

Intramedullary nails in the treatment of trochanteric and subtrochanteric fractures

Kirsten Marie Larsen Grønhaug

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN



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Scientific environment

This PhD project has been a collaboration between the Department of Orthopaedic Surgery, Østfold Hospital Trust and the Norwegian Hip Fracture Register.

After completing my training as an orthopaedic surgeon, I was offered a position as consultant surgeon at Østfold Hospital trust, to work in the field of orthopaedic trauma surgery. After a few years of 100% clinical work my colleague Bengt Østman included me in a research project on the timing of hip hemiarthroplasty and the influence on prosthetic joint infection in collaboration with Sahlgrenska University Hospital in Gothenburg and McMaster University in Canada. After this exciting introduction to the world of orthopaedic research, he asked me to be first author in a study on subsequent femoral fractures after intramedullary nailing. This study became Paper I of my thesis and while working on the study we established contact with Jan-Erik Gjertsen at the Norwegian Hip Fracture Register (NHFR). Together we quickly agreed on two additional studies regarding the use of intramedullary nails in the treatment of trochanteric and subtrochanteric fractures. Research on intramedullary nailing was a well-tailored match with our department's treatment policy of hip fractures over the past two decades. I was accepted as a PhD candidate at the University in Bergen in 2019, with Jan-Erik Gjertsen, head of NFHR and Professor at Department of Clinical Medicine, University of Bergen as main supervisor and Bengt Østman, senior consultant and head of research at the Department of Orthopaedic surgery, Østfold Hospital Trust as co-supervisor. The Department of Research at Østfold Hospital trust lead by professor Whaleed Ghanima, has funded 20% of my position at the Department of Orthopaedics from 2019 – 2023 to complete the PhD.



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“Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won't come in.”

Alan Alda

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I would like to thank my colleague, friend and co-supervisor Dr. Bengt Østman for believing in me as a competent orthopaedic surgeon and researcher, particularly during the times I did not. I have learned so much during the surgery we have performed together and through the scientific work he has included me in. I admire his ability to stay true to method, inspire and teach. I have been allowed to ask the most basic questions and still been met with patience, understanding and brilliant answers. I would not have embarked on my journey towards a PhD had it not been for him.

My main supervisor Dr. Jan-Erik Gjertsen deserves ovations. He has, in spite of all his responsibilities as head of the NHFR, an active clinician and the father of two children, answered all my questions and reviewed every single manuscript draft swiftly and conscientiously be it day or night, working hours or holiday. Despite his experience and vast publication list, he is always patient, down to earth and welcoming. I deeply admire him, as a researcher, clinician, supervisor and person.

I also want to thank Mrs Eva Dybvik, statistician at the NHFR, who has been a patient and understanding teacher and co-author. She has guided me through the incomprehensible jungle of statistics and rescued me every time my very limited competence in computer science was about to put an end to the whole project.

Dr. Kjell Matre, director of the Department of Orthopaedic Surgery at Haukeland University Hospital has been a great inspiration and help, as he conducted analyses similar to those in Paper II in his own PhD. He always keeps the big picture in mind and has on several occasions pointed our research group in the right direction when we were preoccupied by less important details.

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Dr. Asbjørn Sorteberg, head of Department of Orthopaedic Surgery at Østfold Hospital Trust, and Dr. Anders Lippert, Head of Division for Orthopaedic Trauma have given

me time and opportunity to work on this PhD alongside my clinical work. They have respected and protected my research time. They have supported and encouraged me and my fellow PhD candidates in our work, and at the same time allowed me to thrive and develop as an orthopaedic surgeon in my preferred field, orthopaedic trauma surgery.

I also want to thank my wonderful colleagues, past and present, home and abroad, for their friendship and inspiration.

Dr. Waleed Ghanima, professor and Head of Department of Research has enthusiastically supported the evolvement of an orthopaedic research community at our clinic. His department has provided me with 20% research time and economical support in the process of publishing the articles in this PhD.

I will, in my career as in all aspects of life, be grateful to my parents Søren and Elisabeth for their infinite love, support, patience and belief in me. They have inspired me throughout my life, and I still turn to them for comfort, help, enthusiastic discussions and confirmation.

Last, but not least, I want to thank my husband Gudmund. He has given me confidence, happiness, love and our wonderful children, Jakob and Pavel who welcomed me into their lives when we became a family and Pia and Kari, the new amazing arrivals to complete it. Gudmund has supported and inspired me through this PhD as he has through every day of our life together.

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Papers I-III

List of abbreviations

AAOS	American Association of Orthopaedic Surgeons
ADL	Activities of Daily Living
ANOVA	ANalysis Of VAriance
AO/ASIF	Arbeitsgemeinschaft für Osteosynthesefragen / Association for Study of Internal Fixation
AO/OTA	Arbeitsgemeinschaft für Osteosynthesefragen / American Orthopaedic Trauma Association
ASA	American Society of Anesthesiologists
BMD	Bone Mineral Density
BMI	Body Mass Index
calTAD	calcar referenced Tip Apex Distance
CFS	Clinical Frailty Scale
CHS	Compression Hip Screw
CI	Confidence Interval
COS	Core Outcome Set
DFD	Danish Fracture Database
DHS	Dynamic Hip Screw
DMHFR	Danish Multidisciplinary Hip Fracture Register
EBM	Evidence Based Medicine
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version

EWGSOP	European Working Group on Sarcopenia in Older Persons
FLS	Fracture Liaison Services
HRR	Hazard Rate Ratio
HRQL	Health Related Quality of Life
IAFF	Infection After Fracture Fixation
ICD-10	International statistical Classification of Diseases and related health problems
IMN	Intramedullary Nail
IOF	International Osteoporosis Foundation
IQR	InterQuartile Range
MCID	Minimal Clinically Important Difference
mFI	modified Frailty Index
MRI	Magnetic Resonance Imaging
NAR	Norwegian Arthroplasty Register
NHFR	Norwegian Hip Fracture Register
NICE	National Institute for Health and Care Excellence
NCSP	NOMESKO Classification of Surgical Procedures
OHS	Oxford Hip Score
OR	Odds Ratio
PJI	Prosthetic Joint Infection
PROM	Patient Reported Outcome Measures

SD	Standard Deviation
SFR	Swedish Fracture Register
SHS	Sliding Hip Screw
Sffx	Subsequent femoral fracture
SSI	Surgical Site Infection
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TAD	Tip Apex Distance
TSP	Trochanteric Support Plate
RCT	Randomised Controlled Trial
VAS	Visual Analogue Scale
WHO	World Health Organisation

List of publications

Paper I

Grønhaug KML, Dybvik E, Gjertsen JE, Samuelsson K, Östman B. Subsequent ipsi- and contralateral femoral fractures after intramedullary nailing of a trochanteric or subtrochanteric fracture: a cohort study on 2012 patients.

BMC Musculoskelet Disord. 2022 Apr 28;23(1):399.

Paper II

Grønhaug KML, Dybvik E, Matre K, Östman B, Gjertsen JE.

Intramedullary nail versus sliding hip screw for stable and unstable trochanteric and subtrochanteric fractures: 17,341 patients from the Norwegian Hip Fracture Register.

Bone Joint J. 2022;104-B(2):274-282.

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Paper III

Grønhaug KML, Dybvik E, Matre K, Östman B, Gjertsen JE. Comparison of intramedullary nails in the treatment of trochanteric and subtrochanteric fractures. An observational study of 13,363 fractures in the Norwegian Hip Fracture Register.

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Summary in English

A hip fracture is a serious event in the geriatric patient, causing considerable morbidity and increased mortality. Choice of implant in the surgical treatment of trochanteric and subtrochanteric fractures has been debated for decades. The aim of this research project was to describe the impact of an intramedullary nail (IMN) in the event of a subsequent femoral fracture (Sffx), conduct an updated comparison of the sliding hip screw (SHS) and the IMN in stable versus unstable trochanteric and subtrochanteric fractures in Norway and compare the outcomes of different IMN designs.

In Paper I we investigated how an IMN affects the incidence, pattern and localisation of Sffxs in patients treated for a trochanteric or subtrochanteric fracture, without implants or sequelae after previous surgery in either femur. We conducted a retrospective cohort study of 2,012 patients treated at Østfold Hospital trust, all with documented native femora prior to the index fracture. All subsequent fractures were registered. Patients reaching any endpoint (Sffx, other complication requiring surgery, non-fracture related surgery, death) were censored. The total incidence of a Sffx was five times lower on the ipsilateral than the contralateral side following surgery with an IMN, and there was a tenfold increase in the risk of ipsilateral femoral shaft and distal metaphyseal fractures compared to fractures of the shaft and distal metaphysis in the contralateral side. We concluded that an IMN significantly changes the distribution of a Sffx, protecting the proximal femur but increasing the risk of a fracture distal to the implant.

In Paper II we compared the outcomes of SHS and IMN with emphasis on index fracture stability in a prospective cohort study using data from the Norwegian Hip Fracture Register (NHFR), including 17,341 patients treated with a SHS or an IMN from 2013-2019. Primary outcome measure was reoperations in patients treated with an SHS or an IMN in stable versus unstable fractures, and secondary outcome measures were reoperations for individual fracture types, mortality and patient related outcome measures (PROMs) for stable versus unstable fractures. We detected a lower reoperation rate for IMN compared to SHS in unstable fractures, and no difference in

reoperation rate for stable fractures. When analysing individual fracture types there were minimal differences. Mortality was lower one year postoperatively in the group treated with an IMN in stable and unstable fractures alike. PROM data were incomplete, but we found a significant difference in EQ-5D-3L index score, mobility, pain and satisfaction one year postoperatively in favour of the IMN in unstable fractures.

In Paper III we compared reoperation rates for the different brands of IMNs in common use in Norway. We conducted a prospective cohort study including all trochanteric and subtrochanteric fractures treated with an IMN in general use over the past ten years and registered in the NHFR from 2007-2019, identifying 8,283 short nails and 4,949 long nails. Short and long nails were analysed separately. Primary outcome measure was reoperation rate for each brand of short and long nails for all fractures combined, and secondary outcome measure was reoperation rate for the different IMN brands regarding individual fracture types. We discovered similar reoperation rates for the different types of short nails, and a higher reoperation rate for the TRIGEN TAN/FAN in all fractures combined and in AO/OTA A1, A2, and subtrochanteric fractures in subanalyses of individual fracture types.

The results of this thesis support the current international and national guidelines recommending the use of an IMN in the treatment of unstable trochanteric and subtrochanteric fractures. Peri-implant fractures are however, still a challenge, and the presence of an IMN significantly changes the distribution of a subsequent fracture. We have identified significant differences in reoperation rate between different brands of long IMNs, emphasizing the value of registers in the surveillance of performance and outcomes of implants used in the treatment of trochanteric and subtrochanteric fractures.

Summary in Norwegian

Et hoftebrudd er en alvorlig og potensielt dødelig hendelse for et eldre, skrøpelig individ. Et slikt brudd fører svært ofte til økt hjelpebehov, varig nedsatt funksjon og overdødelighet. Valg av implantat i behandlingen av trokantære og subtrokantære brudd har vært diskutert over flere tiår. Målet med dette prosjektet var å beskrive hvordan en intramedullær nagle påvirker lokalisasjon og morfologi ved et nytt brudd i lårben, å gjennomføre en oppdatert sammenlikning av glideskrue og intramedullær nagle i behandlingen av henholdsvis stabile og ustabile trokantære og subtrokantære brudd, samt sammenlikne de ulike intramedullære naglene i utstrakt bruk i Norge.

I Artikkel I har vi undersøkt hvordan en intramedullær nagle påvirker forekomst, lokalisasjon og bruddmønster ved et nytt brudd hos pasienter behandlet for et trokantært eller subtrokantært brudd, uten tidligere implantat eller følgetilstand etter brudd i hverken motsatt eller samme lårben. Vi gjennomførte en retrospektiv kohortstude av 2012 pasienter behandlet ved Sykehuset Østfold, alle med dokumentert friske lårben før det første bruddet inntraff. Alle påfølgende brudd ble registrert. Pasienter som nådde et av følgende endepunkter: påfølgende lårbensbrudd, annen komplikasjon som ledet til reoperasjon, ikke bruddrelatert operasjon i et av lårbena eller død, ble fortløpende sensurert. Den samlede forekomsten av påfølgende brudd i et av lårbena var fem ganger lavere på samme side sammenliknet med motsatt side, mens det var ti ganger så høy forekomst av brudd i skaft og distale metafyse på samme side som implantatet sammenliknet med brudd i skaft og distale metafyse. Vår konklusjon var at en intramedullær nagle påvirker fordelingen av et påfølgende brudd i lårben i betydelig grad. Naglen ser ut til å beskytte mot brudd i øvre del av lårbenet, men øker risikoen for et brudd distalt for implantatet.

I Artikkel II har vi gjennomført en prospektiv kohortstudie der vi sammenliknet utfall av behandling med glideskrue og intramedullær nagle for trokantære og subtrokantære brudd, med tanke på bruddets stabilitet. Utvalget er hentet fra Nasjonalt Hoftebruddregister (NHBR). Vi inkluderte 17 341 pasienter behandlet med glideskrue eller intramedullær nagle og registrert i NHBR i tidsrommet 2013-2019. Det primære

utfallsmålet var reoperasjon etter behandling med glideskrue versus intramedullær nagle ved henholdsvis stabile og ustabile brudd. Sekundære utfallsmål var reoperasjon ved individuelle bruddtyper, mortalitet og pasientrapporterte utfall ved henholdsvis stabile og ustabile brudd. Vi fant lavere reoperasjonsrate ved bruk av intramedullær nagle enn glideskrue for ustabile brudd, og ingen forskjell i reoperasjonsrate for de to ulike implantatene for stabile brudd. Subanalyser av individuelle bruddtyper viste minimale forskjeller. Dødelighet ett år postoperativt var lavere i gruppen behandlet med intramedullær nagle, gjeldende for både stabile og ustabile brudd. Pasientrapporterte data var manglefulle, men vi fant signifikante forskjeller i EQ-5D-3L-indeks, smerte og tilfredshet ett år postoperativt i favør av behandling med intramedullær nagle.

I Artikkel III sammenliknet vi reoperasjonsrate for de ulike typene intramedullære nagler i utstrakt bruk i Norge. Vi gjennomførte en prospektiv kohortstudie der vi inkluderte alle trokantære og subtrokantære brudd behandlet med nagler brukt jevnlig de siste ti år og registrert i NHBR i tidsrommet 2007-2019, totalt 8283 korte nagler og 4949 lange nagler. Korte og lange nagler ble analysert hver for seg. Primært utfallsmål var reoperasjonsrate for de enkelte typer korte og lange nagler for alle bruddtyper samlet, og sekundært utfallsmål var reoperasjonsrate for de ulike korte og lange naglene for hver enkelt bruddtype. Vi fant sammenliknbare resultater for de ulike typene korte nagler, og høyere reoperasjonsrate for TRIGEN TAN/FAN både for alle brudd samlet og for AO/OTA A1, A2 og subtrokantære brudd ved subanalyser på ulike bruddtyper.

Resultatene i dette prosjektet støtter de gjeldende internasjonale og nasjonale retningslinjer, der en intramedullær nagle anbefales i behandlingen av trokantære og subtrokantære brudd. Implantatnære brudd er fremdeles en utfordring, og vi har funnet at en intramedullær nagle påvirker fordelingen av et påfølgende lårbensbrudd i betydelig grad. Vi har identifisert signifikante forskjeller i reoperasjonsrate ved bruk av ulike typer lange intramedullære nagler, noe som understreker verdien av registre for å overvåke implantater i bruk ved behandling av trokantære og subtrokantære brudd.

1 Introduction and background

1.1 Epidemiology of hip fractures and importance of topic

Hip fractures represent a major challenge on an individual as well as a socioeconomical level. North America and Europe, particularly the Scandinavian countries, have the highest incidence of hip fractures¹. Today, approximately 9,000 hip fractures are treated in Norwegian hospitals each year², and with an ageing population the prevalence is likely to increase, nationally and internationally³. There has been a slight decline in age-specific incidence rates of hip fractures in the Western countries, including Norway⁴⁻⁶, possibly due to improved treatment of osteoporosis and vitamin D deficiency, better general health and physical status, as illustrated in Figure 1. However, the increased life expectancy of a growing population counteracts the effect on the total number of fractures^{3,7,8}. The Global Burden of Disease project has estimated an increase in years lived with disability due to a hip fracture of 62% between 1999 and 2019⁷. Approximately 18% of women and 6% of men will experience a hip fracture during their life span^{9,10}. The one-year mortality rate is reported up to 25%⁹, the risk of a subsequent femoral fracture up to 14%¹¹⁻¹³, and 50% of patients never return to their previous level of mobility^{14,15}. The typical hip fracture patient is female, of advanced age and frail. Literature suggests that patients with a fragility fracture in the trochanteric area are even older, less mobile, and have more comorbidities than patients with a femoral neck fracture¹⁴.

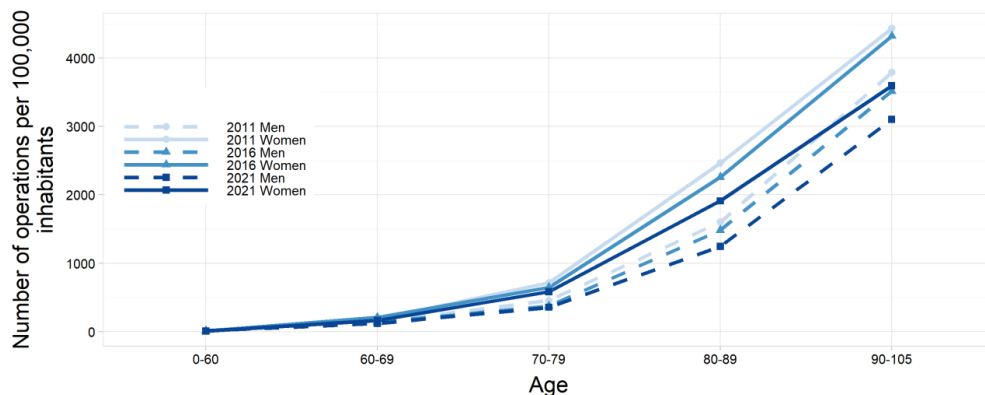


Figure 1: Incidence of hip fractures. Courtesy of Norwegian Hip Fracture Register (NHFR)
(Reprinted with permission)

There is wide consensus concerning multidisciplinary approach to optimize treatment of hip fracture patients¹⁶⁻²⁰. Still, debates concerning surgical techniques and implants in the treatment of different types of hip fractures remain, and the treatment of hip fractures vary greatly both nationally and internationally²¹⁻³⁰. The scope of this PhD is to investigate intramedullary nails in modern surgical treatment of trochanteric and subtrochanteric fractures.

1.1.1 Index fractures

Risk factors for the index fragility fracture of the hip are well described in the available literature. Increasing age, female sex, institutionalization, osteoporosis, and increased fall tendency (due to cognitive impairment, frailty, sensorimotor, and sight disorders, multipharmacy) all increase the risk of an index hip fracture³¹. The vulnerable hip fracture patients run a great risk of adverse outcome following their hip fractures, particularly patients in nursing homes, suffering from severe osteoporosis, cognitive impairment, and sarcopenia³²⁻³⁶. Mortality is generally high in the geriatric population sustaining a hip fracture, but there is a significant excess post-fracture mortality of hip fracture patients compared to peers without hip fractures - attributable to the fracture itself and pre-fracture comorbidity³⁷⁻⁴⁰. A higher category of frailty, defined as the

reduced physiologic capacity of geriatric patients to react to acute stressors such as a hip fracture and measured using the clinical frailty scale (CFS)⁴¹ and the modified frailty index (mFI)⁴², leads to significantly increased mortality. This also applies to pre-fracture institutionalization, diagnosed dementia and delirium, malnutrition, sarcopenia and time to surgery beyond 24-48 hrs that are all independent risk factors for increased mortality and all related to other adverse outcomes of hip fracture surgery^{35,43-47}. Kjærviik et al. recently published results from a large population-based and linked multiregister study concluding that patient and socioeconomic risk factors (non-modifiable factors) had a stronger association with mortality than healthcare-related (modifiable) risk factors⁴⁴.

1.1.2 Subsequent fractures

A patient surviving an index fragility fracture of the hip runs a substantially increased risk of a subsequent femoral fracture, estimated to be up to 14%^{11,13,48,49}. To some extent, risk factors for the second fracture differ from the more investigated risk factors of the index fracture mentioned above, as these patients must be able to survive the stress of an initial hip fracture to be at risk for a subsequent femoral fracture. The Funen County Hip Fracture Study with a follow up of minimum 12 months reported that 50% of Sffxs occurred within the first year, and after 12 months for men and 19 months for women the fracture risk diminished to levels similar to the index hip fracture⁵⁰. The Framingham study, with a substantially longer follow up time of mean 4.2 years and extending to 51 years, found that only 2.5% of Sffxs occurred the first 12 months. A similar discrepancy compared to the Funen County Hip Fracture Study was found in a study based on data from the Danish Multidisciplinary Hip Fracture Register (DMHFR)⁵¹. The one-year mortality has been found to be significantly higher after a Sffx compared to an index femoral fracture, even when adjusting for baseline characteristics¹². In the Framingham study, weight loss and poor perceived health were associated with a Sffx, while estrogen use, physical activity, and normal visual acuity were protective factors¹¹. The majority of the Sffxs occur in the contralateral femur⁵². Previous studies have not specified the presence or absence of other implants or

sequelae in either femur prior to the index fracture, possibly affecting the risk and the pattern of contra- or ipsilateral Sffx. Bone Mineral Density (BMD) at the time of the primary fracture may not indicate who are at risk of a Sffx⁵³. Bone loss after the first hip fracture may have a greater impact, as a rate of loss of 3–7% per year in the contralateral hip has been described^{54,55}, substantially higher than the general age-related bone loss of approximately 1% per year⁵⁶.

1.1.3 Prevention of hip fractures

The main focus of research in the field of orthopaedic surgery has historically been modes of treatment, as reflected in studies regarding hip fractures as well. Although optimized treatment and follow up can improve outcomes after hip fracture surgery, 50% of these fragile patients will never return to their previous mobility, and frequently demand a higher level of care^{14,15}. Initial treatment, postoperative in-hospital and community care, as well as treatment of complications present a major socioeconomic burden. Given the increasing incidence of hip fractures due to an ageing population, primary prevention has a much greater impact than any optimization of treatment. As described above, the risk factors for hip fractures in the elderly are well documented^{1,57}. The primary and secondary prevention of fragility fractures primarily by treating osteoporosis and reducing the risk of falls are of key importance to the current and future epidemiology of hip fracture⁵⁸.

