UNIVERSITY OF COPENHAGEN

FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

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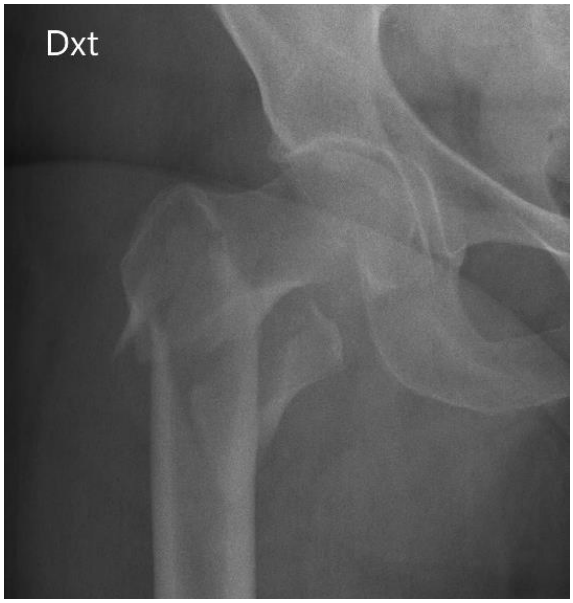
Low-energy femoral fractures and factors influencing death and reoperation

Use of registry-based data for investigating outcomes



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Abbreviations

ASA – Association of anesthesiologists

AO - Arbeitsgemeinschaft für Osteosynthesefragen

CHS – Compression Hip Screw (Smith&Nephew)

CI – Confidence interval (95%)

CRS – CPR registret , The Danish Civil Registration System

DFDB – The Danish Fracture Database

DHR – Danish Hip Arthroplasty Register

DHS – Dynamic Hip Screw (Depuy-Synthes)

FU – Follow up

HR – Hazard ratio

ICD-10 - International Classification of Diseases and Related Health Problems, 10th version

IMHS – Intramedullary Hip Screw (Smith&Nephew)

IMN – Intramedullary nail

LPR – Landspatientregisteret, The national register of treatments performed in Denmark.

OR – Odds ratio

PFN – Proximal Femoral Nail (Depuy-Synthes)

PFNA – Proximal Femoral Nail Antirotation (Depuy-Synthes)

PTN – PeriTrochanteric Nail (Biomet)

RCT – Randomised controlled trial

SHS – Sliding hip screw

Preface and acknowledgements

In my first appointment as a doctor at the orthopedic department at Copenhagen University Hospital Hvidovre I had the fortune of being introduced to a man named Anders Troelsen. This quickly resulted in an invitation to help the active and well-founded research group CORH – Clinical Orthopedic Research Hvidovre. It started with a small work on hip fractures, but soon evolved into this PhD project.

The included studies have been conducted to provide evidence for further optimization of the current treatment of hip fractures and have been planned in close relation to the work of establishing and developing the Danish Fracture Database, to explore the possibilities that lie in the systematic registration of clinically relevant data for fracture patients.

I could not have made this work on my own and would like to thank all the people who made it possible. A special thanks to my supervisors: Anders Troelsen for your excellent guidance, your ability to see the big picture and where I might fit in; Kirill Gromov for help in all details of performing a study and for answering an obscene amount of questions; and Henrik Palm for a great inspiration to the principle that we have to treat the patient as absolutely best possible, and if we do not know what the best is, then to find out. To Thomas Kallemose and Håkon Sandholdt for their invaluable help to try and make me understand a small part the statistical difficulties of research. Thanks to our Chief of staff Peter Gebuhr for your optimism about the work, for making it logistically possible and for the financial support of the thesis. A big thank you to my co-authors Michael Brix and Henrik Malchau for lending your knowledge and integrity to the work. A very large part of the data in this thesis is collected from the DFDB, and the DFDB collaborators have been a great help in providing that. A warm thank you to Cecilia Rogmark, My von Friesendorff, Bjarne Löfgren, Daniel Wenger, Thord von Schewelov and their colleges at the Department

of Orthopedics at Skånes Universitetssjukvård in Malmö for ensuring that my stay with you was both educational and a great experience. A special thank you to Svend Dirksen, senior consultant in orthopedic surgery and my father, and Ruth Ahlburg, family doctor and my mother, for your continuous support to get the work done and for your ongoing help with logistic difficulties.

