical femoral fractures (AFF) in the population, to validate its data on AFFs and to explore possible means to improve data quality.

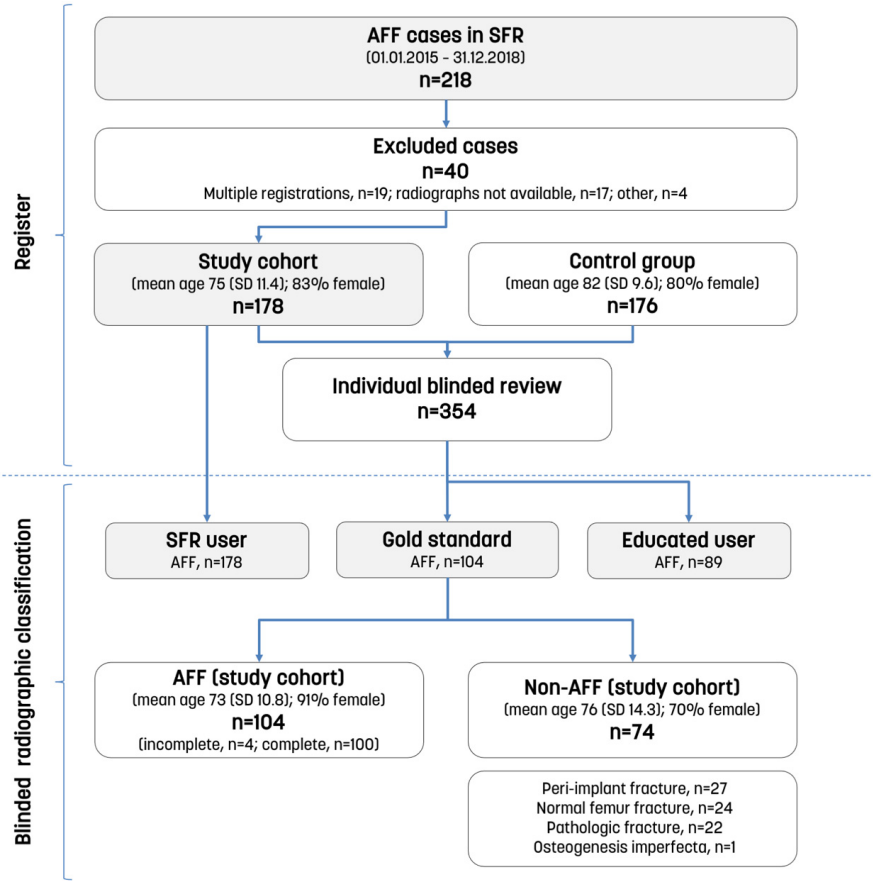
Methods and Results

We identified 218 registrations of AFFs in the SFR from 01.01.2015 until 31.12.2018. With the help of the personal identification numbers, we retrieved radiographs of the fractured femur from radiology departments throughout Sweden. We excluded 40 cases from further analysis: 19 cases due to multiple registrations in the SFR, 17 cases where adequate radiographs could not be retrieved, and four for other reasons. This resulted in a study cohort of 178 patients (83% women) with a mean age of 75 years (SD, 11.4 years). We established an age-matched control group with NFF by randomly searching data from our cohort from study 2. This yielded a control group of 176 patients (80% women) with NFFs, mean age, 82 years (SD, 9.6 years) (figure 4-1).

In the next step we reviewed all the radiographs individually, blinded to all background information. Fractures were classified in either AFFs or NFFs in accordance with the ASBMR case definitions (Shane et al., 2014). Fractures with radiographic features of AFFs but with exclusion criteria were marked separately (e.g. pre-existing implants, pathologic fractures, etc.).