Low bone density doubles the risk of a hip fracture³¹. In Norway, 240,000-300,000 individuals have BMD lower than the threshold of osteoporosis⁵⁹. Several factors affect BMD. Some are non-amenable, like sex and age. Amenable risk factors are low Body Mass Index (BMI), inactivity, smoking, vitamin D-deficiency and long-term cortisone treatment^{60,61}, and low-threshold interventions may reduce the suffering and cost associated with fragility hip fractures considerably.

Several Randomized Controlled Trials (RCTs) as well as register- and population-based studies have reported a cost-effective, significant risk reduction of hip fractures

in postmenopausal women with the use of bisphosphonates⁶²⁻⁶⁴. Nevertheless, rates of testing, diagnosis and treatment among postmenopausal women are low.

The prevention of falls is an obvious measure to reduce hip fracture risk. In a Norwegian population > 75 years old, 50% of women reported that they had fallen once or more the past year, and 13% of the falls had resulted in a fracture⁶⁵. In a WHO report, 30% of people > 65 years of age have one or more falls each year⁶⁶. The National Institute for Health and Care Excellence (NICE) guidelines present a detailed multifactorial risk assessment including identification of falls history, assessment of gait, balance, mobility, sarcopenia, perceived functional ability, visual impairment, urinary incontinence, home hazards, cardiovascular history and medication. Based on the risk assessment, an individualized multifactorial intervention is recommended, including strength and balance training, home hazard intervention, vision correction and modification/withdrawal of medication. These measures require long term involvement of healthcare professionals, information and flexibility in implementation and execution of the programmes⁵⁸. The effect of fall prevention measures has proven difficult to detect. High quality evidence indicates that exercise programs and modifications in the homes of frail elderly persons effectively reduces falls, whereas the quality of evidence supporting vitamin D supplementation, gait-stabilizing devices and psychotropic medication withdrawal is low^{58,66}. External hip protectors have shown a significant reduction in hip fractures⁶⁷⁻⁶⁹. A Cochrane review from 2014 concludes with moderate evidence of effect, but emphasize that long term acceptance and adherence is poor, affecting the results of the included trials⁷⁰.

A prior fragility fracture doubles a patient's future fracture risk^{13,71}. A low energy hip fracture may indicate osteoporosis and several guidelines recommend initiation of bisphosphonate treatment.^{58,72-74} There is evidence of cost-effective treatment with bisphosphonates in women between 65 and 80 years of age with a fragility fracture, whereas this treatment in men and the youngest and oldest female hip fracture patients can be debated⁷⁵. The impact of other explanatory factors than BMD, such as age and impaired balance may be underestimated⁷⁵ To prevent a subsequent hip fracture, multi-national evidence-based models of post fracture care have been suggested⁷⁶. In 2012,

the International Osteoporosis Foundation (IOF) launched the Capture the Fracture Campaign in order to reduce the incidence of subsequent fragility fractures worldwide. To achieve this goal Fracture Liaison Services (FLS) were introduced, and have been successfully implemented in several countries⁷². The core objectives of an FLS are case identification, risk stratification, initiation of treatment in accordance with guidelines and improvement of long-term adherence with therapy⁷². The general measures to prevent fractures are amenable to the subsequent fractures as well. Additionally the accelerated bone loss in the contralateral hip after an initial hip fracture may be prevented by exercise programmes⁷⁷. Although limited, there is also evidence supporting supplementation of vitamin D and dietary protein to prevent subsequent fractures after the index hip fracture. In conclusion, multiple interventions are required, possibly life-long, to reduce the risk of a subsequent hip fracture.

1.2 Classification and stability assessment

1.2.1 Classification of hip fractures

An ideal classification system should be simple, valid, reliable and reproducible. It should indicate stability and dislocating forces at play and provide information regarding the risk and nature of complications. Furthermore, a classification system should communicate the pattern of injury and allow identification and comparison of similar fractures across borders, to facilitate research and the development of treatment guidelines.

Hip fractures can be coarsely divided into neck fractures, trochanteric fractures and subtrochanteric fractures based on anatomical site. Fractures of the head of the femur are considered a different entity, as it is usually seen in younger individuals suffering high energy trauma and rarely occur as a fragility fracture without prior avascular necrosis or other localized pathology⁷⁸.

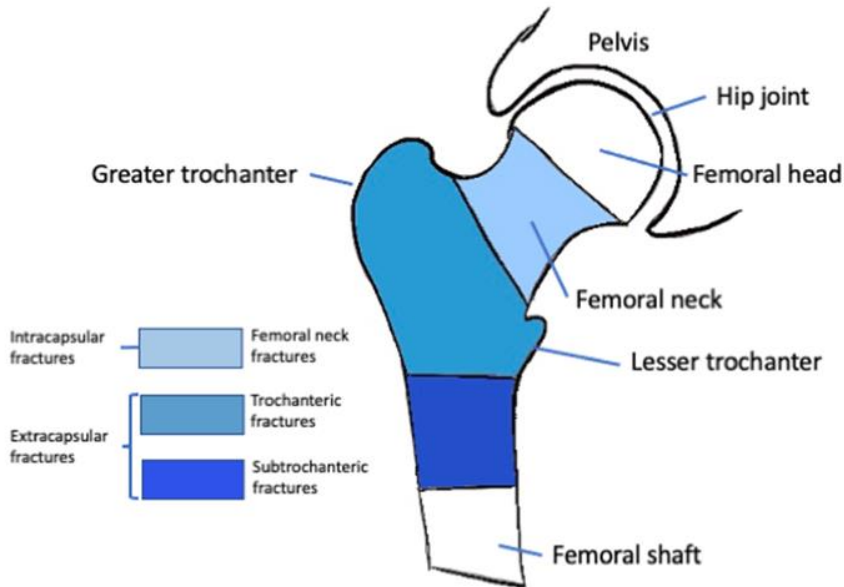


Figure 2: Classification of hip fractures. Courtesy of Eva Dybvik. (Reprinted with permission)

Fractures in the femoral neck are divided into intracapsular (medial) and extracapsular (basocervical fractures (Figure 2), decisive to choice of treatment. Intracapsular fractures are commonly classified according to Garden, originally describing severity of dislocation in the coronal plane (Figure 3). The reliability of the classification improves when the Garden classification is simplified, using the terms: 'non-displaced' (Garden I and II) or 'displaced' (Garden III and IV)^{79,80}. Other classification systems have been introduced (Pauwel⁸¹, Arbeitsgemeinschaft für Osteosynthesefragen / American Orthopaedic Trauma Association (AO/OTA)⁸²) but the simplified Garden classification with the addition of dislocation assessment in the transverse plane appears reliable for practical purposes^{79,83}. Posterior tilt is an independent risk factor of failure in Garden I and II fractures and studies indicate Garden I and II fractures with posterior tilt > 20 degrees should be considered displaced⁸⁴⁻⁸⁷.

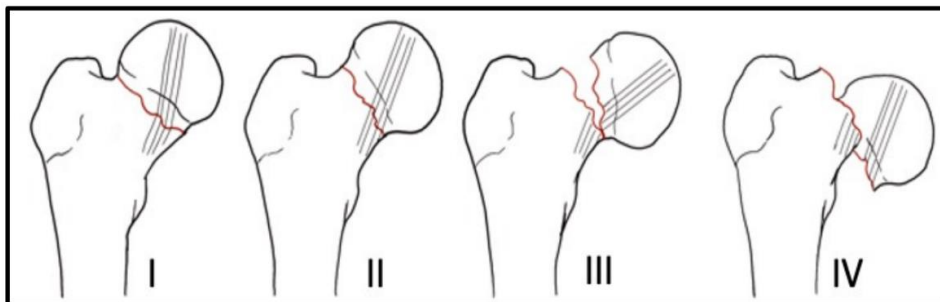


Figure 3: Garden classification of femoral neck fractures. Courtesy of Cato Kjærвик (Reprinted with permission)

Trochanteric fractures occur between the lateral border of the femoral neck and the inferior border of the minor trochanter. Several classification systems describing trochanteric and subtrochanteric fractures have been proposed, but all of them have their flaws⁸⁸. The AO/OTA alphanumeric classification system was originally developed in 1980 by the Arbeitsgemeinschaft für Osteosynthesefragen (AO) and later adopted by the American Orthopedic Trauma Association (OTA)⁸². The unified classification model has been updated regularly, most recently in 2018, and defines simple, two-part trochanteric fractures with inherent stability as A1, multifragmentary trochanteric fractures with potential inherent instability as A2, and intertrochanteric (reverse oblique) fractures with inherent instability as A3. (Figure 4)

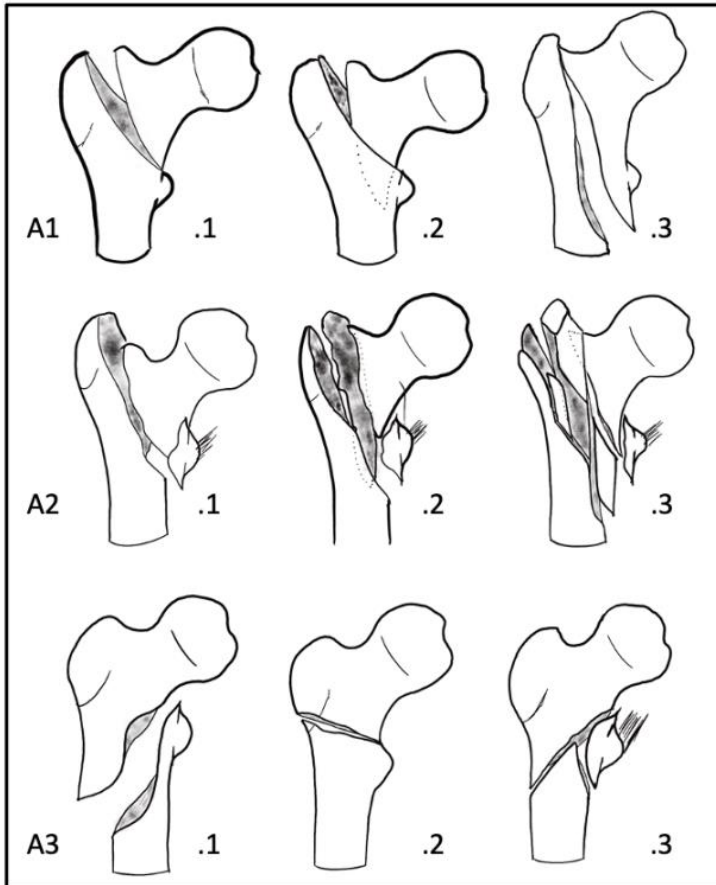


Figure 4: AO/OTA classification of trochanteric fractures. Courtesy of Cato Kjærviik (Reprinted with permission)

Numerous other classification systems have been suggested focusing on either stability and anatomical pattern (Evans⁸⁹, Ramadier⁹⁰, Decoulx⁹¹, Nakano⁹²) or maintaining reduction (Jensens modification of Evans⁹³, Tronzo⁹⁴). All of these classification systems, including the AO/OTA, have challenges when it comes to inter- and intraobserver reliability, but AO/OTA and Evans-Jensen (Figure 5) appear to be the most reliable, reproducible and clinically useful systems^{95,96}. In the Swedish Fracture Register (SFR) a recent validity study has been performed, indicating that the AO classification of femoral fractures in the SFR is accurate and that the data can be reliably used for further research studies⁹⁷.

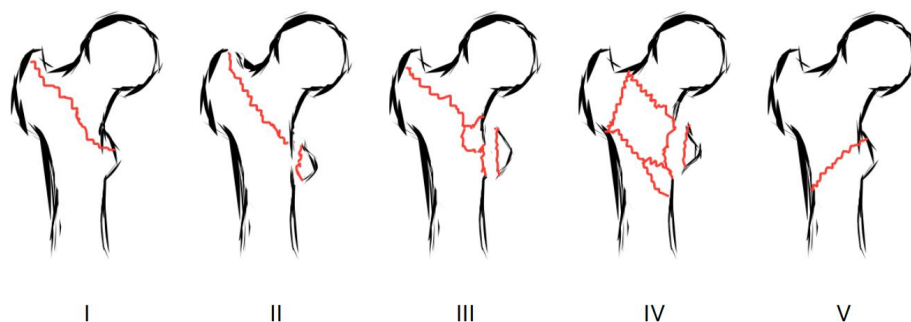


Figure 5: Evans-Jensen classification of trochanteric fractures (Author's illustration)

Subtrochanteric fractures are defined by the AO/OTA classification system as diaphyseal fractures with the centre of the fracture less than three cm distal to the lesser trochanter. Subtrochanteric fractures are unstable and divided into subgroups A1-A3, B1-B2 and C1-C3 according to grade of comminution and severity⁸². In the Norwegian Hip Fracture Register (NFHR), Seinsheimers definition of subtrochanteric fractures as located within five cm distal to the minor trochanter has been applied⁹⁸. Subtrochanteric fractures have been described in several other classification systems as well⁹⁹, the Russel Taylor classification perhaps being the more renown (Figure 6). Debate concerning reproducibility and reliability of this classification system and the evolvement of modern implants have, however, decreased its clinical relevance¹⁰⁰⁻¹⁰².

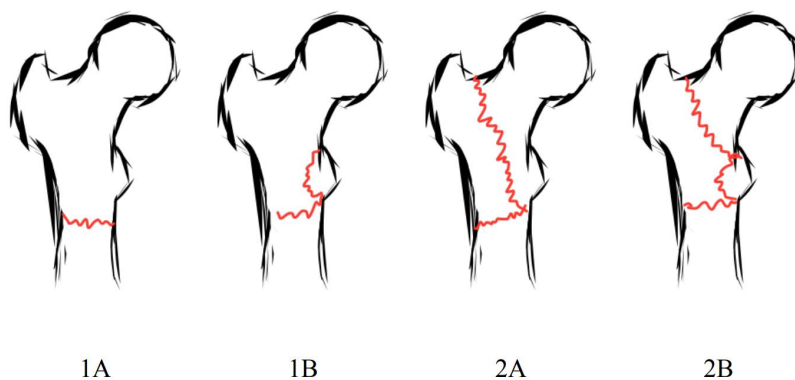


Figure 6: Russel-Taylor classification of subtrochanteric fractures (Author's illustration)

Different fracture characteristics present different challenges and systematic classification prior to surgical treatment is important to counteract dislocating forces and obtain sufficient reduction and stability. Furthermore, the AO/OTA classification system including subgroups provide a universal language important to scientific evaluation of treatment and interpretation of studies.

According to the NHFR approximately 54% of hip fractures are femoral neck fractures, 32% are trochanteric fractures, and 5% are subtrochanteric fractures. The remaining percentages represent combinations of fracture patterns, pathological fractures or missing information (Table 1).

	Number	%
Femoral neck fractures		
Garden 1+2	19,232	14.0
Garden 3+4	55,500	40.4
Basocervical	4,526	3.3
Trochanteric fractures		
AO/OTA A1	21,026	15.3
AO/OTA A2	20,947	15.2
AO/OTA A3	2,436	1.8
Subtrochanteric fractures	7,304	5.3
Other/missing data	6,595	4.7

Table 1: Distribution of hip fractures in the Norwegian Hip Fracture Register²

1.2.2 Stability assessment

Ability to determine fracture stability is the clinically most important role of the various classification systems. Stable fractures, A1 and A2.1 according to AO/OTA and type 1 and 2 according to Evans-Jensen, will withstand medial compressive forces after fixation. Unstable fractures, AO/OTA A2.2, A2.3 and A3, and Evans-Jensen type 3-5

fractures, with compromise of the posteromedial cortex, presence of subtrochanteric extension, or presence of a reversed obliquity fracture pattern, will collapse and/or displace under medial compressive forces despite axial reduction. Additionally, the importance of lateral wall integrity has been highlighted recently. Fractures with insufficiency of the lateral wall (thickness < 20.5 mm)¹⁰³ or lateral wall fracture¹⁰⁴ are considered unstable. Thus, lateral wall integrity should be included as a key component in the assessment of fracture stability in addition to posteromedial comminution, subtrochanteric extension, and presence of a reverse obliquity fracture pattern.

1.3 Historical development of treatment strategies for trochanteric and subtrochanteric fractures

Historically, intramedullary nailing as treatment method in trauma management in general was a controversial subject ever since the first cases were carried out in the 1800s, possibly inspired by the Aztecs use of wooden sticks for pseudarthrosis treatment described by the Spanish in the 1500s¹⁰⁵. Only episodic cases are described until Gerhard Küntscher developed the principles of intramedullary constructs during World War II. Due to academic disagreement the concept of intramedullary nailing was not accepted in North America and Europe until the 1970s, but then developed into the preferred treatment for femoral shaft fractures¹⁰⁵. With the evolvement of cephalomedullary nails for proximal femoral fractures, the indications for intramedullary nailing expanded. The predecessors of modern cephalomedullary nails, shown in Figure 7, were designed by Dr Arsène Grosse and Dr Ivan Kempf, and Dr Thomas Russell and Dr John Charles Taylor and further developed into the first generation of Gamma nails in the early 1990s¹⁰⁶⁻¹⁰⁸.

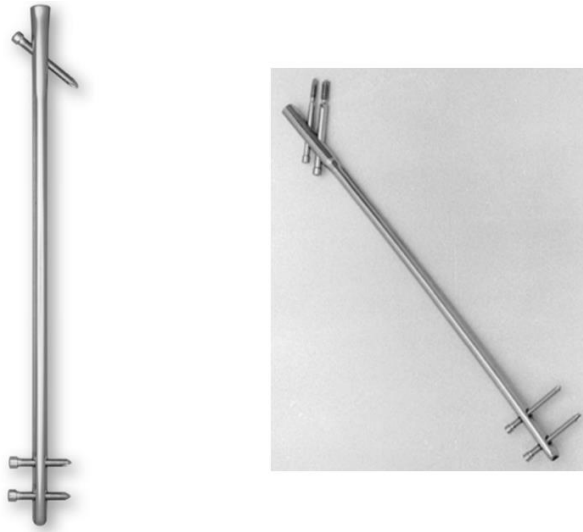


Figure 7: The Grosse-Kempf nail (Stryker Corporation, Kalamazoo, Michigan, USA), **left** and the **Russell-Taylor nail** (Smith and Nephew, Hertfordshire, UK), **right**

The first generations of IMNs for the treatment of trochanteric and subtrochanteric fractures were ridden with a high incidence of peri-implant fractures¹⁰⁹. Further understanding of the biomechanical properties of the implant and bone led to the development of new generations of IMNs with a significantly lower risk of peri-implant fractures¹¹⁰. Modern nails all have an anatomical design, require reaming and allow distal locking.

The SHS has been used in the treatment of trochanteric and subtrochanteric fractures ever since the introduction by Ernst Pohl in 1951^{111,112}. A similar dynamic construct intended for stabilization of femoral neck fractures had been designed by Robert Danis in 1934, but was never taken into use¹¹³. At the end of the 1950s, Pohls design inspired the development of the Richards classic hip screw and the first results were published in 1964¹¹⁴. This coincided with the recognition of high incidences of mechanical failure in the blade plates which were the treatment of choice of the Arbeitsgemeinschaft für Osteosynthesefragen / Association for Study of Internal Fixation (AO/ASIF) in the 1950s and 60s, leading to the development of the Ender nail in the 70s¹¹⁵⁻¹¹⁸. This implant turned out to yield a high percentage of complications as well, preparing the ground for the reintroduction of the SHS¹¹⁹⁻¹²². The AO/ASIF introduced their own

similar implant, including the option of a trochanteric support plate to counteract the inevitable medialization of the femoral shaft¹²³. The SHS became the standard implant in the treatment of trochanteric fractures¹²⁴. The implant is still in use although facing increasing competition from the IMN over the past two decades.

1.4 Contemporary treatment

Most proximal femoral fractures today are treated surgically, with the exception of moribund patients receiving only palliative care and trochanteric fractures only detected in MRI in patients able to mobilise with an acceptable level of pain. Series describing non-operative treatment of all other variations of proximal femoral fractures reveal unacceptable pain, very limited potential for recovery and high mortality. There is a close correlation between ability to mobilise and mortality¹²⁵⁻¹²⁷. The goal of operative treatment of all geriatric hip fractures is swift reduction and stabilisation of the fracture, allowing early mobilisation and load bearing. Prolonged bedrest and insufficient analgesia increase the risk of several complications such as venous thrombosis, pneumonia, muscular atrophy, obstipation and delirium¹⁷. In the following, only the development of surgical treatment of trochanteric- and subtrochanteric fractures will be elaborated, as only this group of fractures are investigated in the individual studies of the thesis. Trochanteric and subtrochanteric fractures are usually treated with a SHS or an IMN¹²⁷

1.4.1 Intramedullary nails

The IMN is introduced into the medullary canal through an entry point on the tip of the greater trochanter or slightly medial to it depending on the nail design. The IMN normally requires a less invasive approach than extramedullary implants and can be combined with other means of fixation such as cerclage wires and reposition plates^{128,129}

One or two lag screws are inserted through the lateral cortex into the femoral neck, allowing compression at the fracture site in the case of a trochanteric fracture. Various designs have been developed over the past decades, such as an additional anti-rotation screw, an integrated anti-rotation screw allowing intraoperative compression of the fracture, and a blade design to increase bone density around the lag screw. Furthermore, implants have evolved from the first generation of straight unreamed nails into second and third generations of implants (Figure 8). Changes have been made with regard to choice of alloy, reaming and distal design, and the historically higher risk of peri-implant fractures compared to the SHS seems to have been reduced significantly^{110,127,130,131}. In the treatment of stable trochanteric fractures, a short nail may be used, whereas a long nail is, in some guidelines, recommended in the treatment of unstable trochanteric and subtrochanteric fractures^{58,132}. There is still debate regarding the benefits of a long nail in these particular settings, as well as the potential hazards of using a short nail in the treatment of unstable fractures^{74,133-135}.