And lastly thank you to Thomas Nyholm and our offspring, Glød and Ask, for being there all the way.

List of papers

I: Nyholm AM, Gromov K, Palm H, Brix M, Kallemose T, Troelsen A, et al. Time to Surgery Is Associated with Thirty-Day and Ninety-Day Mortality After Proximal Femoral Fracture. J Bone Joint Surg Am 2015;97–A:1333–9

II: Nyholm AM, Palm H, Kallemose T, Troelsen A, Gromov K. No association between surgical delay and mortality following distal femoral fractures. A study from the danish fracture database collaborators. Injury 2017. doi:10.1016/j.injury.2017.10.022.

III: Nyholm AM, Palm H, Malchau H, Troelsen A, Gromov K. Lacking evidence for performance of implants used for proximal femoral fractures-A systematic review. Injury 2016;47:586–94. doi:10.1016/j.injury.2016.01.001.

IV: Nyholm AM, Palm H, Sandholdt H, Troelsen A, Gromov K. Minimal effect of implant position in osteosynthesis with parallel implants in femoral neck fractures. Submitted.*

None of the papers have been included in any other thesis.

* The manuscript has now been published as:

Nyholm AM, Palm H, Sandholdt H, Troelsen A, Gromov K, Collaborators D. Osteosynthesis with Parallel Implants in the Treatment of Femoral Neck Fractures - Minimal Effect of Implant Position on Risk of Reoperation. *J Bone Jt Surg Am*. 2018;100-A(19):1682-1690.

English summary

Background – Proximal femoral fractures are the most common fractures treated in Denmark. In recent years several improvements have been made, including the establishment of guidelines, but many questions are still unanswered.

Purpose - This thesis investigates the influence of surgical delay on mortality in low-energy femoral fractures, the data available for long term survival of the cephalomedullary nails and the sliding hip screws, and the surgery-related factors influencing the risk of reoperation following osteosynthesis of the femoral neck fractures.

Methods - *Study I* was a retrospective registry-based study of the association between surgical delay and early mortality following low-energy proximal femoral fractures. *Study II* was identical to *study I*, but performed on distal femoral fractures. *Study III* was a systematic review of the currently available literature on the 1-year performance of the implants used in pertrochanteric fractures. *Study IV* was a retrospective study based on both registry data and x-ray evaluation of several surgical details to evaluate their association to the subsequent risk of reoperation.

Results - In *study I* mortality was 10.8% at day 30 and 17.4% at day 90. For the 30-day mortality risk surgical delay > 12h compared to ≤ 12h, of > 24h compared to ≤ 24 h and of > 48 h compared to ≤ 48 h increased the risk of death. For the 90-days mortality risk only the estimate for surgical delay > 24 h compared to ≤ 24 h was significant. When the surgery was performed by a surgeon with experience level below “attending”, the risk of both 30 day and 90 day mortality increased significantly by approximately 25 %. In *study II* mortality was 7.1% at day 30 and 12.5% at day 90. The logistical regression analysis did not demonstrate any association between surgical delay or the educational level of the surgeon, and mortality following surgery for a distal femoral fracture. *Study III* identified 30 publications for SHS and 54 for

IMN. All studies identified were evidence level II (prospective observational studies and small randomized clinical trials) or III (retrospective observational studies). None of the studies, in which patients were operated after the latest update of the implant was introduced, specify whether the older or the updated version was used. In *study IV* 13% of patients underwent reoperation within 1 year. Of the variables investigating the osteosynthesis only an insufficient reduction of the fracture, placing the implants with an angle to the shaft of ≤125°, and perforating the caput with an implant were significantly associated with an increase in risk of reoperation in the multivariable analysis. We found no association between reoperation and the number of implants used, posterior distance, calcar distance, tip-caput distance or whether the implants were parallel or not.

Conclusion – A short surgical delay in hip fractures may reduce the early mortality. This effect was not demonstrated for distal femoral fractures. The evidence available for performance of the implants used for trochanteric fractures is scarce and better post-marked evaluation may be advised. And for osteosynthesis of a femoral neck fracture, proper patient selection and sufficient reduction seem to be more important for risk of reoperation than the specific details of the implant position.