The review was performed by two experienced researchers in the field of AFFs and a final year orthopaedic registrar who was given a brief introduction on AFFs in general and the ASBMR case definitions. The registrar acted as a representative of an average SFR user after a brief educational intervention. The classification of the two expert reviewers showed agreement for all but nine cases (interrater kappa of 0.93). In a video conference, these nine cases were then discussed and mutually agreed upon to form the *'gold standard classification'*. The classification of the final year orthopaedic registrar was named *'educated user classification'*. Finally, the third classification was named the *'SFR classification'* consisting of the actual registrations in the Swedish Fracture Register.

Figure 4-1: Flowchart showing the selection of radiographs and the results of the different radiographic reviews.



The *'gold standard classification'* yielded 104 AFFs, the *'educated user classification'* 89 patients, with an overlap of 83 cases resulting in an 'almost perfect' inter-observer agreement of 0.81 (Cohen's kappa coefficient) (Landis and Koch, 1977) and a positive predictive value of 0.80 for the *'educated user classification'*. The positive predictive value for the 'SFR classification' was 0.58 when compared to the *'gold standard classification'*.

The 74 cases that were not identified as AFFs by the *'gold standard classification'* comprised 27 peri-implant fractures, 24 normal femoral fractures and 23 pathologic fractures (of which one was a case of osteogenesis imperfecta).

Finally, we estimated the incidence of AFFs in the whole Swedish population for the year 2018. To calculate this estimate we used counties from the SFR that had good data completeness for the year 2018 (>80%, hip

fractures: Västra Götaland, Kalmar, Gävleborg, Dalarna, Blekinge, Uppsala, Värmland and Jämtland) as a surrogate for the entire Swedish population. We retrieved population at risk data (inhabitants and permanent residents, aged 55 years and older) from Statistics Sweden (https://www.scb.se). The estimated incidence for AFFs in the population of the above counties was 1.1.

To allow comparison with our nationwide cohort from 2008–2010 (studies 2, 3) we calculated the yearly incidences and the mean incidence for 2008–2010. The mean incidence of AFF in this cohort was 2.2 (table 4-1).

Table 4-1: Incidence (per 100.000 inhabitants) trends of AFFs over time.

	2008	2009	2010	Mean 2008–2010	2018
AFF rate	23	18	29	23	13
Population*	1 036 859	1 046 832	1 057 143	1 046 945	1 142 417
Incidence	2.2	1.7	2.7	2.2	1.1

*accrued inhabitants and permanent residents, aged 55 years and older in the counties Västra Götaland, Kalmar, Gävleborg, Dalarna, Blekinge, Uppsala, Värmland and Jämtland.