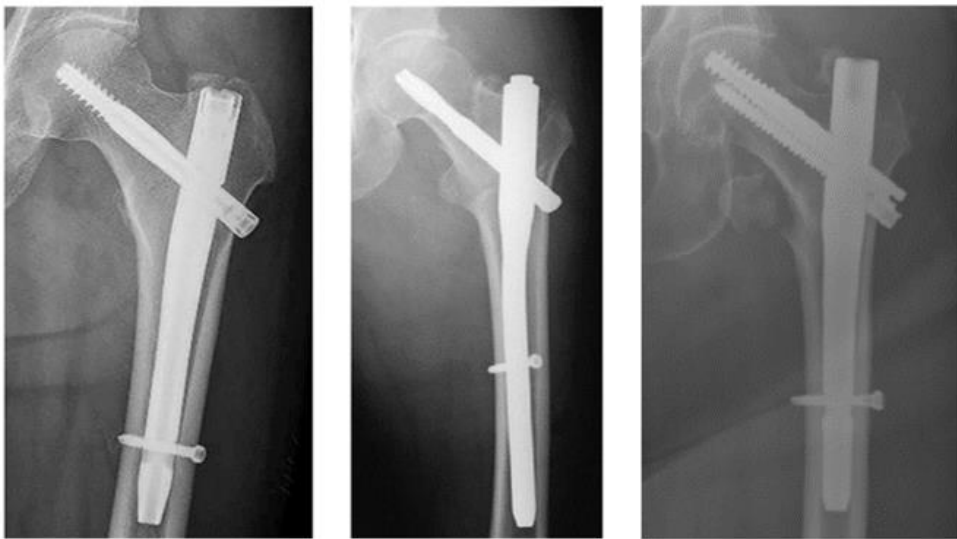


Figure 8: Examples of IMNs A) Gamma3 (Stryker Corporation, Kalamazoo, Michigan, USA), B) PFNA (DePuy Synthes, Oberdorf, Switzerland) and C) TRIGEN INTERTAN (Smith and Nephew, Hertfordshire, UK)

1.4.2 Sliding hip screw

The SHS consists of a lag screw connected to a plate through a barrel, allowing compression at the fracture site with load bearing of a trochanteric fracture, enhancing bone healing and reestablishment of medial cortical contact¹³⁶. This implant requires an open, muscle-splitting approach, even when just detaching vastus lateralis from its insertion on the posterior surface of the femur. SHS implants from different manufacturers, exemplified in Figure 9, present minor variations like lag screw thread design and locking options, but usually offer plate-barrel angles ranging from 130 – 150 degrees and 2-16-hole sideplates. 135 degrees plate-barrel angle and a four-hole sideplate is the standard implant. The sliding of the lag screw in the barrel of the SHS is influenced by angle, barrel length and lag screw length. In the case of an A3 or a subtrochanteric fracture, a trochanteric stabilizing plate (TSP) may be added in attempt to prevent medialization of the shaft^{137,138}. The CHS system has the option of an integrated TSP.



Figure 9: Examples of SHS: A) DHS (DePuy Synthes, Oberdorf, Switzerland), B) CHS (Smith and Nephew, Hertfordshire, UK) and C) CHS with TSP

1.4.3 Biomechanical considerations

The biomechanical properties of the IMN and the SHS differ in terms of their intra- versus extramedullary placement. The placement inside the medullary canal may prevent massive medialisation of the shaft, a challenge in the treatment of unstable A2 and reverse oblique fractures (A3). Femoral medialization is an individual risk factor for a poor outcome regarding pain and mobility one year postoperatively, healing complications and revision, and fractures treated with an SHS are significantly more prone to medialization¹³¹. The IMN also has the theoretical advantage of a shorter lever arm, which may lead to reduced stress on the implant. Biomechanical and clinical studies have not been able to unambiguously conclude that there is a difference in cut-out risk amenable to this feature¹³⁹, whereas the tip-apex-distance (TAD), as described by Baumgaertner and succeeding developments of this measure¹⁴⁰, correlates with cut-out-rate in IMN as well as in SHS^{25,131,141,142}. Nevertheless, an IMN construct appears to be biomechanically stronger and more rigid than an SHS plate construct, leading to less subsidence¹²⁹. Studies indicate that fracture reduction is paramount to ensure stability and uneventful healing of trochanteric and subtrochanteric fractures, regardless of implant chosen. Fractures with varus malalignment > 20 degrees angulation or > 4mm displacement have a significantly increased risk of failure, and tend to fail earlier than adequately reduced fractures¹⁴³. Even though avoiding varus malreduction reduces the load on both IMN and SHS, biomechanical studies indicate an SHS construct may be more affected by varus malalignment and run a greater risk of failure¹⁴⁴. Lateral wall patency is an important factor when using an SHS construct as well as an IMN, and the addition of a TSP to aid lateral wall reconstruction may reduce the risk of failure^{137,145}. Previous studies conclude that a compromised lateral wall is a greater risk when using an SHS compared with an IMN^{103,104}. Some modes of failure are amenable to the particular biomechanical properties of the IMN. The IMN seems to have a persistent increased risk of fractures adjacent to the implant^{146,147}, although not to the extent reported in studies before 2000^{109,130,148}. Development of IMN design have reduced the incidence of peri-implant fractures^{110,149-151}, but some recent studies suggest there is still a higher risk associated with the use of an IMN^{147,148}.

This is likely due to the rigidity of the implant and the stress-shielding amenable to its intramedullary placement.

1.4.4 Time trends for treatment of trochanteric and subtrochanteric fractures

Nationally and internationally, there has been a significant change in the surgical treatment of trochanteric fractures over the past decade, skewing towards increased use of IMNs for all fracture types but particularly for AO/OTA A2, A3 and subtrochanteric fractures^{2,24,152,153} (Figures 10-13). This trend is not necessarily founded in existing evidence^{24,154}. The SHS is still the implant of choice in the treatment of stable trochanteric fractures (A1 and A2.1)^{58,73,104}. Nevertheless, there has been a significant increase in the use of IMNs in these fractures as well, despite the lack of evidence for a better outcome^{155,156}. American and European cost-effectiveness analyses claim the SHS should be the implant of choice in the treatment of stable fracture types^{157,158 159,160}.

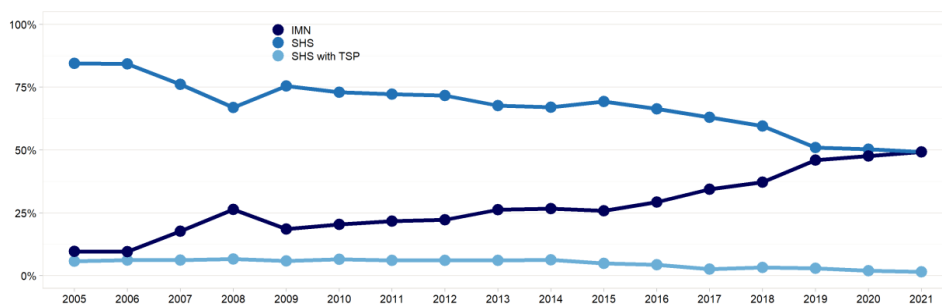


Figure 10: Time trends for treatment of AO/OTA A1 fractures in the NHFR² (Reprinted with permission from NHFR)

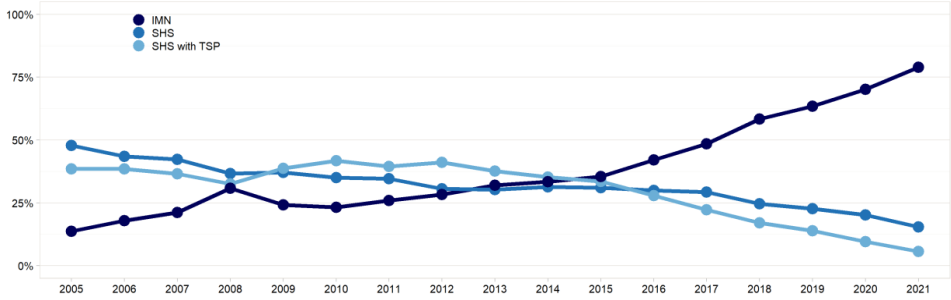


Figure 11: Time trends for treatment of AO/OTA A2 fractures in the NHFR² (Reprinted with permission from NHFR)

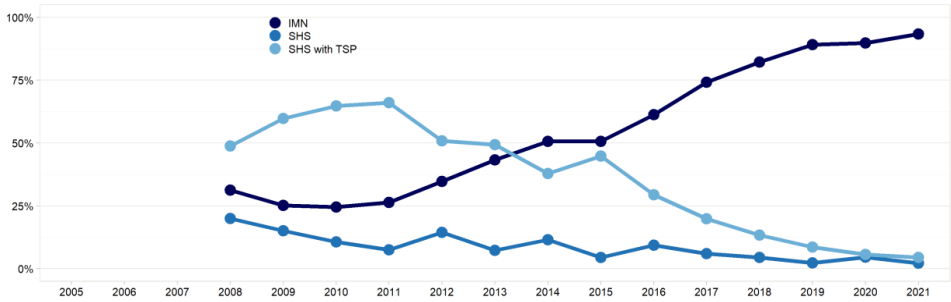


Figure 12: Time trends for treatment of AO/OTA A3 fractures in the NHFR² (Reprinted with permission from NHFR)

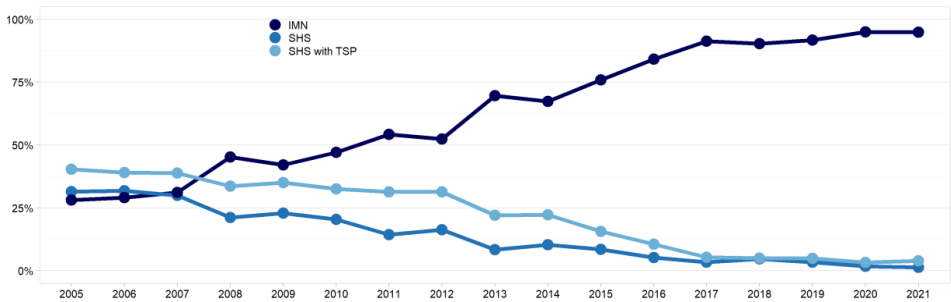


Figure 13: Time trends for treatment of subtrochanteric fractures in the NHFR² (Reprinted with permission from NHFR)

Furthermore, some studies, both RCTs and register based, have even detected higher rates of complications and mortality with the use of an IMN compared to a SHS in trochanteric fractures^{161,162}. Although national and international guidelines now recommend the use of an IMN in the treatment of A3 and subtrochanteric fractures^{73,74}, the last Cochrane report for 2022 with a total of 76 studies (66 RCTs, 10 quasi-RCTs) could not confirm a clear benefit attributable to the IMN in terms of reoperation risk or mortality four months postoperatively. The 2022 Cochrane report describes a reduced risk of infection and non-union with the use of an IMN, but a persistent increased risk of peri-implant fractures¹⁴⁸. However, more than half of the studies included were conducted before 2010, and the evolvement of the third generation of IMNs seem to have reduced their risk of complications. Furthermore, the Cochrane reviews only include RCTs and quasi-RCTs, and the lack of evidence supporting the current trend of increased use of IMNs may be attributable to the challenges an RCT faces in the investigation of rare outcomes such as reoperations following trochanteric and subtrochanteric fractures. Register-based studies have, contrary to the Cochrane report, indicated a benefit of an IMN in the treatment of A3 and subtrochanteric fractures¹⁶³. The heterogeneity of A2 fractures complicates the interpretation of results in studies investigating the treatment of this particular group of fractures and warrants a more specific estimation of stability in the classification systems.

1.5 Complications after trochanteric and subtrochanteric fractures

A complication leading to a reoperation is a devastating event for a frail hip fracture patient, already facing excess mortality after the primary operation. In the 2022 NHFR annual report 3.4% of A1 fractures, 6.9% of A2 fractures, 10.5% of A3 fractures, and 9.5% of subtrochanteric fractures were registered with a reoperation². More than one cause of reoperation may be given. The use of a hierarchy may conceal the true prevalence of coinciding complications, but is necessary when conducting a register-based study to ensure patients are only counted once. A selected list of causes of reoperations is given in Table 2, but as patients reoperated with a THA are registered

int the NAR, it is likely that particularly cut-out is largely underrepresented in this table, as this complication is likely to lead to a THA. Cause of reoperation is not specified to any further extent than “complication leading to THA) in the NAR.

	A1	A2	A3*	Sub-trochanteric
	n (%)	n (%)	n (%)	n (%)
Infection	111 (0.5)	291 (1.4)	47 (1.9)	135 (1.8)
Peri-implant fracture	86 (0.4)	110 (0.5)	11 (0.4)	46 (0.6)
Hardware failure	181 (0.8)	396 (1.9)	74 (3.0)	190 (2.6)
Cut-out	66 (0.3)	114 (0.5)	17 (0.7)	26 (0.3)
Non-union	64 (0.3))	168 (0.8)	33 (1.3)	118 (1.6)

Table 2: Selected causes of reoperation per type of fracture in the NHFR² (List is not exhaustive and more than one cause is possible. Patients reoperated with THA not counted) *registration of A3 fractures started in 2008

1.5.1 Infection

Given the high prevalence of at least one major medical comorbidity in the hip fracture population, these patients are particularly vulnerable to surgical site infections (SSI)¹⁶⁴. The rate of deep infection after hip fracture is reported to be between 1.3 and 3.6¹⁶⁵⁻¹⁶⁷.

Although a relatively rare complication, the consequences are profound on an individual and socioeconomic level^{165,168}. SSI is an independent risk factor for increased 90-day and one-year mortality in the general hip fracture population^{165,168-170}. One-year mortality for patients with SSI is reported to be 35.4–50.0%, substantially higher than those without infection (24.1–30%)^{165,168}. Furthermore, an SSI after hip fracture treatment significantly reduces the prospect of return to previous mobility and level of care^{165,168,171}. For the individual hospital, prolonged length of stay and further

medical and surgical requirements adds a three- to four-fold cost of care^{168,171}. Few studies have singled out trochanteric and subtrochanteric fractures when investigating rate and risk factors for post-operative infection in hip fracture patients¹⁶⁶, but existing literature suggests the risk of an SSI is lower for trochanteric fractures treated with osteosynthesis compared with femoral neck fractures treated with hemi- or total arthroplasty^{166,167,169,172}.

Definitions of SSI in fracture patients – “infection after fracture fixation” (IAFF) vary in the existing literature, causing difficulty estimating the incidence and impact of this complication, as well as creating treatment guidelines^{173,174}. Periprosthetic joint infections (PJIs) are more unanimously defined, and guidelines are largely agreed upon. Many of the surgical and medical treatment concepts applied to IAFF have been adopted from PJI treatment algorithms^{175,176}. IAFF and PJI do have similar clinical properties, but there are important distinctions between the elective arthroplasty patient and the trauma patient. Attempts have been made to create consensus and facilitate diagnosing and related research^{173,174}.

In a previous study based on NHFR data, risk factors for SSI in surgically treated hip fractures were cognitive impairment, an intraoperative complication, and increasing duration of surgery, but after controlling for observed confounding, the association between duration of surgery and early and delayed deep SSI was not statistically significant¹⁶⁹. Other studies have both confirmed¹⁷⁷ and contradicted^{170,178} this result. Age is related to increased risk of an SSI, but mainly due to the increasing comorbidity associated with advanced age. Charlson Comorbidity Index > 3 has been reported as an individual risk factor for SSI following hip fracture surgery¹⁶⁷, and an association between increasing ASA score and SSI has been described¹⁷⁹. Nutritional deficiency has also been confirmed to be an independent risk factor of postoperative complications, including infection¹⁸⁰. The relationship between BMI and SSI in hip fracture patients has been extensively studied, and there appears to be a significant increase in SSIs with increasing BMI in obese patients (BMI > 28)^{170,181}.

Choice of implant may affect the risk of an SSI in trochanteric and subtrochanteric fractures, namely an increased risk associated with an SHS compared with an IMN¹⁷⁷.

Previous register-based studies have found this to only apply to unstable trochanteric fractures and subtrochanteric fractures^{156,163}, and in the most recent Cochrane reviews comparing extra- and intramedullary devices in the treatment of extracapsular hip fractures no such distinction could be made^{109,126}.

Another topic of debate is the impact of surgeon and anaesthesiologist experience on risk of an SSI, where large register-based studies have come to contradicting conclusions^{104,168,177,182}.

Staphylococci (*Staph aureus*), methicillin-sensitive or -resistant, are the most common causative organisms in SSI following surgical treatment of hip fractures, regardless of implant^{168,183 184,185}. Targeted systemic prophylactic antibiotics administered correctly is the single most important measure against SSIs, and significantly reduce the risk¹⁸⁶. This is reflected in international and national treatment guidelines^{73,74}. Prophylactic antibiotics should be administered within 60 minutes of the incision¹⁸⁶⁻¹⁸⁸. There is less high-quality evidence determining the ideal duration of prophylaxis. Studies from arthroplasty surgery are commonly used to substantiate guidelines regarding prophylaxis in hip fracture treatment. The risk of SSI after THA decreases with every added dose up to four doses the first 24 hours, but there seems to be no further benefit of administration of prophylactic antibiotics beyond 24 hours¹⁸⁸, confirmed in other studies¹⁸⁹. Some authors even claim one dose administered preoperatively may be sufficient in both arthroplasty surgery and in the treatment of closed fractures^{190,191}, although not reflected in current practice.

There is little evidence substantiating choice of antibiotic in prophylactic treatment. Furthermore, the pattern of resistance in microbes varies between continents and countries and international guidelines are not necessarily ideal for all countries¹⁹². In Norway too, the most common causative microbe is staphylococcus aureus, but the occurrence of methicillin resistance is much lower^{193,194}.

In the era of worldwide evolving antibiotic resistance, orthopaedic surgeons too have an individual responsibility to choose as narrow spectered antibiotics as possible, including prophylaxis, and pay respect to evidence based guidelines regarding duration.

1.5.2 Peri-implant fracture

In the treatment of trochanteric and subtrochanteric fractures, an implant will affect the acting forces in the case of a second trauma and may increase the risk of some fracture types and decrease the risk of others. The risk of a peri-implant fracture is higher after an initial trochanteric, subtrochanteric or femoral shaft fracture compared to a femoral neck fracture^{195,196}. The choice of implant may influence the risk of an ipsilateral subsequent fracture^{146,147}. Historically, the IMNs have been associated with more peri-implant fractures than the SHS^{109,130,148}, but modern nails seem to have reduced the discrepancy^{110,149-151}. Nevertheless, even recent studies have detected a persistent higher risk of peri-implant fractures associated with the use of an IMN^{147,148}, and although the incidence has decreased with the evolution of new generations of IMNs, peri-implant fractures still represent a challenge to the orthopaedic surgeon. A peri-implant fracture will typically occur in the femoral shaft or distal metaphyseal area^{146,196,197}. However, previous studies have not specified the presence or absence of other implants or sequelae in either femur prior to the index fracture, possibly affecting risk and distribution of fractures.

There is an ongoing discussion regarding the possible benefit of a long nail in the treatment of unstable intertrochanteric and subtrochanteric fractures. In the AAOS and NICE guidelines, no specification of nail length is given, whereas the Norwegian national guidelines recommend a long nail^{58,74,132,198}. Most studies conclude that there is no significant difference in the rates of peri-implant fracture between short and long nails^{135,199}, but a recent study from the Danish Multidisciplinary Hip Fracture Registry (DMHFR) indicates there might be a benefit to long nails¹³³.

Distal locking may reduce the risk of peri-implant fracture in both short and long nails. Current evidence supports distal locking in axially or rotationally unstable fractures, including those with subtrochanteric extension or comminution, or in osteoporotic femora²⁰⁰.

1.5.3 Hardware failure

Hardware failure is not consistently defined but can in general be argued to include implant fracture or dislocation, implant deformation, and component displacement like screw back-out. Predisposing factors are implant or component malposition, suboptimal surgical approach and implant design. In the NHFR data, hardware failure includes screw, nail and plate breakage, and excessive sliding of the lag screw in the SHS or IMN, causing significant shortening of the femoral neck. Failure modes of an SHS construct typically includes excessive sliding of the lag screw and pull-out of the screws securing the side-plate. Failure is associated with unstable fracture patterns with lateral wall incompetence, varus displacement, femoral shaft medialisation and shortening^{145,201-203}. Biomechanically the SHS runs a greater risk of medialisation of the femoral shaft in unstable fractures with a compromised lateral wall, due to loss of integrity with osteoporosis or fracture, confirmed by several studies^{103,104,203,204}. These fracture patterns lack the bony support to counteract the pull of the adductor muscles and allow the distal fragment to displace medially. The adjunct of a TSP has been advocated to reduce the risk of medialisation¹³⁷, but its value has been debated^{138,205}. Breakage of the lag screw or the plate are rare complications but may occur if the sliding capability of the lag screw in the barrel of the SHS is affected^{202,206,207}. More commonly, screw or plate breakage will occur in the case of concomitant non-union. The IMN has, with its intramedullary placement and thus shorter lever arm, a theoretically lower risk of medialisation of the femoral shaft, and a decreased tensile strain on the implant. The IMN has some unique failure modes. The z-effect phenomenon can occur in intramedullary nail designs with two separate or integrated lag screws. In these cases the inferior lag screw migrates laterally, and the superior lag screw migrates medially during loading. Biomechanical studies suggest an increased risk of the z-effect in unstable fracture patterns, as bone density of the femoral head exceeds that of the femoral neck²⁰⁸. Causes of the z-effect are not exhaustively defined, but appear to include loss of medial support, varus collapse, posterior or anterior entry point of the nail, and poor bone quality. Furthermore, one biomechanical study suggests a neck-shaft angle < 125 degrees predisposes of the z-effect²⁰⁹. A neck-shaft angle of < 125 degrees has also been linked to a significant increase in fixation failure for all

causes combined²¹⁰. Nail or screw breakage are rare events, but described to be associated with unamenable factors like unstable fracture types, subtrochanteric fractures in particular, and pathological fractures²¹¹, as well as amenable factors like varus malreduction, suboptimal implant positioning and damage to the lag screw aperture upon reaming²¹²⁻²¹⁴. Non-union due to biological or mechanical causes will in the case of treatment with either IMN and SHS cause fatigue and increase the risk of implant breakage²¹⁵⁻²¹⁷.

1.5.4 Cut-out

Cut-out is, in the presence of an SHS or an IMN, defined as protrusion of the lag-screw through the femoral head surface as a consequence of varus collapse of the fracture. The prevalence of cut-out in the treatment of trochanteric and subtrochanteric fractures is in various studies estimated to be 1.85%–16.5%^{142,218,219}, and poses a challenge with the use of SHS and IMN alike. Tip-apex-distance (TAD), fracture classification, position of the screw in the femoral head, and fracture reduction are identified as predictors for screw cut-out²¹⁸. TAD, described by Baumgaertner¹⁴⁰, is considered to be a reliable predictor of cut-out risk, relevant to the positioning of both IMN and SHS²²⁰⁻²²², and an optimal TAD is, in some studies, regarded the most important factor in the prevention of cut-out²²³. TAD is defined as the sum of the distances between the tip of the lag screw and the apex of the femoral head, as measured in an antero-posterior and lateral view, and adjusted for radiograph magnification by using the diameter of the lag screw as reference, illustrated in figure 14.