Danish summary

Baggrund – Øvre lårbensbrud er den hyppigst forekomne fraktur, som bliver behandlet med operation I Danmark. I de forgangne år er der indført adskillige forbedringer i behandlingen, bl.a. udformningen af generelle retningslinjer, men der forligger stadig mange ubesvarede spørgsmål.

Formål – Denne afhandling undersøger virkningen af ventetiden til operation på risikoen for død efter lavenergi lårbensbrud, evidensen for overlevelsen af cephalomedullære søm (IMN) og glideskruer (SHS), samt de kirurgi-relaterede detaljers indflydelse på risikoen for reoperation efter osteosyntese af brud i lårbenshalsen.

Metode – *Studie I* er et retrospektivt register studie af sammenhængen mellem ventetiden på operation og den tidlige dødelighed efter lavenergi hoftebrud. *Studie II* er identisk med studie I, men udført på knænære lårbensbrud. *Studie III* er et systematisk review af den tilgængelige litteratur for 1-års overlevelsen af implantater til trochantære brud. *Studie IV* er et retrospektivt studie baseret på registerdata og målinger af røntgenbilleder, der undersøger flere kirurgiske detaljers sammenhæng med risikoen for reoperation efter osteosyntese af brud i lårbenshalsen.

Resultater – I *studie I* var dødeligheden efter 30 dage 10.8%, og efter 90 dage 17.4%. Ventetid på > 12 timer versus ≤ 12 timer, på > 24 timer versus ≤ 24 timer og på > 48 timer versus ≤ 48 timer øger risikoen for død efter 30 dage. For 90 dage var det kun estimaterne for ventetid på > 24 timer versus ≤ 24 timer, der gav en signifikant forskel. Når operationen blev udført af en kirurg, der endnu ikke var speciallæge, uden supervision, steg risikoen både for 30 dages dødelighed og 90 dages dødelighed signifikant med omkring 25 %. *I studie II* var dødeligheden efter 30 dage 7.1% og efter 90 dage 12.5%. Ved logistisk regressionsanalyse var det ikke muligt at vise nogen sammenhæng mellem ventetiden på operation eller kirurgens erfaringsniveau, og

risikoen for død efter knænære lårbensbrud. *Studie III* identificerede 30 artikler omhandlende SHS og 54 omhandlende IMN. Alle studier havde et evidensniveau på II (prospektive observationelle studier eller små randomiserede kliniske studier) eller III (retrospektive studier). Ingen af studierne, der potentielt kunne være udført med den nyeste version af et implantat, angav hvilken version der var blevet brugt. I *studie IV* blev 13% af patienterne reopereret indenfor 1 år. Af de undersøgte variable for operations-detaljerne var det kun utilstrækkelig reponering, at placere implantaterne med en vinkel til skaftet på lårbenet på ≤125°, samt at skruen stak ud i leddet, der havde en sammenhæng med risikoen for reoperation. Der blev ikke fundet nogen sammenhæng mellem antallet af implantater, posterior distance, calcar distance, tip-caput distance, eller om implantaterne var parallelle, og risikoen for reoperation.

Konklusion – En kort ventetid på operation reducerer den tidlige dødelighed for hoftebrud. Denne effekt er ikke til stede ved knænære lårbensbrud. Størrelsen af den tilgængelige evidens for overlevelsen af implanter til trochantære frakturer er lille og bedre monitorering efter indførelsen af implantater kunne overvejes. Og så virker det til at korrekt udvælgelse af patienter, samt omhyggelig reponering af frakturen inden osteosyntese er vigtigere end den præcise placering af implantaterne ved osteosyntese af brud på lårbenshalsen.

Introduction

Hip fractures and patient demographics

Fractures of the hip, or proximal femoral fractures, are the most common fractures treated in orthopedic departments in Denmark, accounting for 35% of all fracture surgeries reported to the DFDB in 2016[1] and with an yearly incidence around 8.000[2–4]. The incidence has been declining[4], however, as the number of elderly increases with general improvements in population health and better survival of other diseases, the incidence may rise again.