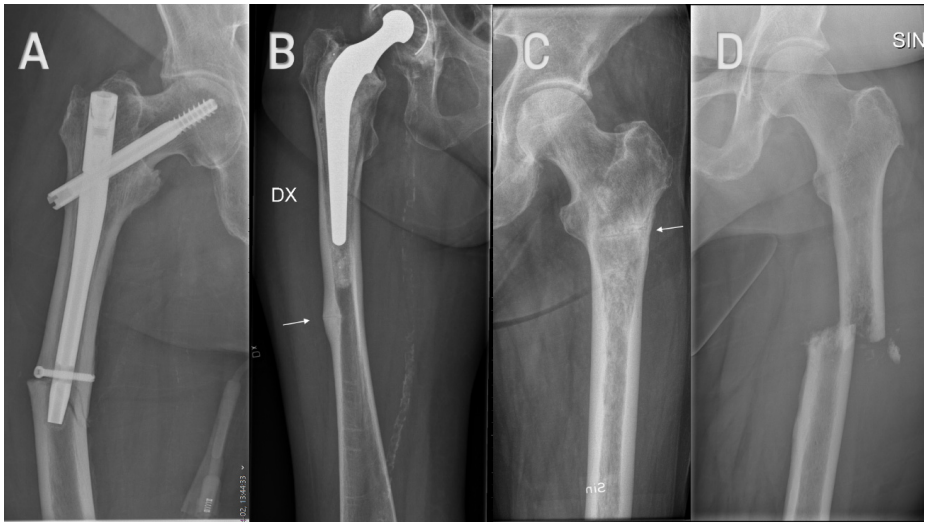
Discussion and Conclusions

Our *'gold standard classification'* identified 58% of the cases (104 of 178) in the SFR as true AFFs. This proportion appears low at first glance, when considering the appropriateness of the SFR as a surveillance tool for AFFs. However, compared to a detection rate of less than 5% on diagnostic radiographic reports (Harborne et al., 2016) and poor reporting to the Swedish Medical Products Agency's register for adverse drug reactions, the SFR represents an attractive alternative. Another advantage of the register is its ease of access as a web-based application with real-time data.

We observed a marked improvement in positive predictive values from 0.58 in the *'SFR classification'* to 0.80 in the *'educated user classification'* when using the *'gold standard classification'* as a reference, indicating a positive impact of our educational intervention. Even if it is not possible to draw any final conclusions from these preliminary data, it appears not unreasonable to believe that a limited educational intervention in the SFR may improve data quality. The majority of the physicians attending the

emergency departments are at junior level and are probably not familiar with the ASBMR case definitions for AFFs. The larger part of the cases erroneously classified as AFFs in the Swedish Fracture Register (68%) showed features of the exclusion criteria of the ASBMR case definitions for AFFs (i.e. pre-existing implants, pathologic fracture, etc.), but had a radiologic appearance not unlike AFFs (Figure 4-2). This proportion of erroneous registrations is likely to be reduced with an increased awareness of the exclusion criteria of the ASBMR case definitions.

Figure 4-2: Frequent erroneous registrations of AFF in the Swedish Fracture Register. (A) Peri-implant fracture, (B) incomplete AFF in the presence of pre-existing implants, e.g. total hip arthroplasty, (C) pathological fracture, metastasis of a prostate cancer and (D) pathological fracture due to myeloma. Each showing some of the ASBMR case definition features for AFF but fulfilling the exclusion criteria.



As a consequence of the above we introduced a brief educational video on AFFs in the Swedish Fracture Register in 2020 that can be viewed during the registration process (https://stratum.blob.core.windows.net/sfr/Movies/AtypFemureFract.mp4). Our hope is that this will improve the data accuracy in future.

Our estimate of the incidence AFFs in the Swedish Fracture Register is only half of the mean estimate of our historic cohort. Even if the estimates of our historic cohort appear robust, the true incidence of AFFs in Sweden in 2018 remains unknown. Therefore, it is somewhat speculative to extrapolate our historic estimates to 2018, particularly when considering the

long time span between the two cohorts. As prescription rates for bisphosphonates have dropped in recent years and a treatment duration of three to five years is more frequently followed by a drug holiday compared to before, the incidence of AFFs is likely to have dropped as well (Jha et al., 2015, Black et al., 2020).

In summary, the Swedish Fracture Register provides a solid basis for the surveillance of the rare fracture type of AFFs with easy access to its real-time data. The accuracy of its data on AFFs is likely to be improved markedly by providing more detailed information on the case definitions for AFFs during the registration process. If this can be confirmed in the future, the SFR represents an excellent database for future research on AFFs and surveillance of epidemiologic developments. To my knowledge, the SFR is the only nationwide register with 100% national coverage, providing an option for the registration of AFFs.

FUTURE IMPLICATIONS

The studies included in this thesis show that patients with atypical fractures have a good capacity to generate callus and therefore to heal fractures. The surgical treatment of AFFs is burdened with complications such as high reoperation rates. However, these reoperations are unlikely to be related to the nature of the fracture itself. It is more likely that background factors contribute to the high reoperation rates and that these factors have not previously been appropriately acknowledged and accounted for. Patient factors like age, gender, comorbidities, drug use and mortality, despite their impact on surgical outcomes, cannot be influenced. However, as shown in this thesis, the choice of implant has the potential to improve outcomes in this fragile patient population.