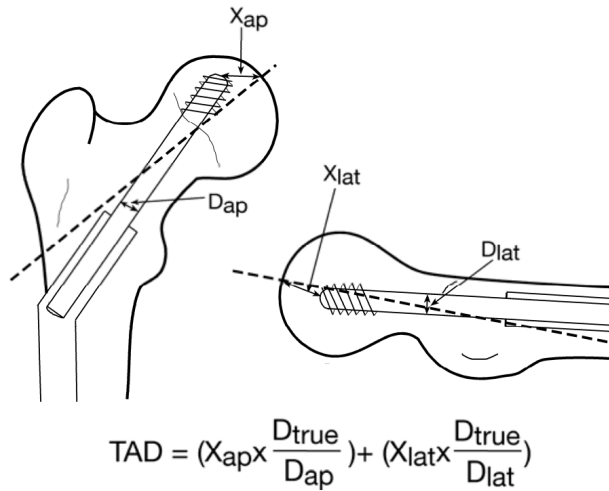


Figure 14: Calculation of TAD D_{true} : actual diameter of lag screw (courtesy of dr Kjell Matre, reprinted with permission)

Clinical and biomechanical studies have attempted to determine the optimal range in TAD-value, where the risk of cut-out is minimized^{140,221,224}, and is suggested to not exceed 25 mm. With the development of more refined imaging techniques, the accuracy and relevance of the TAD has been questioned²²⁵. Furthermore, a recent biomechanical study²²⁶, and a finite-element study²²⁷ have shown that inferior middle and inferior posterior positions are preferable, challenging the importance of a TAD > 25 mm cut-off for prediction of cut-out, as this suggests a higher rate of cut-out with a more inferior placement of the lag screw and implies a central–central placement is optimal. This may indicate that a calcar referenced tip-apex distance (CaTAD) is more accurate to predict cut-out¹⁴². Screw placement is recommended central-inferiorly or anterior-inferiorly based on clinical, biomechanical and mathematical analyses²²⁶⁻²²⁸. Even when the TAD exceeds the recommended measure, these screw positions are still protective of cut-out²¹⁸. Fracture classification is closely related to cut-out risk, even when adjusted for TAD and screw position. A3 fractures are significantly more at risk than A1 fractures²¹⁸, whereas the risk in A2 fractures is more difficult to assess in studies due to the heterogeneity of this group and the following uncertainty in subclassification of these fractures. The importance of screw placement and TAD in subtrochanteric fractures is debatable. A varus malreduction of the fracture has been

associated with a higher cut-out rate in fractures treated with either SHS and IMN^{139,142,229}.

More recent studies have found that a combination of the known risk factors of cut-out are more likely to cause cut-out than any single factor^{142,222,230}.

1.5.5 Non-union

Non-union describes a fracture where failure of normal fracture healing processes has occurred and where there is no possibility of healing without further intervention²³¹. In the 2022 NHFR report, non-union was reported as a cause of reoperation in 8.7% of A1 fractures, 11.5% of A2 fractures, 12.8% of A3 fractures and 17.0% of subtrochanteric fractures². Several causes of reoperation may be given though, and non-union may be a consequence of, or a predisposing factor for other complications documented in previous literature, such as infection, hardware failure and cut-out^{143,232}. Causes of non-union are multifactorial, including biological, mechanical and patient factors²³¹. The trochanteric region is well vascularized and non-union as such relatively rare. Hypertrophic nonunions typically occur when there is adequate vascularity but inadequate stability, whereas atrophic non-union lack sufficient blood supply at the fracture site and additional stabilizing procedures may be futile^{231,233}. Nonunions caused by surgeon induced fixed diastasis may have variable vascularity and stability²³³. Vitamin D and calcium deficiency, abnormalities in thyroid function and other hormonal systems are associated with delayed fracture healing and may increase risk of nonunion²³⁴. Revision options in the face of a nonunion following treatment for trochanteric or subtrochanteric fractures are revision nailing with or without bone grafting, arthroplasty with THA or HA, or revision fixation with a proximal femur locking- or blade-plate. Results of revision surgery after non-union, regardless of modality, are somewhat disheartening, with a high rate of re-revision and mortality¹⁴³. Emphasis should be placed on the importance of initial reduction and stability, appropriate fixation method and maximising bone healing capabilities.

2 Aims of the studies

The overall aim of this thesis was to evaluate the outcomes of trochanteric and subtrochanteric fractures treated with an IMN, using data from a local quality database and the Norwegian Hip Fracture Register.

The specific aims of the three studies included in the thesis were:

Paper I:

- To investigate how an IMN affects the incidence, pattern, and localisation of subsequent femoral fractures in patients without implants or sequelae after previous surgery in either femur.

Paper II:

- To compare reoperation rates for SHS and IMN for stable fractures (A1) and unstable fractures (A2, A3, and subtrochanteric combined) one and three years postoperatively.
- To compare reoperation rates for SHS and IMN for A2, A3, and subtrochanteric fractures separately one and three years postoperatively.
- To compare mortality and patient-reported outcomes after SHS and IMN for stable and unstable fractures one year postoperatively.

Paper III:

- To compare reoperation rates between different IMNs used in the treatment of trochanteric and subtrochanteric fractures.
- To report reoperation rates for the various types of short and long nails regarding fracture type.

3 Patients and methods

3.1 Registration of hip fractures at Østfold Hospital Trust

In *Paper I* patients were identified by searching the hospital database at Østfold Hospital Trust using the International Statistical Classification of Diseases and Related Health Problems (ICD10) and the NOMESKO Classification of Surgical Procedures (NCSP) codes. Patients with ICD10 codes S72.1 (trochanteric fractures) or S72.2 (subtrochanteric fractures) and NCSP codes NFJ51 or NFJ52 (intramedullary nailing of trochanteric or subtrochanteric fractures respectively) were identified. Electronic health records and X-ray images were reviewed. Variables collected are shown in Appendix 1. Handwritten documentation provided by the surgeons postoperatively was reviewed and compared with the electronic health records. The American Society of Anesthesiologists Physical Status scoring system (ASA score) was used to assess the overall health status of the patient. Pre- and postoperative X-ray images, as well as all follow-up X-ray images taken of the proximal femur and the pelvis, were examined to identify, classify and localise index fractures and any subsequent fractures. Fracture type was registered according to the AO/OTA classification system²³⁵. Pelvic X-ray images visualising the contralateral hip and all follow-up X-ray images were included for all patients to identify any pre-existing implant, added implant, or sequelae in either proximal femur. The completeness of local data obtained from electronic health records was validated by comparison with data from the NHFR. Patients missing from either database were supplemented.

3.2 The Norwegian Hip Fracture Register

Papers II and III are based on data from the Norwegian Hip Fracture Register (NHFR).

The NHFR was established in January 2005 to collect information about patients treated for hip fractures in Norway²³⁶. Data collection is approved by the Norwegian Data Protection Authority. Until July 2021 patients' written consent was required for registration in the NHFR, whereas patients are now included without consent but can withdraw at any time. Registration completeness when compared to the Norwegian Patient Registry has been found to be 86% for primary osteosyntheses and 78% for reoperations after osteosyntheses². All hospitals in Norway treating hip fractures report to the NHFR². Regular reports from the NHFR are presented on their website.

3.2.1 Registration of primary operations

After each primary operation the surgeons fill in a standardized 1-page form with the unique identification number assigned to all Norwegian residents revealing age and sex, comorbidity according to the ASA classification, cognitive status, time of injury and type of fracture (Appendix 2). Trochanteric fractures are classified according to the AO/OTA classification system as AO/OTA type A1 (simple two-part), A2 (multifragmentary), and A3 (intertrochanteric/reverse oblique). Subtrochanteric fractures are defined as diaphyseal fractures with the centre of the fracture less than five cm distal to the lesser trochanter. Additionally, intraoperative details including timing and duration of surgery as well as type of surgery and implant are reported. Details of implants are given in product labels attached to the registration form. This allows identification of each implant on catalogue number level.

3.2.2 Registration of reoperations

All reoperations should be reported to the NHFR, also reoperations without exchange or removal of implants. Reoperations including failure of osteosynthesis, non-union,

avascular necrosis of the femoral head, local pain, malunion, superficial or deep infection, haematoma, cut-out, peri-implant fracture and “other” are recorded using the same form as for primary operations (Appendix 2) and can be linked to the primary operation using the unique identification number assigned for each Norwegian resident. More than one cause may be given for each reoperation in the NHFR. Two or more complications may very well present themselves concomitantly, like infection and non-union, infection and hardware failure, hardware failure and non-union and so on so forth. In *Paper I* all reoperations registered with peri-implant fracture as cause were counted, and reoperations for other causes censored. In *Papers II and III* hierarchies based on assumed severity of the different causes of reoperation was suggested to avoid counting each reoperation more than once. In *Paper II* infection, peri-implant fracture, mechanical complications (non-union, implant failure, cut-out), unspecified sequelae (treated with THA), pain alone, other, was chosen. Collapsing individual causes of mechanical complications into one group was done to create larger groups and thus give more robust statistical analyses. In *Paper III* we chose a more detailed hierarchy (infection, peri-implant fracture, hardware failure, cut-out, non-union, unspecified sequelae (treated with THA), pain alone, other) to possibly identify specific modes of failure linked to particular nail designs.

3.2.3 Registration of patient-reported outcomes

Patient-reported outcomes were included as secondary outcome in *Paper II*. A standardized questionnaire including health-related quality of life (EQ-5D), a visual analogue scale (VAS) 0-100 for pain (0 = no pain, 100 = unbearable pain), and a VAS 0-100 for satisfaction (0 = least satisfied, 100 = most satisfied) is sent to the patients 4, 12, and 36 months postoperatively. The pre-fracture EQ-5D is collected in the questionnaire sent to patients 4 months postoperatively. The multi-item, generic EQ-5D questionnaire (EQ-5D-3L, EuroQol Group, Rotterdam, The Netherlands) consists of the following dimensions (walking ability, ability of self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression), and is regarded as a useful and relevant outcome measure for this patient population. The EQ-5D-3L is a non-

disease-specific questionnaire offering the opportunity of assessment and comparison of patients' perceived outcomes from different populations. Index score is calculated based on the response for each dimension. A score of 1 indicates the best possible health state, and a score of 0 indicates a perceived health state of no more value to the patient than death. The preference scores (EQ-5D index scores) generated from a large European population were used²³⁷. The response rate for PROM questionnaires is 57%². Although most frequently analysed as an index score, level of function can be explored within each dimension and compared to reference groups. Such comparisons have been done between hip fracture patients and the peer population²³⁸.

3.2.4 Mortality

In *Paper II* one-year mortality was a secondary outcome measure. In the NHFR, mortality data are collected from the Norwegian Population Register, allowing analyses on mortality associated with patients' baseline data, type of fracture, type of implant, time to surgery, duration of surgery and intraoperative complications. In the annual reports, one-year mortality of patients sustaining different fracture types is calculated for each individual hospital.

3.3 Inclusion and exclusion of patients

The inclusion and exclusion criteria for *Papers I-III* are summarized in Table 3.

	Inclusion criteria	Exclusion criteria
<i>Paper I</i> (local database)	<p>ICD10 codes:</p> <p><i>S72.1</i> (trochanteric fractures)</p> <p><i>S72.2</i> (subtrochanteric fractures)</p> <p>NCSP codes</p> <p><i>NFJ51</i> (intramedullary nailing of trochanteric fractures)</p> <p><i>NFJ52</i> (intramedullary nailing of subtrochanteric fractures)</p> <p>Preoperative X-ray images without prior implants or sequelae in either femur</p>	<p>< 60 years of age</p> <p>Non-Norwegian citizens</p> <p>Primary care episode at a non-orthopaedic department</p> <p>Pre-existing implant in either femur</p> <p>High-energy trauma</p> <p>Multiple simultaneous fractures in the lower extremities</p> <p>Pathologic fracture (other than osteoporosis)</p>
<i>Paper II</i> (NHFR data)	<p>Trochanteric and subtrochanteric fractures operated 2013-2019</p> <p>Treatment with a short or long IMN or a</p> <p>SHS w/wo TSP</p>	<p>< 60 years of age</p> <p>Fractures treated with other implants than SHS or IMN</p> <p>Pathologic fracture (other than osteoporosis)</p> <p>Fractures with missing data</p>
<i>Paper III</i> (NHFR data)	<p>Trochanteric and subtrochanteric fractures operated 2007-2019</p> <p>Treatment with a short or long IMN</p>	<p>< 60 years of age</p> <p>Fractures treated with other implants</p> <p>Pathologic fracture (other than osteoporosis)</p> <p>Fractures with missing data</p> <p>Implant used < n=150</p> <p>Implant not in general use the past 10 years</p>

Table 3: Inclusion and exclusion criteria in Papers I-III

3.4 Statistics

Pearson chi-square test was used for comparison of categorical variables and the independent t-test (Student's test) and Analysis of Variance (ANOVA) were used to compare mean values in continuous variables in independent groups. The significance level was set at 0.05 in *all Papers*.

In *Paper I* data was summarised using frequencies and percentages for categorical variables. The mean, standard deviation (SD) and range were calculated for continuous variables. The mean time to subsequent fracture, range and 95% confidence interval (CI) were calculated. The odds ratio (OR) was calculated using robust variance estimates in logistic regression. The follow-up time was calculated from the primary operation until a new fracture-related operation on the ipsilateral side, fracture-related surgery on the contralateral side, other operation not related to a fracture, death, or 31 January 2020, whichever came first. The patients who reached any of the endpoints were censored along the way.

In *Paper II* hazard rate ratios (HRRs) of reoperations and hierarchical cause of reoperation were calculated using Cox regression analyses, adjusted for age, sex, and ASA classification²³⁹. Patients were followed from primary operation to reoperation, death, or 31 December 2019 (end of study), whichever occurred first. One-year mortality for SHS and IMN was calculated for stable and unstable fractures using Cox regression analysis adjusted for age, sex, and ASA classification. The proportional hazards assumption was tested using log-minus-log plots and was fulfilled. Patient-reported quality of life (EQ-5D-3L), pain (VAS 0-100), and satisfaction (VAS 0-100) twelve months postoperatively were analyzed using the independent sample t-test to compare means between SHS and IMN

In *Paper III*, short and long nails were analysed separately. Median and interquartile range (IQR) was chosen to describe duration of surgery due to the extreme outliers that may represent errors in the registration process. HRRs of reoperations were calculated using Cox regression analysis, adjusted for age, sex, and ASA classification. Gamma3 was the most common nail in the analyses of both short and long nails and was used as

reference. Patients were followed from primary operation to reoperation, death, or December 31, 2019 (end of study), whichever occurred first.

The statistical analysis was performed using IBM SPSS Statistics, version 24 in *Paper I*, version 26 in *Paper II* and version 29 in *Paper III* (IBM Corp, Armonk, NY, USA), the statistical package R version 3.4.0 (<http://CRAN.R-project.org>) in *Papers I, II and III*, and, in *Paper I*, Stata/SE (Version 16.0, StataCorp LLC, College Station, TX, USA).

The STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) guidelines were followed²⁴⁰.

4 Summary of Papers I-III

4.1 Paper I

Grønhaug KML, Dybvik E, Gjertsen JE, Samuelsson K, Östman B.

Subsequent ipsi- and contralateral femoral fractures after intramedullary nailing of a trochanteric or subtrochanteric fracture: a cohort study on 2,014 patients.

BMC Musculoskelet Disord. 2022 Apr 28;23(1):399.

Background The incidence of a subsequent femoral fracture (Sffx) is significant among patients who have suffered an initial hip fracture. The pattern of an Sffx will be influenced by the presence and type of the given implant at the time of a second injury. An implant may increase the risk of some fracture types and decrease the risk of others. Previously published literature does not provide sufficient information regarding the impact of an intramedullary nail. Based on data from the hospital electronic health records we investigated how an intramedullary nail affects the incidence, pattern, and localization of subsequent femoral fractures in patients without implants or sequelae after previous surgery in either femur.

Patients and methods A cohort of 2,012 patients treated with a short or long intramedullary nail for the management of trochanteric or subtrochanteric fracture between January 2005 and December 2018 was retrospectively analysed. Subsequent presentations with ipsi- and contralateral femoral fractures were documented. Only patients with no previous femoral surgery were followed, and consecutive censoring of patients reaching either end-point (Sffxs, death, non-fracture complications or new implant) enabled analysis of the risk of a Sffx. Odds ratios (ORs) for subsequent femoral fracture were calculated using robust variance estimates in logistic regression. The information based on data from the hospital electronic health records was validated by comparison with data from the NHFR.

Results The mean age of the cohort was 82.4 years and 72.1% were female. The total number of patients presenting with subsequent femoral fractures was 299 (14.9%). The number of patients presenting with subsequent ipsilateral and contralateral femoral

fractures was 51 (2.5%) and 248 (12.3%) respectively (OR: 5.0, 95% CI: 3.7 to 6.9). Twenty-six (8.7%) of all subsequent femoral fractures occurred in the ipsilateral shaft, 14 (4.7%) in the ipsilateral metaphyseal area, one (0.33%) in the contralateral shaft, and three (1.0%) in the contralateral metaphysis (OR: 10, 95% CI: 3.6 to 29).

Conclusion An intramedullary nail significantly changes the fracture pattern in the event of a second low-energy trauma, reducing the risk of subsequent proximal ipsilateral femoral fractures and increasing the risk of subsequent ipsilateral femoral fractures in the shaft and distal metaphyseal area compared with the native contralateral femur. The overall risk of Sffx is substantially higher in the contralateral, native femur indicating the protective effect of the IMN regarding a proximal ipsilateral Sffx is much higher than the increased risk of sustaining an ipsilateral peri-implant fracture.

The increased incidence of ipsilateral versus contralateral Sffxs in the shaft and distal metaphyseal area following the implantation of an IMN in this study may indicate a redistribution of forces in the event of a second trauma to the femur, morphological changes in adjacent bone or altered falling pattern.

4.2 Paper II

Grønhaug KML, Dybvik E, Matre K, Östman B, Gjertsen JE.

Intramedullary nail versus sliding hip screw for stable and unstable trochanteric and subtrochanteric fractures in 17,341 patients from the Norwegian Hip Fracture Register.

Bone Joint J. 2022;104-B(2):274-282.

Background The choice of implant in the treatment of trochanteric fractures and subtrochanteric fractures has been debated for decades without reaching consensus. The most common implants are extramedullary sliding hip screws (SHS) and intramedullary nails (IMN), skewing towards IMN over the past two decades. The primary aim of this study was to compare reoperation rates for SHS and IMN for stable fractures (A1) and unstable fractures (A2, A3, and subtrochanteric combined) one and three years postoperatively. Secondary aims were to compare reoperation rates for SHS and IMN for A2, A3, and subtrochanteric fractures separately one and three years postoperatively and to compare mortality and patient-reported outcomes after SHS and IMN for stable and unstable fractures one year after surgery.

Patients and methods Data from 17,341 patients registered in the Norwegian Hip Fracture Register with trochanteric or subtrochanteric fractures treated with SHS or IMN from 2013 to 2019 was assessed. Primary outcome measures were reoperations for stable fractures (AO/OTA type A1) and unstable fractures (AO/OTA type A2, A3 and subtrochanteric fractures). Secondary outcome measures were reoperations for A2, A3 and subtrochanteric fractures individually, one-year mortality, quality of life (EQ-5D-3L), pain (Visual Analogue Scale (VAS)), and satisfaction (VAS) for stable and unstable fractures. Hazard rate ratios (HRRs) for reoperation were calculated using Cox regression analysis with adjustments for age, sex and ASA-score.

Results Reoperation rate was lower after surgery with IMN for unstable fractures one year (HRR: 0.82, 95% CI: 0.70 to 0.97, $p=0.02$) and three years postoperatively (HRR: 0.86, 95% CI: 0.74 to 0.99, $p=0.036$), compared to SHS. For individual fracture types, no clinically significant differences were found. Lower 1-year mortality was found for

IMN compared to SHS for stable (HRR: 0.87, 95% CI: 0.78 to 0.96, $p=0.007$), and unstable fractures (HRR: 0.91, 95% CI: 0.84 to 0.98, $p=0.014$).

Conclusion This national register-based study indicates a lower reoperation rate for IMN than SHS for unstable trochanteric and subtrochanteric fractures, but not for stable fractures or individual fracture types. The choice of implant may not be decisive to the outcome of treatment for stable trochanteric fractures in terms of reoperation rate. One-year mortality rate for unstable and stable fractures was lower in patients treated with IMN. The lower one-year mortality rate for unstable and stable fractures in patients treated with IMN should be further investigated.

4.3 Paper III

Grønhaug KML, Dybvik E, Matre K, Östman B, Gjertsen JE.

Comparison of intramedullary nails in the treatment of trochanteric and subtrochanteric fractures. An observational study of 13,363 fractures in the Norwegian Hip Fracture Register.

Submitted JBJS Am.

Background Different brands of intramedullary nails vary with respect to lag screw/blade design, single or double lag screw, proximal diameter, entry point, and for long nails, antecurvature. In this prospective, register based study we aimed to investigate if there are any differences in reoperation rate between the various brands of IMNs in widespread use for treatment of trochanteric and subtrochanteric fractures in Norway.

Patients and methods Data from 13,363 trochanteric or subtrochanteric fractures treated with an IMN and registered in the Norwegian Hip Fracture Register (NHFR) between 2007 and 2019 was assessed. Primary outcome measure was risk of reoperation for various types of short and long IMNs. Secondly, reoperation rates for the selected nails regarding fracture type (AO/OTA type A1, A2, A3, and subtrochanteric fractures) were compared. Hazard rate ratios (HRRs) for reoperation were calculated using Cox regression analysis adjusted for age, sex, and ASA-score.

Results Mean age was 82.9 years and 72.8% were female. We included 8,414 short nails and 4,949 long nails. A1 fractures accounted for 29.8%, A2 for 40.6%, A3 for 7.2%, and subtrochanteric fractures for 22.4%. When comparing short nails regardless of fracture type, TRIGEN INTERTAN had an increased risk of reoperation one (HRR: 1.31, 95% CI: 1.03 to 1.66, $p=0.028$) and three years (HRR: 1.31, 95% CI: 1.06 to 1.61, $p=0.011$) postoperatively compared to Gamma3. For individual fracture types, we found no statistically significant differences in reoperation risk between the various types of short nails. Most failures occurred when the short TRIGEN INTERTAN was used in unstable fractures. When comparing long nails, TRIGEN TAN/FAN had an increased risk of reoperation one (HRR: 3.05, 95% CI: 2.10 to 4.42, $p<0.001$) and three

years (HRR: 2.54, 95% CI: 1.82 to 3.54, $p < 0.001$) postoperatively compared with long Gamma3, persistent in A1, A2, and subtrochanteric fractures.

Conclusion This study indicates comparable reoperation rates for short nails in widespread use in Norway. The short TRIGEN INTERTAN nail was associated with a higher risk of reoperation, but mostly when used in unstable fractures contrary to recommendations of using a long nail for these fractures in the Norwegian interdisciplinary guidelines for treatment of hip fractures. In analyses of long nails, the TRIGEN TAN/FAN nail was associated with a higher risk of reoperation in the treatment of trochanteric and subtrochanteric fractures, applicable for both less and more experienced surgeons.