Hip fractures occur in a population of mainly elderly patients with a mean age of 80 years. Approximately 70% are female. More than 35% have at least 1 comorbidity and approximately 50% of patients get classified as ASA 3 or more in relation to the surgery[5–7]. Malnutrition and medical comorbidities such as chronic pulmonary or cardiovascular disease are often presents, and represent a challenge in the perioperative management of the patient[8,9]. Furthermore, dementia or cognitive impairment is frequent, in some studies reported to be in the range 19-41%[6,10,11]. The mortality following fracture is quite high: 10% of the patients die within 30 days[5] and around 25-30%[11,12] die within the first year. 7-10% undergo reoperation within 2 years of surgery[4,6], of which 80% are due to mal-union, necrosis of the femoral head, failure of osteosynthesis or arthroplasty dislocation[2]. Furthermore, even when the treatment is successful and no reoperations occur, the fracture quite often leaves sequelae in terms of pain as well as reduced mobility and independence following fracture[13–15].

Anatomy of the proximal femur

The proximal femur is generally viewed as the proximal part of the femur to a line approximately 5 cm below the trochanter minor. It consists of the femoral head, the femoral neck, the trochanteric region and the sub-trochanteric region (figure 1). The

femoral head consists of mainly trabecular bone with a thin cortical surface covered in cartilage. Biomechanical studies have demonstrated that the strongest trabecular bone is located in the epiphyseal scar in the center of the femoral head[16], with weaker bone in the apical half. In the femoral neck and the trochanteric region the cortex thickens, especially the inferior/medial part of the cortex, named the calcar.

Based on the attachment of the joint capsule, the proximal femur is divided into two fractions: an intracapsular and an extracapsular part. This division is clinically practical due to the blood supply to the femoral head (figure 1)[17]. In femoral neck fractures this blood supply is disturbed, resulting in a reduced perfusion of the femoral head, which is more pronounced in displaced fractures[18]. As a result, the femoral neck fractures have a considerable risk of AVN. This is reflected in the higher risk of reoperation for the femoral neck fractures[4] compared with the extracapsular fractures.