We are convinced that the choice of implant is a critical factor in minimising reoperation rates in elderly patients with femoral shaft fractures. In study 3, we saw a strong protective effect on reoperation risks when using femoral neck protecting nails. Using these nails, no subsequent ipsilateral hip fractures occurred. This effect of protecting against future fractures in the specific subgroup of patients with a femoral shaft fracture is much stronger than any other available fracture prophylaxis available today. To be able to make a correct choice, the biomechanical understanding of the fracture and its fixation is of paramount importance and warrants further investigation.

In order to inform treating surgeons about our findings, we cooperate with the Swedish Fracture Register (SFR). Implant choices can be influenced by multiple factors, such as local traditions, own experiences, economic factors such as limited storage capacities, and the sterility of the implants. Together with the SFR, we aim to study three projects: firstly, we want to evaluate the rationales behind surgeons' implant choices through using a web-based questionnaire integrated into the register; secondly, we aim to provide information on the current evidence on the benefits of femoral neck-protecting nails, and thirdly, we aim to evaluate trends in implant choices for femoral shaft fractures over time and the possible impact of this new information as provided by the register. Trends in implant choices can easily be followed in a continuous manner in the SFR due to its real-time data access, in a national perspective. Since the beginning of 2021, all Swedish hospitals taking care of fracture patients have joined the SFR, and its data shows good completeness and validity (Wennergren, 2019).

These future projects will hopefully provide important information about the factors that influence surgeons' implant choices in daily practice. The results may provide more customised information for surgeons and

health care providers. Through a longitudinal follow-up of implant frequencies, researchers and health care providers are enabled to follow trends over time.

The understanding of the biomechanics of the fracture and its fixation is crucial for successful outcomes with low reoperation rates. One interesting biomechanical aspect is the question about how strains are distributed in the femur upon different loading conditions and how the bone's morphology (i.e. osteoporosis) and orthopaedic implants such as intramedullary nails alter the strain distribution. With the results of study 3 in mind, it is not unreasonable to assume that strains in the area 'protected' by the implant are attenuated by means of stress shielding. At the same time, it is should be expected that excessive strains will occur in transition zones from bone surrounding the implant to genuine bone, leading to an increased fracture risk (Zhou et al., 2019). If that is the case, implants with the longest possible working length should prevent stress-risers occurring through a distribution of forces along the entire length of the bone (figure 5-1). Nails with an optimised working length, an individualised radius of curvature and the option for stable angle locking at either end of the nail might be valuable means to minimise the risk for subsequent peri-implant fracture. In order to achieve a better understanding of the implications of femoral strain distributions throughout the femur, we are currently planning two biomechanical studies to elucidate these important yet unanswered questions, in collaboration with implant makers.

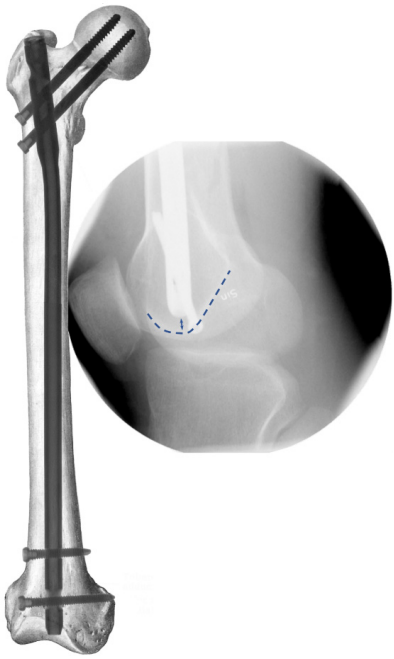
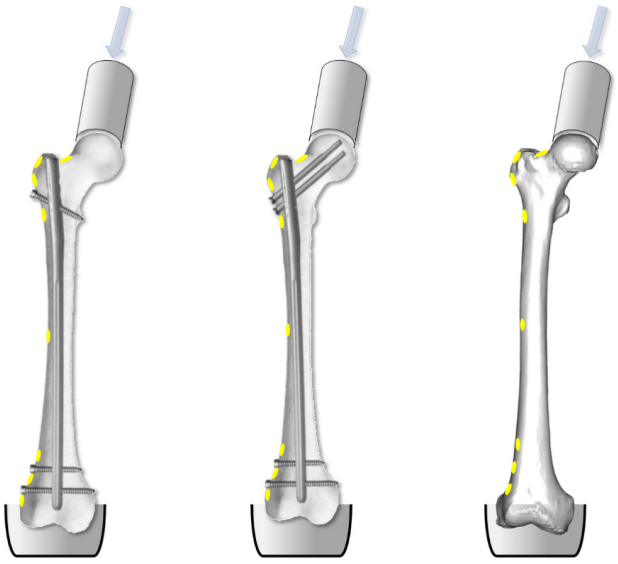