5 Discussion

5.1 Methodological considerations

5.1.1 Retrospective studies

Retrospective studies, considered inferior to prospective, randomized, and controlled clinical trials, can have strength and validity not necessarily recognized in the hierarchy of clinical data. A retrospective cohort study considers events that have already occurred. Health records of a certain group of patients are already collected and stored in a database, so it is possible to identify a group of patients – the cohort – and reconstruct their experience as if it had been prospectively followed up. Use of previously collected and stored records indicates that the retrospective cohort study is relatively inexpensive, and analyses often relatively quick and easy to perform. Furthermore, it enables the researcher to examine the temporal relationship between exposure and outcome. The information about patients may be collected without any thought for later research use and is usually not collected in a homogenous manner. In a retrospective study, it is likely that not all relevant risk factors have been recorded. The researcher will not be able to identify all exposure factors, covariates, and potential confounders, affecting the validity of a reported association between risk factor and outcome. In addition, it is likely that the measurement of risk factors and outcomes is not as accurate as in a prospective cohort study where documentation is done after defining a hypothesis and collection of information is structured. In *Paper I* a retrospective study design was applied to identify subsequent femoral fractures after initial treatment of a trochanteric or subtrochanteric fracture. An advantage to this design is its ability to study a rare outcome like a subsequent fracture, the ipsilateral fractures in particular. Furthermore, the retrospective design allows inclusion of a large population and long follow-up time. Important limitations were as described above, the inability of the retrospective design to identify relevant variables like BMD or fall pattern.

5.1.2 Register-based studies

The introduction of personal identification numbers in the Nordic countries in the 1960s paved the way for further development of medical registers in these countries, and their political stability and peaceful history have enabled them to establish reliable and relatively complete medical registries. The personal identification numbers allow linkage on an individual level between different registries, releasing an increasing amount of health-related data for epidemiological research. Registration systems like these are valuable as they offer a large number of recorded events, long follow up time, and a low influence of chance given the high number of observations in the data sets.

The main purpose of orthopaedic registers is collection of information regarding patients, implants, and procedures to monitor, and hopefully improve, outcome. Register-based studies require specific methodological considerations. Data collection in register-based studies differ from researcher collected data. Nevertheless, studies based on register data must be designed with the same scrutiny and critical approach to one's hypotheses as any other research.

In the following, the main strengths and limitations of register-based studies will be discussed.

5.1.2.1 Strengths of register-based studies

When conducting a register-based study, the relevant data have already been prospectively collected, minimizing cost and time spent. Sample size is much larger than what is possible in a traditional researcher-collected data set, yielding great statistical power and facilitating studies of less frequent outcomes and complications. When investigating rare outcomes, like reoperations after hip fracture surgery in **Papers II and III**, a very high number of cases is required to reach sufficient statistical power. Accordingly, a RCT within a reasonable time frame would be very difficult to conduct. Linkage of different registers will enable calculation of completeness, ensuring the data regarding the population in question is representative. The NHFR has high completeness, minimizing the effects of selection bias, and allowing investigation of smaller sub-populations, such as patients with particular fracture types and implant

brands. Furthermore, the data have been collected prior to, and independent of, the study in question. This may reduce influence of any diagnostic process or treatment, that may represent obstacles in other research models. When investigating register data, valuable time has passed. Some complications develop months and years after exposure, surgery etc. Existing registers allow us to study long-term effects and outcomes, even when there is latency between exposure and manifestation of effect. Register-based studies can also be used to identify research questions suited for RCTs, and register data may even be used as a data pool for inclusion of patients into an RCT. Furthermore, given the large number of cases, register-based studies can supplement and substantiate results from RCTs. A study based on data from a register with high coverage and completeness will have high external validity as it describes the whole country, not just selected centres, surgeons or patients.

5.1.2.2 Limitations of register-based studies

Register-based studies certainly come with limitations that are important to recognize too. The most important limitation is that a register-based study can only describe associations, not causality. Data selection and content are not defined by the researcher and normally collected prior to the formulation of a particular research question, and the researcher is limited to use the pre-defined variables in the register. Certain information may be unavailable, like x-ray images in *Papers II and III*. This prevented us from subclassification of fracture types influencing stability assessment of AO/OTA A2 fractures and verifying correct classification of fractures. Information in a register may be inaccurate, and the level of detail is limited. In health registers, coding of diagnoses and surgical procedures are used, and there may be variations in coding practice between health personnel, departments, institutions and even over time as coding systems are revised. The registers may lack information crucial to the interpretation of results and fail to identify and acknowledge confounders. Incomplete information regarding confounding factors, and the fact that register-based studies provide large samples and have great statistical power to detect small effect sizes, makes register-based studies prone to confounding. To reduce the risk of confounding in *Papers II and III* we adjusted for ASA, sex and age groups but there is a risk of residual confounding. Missingness is another important limitation in research methodology, also applicable to handling of data from the NHFR. An example in long-term medical studies is drop-out of participants because of deteriorating health or cognitive status, where the final dataset may include only the

healthiest individuals – attrition bias. We have no reason to believe we have a significant risk of attrition bias in *Papers II and III* as baseline data were comparable for all groups and mortality and loss to follow-up are assumed to be comparable in all groups. Evaluation of data quality is a limitation in register-based studies. Register data can be difficult to validate, as a golden standard cannot be established. Furthermore, the large amount of available data may lead to misleading post-hoc analyses. A research question posed after processing the data may be biased and lead to the wrong conclusions. Finally, clinically insignificant differences may reach statistical significance in register studies with large numbers of observations. The size of risk estimates must be interpreted, and clinical relevance taken into consideration upon conclusion.

In *Paper II* PROM-analyses were included. A core outcome set (COS) has been suggested for clinical trials investigating patients with hip fractures²⁴¹, including mortality, pain, activities of daily living, mobility and health related quality of life (HRQL). EQ-5D was recommended as measure of HRQL. The EQ-5D correlates with the hip specific PROM Oxford Hip Score (OHS)^{238,242}, and is regarded responsive for the hip fracture population, including proxy scores for patients with cognitive impairment^{243,244}. When using PROMs the minimal clinically important difference (MCID) must be taken into consideration²⁴⁵, which is estimated to be 0.06-0.07 for the EQ-5D index score²⁴⁶. The response rate from the patients receiving the 4-months questionnaire was only approximately 52% in *Paper II*. We found a statistically significant higher EQ-5D-3L score at one year for patients with an A2 fracture treated with an IMN, but the difference only amounted to 0.04. Thus, we cannot conclude upon a clinically relevant difference in EQ-5D-3L score between treatment groups in our study, although statistically significant. Earlier studies have shown that the patients responding to the 4-months questionnaire are younger and healthier than the patients not responding, indicating selection bias. Furthermore, recall bias is likely as these data are collected 4 months postoperatively²⁴⁷. The PROM data reported in *Paper II* probably represent a best-case scenario as a recent study from the NHFR indicates that the frailest patients more seldom respond²⁴⁸. However, in their report based on two large prospective studies, Parsons et al provide evidence for the reliability of retrospective assessment of pre-injury health and functional status using the EQ-5D²³⁸. We decided to include PROM analyses despite a large amount of missing data, as we have no reason to believe there would be more non-responders in either group compared to the other. Nevertheless, after one year, 24% of the study

population had died, and only 52% of the remaining patients answered the questionnaire. With such a large amount of missing data we cannot draw any inferences based on PROM analyses.

When using health register data, validity must be evaluated. Validity can be described as completeness, holding two dimensions. The first dimension refers to the proportion of individuals in the population in question with the condition of interest that are correctly reported and entered in the register. Completeness can be calculated by comparison to another register or data source with high credibility, such as national patient registers containing all admitted patients in all hospitals. Such completeness analyses have been made in the NHFR²⁴⁹. Lower completeness for reoperations compared to primary operations implies that the reported risk of reoperation describes a best-case scenario. We have no reason to believe there is a systematic under-reporting of reoperations for any particular operation method in *Paper II* or for any particular type of IMN in *Paper III*, and thus conclude the risk estimates can be trusted.

Another option to calculate completeness is to review hospital discharge reports, where all patients should be registered, but may be misclassified or lack classification. This is costly and time consuming, but a more accurate way of determining completeness of the register in question. The second dimension is validity of the variables, describing to what extent the variables in fact measure what they were intended to. In this sense, core measures for validity are sensitivity, specificity and positive and negative predictive value. An example relevant to *Papers II and III* is validity of fracture classification.

5.1.3 Register-based studies versus RCTs

Evidence-based medicine (EBM) categorizes various sources of information based upon their ability to provide reliable evidence. Meta-analyses and systematic reviews hover at the top of the hierarchy, followed by randomized clinical trials (RCTs), preferably blinded and controlled (Figure 15). RCTs are considered the golden standard of clinical research, providing the raw material for meta-analyses and systematic reviews. RCTs are designed to verify or falsify a pre-defined hypothesis and allow the researcher to infer causality from observed associations. Pre-defined inclusion and exclusion criteria and the process of randomization ensure homogenous study populations where the only difference between the intervention group and the control group is the intervention in question. Register-based studies are observational studies and are classified as low-level evidence according to the EBM hierarchy.

The Agency for Healthcare Research and Quality define a patient register as “*an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more pre-defined scientific, clinical, or policy purposes.*” Information from a register database reflect real-life clinical practice whereas in RCTs, intervention is decided by a protocol. In a register, information regarding a large number of various patients and over long periods of time is collected, allowing subgroup analyses. In an RCT, a limited number of similar patients are enrolled based on sample size calculation and power analyses, and followed for a limited period, most often with strict inclusion criteria, causing selection bias and low external validity. These studies have high internal validity. The large populations available in register-based studies can provide sufficient information to identify associations regarding rare diagnoses and outcomes with low prevalence and incidence. In these cases, RCTs will be too costly and time-consuming to perform. Rare adverse events are less likely to be captured in RCTs given their limited size and duration, and register-derived information is necessary for surveillance and documentation of safety. Medical decision-making will sometimes have to just rely on register-derived evidence, as RCTs may be impossible or unethical to perform. As discussed previously, there are limitations to register-based studies as well as to RCTs. The risk of bias is higher in a register-based study, such as *Papers II and III*, than in an RCT and must be taken into careful consideration upon designing, conducting, and concluding. Methodological tools like Cox regression analysis and logistic regression allow adjustment for known confounders, but these are not exhaustive and a register-based study can never be as conclusive as an RCT. External validity, however, is higher in register-based studies.

In conclusion, well-designed RCTs and register-based observational studies both provide useful information and should both be considered when creating treatment guidelines.

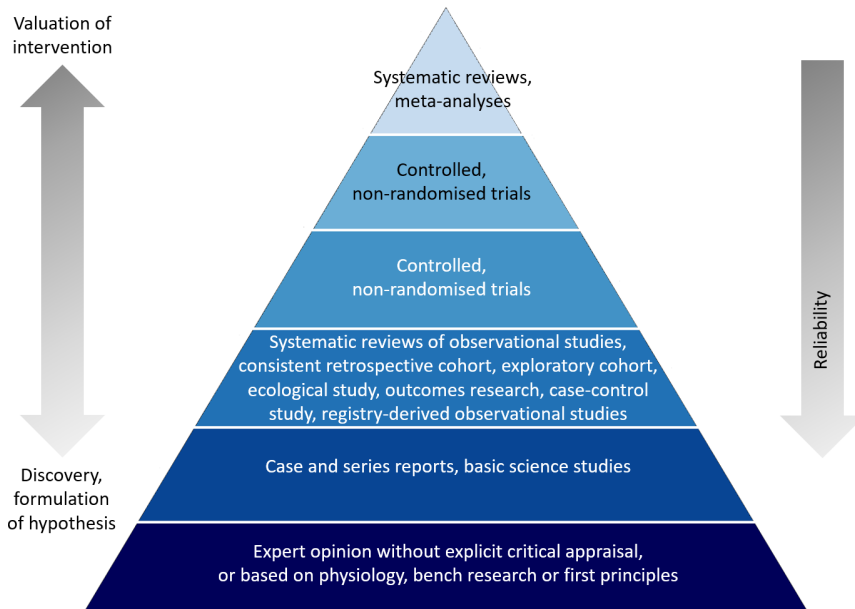


Figure 15: Pyramid of medical evidence hierarchy. Based on: Vandembroucke JP. Observational Research, Randomized Trials and two views of medical science. PLoS Medicine 2008²⁵⁰.

5.1.4 Limitations of the AO/OTA classification model

Detailed classification systems challenge accuracy in reporting when collecting fracture classification data at a largescale, like a national register. The AO/OTA classification is the most commonly used system and is also the classification chosen in the NHFR. After the initial publication in 1990 the system has been revised several times but has had persistent faults regarding inter- and intra-observer reliability^{88,251}. In a clinical setting, particularly the AO/OTA A2 fracture type is challenging as it comprises of both relatively stable and unstable patterns. The AO/OTA classification system was revised in 2018 with the aim of re-classifying and further defining the 31-A2 group. Agreement for the subtypes of extracapsular fracture did not substantially improve; most centres achieved no better than “fair” agreement²⁵². The AO/OTA classification remains sub-optimally reliable with only a “moderate” inter-observer reliability at group level with this falling to “fair” when sub-group classifications are made. Identification of stable and unstable injuries using the new AO/OTA system remains difficult and is challenging to apply with consistent accuracy⁹⁶. There are indications of increased

diagnostic reliability when CT images with 3D reconstruction are available²⁵³, but few centres routinely use CT-scans in the investigation of trochanteric and subtrochanteric fractures. In *Papers II and III* data on sub-classification of the AO/OTA A2 were unavailable. Accordingly, the AO/OTA A2 fractures in these papers may consist of both stable and unstable subtypes of fractures.

5.2 Discussion of results

5.2.1 Subsequent fractures following treatment with intramedullary nail

Patients surviving a hip fracture have a substantially increased risk of a Sffx, as described in several large epidemiological studies^{13,195}. To be able to address this increased risk, orthopaedic surgeons need information regarding a multitude of factors, among these a deeper understanding of the biomechanical impact of the implants. A number of previous studies have investigated the occurrence and morphology of a second hip fracture in general^{13,195} or described the incidence of peri-implant fractures distal to an IMN in particular^{146,196,254}, but no studies have eliminated the impact of previous implants or sequelae in either femur to isolate the impact of the IMN. In *Paper I* we attempted to achieve this distinction by excluding patients with pre-existing implants or fracture sequelae in either femur, and censoring patients receiving a new implant during follow-up. The distribution of Sffxs is illustrated in Figure 16.

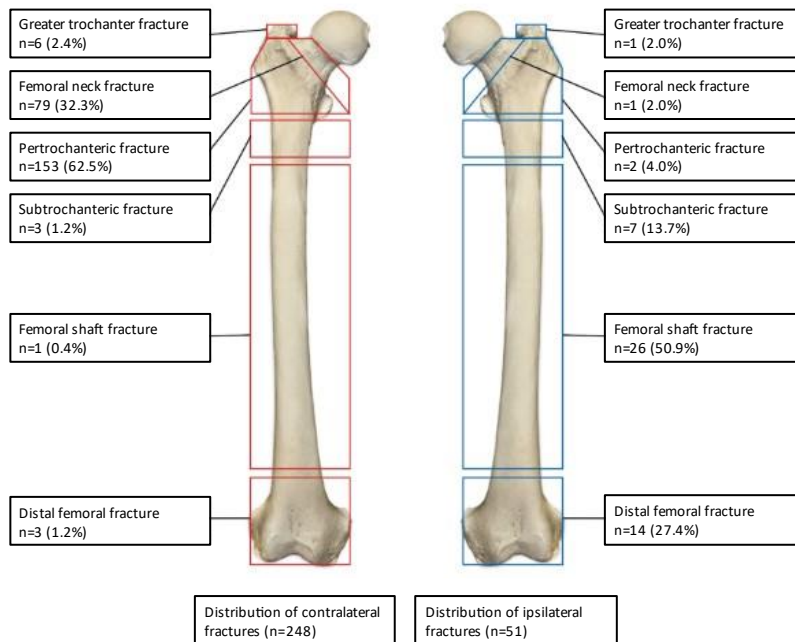


Figure 16: Distribution of subsequent femoral fractures (From *Paper I*)

In *Paper I*, we found a total incidence of a Sffx five times lower on the ipsilateral than on the contralateral side following trochanteric and subtrochanteric fractures treated with an IMN. The risk of femoral shaft and distal metaphyseal Sffx was ten times higher on the ipsilateral than on the contralateral side, given the much lower risk of a femoral shaft fracture than a proximal femur in a native femur. The occurrence of subsequent fractures has been investigated in large observational studies and register based studies^{48,50,51}, and the results of *Paper I* confirm their conclusion that the overall risk of a Sffx is significantly higher than the risk of an index hip fracture, particularly during the first 1-2 years. This also applies to Sffxs occurring after other types of low-energy fractures^{48,255}. According to Center et al⁵², the majority of Sffxs occur in the contralateral side, in agreement with our results. Bögl et al concluded upon overall reduced risk of reoperations and Sffx in particular with the use of IMN with femoral neck protection in the treatment of low energy femoral shaft fractures in a retrospective

study of 897 patients²⁵⁶. An increased risk of Sffx distal to an IMN similar to our findings was reported in the 2022 Cochrane review of surgical treatment of extracapsular hip fractures¹²⁶, a systematic review of 13,568 patients by Norris et al¹⁴⁶, and a register-based study from the Finnish Health Care Register by Yli-Kyyni et al¹⁹⁷. Both the latter were published in 2012, thus including third generation IMNs. In *Paper I*, we discovered an increased risk of a Sffx over a longer period compared to other register-based studies^{50,197}. These studies report a substantially increased risk over the first 12-19 months, but thereafter a normalization of risk comparable to that of an index hip fracture. Schemitsch et al and Balasubramanian et al have reported a persistent higher risk of subsequent hip fracture for 5 years, although declining after a clustering during the first 1.5 years^{48,257}, in line with our results.

The incidence of ipsilateral Sffxs occurring in the shaft and distal metaphyseal area, are consistent with the existing literature^{109,146,197}. In these previous studies, however, there is no information regarding previous implants or sequelae in either femur.

The increased risk of an ipsilateral Sffx in the shaft and distal metaphyseal area in the presence of a short versus a long IMN suggested in our material is in agreement with the results presented by Frisch et al in a retrospective cohort of 169 patients and a recent study from the Danish Multidisciplinary Hip Fracture Registry^{133,258}, but contradictory to the results in other retrospective cohort studies^{199,259}, recent systematic literature reviews^{27,260} and a randomized prospective study of 220 patients²⁶¹. The event of an ipsilateral Sffx is relatively rare and the low quantity analyzed in *Paper I* did not allow us to draw any interferences regarding differences between short and long IMNs.

Several variables are likely to contribute to the observed changes in distribution and morphology in the case of a Sffx following treatment with an IMN. All Sffxs in *Paper I* occurred following a low-energy trauma. The risk of a low-energy Sffx in the shaft, which is normally able to withstand substantial force even in osteoporotic individuals, is increased following the implantation of an IMN, indicate other explanatory factors in addition to general osteoporosis.

Factors amenable to the properties of the implant itself, like the modulus of elasticity are suggested to affect the incidence of adjacent fractures in biomechanical studies²⁶². Ideally, the implant should counter bending, torsion and shear stress adequately, whilst allowing compression at the fracture site. The increased incidence of ipsilateral versus contralateral Sffxs in the shaft and distal metaphyseal area following the implantation of an IMN seen in *Paper I* may indicate a redistribution of forces in the event of a second trauma to the femur – protecting the proximal femur but increasing the risk of fracture distal to the IMN. Morphologic changes in adjacent bone may also increase the incidence of low-energy Sffxs distal to the implanted IMN, as seen in *Paper I*. The implant bears the load following treatment of fractures in the lower extremity, causing bone resorption and localized osteopenia due to stress-shielding as described in association to other implants in fracture treatment as well²⁶³⁻²⁶⁵. Postoperative immobilization causes both localized and general reduction of bone mineral density (BMD) in the femur, confirmed in previous studies^{53,266-268}, and possibly contributes to the increased incidence of ipsilateral Sffxs in the shaft and distal metaphyseal area seen in *Paper I*. Previous studies have targeted impaired balance and an increased risk of falling as major risk factors for index and subsequent hip fractures, and with a higher impact than low BMD²⁶⁹⁻²⁷¹. This is reflected in guidelines for the secondary prevention of hip fractures^{58,72}. Closely related to the increased risk of falling, sarcopenia, as defined by the European Working Group on Sarcopenia in Older Persons (EWGSOP): low muscle mass with low muscle strength or low physical performance, is typically seen in the frail hip fracture patient²⁶⁹. Sarcopenia inevitably develops further after the index hip fracture²⁷²⁻²⁷⁴ due to lower activity, mobility, pain, and avoidance, thereby increasing the risk of falling and the risk of a Sffx⁵³.

Paper I provides a large sample size indicating high external validity. The retrospective design allows a long follow-up time reducing the risk of not identifying Sffxs occurring a long time after the index fracture. The exclusion of patients with pre-existing implants or sequelae in either femur allowed us to investigate the true impact of the IMN in this setting, and our data were validated by comparison to NHFR data. In *Paper I*, information regarding BMD, sarcopenia or fall pattern before the index operation was

not available, but we assumed comparable BMD in both femurs as only patients without previous implants or sequelae in either femur at the time of index fracture were included and patients receiving other implants during follow-up were censored. The existing literature indicates that fracture type may affect the risk of a Sffx^{196,275-277}, but as ipsilateral Sffxs are less frequent, we did not have sufficient sample sizes to allow meaningful subanalyses of index fracture type or stability. *Paper I* only included patients treated with IMNs. A short Gamma3 accounted for 55.8% of implants used, followed by long Gamma3 (21.1%), and although we found a significant impact of the implant on the localization and incidence of a Sffx we cannot conclude whether this effect is specific only to IMNs, just Gamma3, or apply to other femoral implants as well, such as sliding hip screws or arthroplasty femoral stems.

5.2.2 Choice of implants in trochanteric and subtrochanteric fractures

The results in *Paper II* may indicate that IMN is the preferable implant in the treatment of unstable fractures (A2, A3 and subtrochanteric fractures combined), as we found the IMN to be associated with lower reoperation rates than SHS. We found similar reoperation rates for SHS and IMN in the treatment of A1 fractures, but peri-implant fracture was a more prevalent cause of reoperation in patients with A1 fracture treated with an IMN. Otherwise, there were no clinically relevant differences in individual fracture types between SHS and IMN in terms of reoperation rates or PROM data. There was a lower 1-year mortality rate in patients treated with IMN compared to SHS for stable and unstable fractures alike.