Figure 5-1: Reconstruction nail with optimised working length. Note the minimal distance between the tip of the nail and the tip of the Blumensaat line (marked in blue)

The first project involves mechanical testing of an osteoporotic bone model by measuring strain distributions at the lateral femoral cortex, where tensional forces dominate (figure 5-2).

Figure 5-2: Biomechanical testing of an osteoporotic bone model. From left to right: antegrade femoral nail with standard locking. The same nail but with locking into the femoral neck. A genuine bone model as a baseline reference.



As a second study design, we plan to use the technique of finite element analysis. This modelling approach is based on quantitative CT scans of full-length femur bones and known mechanical properties of the nail design, only differing in the mode of proximal locking. With predefined Young's modulus and Poisson's ratio and the mechanical axis defined from the centre of the femoral head to the centre of the femoral condyles, the stress distribution along the femur can be calculated by finite element modelling (Oh et al., 2017). This can identify zones of stress-risers and quantify strains after implantation of the two types of locking modes of intramedullary nails. The results might add important information that can help to explain our results from study 3. Also, additional evidence will be provided to support our advocation of the use of femoral neck protecting nails in the fixation of femoral shaft fractures in the elderly.

ETHICAL CONSIDERATIONS

All the studies involved large amounts of patient data from different Swedish registries. To identify patients and to allow comparisons of data from different registers, the unique Swedish Personal Identity Number issued by the Swedish Taxation Agency was used. This number was replaced with study numbers and all data were only handled by study personnel.

All imaging was stored on dedicated research Picture Archiving and Communication Systems (PACS).

All study protocols were reviewed and approved by the local ethical board with the following registration numbers:

- Study 1: DNR M14-09 and DNR 2011/358-31
- Study 2: DNR 2014/407-31 and DNR 2015/382-32
- Study 3: DNR 2014/407-31 and DNR 2015/382-32
- Study 4: DNR 2014/407-31 and DNR 2017/1-32

An ethical dilemma in register research

An AFF is a rare condition with a strong association to bisphosphonate use. Ideally, it should be diagnosed early, when the fracture is still in the incomplete stage, to avoid the propagation of the fracture to become complete with all its related risks. Deteriorated functional outcomes, increased and prolonged suffering for the patient and higher costs for health care providers and society are only a few drawbacks to mention when diagnosis is delayed. Incomplete AFFs generally have good outcomes when an appropriate treatment is initiated early. Health care providers should report AFFs to the Swedish Medical Products Agency's register for adverse drug reactions in cases with known anti-resorptive treatment (roughly 80% of the cases). This would allow governmental agencies, but also pharmaceutical companies to get a better picture of the frequencies and the extent of the drug-related adverse reaction to bisphosphonates. Unfortunately, AFFs are very rarely diagnosed in the early, incomplete stage, but most commonly when the fracture has become complete, and the patient is unable to ambulate.

During the review of thousands of radiographs in studies 2–4, we frequently came across cases where general practitioners had probably initiated radiographic investigations based on the patient's complaints. In our experienced eyes we could easily detect and reliably diagnose incomplete AFFs despite the lack of background data (i.e. medication) on these patients. Very sadly, these diagnoses were frequently missed by the examining radiologist, and reports leaving the radiological findings unreported

were returned to the referring physician. As a result, appropriate action to prevent a complete fracture could not be taken.

We identified in total more than 250 AFFs in our two cohorts. These were patients that had been exposed to a rare but yet such significant condition that is very likely related to the use of anti-resorptive drugs. With the risk of propagation in cases of incomplete AFFs, but also the risk of a contralateral engagement in all cases, it appeared reasonable to contact the patients and inform them about our important findings. Unfortunately, this was not possible due to data protection regulations in Sweden. Neither are we allowed to report our findings as adverse drug reactions to the Swedish Medical Products Agency for the same reasons. Our findings pose a significant yet unsolved ethical dilemma for us as researchers and physicians.

ACKNOWLEDGEMENTS

This thesis would of course never have been written if certain people had not blessed me with their unconditional support during this journey in science.

It all began with a common social discussion at a breakfast table in May 2016 at Säröhus in Särö where my primary supervisor Jörg Schilcher 'infected' me with the proposition of getting involved in orthopaedic research. Jörg is one those persons that I look at with a hint of envy and admiration. As assistant professor in orthopaedics, he is one of the most dedicated researchers I have met and at the same time a skilled surgeon who never loses sight of the patient's best interests. A very rare and yet so admirable combination! I am sure his days last longer than 24 hours. Ever since this lovely breakfast in Särö with the archipelago of the Swedish west coast in sight, he has been an endless source of inspiration and consideration. He really taught me that there are no boundaries; the only limit is the sky. I am certain that the countless stimulating hours of discussing interesting aspects of orthopaedics and beyond will continue in the future. I am looking forward to that!

Per Aspenberg, late professor in orthopaedics from Linköping had a unique ability to stimulate critical thinking. His charismatic personality and his ingeniousness with a touch of artistry really made me curious and were instrumental in my decision to take on a postgraduate education that led to this thesis. I am deeply grateful for the short time Per acted as my assistant supervisor until he sadly passed away in 2018. His critical voice is badly missed in the orthopaedic community.

Gösta Ullmark, associate professor and valued colleague at my home base at Gävle hospital. Gösta acted from the beginning as a local senior mentor, always open to any questions and a great person with which to discuss practical aspects of both research and clinical matters. His pragmatic ways of problem-solving are unique.

Anna Fahlgren, professor at the department of biomedical and clinical sciences at Linköping University took me on as an initial main supervisor until the autumn of 2017 while Jörg was waiting for his paperwork to become associate professor. Since then, Anna has stood by my side as my assistant supervisor.

Then there is this long list of people that contributed significantly to this thesis. First off is Georg Zdolsek, his inexhaustible endeavours in collecting, recovering and analysing radiographs contributed greatly to papers

2-4. Thanks go to Lukas Barnisin a colleague from Västra Götaland for his help in collecting and analysing data in paper 4. I thank Professor Karl Michaëlsson and Jonas Höijer from Uppsala University for opening doors in the maze of statistics and epidemiology.

Special thanks go to Gösta Ullmark and Daphne Wezenberg for proofreading this thesis and improving it with input derived from years of experience in academic publishing and orthopaedic research. Furthermore, I give deepest thanks to my wife Karin for her linguistic input when proofreading. Pure scientific facts were boring if there was not a note of word artistry involved. I owe my daughter Lene for her help with the graphics, it is impressive what can be done on an iPad. Thanks again, much appreciated!