The latest Cochrane review from 2022 confirms the conclusion of the 2010 report and continues the recommendation of an SHS for the majority of trochanteric fractures, mainly due to the higher incidence of peri-implant fractures associated with IMNs^{109,148}. The 2022 report describes a higher incidence of infection after treatment with an SHS compared to an IMN, in line with the increased risk of infection following treatment with an SHS in unstable fractures found in *Paper II*, but the overall risk of a complication was higher for patients treated with an IMN in their report, contrary to the results of our analyses of unstable fractures¹⁴⁸. In the Cochrane reports only RCT

and quasi-RCTs are reviewed, whereas *Paper II* is a register-based study, and thus the results are not necessarily comparable. Some research questions, such as differences in rare outcomes like reoperations after trochanteric and subtrochanteric fractures, may be difficult to assess in RCTs. The necessary sample size of an RCT intended to detect significant differences in complications between implants in the treatment of these fractures is estimated to be $n > 1,000$. A recent propensity-matched comparative study of 8,000 patients with A1, A2 and A3 fractures did not identify any major differences between SHS and IMN²⁷⁸. Similar results were reported in a multicentre RCT comparing SHS and IMN (TRIGEN INTERTAN) in 684 patients with A1, A2, A3 and subtrochanteric fractures²⁷⁹.

In *Paper II* we chose to focus on fracture stability indicated through classification rather than individual fracture type when investigating differences in reoperation rate between SHS and IMN. We believe this approach may be clinically more relevant and provide a more robust statistical analysis, as the stability assessment in the AO/OTA classification system is uncertain in the case of A2 fractures. Studies have reported moderate inter- and intra-observer reliability regarding stability assessment, even in the revised AO/OTA classification of 2018, indicating reservations when using this system in day-to-day decision making and analyses of register data^{96,252}. As the A2 fractures are not further subclassified in the NHFR data and account for a considerable amount of investigated fractures, we chose to include A2 in the group of unstable fractures as suggested by Pervez⁸⁸. In previous studies from the NHFR investigating the outcome of SHS versus IMN in the treatment of trochanteric and subtrochanteric fractures, lower reoperation rates were found in for SHS compared with IMN in type A1 fractures one and three years postoperatively¹⁵⁶, and higher reoperation rates for SHS compared with IMN in type A3 and subtrochanteric fractures combined¹⁶³. A2 fractures were not included and remain a less properly defined entity in terms of stability and prediction of outcome. Lateral wall thickness appears to play a key role in the prediction of success with treatment, indicating the majority of A2 fractures should be considered unstable¹⁰³. A2 fractures have been singled out in previous studies comparing IMN and SHS, but the results are conflicting^{25,280,281}. The differences in reoperation rate for

individual fracture patterns found in the previous NHFR studies were not confirmed in *Paper II*, but when analysing all unstable fractures pooled together, there was a statistically significant lower risk of reoperation with the use of IMN compared to SHS. Our results support the conclusion in the previous study from the NHFR that recommended the use of IMN in the treatment of A3 and subtrochanteric fractures¹⁶³. In *Paper II* we included A2 fractures in the analysis of unstable fractures, thus also extending the recommendation to this group of fractures.

In *Paper II* subanalyses of cause of reoperation revealed more cases of infection as primary cause in patients with unstable fractures treated with SHS compared to those treated with IMN, persistent in subanalyses of A2 and A3 fractures. The risk of complications leading to revision with THA was also higher in patients with unstable fractures treated with an SHS, persistent in subanalyses on fracture type. This is contrary to a recent register-based study from the Swedish Fracture Register (SFR), concluding there is probably no difference in conversion rate to THA after IMN or SHS for extracapsular hip fractures, also including subanalyses regarding fracture type. That study did in fact find a higher risk of conversion to THA in A2 fractures treated with an IMN, although the authors did not perceive this difference as clinically important²⁸². In the treatment of stable (A1) fractures, peri-implant fracture was a more prevalent cause of reoperation with the use of IMN, but the total reoperation rate was comparable between SHS and IMN. Peri-implant fractures were not overrepresented as cause of reoperation in A2, A3 and subtrochanteric fractures individually or pooled together. Existing literature is inconclusive regarding the possible beneficial effects of a long versus a short IMN¹⁹⁹. Although a cephalomedullary device is recommended in international guidelines for the treatment of unstable intertrochanteric fractures, reverse obliquity fractures and subtrochanteric fractures, no recommendation regarding short or long IMN is given^{58,73}. The Norwegian national guidelines include a specification of a long IMN in the treatment of A3 and subtrochanteric fractures⁷⁴. Two meta-analyses from 2017²⁶⁰ and 2020¹³⁴, and a retrospective study by Boone in 2014²⁸³, among others have not found any differences in risk of reoperation between short and long IMNs in the treatment of unstable trochanteric fractures. There is, however, a recent study from the Danish Hip Fracture Register reporting higher risk of reoperation when a short IMN

is used in subtrochanteric fractures¹³³. In *Paper II* we were not able to compare outcomes of long vs short nails, nor outcomes of SHS vs SHS with TSP, given the heterogeneity of the groups. A3 and subtrochanteric fractures were almost exclusively treated with a long IMN/SHS with TSP and A1 fractures almost exclusively treated with a short IMN/regular SHS.

In *Paper II* we focused on time to reoperation, and the results from Cox regression analyses are straightforward to interpret. The statistical interpretation from Kaplan-Meier and Cox analysis for analysis of reoperation have been advocated^{284,285}.

We found a lower mortality rate in patients treated with IMN compared to patients treated with SHS, applicable to both stable and unstable fractures. Previous studies have, contradictory to our result, found a higher mortality in patients treated with IMN compared to SHS^{161,162}, or claim choice of implant does not affect mortality^{148,286}. The studies in question are not fully comparable. As opposed to the study of Whitehouse et al¹⁶¹ our study included both trochanteric and subtrochanteric fractures, whereas they only included unstable A2 and A3 fractures. Pathological fractures were excluded, and our patients were treated during a later period. Wolf et al¹⁶² only investigated A1 and A2 fractures in their register-based study where an IMN was associated with higher 30-day mortality. Pathological fractures were not explicitly excluded. A large register-based study from the Danish Fracture Database investigating mortality in trochanteric fractures (A1, A2, A3) concludes upon a higher crude mortality in patients treated with IMN compared to SHS at 30 days, 90 days and one year, but the differences were not significant after adjusting for confounders²⁸⁷. A recent study by Lynch-Wong et al found a lower 30-day mortality in patients treated with IMN compared to SHS, including all trochanteric fracture types but excluding subtrochanteric fractures²⁸⁸. The 2022 Cochrane report similarly concludes that there is probably no significant difference in mortality risk between patients treated for extracapsular hip fractures with IMN and SHS¹⁴⁸. The discrepancy of results investigating mortality and choice of implant may indicate it is not the most important factor in predicting mortality in this group of patients.

The choice of implant is an important issue that affects patient outcomes, at least for certain groups of patients and fractures, but other factors might be even more important. More emphasis should probably be placed on fracture reduction, correct implant positioning and pre- and postoperative care to reduce reoperation rates and improve patient satisfaction⁷⁴. Furthermore, economic considerations inevitably play a role in choice of implants in all fracture treatment¹⁵⁷. In a public healthcare system under increasing economic pressure world-wide as well as expectations of evidence based best practice guidelines including socioeconomic evaluations, orthopaedic surgeons cannot expect to be able to choose implant based on preference, habit or personal conviction.

The RCTs available investigating different treatment options for hip fractures in general, including trochanteric and subtrochanteric fractures, rarely include patient-relevant outcome measures like pain, activities of daily living (ADL), health-related quality of life and mobility¹⁴⁸. The NHFR monitors PROMs using a visual analogue scale to describe pain and overall satisfaction, as well as the EQ-5D-3L containing dimensions describing mobility and ADL. The EQ-5D has evolved over time into a validated and relevant tool to measure softer, and less accessible outcomes for this patient population^{238,289}. In *Paper II*, patients with unstable fractures treated with an SHS reported lower EQ-5D-3L index score one-year post-fracture compared to patients treated with an IMN, and a lower VAS satisfaction score. The differences in mean EQ-5D-3L index score and mean VAS satisfaction score between the two groups were small, but a sizable number of patients in one of the groups may still have reported a clinically significant better outcome. The PROM values registered one year postoperatively do not correspond directly to the pre-fracture values provided in the four-month questionnaires, and do not represent a delta-value. Additional analyses to identify the number of patients returning to their pre-fracture EQ-5D-3L score, VAS satisfaction score and walking ability were performed, confirming the significant differences between patients treated with SHS versus IMN found in the crude comparison of PROM values one year postoperatively. Analyses of PROM data must be interpreted with great reservation, and we cannot draw any interferences because of the large amount of missing data. We chose to include the PROM analyses in *Paper II*

as we do not have reason to believe the number of non-responders is skewed. Baseline data were similar for the compared groups and as described, the delta values when coupling pre-fracture PROMs and PROMs one year postoperatively for the patients having responded to both questionnaires confirmed the observed differences for the whole population, although the incomplete datasets cause great uncertainty. After one year, 24% of the study population had died, and only 52% of the remaining patients answered the questionnaire.

The large sample size studied in *Paper II* provides great statistical power and external validity as register data describes the average surgeon, hospital and patient. Large study populations and a long perspective are required to reveal statistically significant differences in implant performance, and an adequately powered RCT with sufficient follow-up time nearly impossible to perform. Register-based studies allow investigation of rare outcomes like reoperations and subanalyses of smaller groups like the A3 and subtrochanteric fractures but is prone to confounding as all relevant variables for all future studies cannot be foreseen when establishing a register. Furthermore, in order to achieve high completeness questionnaires have to be short and concise. Selection bias is not likely in *Paper II* as baseline characteristics were comparable for the two groups of patients, and choice of implant decided upon by tender at a regional level and not by the individual orthopaedic surgeon.

Register-based studies cannot claim to prove causality. Missingness is an issue in register-based research like *Paper II* and can only describe associations. In the NHFR as in other national registries, completeness regarding reoperations is lower than for primary operations, namely 80% versus 88%²⁹⁰. We do not have reason to believe there is a discrepancy in reporting of reoperations between implants although underreporting of complications certainly is a possible bias in *Paper II*. All IMN and SHS brands were grouped together, respectively, and we cannot be ascertained our results are representative for all implant brands. Further, we must suspect fracture classification errors affecting interpretation of our results, as NHFR data do not contain x-ray images. Thus, we were not able to confirm correct classification of fracture type or identify combinations of fracture patterns. Previous studies have indicated that there is a fair

amount of classification errors, even with the most recently updated AO/OTA classification system^{88,96,252}. In *Paper II* all A2 fractures were considered unstable, although A2-1 fractures have a stable fracture pattern. Subgroups of the AO/OTA fracture types cannot be identified in the NHFR data, and as all other subgroups of A2 fractures are unstable we believe including all A2 fractures is sound. This increases statistical power in our analyses and may be more clinically relevant.

5.2.3 Comparison of intramedullary nails

In *Paper III*, the comparison of different short IMN brands in all fracture types combined revealed a slightly increased reoperation rate associated with the use of a short TRIGEN INTERTAN nail, but the clinical significance is questionable. Although most of these reoperations occurred in patients treated for A3 and subtrochanteric fractures no significant differences were detected in the analyses of individual fracture types, indicating similar outcomes. In the comparison of different long IMNs, there was a significantly increased risk of reoperation with use of a long TRIGEN TAN/FAN nail compared to the long Gamma3. Sub-analyses confirmed the increased risk of reoperation in A1, A2, and subtrochanteric fractures. Risk of reoperation increased further when the operating surgeon had less than three years of experience.

Previous studies have identified cut-out as the major cause of failure leading to reoperation^{219,291}. In *Paper III* hardware failure was the most common cause of reoperation for short and long nails. This does not rule out the possibility of a concomitant cut-out, in line with existing literature. In the NHFR form, more than one cause of reoperation may be given. To avoid counting each reoperation more than once in *Paper III*, the following hierarchy was chosen to identify the more serious cause: infection, peri-implant fracture, hardware failure, cut-out, non-union, unspecified sequelae (treated with THA and registered to the Norwegian Arthroplasty Register), pain alone, other. Thus, cut-out may have been present in addition to hardware failure, but not registered as main cause of reoperation.

To the best of our knowledge, *Paper III* is the first national register-based study investigating reoperation risk including all IMNs in general use. Previous studies have compared IMN and SHS^{148,292}, short and long nails^{28,134,135,199,261,293-295} or two different nail designs^{27,199,259,296}. A clear benefit to any particular IMN design or to a long nail in the treatment of unstable intertrochanteric and subtrochanteric fractures has not been established. The AAOS and NICE guidelines advocate the use of an IMN in the treatment of unstable fractures, but do not specifically recommend a long IMN^{58,73}. The Norwegian national guidelines have a specification of a long IMN⁷⁴. The slightly increased reoperation risk with the use of the short TRIGEN INTERTAN, primarily in unstable fracture patterns, seen in *Paper III* is far from conclusive, and the number of patients in some subgroups was too low to compare short and long nails in individual fracture types. Further research is certainly indicated, supported by recent study from the DMHFR suggesting there may be a benefit to long IMNs in unstable fracture patterns¹³³.

In order to obtain a stable construct allowing early weightbearing, adequate fracture reduction and correct positioning of the lag screw are crucial factors^{204,293,297}. New variations of IMNs have been introduced over the past two decades and features like a helical blade and double or integrated lag screw have been investigated regarding risk of reoperation^{293,294}, but there is no clear evidence of superiority of any particular design. The helical blade is intended to increase adjacent bone density and reduce risk of cut-out. In *Paper III* the nail brands providing a helical blade (short and long PFNA) had comparable revision rates to the other brands, even when investigating risk of cut-out specifically. The introduction of double or integrated lag screws is intended to reduce the risk of failure due to rotational instability and fracture collapse, and although smaller series of patients and biomechanical studies may indicate an effect²⁹⁸, definite clinical evidence to support this assumption is lacking^{299,300}. In *Paper III*, nail brands with double or integrated lag screws were included, namely the long TRIGEN TAN/FAN, the long T2 Recon nail, and short and long TRIGEN INTERTAN nails respectively. The results of our analyses did not indicate any significant benefit of these features, in fact the short TRIGEN INTERTAN and the long TRIGEN TAN/FAN had

a higher risk of reoperation when analysing all fracture types combined. There were no statistically significant differences in sub-analyses regarding individual fracture types, but as a long nail is recommended in the treatment of A3 and subtrochanteric fractures in the Norwegian guidelines⁷⁴, the number of such fractures treated with a short TRIGEN INTERTAN was low. Most failures occurred when used in unstable fracture patterns. This tendency could not be found in the subanalyses of other short nail brands. The TRIGEN TAN/FAN had a higher reoperation rate in all fracture types except A3. Hardware failure, theoretically including breakage of the nail or lag screws, exaggerated sliding and failure due to a z-effect, was the most frequently observed cause of reoperations in the short TRIGEN INTERTAN group and the long TRIGEN TAN/FAN group. The T2 Recon provides double lag screws, similar to the TRIGEN TAN/FAN, but did not have a higher rate of reoperations, indicating this particular feature may not explain the increased risk of reoperations.

The large sample size in *Paper III* provides high external validity and statistical power. Some fracture types are less common and certain IMN brands used less frequently, and although this causes uncertainty in the analysis of our register-based studies as well, a sufficiently powered RCT with a timeframe long enough to detect differences would be very difficult to perform. Analyses of data from the NHFR, given its high coverage and completeness², allowed analyses of subgroups and identification of statistically significant differences in baseline characteristics and rare outcomes like reoperations, and sample sizes were large enough to compare various brands of short and long nails used in the treatment of different fracture types. The risk of selection bias is low as baseline characteristics were similar for patients in the compared groups, and the choice of implant is undertaken by a tender process in the Norwegian health care system.

Registration completeness in the NHFR is calculated by comparison to information from the Norwegian National Population Register. Underreporting of complications is a possible bias in *Paper III*, as registration completeness in the NHFR is lower for reoperations than for primary operations²⁹⁰. The coverage is high though, as 100% of Norwegian hospitals report to the NHFR, and systematic differences in the reporting of reoperations between implants is unlikely. There is a documented difference in

reporting practice between the hospitals in Norway², but none of the implants included in the analyses in *Paper III* were limited to one hospital alone. Furthermore, none of the implants were used exclusively in hospitals with low reporting percentage, reducing the risk of underreporting of reoperations related to particular implants.

Given the different designs of some of the implants included in *Paper III*, one might expect unique hardware failure modes. Unfortunately, mechanical complications are not specified in any further detail in the NHFR than hardware failure, cut-out, and non-union, and more specific patterns of failure cannot be identified. Several factors related to surgical treatment, but not to choice of implant are associated with an increased risk of reoperation, like malreduction or suboptimal nail placement^{204,291,297}. X-ray images are not available in the NHFR and we were not able to identify such confounders. Furthermore, the higher risk of reoperation found when a short TRIGEN INTERTAN nail was used by surgeons with more than three years of experience is likely to be influenced by unknown confounders. Challenging fracture patterns like reverse obliquity and subtrochanteric fractures are probably more often dealt with by more experienced surgeons. We did not have access to x-ray images and this possible distribution bias could neither be confirmed nor ruled out.

In the analyses in *Paper III*, we found that some stable fractures (A1) had received a long IMN and some unstable fractures (A3 and subtrochanteric) a short IMN, eligible for all brands. The Norwegian national guidelines specifically recommend a long nail in the treatment of A3 and subtrochanteric fractures and an SHS or a short IMN in the treatment of A1 fractures⁷⁴. The deviations identified in *Paper III* indicate variable adherence to these guidelines in the Norwegian orthopaedic population. Internationally recognized guidelines like the AAOS and NICE do not include specification of nail length^{58,73}. Better outcome of a long IMN in reverse obliquity and subtrochanteric fractures compared to a short IMN has not been irrevocably confirmed in the existing literature^{133,134,260,283}. We were not able to compare short and long IMNs in the treatment of different fracture types in *Paper III*. We did find a slightly increased reoperation rate following treatment with the short TRIGEN INTERTAN, dominantly

A3 and subtrochanteric fractures, but there was no correlation between reoperation rate and individual fracture types for neither short TRIGEN INTERTAN nails nor any of the other short IMN brands. We cannot draw any inferences due to the limited number of short IMNs used in unstable fracture types.

In *Paper III*, we were not able to establish if surgeon experience influences performance of the different nail brands, as the majority of operations were performed by surgeons with more than three years of experience. The NHFR data do not describe surgeon volume, but the learning curve is likely to be comparable for all IMN brands. Furthermore, we cannot be ascertained that reported experience does in fact reflect experience with hip fracture surgery in particular, although that is specified in the NHFR form. The operating surgeon may in some cases just have stated his or her experience in orthopaedic surgery. One previous study from Denmark has suggested that experienced surgeons have better outcomes when treating unstable trochanteric and subtrochanteric fractures^{104,182}, but this was not confirmed in a previous study based on NHFR data¹⁸².

6 Conclusions

Paper I:

- An intramedullary nail significantly changes the fracture pattern in the case of a second low-energy trauma, reducing the risk of subsequent proximal ipsilateral femoral fractures and increasing the risk of subsequent ipsilateral femoral fractures in the shaft and distal metaphyseal area compared with the native contralateral femur.
- The overall risk of Sffx is substantially higher in the contralateral, native femur indicating the protective effect of the IMN with regard to a proximal ipsilateral Sffx is much higher than the increased risk of sustaining an ipsilateral peri-implant fracture.

Paper II:

- IMN had lower reoperation rate after one and three years than SHS for unstable trochanteric and subtrochanteric fractures, but not for stable fractures or individual fracture types.
- One-year mortality rate for unstable and stable fractures was lower in patients treated with IMN.
- Patients with unstable fractures treated with an SHS reported a lower EQ-5D-3L index score, inferior walking ability and were less satisfied one year postoperatively than patients treated with an IMN.

Paper III:

- Reoperation rates for different brands of short nails in widespread use in Norway were comparable.
- Use of a short TRIGEN INTERTAN was associated with a subtly increased risk of reoperation compared to the short Gamma3. Most failures occurred when used in unstable fractures contrary to national Norwegian guidelines for treatment of unstable intertrochanteric fractures, reverse obliquity and subtrochanteric fractures, where the recommendation of a long nail is specified, and the clinical importance of this difference is uncertain.
- The TRIGEN TAN/FAN nail was associated with a higher risk of reoperation compared to other long nails in the treatment of trochanteric and subtrochanteric fractures, applicable to both less and more experienced surgeons.

7 Implications of studies

This thesis elaborates on the use of intramedullary nails in the treatment of trochanteric and subtrochanteric fractures. In *Paper I* we identified a significant alteration of fracture incidence, localization and morphology indicating a significantly increased risk of a contralateral proximal femoral fracture and a significantly reduced incidence of ipsilateral proximal fractures. The incidence of ipsilateral fractures in the shaft and distal metaphysis was significantly increased, despite the fact that even an osteoporotic femoral shaft should be able to resist the applied forces in the case of a low energy trauma like a fall from standing height. Given the serious nature of peri-implant fractures, further biomechanical studies and clinical research to investigate why IMNs lead to increased fracture rates distal to the implant are called for, as well as similar studies investigating the risk of Sfx after other intra- and extramedullary implants in the treatment of proximal femoral fractures. The results of *Paper II* support the recommendations in national and international guidelines suggesting an IMN should be used in A3 and subtrochanteric fractures. Furthermore, we collapsed the presumed unstable fracture types and included A2 fractures in the group of unstable fracture patterns, as only A1 fractures can with certainty be regarded as stable. This decision may of course be questioned, but the existing literature confirms the uncertainty of stability assessment particularly in A2 fractures. Including A2 fractures in the group of unstable fractures might be more clinically relevant and provide a more robust statistical analysis.

The options for surgical treatment of trochanteric and subtrochanteric fractures has been extensively investigated and compared over the past two decades. Although the heterogeneity of A2 fractures still impedes a conclusion upon ideal treatment for this particular group, the orthopaedic community should probably focus on other factors than implant choice to improve outcome for these fragile patients – secondary fracture prevention, optimisation of physical and mental health, nutrition and maintenance of physical and social activity after a hip fracture. This has also been suggested by senior researchers in the hip fracture register communities³⁰¹. Nevertheless, all modes of treatment must be monitored, and with the development of large national registers with

high completeness and validity, we have a valuable tool for surveillance of outcome. New implants in fracture treatment are introduced regularly, as demonstrated in *Paper III*, and not necessarily preceded by RCTs comparing them to existing implants as complications are relatively rare and reliable results are difficult to obtain through RCTs given their limited sample sizes and follow-up time. Thus, register-based studies will continue to be important sources in evidence-based treatment of hip fractures.

8 Future perspectives

8.1 Validation of classification models of trochanteric and subtrochanteric fractures

During the research resulting in *Papers I-III* we have become further aware of the uncertainty regarding accuracy in the classification of trochanteric and subtrochanteric fractures. In *Paper I*, all x-ray images were reviewed, revealing several cases of misclassification. A1 fractures were seldom misclassified, but we detected considerable confusion regarding the classification of A2, A3 and subtrochanteric fractures. We have only reviewed images relevant to *Paper I*, and thus only from patients treated at Østfold Hospital Trust. Previous studies have highlighted only moderate to fair inter- and intraobserver reliability in the AO/OTA classification system regarding proximal femur fractures, particularly with regards to stability assessment of A2 fractures^{96,252}. This represents a non-negligible uncertainty when dealing with NHFR data, as we cannot be sure if the classification given in the form filled in by the surgeons is correct. This may have profound implications and we believe a validation of the classification model would be valuable. On the same note, the A2 fractures represent a large percentage of the total number of trochanteric fractures, and it is in this group the uncertainty of not just stability but also choice of implant is most evident. Given the higher cost of an IMN compared to an SHS it is important to determine whether there actually is an advantage to the IMN in this particular group.

8.2 The importance of intramedullary nail length

Nationally and internationally, there is at least a reasonable degree of agreement that A3 and subtrochanteric fractures should be treated with an IMN^{58,73,74}. There is still uncertainty regarding the indications of a short versus a long IMN in the existing literature^{133,134,260,283}. Further studies to determine whether there is an advantage to a

long nail in any particular fracture types are necessary as there is an additional cost to these implants as well as longer operation time and blood loss.

8.3 Peri-implant fractures

In *Paper I*, we aimed to investigate the true impact of an IMN by excluding patients with pre-existing implants or sequelae in either femur. Given the serious nature and consequences of a peri-implant fracture, similar studies regarding the impact of other extra- and intramedullar implants such as SHS and femoral stems would be valuable to guide and substantiate implant choice in the treatment of hip fractures.

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Appendices

Appendix 1: Operation form, Norwegian Hip Fracture Register

Appendix 2: Patient questionnaire, Norwegian Hip Fracture Register

**NASJONALT HOFTEBRUDDREGISTER**

Nasjonalt Register for Leddproteser
 Helse Bergen HF, Ortopedisk klinikk
 Haukeland universitetssjukehus
 Møllendalsbakken 7
 5021 BERGEN
 Tlf: 55973742

F.nr. (11 sifre).....

Navn:.....

(Skriv tydelig ev. pasientklirelapp – spesifiser sykehus.)

Sykehus:.....

HOFTEBRUDD

PRIMÆRE OPERASJONER PÅ BRUDD I PROKSIMALE FEMURENDE og ALLE REOPERASJONER, inkludert lukket reponering av hemiproteser. Ved primæroperasjon med totalprotese og ved reoperasjon til totalprotese brukes kun hofteproteseskjema. Alle produktklirelapper settes i merket felt på baksiden av skjemaet.

AKTUELLE OPERASJON 1 Primæroperasjon 2 Reoperasjon**SIDE (ett kryss)** (Bilateral opr. = 2 skjema) 1 Høyre 2 Venstre**OPR TIDSPUNKT** (dd.mm.åå) | | | | | | | | kl | | | |**BRUDD TIDSPUNKT** (dd.mm.åå) | | | | | | | | kl | | | |

Dersom det er usikkerhet om bruddtidspunkt, fyll ut neste punkt.

TID FRA BRUDD TIL OPERASJON I TIMER 1 0-6 2 >6-12 3 >12-24 4 >24-48 5 >48**KOGNITIV SVIKT** 0 Nei 1 Ja (Se test på baksiden) 2 Usikker**ASA-KLASSE** (se bakside av skjema for definisjon)

- 1 Frisk
- 2 Asymptomatisk tilstand som gir økt risiko
- 3 Symptomatisk sykdom
- 4 Livstruende sykdom
- 5 Moribund

TYPE PRIMÆRBRUDD (ÅRSÅK TIL PRIMÆROPERASJON) (Kun ett kryss)

Se baksiden for klassifikasjon

- 1 Lårhalsbrudd udislokert (Garden 1 og 2)
- 2 Lårhalsbrudd dislokert (Garden 3 og 4)
- 3 Lateralt lårhalsbrudd
- 4 Pertrokantært tofragment (AO klassifikasjon A1)
- 5 Pertrokantært flerfragment (AO klassifikasjon A2)
- 6 Intertrokantært (AO klassifikasjon A3)
- 7 Subtrokantært
- 7 Annet, spesifiser

TYPE PRIMÆROPERASJON (Kun ett kryss)

(Fyller ut bare ved primæroperasjon - eget skjema for totalproteser)

(Fest produktklirelapp på baksiden eller spesifiser nøyaktig produkt)

- 1 To skruer eller pinner
- 2 Tre skruer eller pinner
- 3 Bipolar hemiprotese
- 4 Unipolar hemiprotese
- 5 Glideskrue og plate
- 6 Glideskrue og plate med trokantær støtteplate
- 7 Vinkelplate
- 8 Kort margnagle uten distal sperre
- 9 Kort margnagle med distal sperre
- 10 Lang margnagle uten distal sperre
- 11 Lang margnagle med distal sperre
- 12 Annet, spesifiser

Navn / størrelse og katalognummer

ÅRSÅK TIL REOPERASJON (Flere enn ett kryss kan brukes)

- 1 Osteosyntesevikt/havar
- 2 Ikke tilhelet brudd (non-union/pseudartrose)
- 3 Caputnekrose (segmentalt kollaps)
- 4 Lokal smerte pga prominierende osteosyntesemateriale
- 5 Brudd tilhelet med feilstilling
- 6 Sårinfeksjon – overfladisk
- 7 Sårinfeksjon – dyp
- 8 Hematom
- 9 Luksasjon av hemiprotese
- 10 Osteosyntesematerialet skåret gjennom caput
- 11 Nytt brudd rundt implantat
- 12 Løsning av hemiprotese
- 13 Annet, spesifiser

TYPE REOPERASJON (Flere enn ett kryss kan brukes)

(Fest produktklirelapp på baksiden eller spesifiser nøyaktig produkt)

- 1 Fjerning av implantat (Brukes når dette er eneste prosedyre)
- 2 Girdlestone (= fjerning av implantat og caput)
- 3 Bipolar hemiprotese
- 4 Unipolar hemiprotese
- 5 Re-osteosyntese
- 6 Debridement for infeksjon
- 7 Lukket reposisjon av luksert hemiprotese
- 8 Åpen reposisjon av luksert hemiprotese
- 9 Annet, spesifiser

Navn / størrelse og katalognummer

FIKSASJON AV HEMIPROTESE

(For totalprotese sendes eget skjema til hofteproteseregisteret)

- 1 Usementert 1 med HA 2 uten HA
- 2 Sement med antibiotika Navn.....
- 3 Sement uten antibiotika Navn.....

PATOLOGISK BRUDD (Annen patologi enn osteoporose) 0 Nei 1 Ja, type.....**TILGANG TIL HOFTELEDDET VED HEMIPROTESE** (Kun ett kryss)

- 1 Fremre (mellom sartorius og tensor)
- 2 Anterolateral (mellom gluteus medius og tensor)
- 3 Direkte lateral (transgluteal)
- 4 Bakre (bak gluteus medius)
- 5 Annet, spesifiser

ANESTESITYPE 1 Narkose 2 Spinal 3 Annet, spesifiser**PEROPERATIVE KOMPLIKASJONER** 0 Nei 1 Ja, hvilke(n).....**OPERASJONSTID** (hud til hud).....minutter.**ANTIBIOTIKAPROFYLAKSE** 0 Nei 1 Ja

Navn	Dosering	Varighet i timer
Medikament 1.....timer
Medikament 2.....timer
Medikament 3.....timer

TROMBOSEPROFYLAKSE 0 Nei 1 Ja: Første dose 1 Preoperativt 2 Postoperativt

Medikament 1	Dosering opr.dag.....
.....	Dosering videre	Varighet døgn
Medikament 2	Dosering	Varighet døgn

FAST TROMBOSEPROFYLAKSE 0 Nei 1 Ja, type:.....**FIBRINOLYSEHEMMER** 0 Nei 1 Ja, medikament : Dosering**OPERATØRERFARING**Har en av operatørene mer enn 3 års erfaring i hoftebruddkirurgi? 0 Nei 1 Ja

Lege.....
 Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

RETTLEDNING

Registreringen gjelder alle operasjoner for hoftebrudd (lårhals, pertrokantære og subtrokantære) og alle reoperasjoner, også reposisjoner, på pasienter som er primæroperert og reoperert for hoftebrudd. **Ved primæroperasjon med totalprotese og ved reoperasjon til totalprotese sendes bare skjema til hofteproteseregisteret.**

Ett skjema fylles ut for hver operasjon. Originalen sendes Haukeland universitetssjukehus og kopien lagres i pasientens journal. Pasientens fødselsnummer (11 sifre) og sykehuset må være påført. Aktuelle ruter markeres med kryss. Pasienten skal på eget skjema gi samtykke til registrering i Nasjonalt hoftebruddregister.

Kommentarer til enkelte punkt:

OPERASJONS- OG BRUDDTIDSPUNKT

Operasjonstidspunkt (dato og klokkeslett) må føres opp på alle primæroperasjoner. Det er også sterkt ønskelig at dato og klokkeslett for *bruddtidspunkt* føres opp. Dette bl.a. for å se om tid til operasjon har effekt på prognose. (Hvis en ikke kjenner klokkeslettet for bruddtidspunkt lar en feltet stå åpent. En må da prøve å angi omtrentlig tidsrom fra brudd til operasjon på neste punkt).

Ved reoperasjon er ikke klokkeslett nødvendig.

KOGNITIV SVIKT

Kognitiv svikt kan eventuelt testes ved å be pasienten tegne klokken når den er 10 over 11. En pasient med kognitiv svikt vil ha problemer med denne oppgaven.

ASA-KLASSE (ASA=American Society of Anesthesiologists)

ASA-klasse 1: Friske pasienter som røyker mindre enn 5 sigaretter daglig.

ASA-klasse 2: Pasienter med en asymptomatisk tilstand som behandles medikamentelt (f.eks hypertensjon)

eller med kost (f.eks diabetes mellitus type 2) og ellers friske pasienter som røyker 5 sigaretter eller mer daglig.

ASA-klasse 3: Pasienter med en tilstand som kan gi symptomer, men som holdes under kontroll medikamentelt

(f.eks moderat angina pectoris og mild astma).

ASA-klasse 4: Pasienter med en tilstand som ikke er under kontroll (f.eks hjertesvikt og astma).

ASA-klasse 5: Moribund/døende pasient

GARDENS KLASSIFISERING AV LÅRHALSBRUDD

Garden 1: Ikke komplett brudd av lårhalsen (såkalt innkilt)

Garden 2: Komplet lårhalsbrudd uten dislokasjon

Garden 3: Komplet lårhalsbrudd med delvis dislokasjon. Fragmentene er fortsatt i kontakt, men det er feilstilling av lårhalsens trabekler.

Caputfragmentet ligger uanatomisk i acetabulum.

Garden 4: Komplet lårhalsbrudd med full dislokasjon. Caputfragmentet er fritt og ligger korrekt i acetabulum slik at trabeklene er normalt orientert.

AO KLASSEFIKASJON AV TROKANTÆRE BRUDD



A1: Pertrokantært tofragment brudd

A2: Pertrokantært flerfragment brudd

A3: Intertrokantært brudd

Subtrokantært brudd*

*Subtrokantært brudd: Bruddsentrum er mellom nedre kant av trokanter minor og 5 cm distalt for denne.

REOPERASJONSÅRSÅK

Dyp infeksjon defineres som infeksjon som involverer fascie, protese, ledd eller periprotetisk vev.

IMPLANTAT

Implantattype må angis entydig. Produktklistrelapp er ønskelig for å angi katalognummer for osteosyntesematerialet eller protesen som er brukt.

PEROPERATIVE KOMPLIKASJONER

Vi ønsker også å få meldt dødsfall på operasjonsbordet og peroperativ transfusjonstrengende blødning.

ANTIBIOTIKAPROFYLAKSE

Her føres det på hvilket antibiotikum som er blitt benyttet i forbindelse med operasjonen. Det anføres dose, antall doser og profylaksens varighet. F.eks. Medkament 1: Keflin 2g x 4, med varighet 4,5 timer.

TROMBOSEPROFYLAKSE

Medikament, dose og antatt varighet av profylaksen skal angis separat for operasjonsdagen og senere. Det skal også oppgis om pasienten står fast på tromboseprofylakse (AlbyE, Marevan, Plavix ol).

FIBRINOLYSEHEMMER

Her føres det på om en benytter blødningsreducerende legemidler i forbindelse med operasjonen (f.eks. Cyklokapron).

Kontaktpersoner vedrørende registreringsskjema er:

Overlege Jan-Erik Gjertsen, Ortopedisk klinikk, Haukeland universitetssjukehus. Tlf. 55 97 56 86 (email: jan-erik.gjertsen@helse-bergen.no)

Konsulent Nasjonalt Hoftebruddregister: Randi Fumes. Tlf. 55 97 37 42 (email: nrl@helse-bergen.no)

Internett: <http://nrlweb.ihelse.net/>



NASJONALT HOFTEBRUDDREGISTER

Nasjonalt Register for Leddproteser
Helse Bergen HF, Ortopedisk klinikk
Haukeland Universitetssykehus
Møllendalsbakken 7
5021 BERGEN

PASIENTSPØRRESKJEMA NASJONALT HOFTEBRUDDREGISTER

1. Dato for utfylling av skjema: |__| |__| |__|

2. Spørreskjemaet er besvart av:

¹ Meg selv

eller ved hjelp av....(kryss av i ruten som gjelder)

² Slektning (ektefelle, barn)

³ God venn eller annen nærstående

⁴ Annen privat person

⁵ Hjemmesykepleier/hjemmehjelp

⁶ Annen person, angi hvem: _____



NASJONALT HOFTEBRUDDREGISTER

Nasjonalt Register for Leddproteser
Helse Bergen HF, Ortopedisk klinikk
Haukeland Universitetssykehus
Møllendalsbakken 7
5021 BERGEN

I de neste 5 spørsmålene ønsker vi å vite hvordan livssituasjonen din var FØR du fikk hofte/lårhalsbruddet som du ble operert for.

3. Hvordan opplevde du gangevnen din?

- ¹ Jeg hadde ingen problemer med å gå omkring
- ² Jeg hadde litt problemer med å gå omkring
- ³ Jeg var sengeliggende

4. Hvordan klarte du personlig stell?

- ¹ Jeg hadde ingen problemer med personlig stell
- ² Jeg hadde litt problemer med å vaske meg eller kle meg
- ³ Jeg klarte ikke å vaske meg eller kle meg

5. Hvordan klarte du dine vanlige gjøremål (f.eks. arbeid, studier, husarbeid, familie- og fritidsaktiviteter)?

- ¹ Jeg hadde ingen problemer med å utføre mine vanlige gjøremål
- ² Jeg hadde litt problemer med å utføre mine vanlige gjøremål
- ³ Jeg var ute av stand til å utføre mine vanlige gjøremål

6. Smerter eller ubehag?

- ¹ Jeg hadde verken smerte eller ubehag
- ² Jeg hadde moderat smerte eller ubehag
- ³ Jeg hadde sterk smerte eller ubehag

7. Angst eller depresjon?

- ¹ Jeg var verken engstelig eller deprimer
- ² Jeg var noe engstelig eller deprimer
- ³ Jeg var svært engstelig eller deprimer



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I de 5 neste spørsmålene ønsker vi å vite hvordan livssituasjonen din er **NÅ**:

8. Hvordan opplever du gangevnen din?

- ¹ Jeg har ingen problemer med å gå omkring
 ² Jeg har litt problemer med å gå omkring
 ³ Jeg er sengeliggende

9. Hvordan klarer du personlig stell?

- ¹ Jeg har ingen problemer med personlig stell
 ² Jeg har litt problemer med å vaske meg eller kle meg
 ³ Jeg klarer ikke å vaske meg eller kle meg

10. Hvordan klarer du dine vanlige gjøremål (f.eks. arbeid, studier, husarbeid, familie- og fritidsaktiviteter)?

- ¹ Jeg har ingen problemer med å utføre mine vanlige gjøremål
 ² Jeg har litt problemer med å utføre mine vanlige gjøremål
 ³ Jeg er ute av stand til å utføre mine vanlige gjøremål

11. Smerter eller ubehag?

- ¹ Jeg har verken smerte eller ubehag
 ² Jeg har moderat smerte eller ubehag
 ³ Jeg har sterk smerte eller ubehag

12. Angst eller depresjon?

- ¹ Jeg er verken engstelig eller deprimert
 ² Jeg er noe engstelig eller deprimert
 ³ Jeg er svært engstelig eller deprimert



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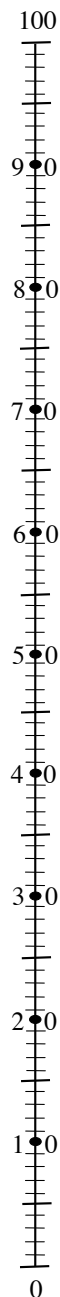
13. Din helsetilstand i dag.

For å hjelpe folk til å si hvor god eller dårlig en helsetilstand er, har vi laget en skala (omtrent som et termometer) hvor den beste tilstanden du kan tenke deg er merket 100 og den verste tilstanden du kan tenke deg er merket 0.

Vi vil gjerne at du viser på denne skalaen hvor god eller dårlig helsetilstanden din er i dag, etter din oppfatning. Vær vennlig å gjøre dette ved å trekke en linje fra boksen nedenfor til det punktet på skalaen som viser hvor god eller dårlig din helsetilstand er i dag.

**Din egen
helsetilstand
i dag**

Best tenkelige
helsetilstand



Verst tenkelige
helsetilstand



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16. Har du besvær fra den andre hoften?

¹ Ja

² Nei

17. Er det andre årsaker til at du har problemer med å gå?

(For eksempel smerter fra andre ledd, rygg smerter, hjerte-karsykdom eller andre sykdommer som påvirker gangevnen din)

¹ Ja

² Nei

18. Har du hatt nye operasjoner i den samme hoften som ble operert for hoftebrudd?

¹ Ja

² Nei

Takk for at du tok deg tid til å svare på spørsmålene. Dine svar er svært nyttige for oss. Vennligst send spørreskjemaet i retur til oss i den ferdig frankerte svarkonvolutten.

Papers I-III

RESEARCH

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Subsequent ipsi- and contralateral femoral fractures after intramedullary nailing of a trochanteric or subtrochanteric fracture: a cohort study on 2012 patients

Kirsten Marie Larsen Grønhaug^{1,2*}, Eva Dybvik³, Jan-Erik Gjertsen^{2,3}, Kristian Samuelsson^{4,5} and Bengt Östman¹

Abstract

Background: The literature is inconclusive as to whether an intramedullary nail changes the distribution of a subsequent ipsi- or contralateral fracture of the femur. We have compared the incidence, localisation, and fracture pattern of subsequent femoral fractures after intramedullary nailing of trochanteric or subtrochanteric fractures in patients without previous implants in either femur at the time of surgery.

Methods: Retrospective analysis was performed of a two-centre cohort of 2012 patients treated with a short or long intramedullary nail for the management of trochanteric or subtrochanteric fracture between January 2005 and December 2018. Subsequent presentations with ipsi- and contralateral femoral fractures were documented. Only patients with no previous femoral surgery performed, other than the index nailing were followed. Odds ratios (ORs) for subsequent femoral fracture were calculated using robust variance estimates in logistic regression.

Results: The mean age of the cohort was 82.4 years and 72.1% were female. The total number of patients presenting with subsequent femoral fractures was 299 (14.9%). The number of patients presenting with subsequent ipsilateral and contralateral femoral fractures was 51 (2.5%) and 248 (12.3%) respectively (OR 5.0; CI 3.7–6.9). Twenty-six (8.7%) of all subsequent femoral fractures occurred in the ipsilateral shaft, 14 (4.7%) in the ipsilateral metaphyseal area, one (0.33%) in the contralateral shaft, and three (1.0%) in the contralateral metaphysis (OR 10; CI 3.6–29).

Conclusion: An intramedullary nail significantly changes the fracture pattern in the event of a second low-energy trauma, reducing the risk of subsequent proximal ipsilateral femoral fractures and increasing the risk of subsequent ipsilateral femoral fractures in the shaft and distal metaphyseal area compared with the native contralateral femur.

Keywords: Subsequent femoral fracture, Intramedullary nail, Trochanteric fracture

Background

The incidence of a subsequent femoral fracture (Sffx) is significant among patients who have suffered an initial hip fracture [1–3]. Previous studies have stated that 2–12% of patients with a hip fracture of any type sustain

a contralateral Sffx. Sffx pattern will be influenced by the presence and type of implant in situ at the time of reinjury [3–6]. Ipsilateral Sffxs appear to be less common [3]. An implant may increase the risk of some fracture types and decrease the risk of others. Without securing a native contralateral femur pre- and postoperatively, it is impossible to evaluate the true impact of the implant on Sffx.

Schröder et al. [3] reported that 92% of all Sffxs are contralateral, but without documenting any

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pre-existing implant in the contralateral femur at the time of surgery. The risk of an ipsilateral Sfx is higher after an initial fracture in the trochanteric, subtrochanteric or shaft region, as compared to a femoral neck fracture [6–8].

For the past several decades, fractures in the trochanteric area have been treated with either a variation of a sliding hip screw (SHS) or a short or long intramedullary nail (IMN) [9–11]. SHS is regarded as the gold standard for the stable two-fragment fractures (AO/OTA 3 1 A1) [12]. However, in the treatment of intertrochanteric (AO/OTA 3 1 A3) and subtrochanteric fractures (AO/OTA 3 2 A/B/C 1–3), the literature suggests that an IMN is a more favorable treatment option [13–17], due to the shorter lever arm and the reduced potential for medialization the nail device provides. Despite the biomechanical benefits, IMNs have been associated with an increased risk of ipsilateral Sfx, although this appears to be less frequent with contemporary nail designs [18, 19]. The choice of implant may influence the incidence, localisation and morphology of a Sfx [20, 21]. In a recent retrospective study, no differences could be found when comparing the incidence of a contralateral Sfx after an initial trochanteric fracture treated with either an IMN or an SHS [22].

This study aimed to investigate how an IMN affects the incidence, pattern and localisation of Sffxs in patients treated for a trochanteric or subtrochanteric fracture with documented normal femora without implants or sequelae after previous surgery in either femur. A comparison between an operated femur and a persistently native contralateral femur will inevitably require exclusion of patients with any femoral implant initially and consecutive censoring of patients having subsequent implant surgery in either femur. The chosen design intends to reduce the influence of individual characteristics difficult to account for, such as risk behavior, drug or alcohol abuse, fall tendency, and comorbidity.