Finally yet importantly, I thank all staff at Linköping University involved in the postgraduate PhD programme. You have all opened my eyes to a new world called science! A special mention goes to Annelie Lindström, director of postgraduate studies at the medical faculty at Linköping University. Annelie was an invaluable resource during my studies. Her friendliness and courteous manner when answering questions always eradicated any doubts in a blink of an eye. Many thanks for that; you certainly made my student life even more enjoyable!

Moreover, not to forget CFUG, the Centre for Research and Development, Uppsala University / Gävleborg Region not only for providing generous financial support, but also for a great time writing on its premises. Thanks also go to the head of my orthopaedic department, Anette Lund, for letting me take on this journey into unknown territory, despite the fact that I was needed at the unit as well. I think we found a good compromise that worked well for all of us.

Many thanks go to my fellow doctoral students at CFUG for great scientific and diversional discussions over a coffee break or a lunch. I really enjoyed these hours of dedication and compassion!

I dare not to forget my dear colleagues and adjunctive staff at the orthopaedic department at Gävle hospital. I feel a little bit sorry for being away trying to get my heads around orthopaedic research and them having to compensate for it. But only a very little bit :-), you are a great bunch of people!

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SUPPLEMENTARY MATERIAL

ASBMR Task Force 2013 Revised Case Definitions of Atypical Femoral Fractures

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.

Major features*

- The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
- The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
- The fracture is non-comminuted or minimally comminuted
- Localised periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

Minor features

- Generalised increase in cortical thickness of the femoral diaphysis
- Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral incomplete or complete femoral diaphysis fractures
- Delayed fracture healing

*Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumours and miscellaneous bone diseases (e.g., Paget's disease, fibrous dysplasia) (Shane et al., 2014).

Papers

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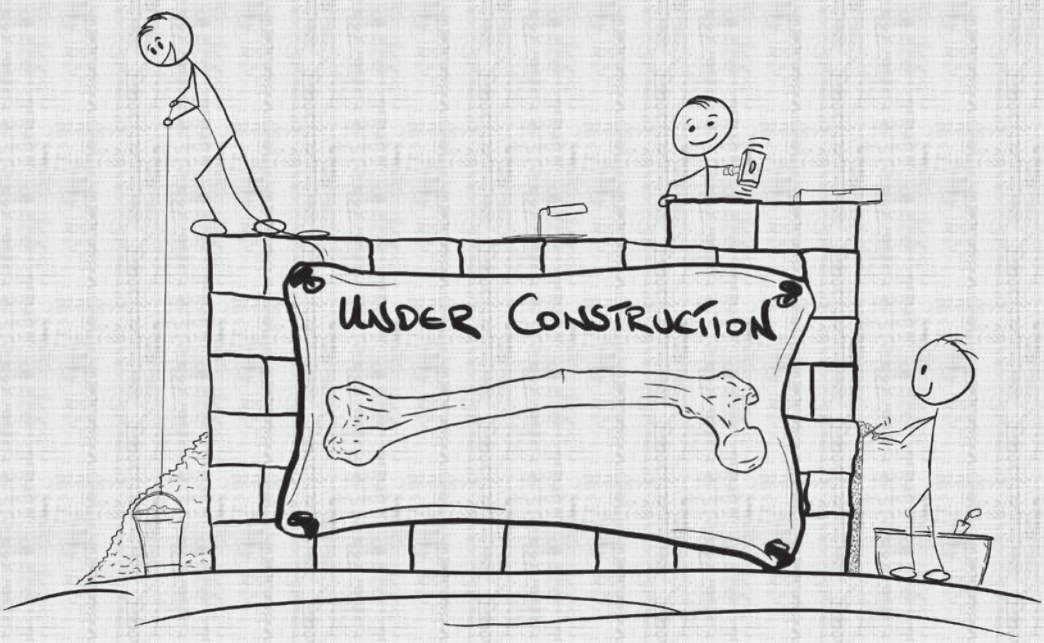

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