Methods

Study design

In this retrospective cohort study all patients with a trochanteric or subtrochanteric femoral fracture treated with a short or long IMN at Østfold Hospital Trust between 2005 and 2018 ($n = 2525$) were eligible for inclusion. To study the true impact of an IMN on the distribution of Sffxs after intramedullary nailing of trochanteric and subtrochanteric fractures, the pre-operative status in both femora was investigated. Comparison of the operated femur with the contralateral femur was only continued as long as no major surgery was performed on either femur. The occurrence of and time to a new admission due to a Sfx was registered, yielding total exposure time.

Sources of data

Patients were identified by searching the hospital databases using the International Statistical Classification of Diseases and Related Health Problems (ICD10) and the NOMESKO Classification of Surgical Procedures (NCSP) codes. Patients with ICD10 codes S72.1 (per- or intertrochanteric fractures) or S72.2 (subtrochanteric fractures) and NCSP codes NFJ51 or NFJ52 (intramedullary nailing of trochanteric and subtrochanteric fractures respectively) were identified. Electronic health records and X-ray images were reviewed. Handwritten documentation provided by the surgeons postoperatively was reviewed and compared with the electronic health records. The American Society of Anesthesiologists Physical Status scoring system (ASA score) was used to assess the overall health status of the patient.

Identification of cohort

Pre- and postoperative X-ray images, as well as all follow-up X-ray images taken of the proximal femur and the pelvis, were examined to identify, classify and localise index fractures and Sffxs. Fracture type was registered according to the AO/OTA classification system [23]. Pelvic X-ray images visualising the contralateral hip and all follow-up X-ray images were included for all patients to identify any pre-existing implant, added implant, or sequelae in either proximal femur.

Exclusion process

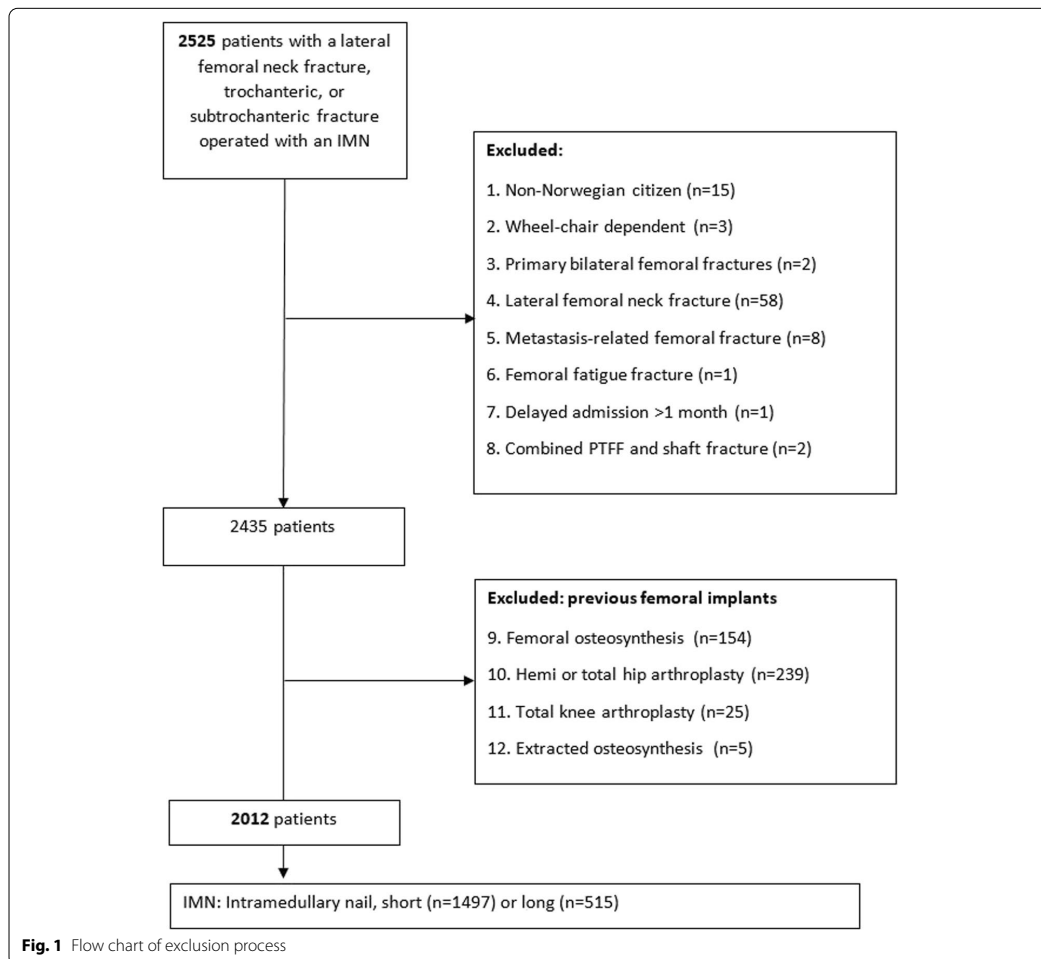
Patients <60 years of age, non-Norwegian citizens, patients with the primary care episode at a non-orthopaedic department, a pre-existing implant in either femur, high-energy trauma, multiple simultaneous fractures in the lower extremities or pathologic fracture (other than osteoporosis) were excluded from the study. Finally, 2012 patients met the inclusion criteria. The exclusion process is illustrated in Fig. 1.

Censoring

The following endpoints were registered: ipsi- and contralateral Sffxs (medial or lateral femoral neck fractures, trochanteric avulsions, per- or subtrochanteric fractures, femoral shaft fractures, distal femoral fractures), infection, cut-out, failure of osteosynthesis, non-union, mal-union, local pain, local hematoma, lag screw complications leading to surgery and surgery involving a non-fracture-related implant in either femur (total or hemi-arthroplasty in the hip or knee).

Validation

Data obtained from electronic health records were validated using a comparison with data from the



Norwegian Hip Fracture Register (NHFR) [24]. A total of 329 (16.4%) patients who underwent surgery were not registered in the NHFR while 42 (2.1%) patients were registered in the NHFR but not in the local electronic health records. All patients were included.

Ethics

The study was approved by the Norwegian Regional Ethics Committee (REC South-East). The STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) guidelines were followed [25].

Statistical analysis

The data was summarised using frequencies and percentages for categorical variables. The mean, standard deviation (SD) and range were calculated for continuous variables. The mean time to subsequent fracture, range and 95% confidence interval (CI) were calculated. The alpha value was set at 0.05. The odds ratio (OR) was calculated using robust variance estimates in logistic regression. The follow-up time was calculated from the primary operation until a new fracture-related operation on the ipsilateral side, fracture-related surgery on the contralateral side, other operation not related to a fracture, death,

or 31 January 2020, whichever came first. The patients who reached any of the endpoints were censored along the way. The statistical analyses were performed using IBM-SPSS Statistics (Version 24.0, IBM, Armonk, NY, USA), the R, version 3.4.0, statistical package (<http://www.R-project.org>) and Stata/SE (Version 16.0, Stata-Corp LLC, College Station, TX, USA).

Results

Table 1 presents the baseline characteristics of the 2012 patients included. The mean age was 82.4 years and 72.1% were female. Out of the 2012 patients, 1890 (93.9%) were classified as ASA 2 or ASA 3 prior to surgery. The index fracture was pertrochanteric in 1959 (97.4%) cases. Laterality was near symmetrically distributed (right: 48.8%, left: 51.2%). The mean exposure time was 1031 days (SD 1036).

A Short Gamma3 Intramedullary Nail (Stryker Corporation, Kalamazoo, Michigan, USA) alone accounted for 55.8% of the implants used, followed by long Gamma3 (21.1%), (Table 2). The remaining implants were divided between the GammaT nail, the TRIGEN InterTan Nail (Smith and Nephew, Hertfordshire, UK), the AFFIXUS Hip Fracture Nail (Zimmer Biomet, Indiana, USA) and, in a single case, the TRIGEN Trochanteric Nail (Smith and Nephew, Hertfordshire, UK). A long nail was used in 515 (25.6%) cases.

The total number of Sffxs was 299 (14.9%). Ipsilateral Sffxs occurred in 51 (2.5%) and contralateral in 248 (12.3%) of all patients (OR 5.0; CI 3.7–6.9, $p < 0.001$).

Table 1 Baseline data

Characteristics	2012
Total n	2012
Gender, n (%)	
Male	562 (27.9)
Female	1450 (72.1)
Mean age, (SD)(range)	82.4 (8.5) (60–103)
ASA, n (%)	
1	31 (1.5)
2	829 (41.2)
3	1059 (52.6)
4	89 (4.4)
Missing	4 (0.20)
Type of fracture, n (%)	
Pertrochanteric	1959 (97.4)
Subtrochanteric	53 (2.6)
Laterality, n (%)	
Right	981 (48.8)
Left	1031 (51.2)
Mean exposure in days, (SD)(range)	1031 (1036) (0–5379)

Table 2 Type of implant

Implant	Type	Number (% of total)	With distal locking (%)
Short nail	Total	1497 (74.4)	1326 (88.6)
	GammaT	198 (9.8)	129 (65.2)
	Gamma3	1122 (55.8)	1020 (90.9)
	InterTan	174 (8.6)	174 (100.0)
Long nail	Affixus	3 (0.15)	3 (100.0)
	Total	515 (25.6)	513 (99.6)
	GammaT	32 (1.6)	31 (96.9)
	Gamma3	424 (21.1)	423 (99.8)
	InterTan	57 (2.8)	57 (100.0)
	Affixus	1 (0.05)	1 (100.0)
Trigen	1 (0.05)	1 (100.0)	

[Stryker GammaT Intramedullary Nail TM (2005–2007), Stryker Gamma3 Intramedullary Nail TM (2007–2017), Smith and Nephew TRIGEN Trochanteric Nail TM (2015), Smith and Nephew TRIGEN InterTan Nail TM (2016–2017), Zimmer Biomet AFFIXUS Hip Fracture Nail TM (2017)].

The distribution of Sffxs is illustrated in Fig. 2. A significantly higher rate of ipsilateral Sffxs in the shaft and distal metaphyseal area was detected compared with the corresponding types of contralateral Sffxs (OR 10; CI 3.6–29, $p < 0.001$). Ipsilateral Sffxs in the shaft accounted for 8.7% ($n = 26$) and in the metaphyseal area 4.7% ($n = 14$) of all Sffxs. The corresponding figures for contralateral Sffxs was 0.33% ($n = 1$) and 1.0% ($n = 3$) respectively. In the contralateral femur, 238 (79.6%) Sffxs occurred in the femoral neck and per- and subtrochanteric area, compared to 10 (3.3%) in the ipsilateral femur.

Of 1497 patients treated with a short nail, six (0.4%) sustained an ipsilateral subtrochanteric fracture, 23 (1.5%) sustained a shaft fracture, and 10 (0.6%) sustained a Sfx in the metaphyseal area. Of 515 patients treated with a long nail, one (0.19%) sustained an ipsilateral subtrochanteric fracture, three (0.6%) sustained a shaft fracture, and five (1.0%) sustained a Sfx in the metaphyseal area. Three (0.6%) ipsilateral Sffxs occurred in the proximal part of the femur and only in patients treated with a short nail.

Patients reaching any endpoint were censored along the way. Table 3 shows the distribution of all endpoints. Non-fracture-related complications leading to reoperation and non-fracture-related operations in either femur reached a total of 123 (6.1%) censored patients. Cut-out and other lag screw complications were the most prevalent non-fracture complications leading to reoperation in 40 (2.0%) and 17 (0.8%) patients respectively. When ruling out contra- and ipsilateral coxarthrosis, 118 (5.9%) complications directly related to the primary operation were identified. A total of 1226 (60.9%) patients died without experiencing a Sfx or any non-fracture complications.

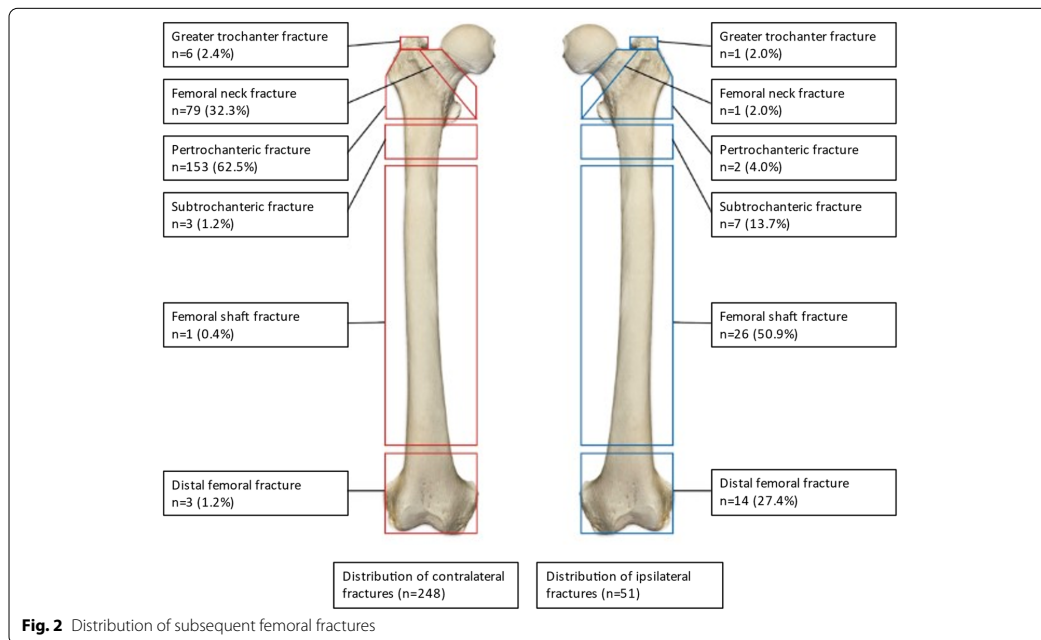


Table 3 Endpoints of study

Endpoint		N	%	
Subsequent femoral fracture	Total	299	14.9	
	Ipsilateral	51	2.5	
	Contralateral	248	12.3	
Other complications requiring surgery	Total	118	5.9	
	Infection	16	0.8	
	Cut-out	40	2.0	
	Failure of osteosynthesis	5	0.25	
	Non-union	21	1.0	
	Mal-union	2	0.10	
	Local pain	17	0.8	
	Screw complications	17	0.8	
	Non-fracture related surgery	Coxarthrosis –THA	17	0.8
	Death		1226	60.9

THA Total hip arthroplasty.

The number of patients left at risk nearly halved every two years. Table 4 shows the distribution of endpoints in two-year intervals.

Discussion

This retrospective study of 2012 patients treated with an intramedullary nail for a pertrochanteric or subtrochanteric fracture investigated the occurrence of subsequent femoral fractures. Patients with coexisting implants or fracture sequelae in either femur were excluded to assess the impact of the IMN alone. The total incidence of a Sffx was five times lower on the ipsilateral than the contralateral side following surgery with an IMN. However, the study demonstrated a tenfold increase in the risk of ipsilateral femoral shaft and distal fractures after receiving an IMN for a trochanteric or subtrochanteric fracture, compared with a contralateral side without implants or fracture sequelae.

To the best of our knowledge, no previous study has compared the impact of IMN in the treatment of trochanteric or subtrochanteric fractures in elderly patients with no previous implant in either femur at the time of surgery. The incidence of peri-implant femoral fractures distal to an IMN has been described [20, 26]. Although the incidence has decreased with the evolution of new generations of IMNs, peri-implant fractures still represent a challenge to the orthopaedic surgeon. The overall lower risk of an ipsilateral Sffx, as well as the increased incidence of those ipsilateral Sffxs occurring in the shaft and distal metaphyseal area, are consistent with the

Table 4 Risk of ipsi- and contralateral fracture. Censored data are subtracted consecutively

Endpoint	Years					
	0–2	2–4	4–6	6–8	8–10	> 10
Number left at risk	2012	1029	566	283	137	53
Death	714	258	152	59	24	16
Non-fracture rel. Reoperation	104	9	3	2	1	1
Ipsilateral Sffx ^a	35	9	5	1	0	1
Contralateral Sffx ^a	122	68	27	18	10	3
End of follow-up	8	119	96	66	49	32

^a Subsequent femoral fracture

existing literature [7, 20, 27–30]. However, previous studies have not specified the presence or absence of other implants or sequelae in either femur prior to the index fracture. Bögl et al. concluded that there was a reduced risk of subsequent hip fracture with the use of IMNs with femoral neck protection in the treatment of low energy femoral shaft fractures in a retrospective study of 897 patients, but discuss that national register data are incomplete regarding laterality [31]. Schröder et al. did not review x-ray images until a subsequent femoral fracture was present [3]. By reviewing all x-ray images to exclude patients with pre-existing implants in the present study we were able to further assess the impact of the IMN.

All the Sffxs in our study occurred as a result of low-energy trauma, as high-energy injured patients were excluded. Biomechanical studies and clinical experience suggest that the incidence of peri-implant fractures is affected by the modulus of elasticity of the implant [32]. The increased incidence of ipsilateral versus contralateral Sffxs in the shaft and distal metaphyseal area following the implantation of an IMN in this study may indicate a redistribution of forces in the event of a second trauma to the femur – protecting the proximal femur but yielding an increased risk of fractures distal to the nail. However, the protective effect of the IMN with regard to an ipsilateral proximal Sffx is far greater than the increased risk of an ipsilateral peri-implant fracture. Extracting an IMN increases the risk of sustaining an ipsilateral trochanteric fracture substantially compared with the risk of sustaining an ipsilateral peri-implant fracture with the implant in place.

The increased incidence of low-energy Sffx distal to an implanted IMN, as seen in this study, may be a result of morphologic changes in the adjacent bone secondary to the implant. The rigidity of the chosen implant causes the implant to bear the majority of the load [33], resulting in stress-shielding and bone resorption around the implant over time [34–36]. The stress-shielding effect causes

localised osteopenia as well as inactivity osteopenia and is likely to contribute to the increased risk of ipsilateral Sffxs in the shaft and distal metaphyseal area demonstrated in this study. Previous studies have confirmed the rapid reduction of bone mineral density (BMD) following postoperative immobilisation [30, 37–39]. Postoperative restraints reduce BMD in the entire femur and may contribute to the increased incidence of ipsilateral Sffxs in the shaft and distal metaphyseal area. Furthermore, previous studies rate impaired balance and an increased risk of falling as even more important risk factors for hip fractures than low BMD [40–42].

The overall risk of an Sffx is significant after any low-energy index fracture, as demonstrated in the work of Center [43] and Kanis [2]. In a population-based Finnish study, the risk of an Sffx was significantly higher than the risk of a primary hip fracture during the first twelve to fifteen months postoperatively [44]. The population most vulnerable to fractures in the trochanteric area typically display sarcopenia, as defined by the European Working Group on Sarcopenia in Older Persons (EWGSOP): low muscle mass with low muscle strength or low physical performance [45]. This deteriorates further after the index hip fracture [46–48]. Reduced activity, mobility, pain, fear, and avoidance enhance sarcopenia, thereby increasing the risk of falling [38].

Strengths and weaknesses

The strengths of this study include the large sample size, the long follow-up, the exclusion of patients with pre-existing implants or sequelae in either femur prior to the index nailing and validation by comparison with data from NHFR. The discrepancy identified during the validation process may be due to surgeons forgetting to report to the NHFR, missing data in received forms, forms lost in transit and patients with comorbidities warranting the complete care episode at a non-orthopedic department.

The study has several limitations. Due to the retrospective design, no information was available on BMD or fall pattern before or after the index operation. However, by only including patients without previous implants in either femur, we assumed a similar BMD in both femurs at the time of index fracture. Although fracture type may influence the risk of Sffx [3, 6–8], subanalyses of index fracture type or stability were not conducted, as ipsilateral Sffxs are relatively uncommon. As this study aimed at comparing a native femur, operated with an IMN, with a persistently native contralateral femur, we excluded patients with any femoral implant initially, and even censored patients having subsequent non-fracture related surgery in either femur later on. Such a study design is advantageous in view of our aim but significantly limits the ability to compare the influence of nail length on the distribution of ipsilateral Sffxs. This study only included patients treated with IMNs, and it cannot be ascertained whether the incidence and fracture pattern of Sffxs found in this study are specific to IMNs or apply to other femoral implants as well, such as sliding hip screws or arthroplasty femoral stems.

Conclusion

An IMN significantly changes the fracture pattern in the event of a second low-energy trauma by reducing the risk of proximal Sffxs but increasing the risk of Sffxs in the shaft and distal metaphyseal area compared with the native contralateral femur. The overall risk of Sffx is substantially higher in the contralateral, native femur indicating the protective effect of the IMN with regard to a proximal ipsilateral Sffx is much higher than the increased risk of sustaining an ipsilateral peri-implant fracture.

Given the serious nature of peri-implant fractures, further biomechanical studies and clinical research to investigate why IMNs lead to increased fracture rates distal to the implant are called for, as well as similar studies investigating the risk of Sffx after other intra- and extramedullary implants in the treatment of proximal femoral fractures.

Abbreviations

AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association; ASA: The American Society of Anesthesiologists; BMD: Bone Mineral Density; EWGSOP: European Working Group on Sarcopenia in Older Persons; ICD-10: International Statistical Classification of Diseases and Related Health Problems; IMN: Intramedullary Nail; NHFR: Norwegian Hip Fracture Register; NCSF: NOMESKO Classification of Surgical Procedures; REC: Norwegian Regional Ethics Committee; Sffx: Subsequent femoral fracture; SHS: Sliding Hip Screw; STROBE: STrengthening the Reporting of OBServational studies in Epidemiology.

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Authors' contributions

Bengt Østman and Kristian Samuelsson designed the study. Kirsten Marie Larsen Grønhaug wrote the manuscript. Eva Dybvik performed the statistical analyses. All authors contributed to the interpretation of the results, and improvement of the manuscript. All authors approved the final version of the manuscript.

Funding

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Availability of data and materials

The regulations of the Norwegian Data Protection Authority and the Norwegian personal protection laws prohibit the publication of the complete dataset. The data that support the findings of this study are available from the Norwegian Hip Fracture Register but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon request and with permission of the Norwegian Hip Fracture Register.

Declarations

Ethics approval and consent to participate

The study was approved by the South Eastern Norway Regional Ethics Committee. The STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) guidelines were followed and the methods are in accordance with the WMA declaration of Helsinki. The NHFR has permission from the Norwegian Data Protection Authority to collect and store data on hip fracture patients (permission issued January 3, 2005; reference number. 2004/1658–2 SVE/–). The patients signed a written, informed consent declaration, and when unable to understand or sign, their next of kin could sign the consent form on their behalf.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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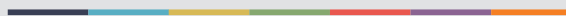
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