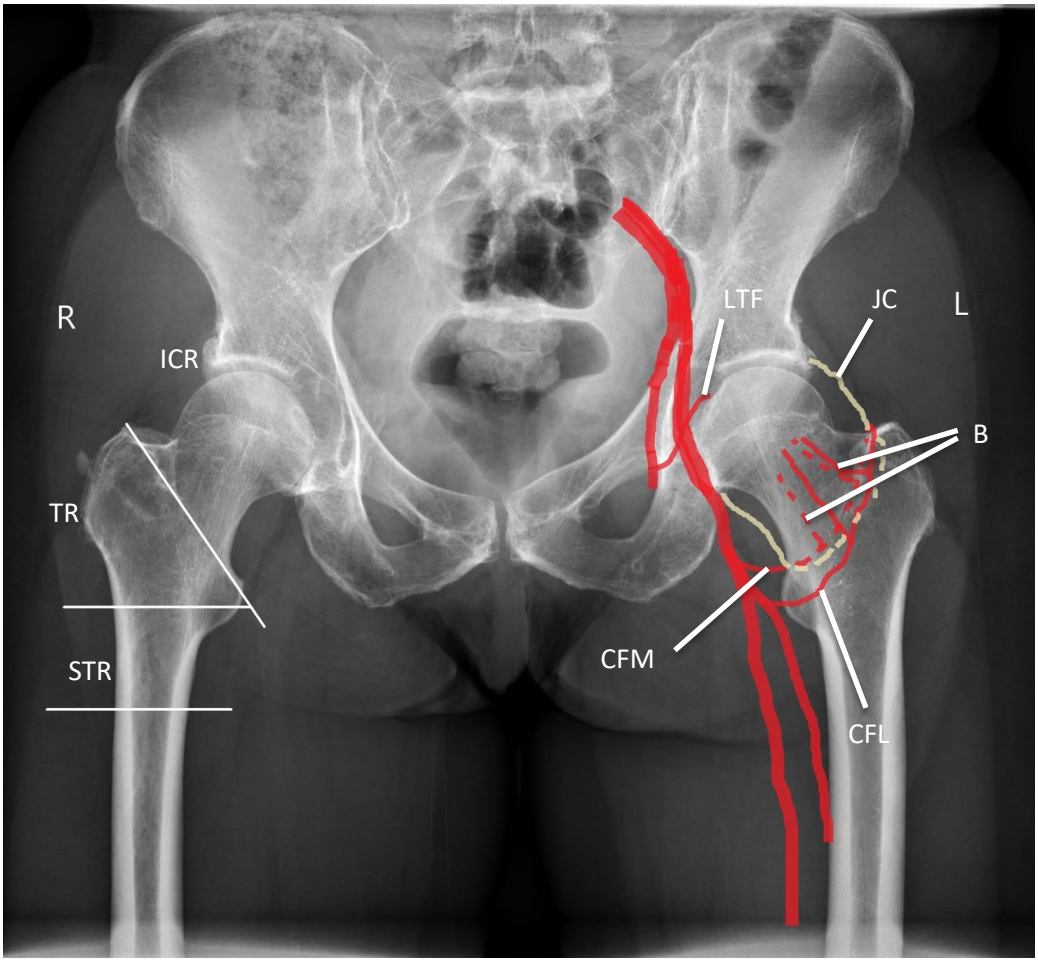


Figure 1 – The proximal femur is divided into the intracapsular region (ICR), the trochanteric region (TR) and the subtrochanteric region (STR). The blood supply derives primarily from the femoral artery via the aa. circumflexae femoris medialis et lateralis (CFM and CFL). The branches (B) for the femoral head enter the periosteum of the femoral neck distally to the insertion of the capsule and runs proximally towards the femoral head. No vessels traverse the joint cavity (JC). A minor part of the blood supply is by small vessels within the lig. Teres femoris (LTF).

Guidelines, registers and monitoring of treatment

The treatment of diseases is constantly evolving as new knowledge is obtained, with introduction of technology as well as modification of well-established treatments and implants. Awareness of need for best possible evidence-based treatment is emerging and as a consequence, guidelines for treatment of hip fractures have been established during the 90s[19,20]; as examples the Danish reference program for management of hip fractures was published in 1999, with a revision published in 2008[20], and the British NICE (the National Institute for Clinical Excellence) was established in 1999 to *"reduce variation in the availability and quality of NHS treatments and care"*[21] and have published and updated several guidelines, including a guideline concerning hip fractures[22].

In parallel with the guidelines, registers with systematic collection of data on several factors in the treatment of hip fractures have been implemented in several countries, such as "Rikshöft" in Sweden from the early 1990s[23], "Det Nationale Indikatorprojekt" (NIP)) in Denmark from 2004[4], "Nasjonalt Hoftebruddregister" in Norway from 2005[24] and the "National Hip Fracture Database" in England, Wales and Cornwall from 2007[25]. These registers perform a continuous monitoring of the treatment of hip fractures, follow time-trends and benchmark the different aspects of the treatment. The specifics of the registers vary, with some being more extensive than others. All report surgical delay, fracture type, implant type, death and reoperations, but some have included patient reported outcome measures, evaluating pain and function at several time-points postoperatively[23,24], and (to the best of my knowledge) only the Norwegian register systematically collects information regarding the specific implants, antibiotics and thromboprophylaxis used[24].

This systematic collection of data furthermore provides a basis for performing larger observational studies. This is of great value in the hip fracture population that, due to its inhomogeneous composition, high proportion of cognitive impairment and high

mortality, has proven quite difficult to investigate. And for less frequent fractures, this systematic registration may ensure accumulation of data to provide sufficient power for studies, which may not be possible in single-center setups.

DFDB

A growing awareness of the lack of high quality studies in traumatology lead to the establishment of the Danish Fracture Database (DFDB, approved by Danish Data Protection Agency ID: 02716) in 2011[26]. The DFDB was established as an online based database for registration of all fracture related surgery performed. The specific aim of the database was to establish a continuous monitoring of all fracture-related surgery to ensure and improve the quality of fracture surgery[27]. The data is entered in the database by the primary surgeon immediately after the surgical procedure has been completed and includes patient-related, trauma-related and surgery-related factors[28]. It was primarily implemented in 2 departments (Hvidovre and Odense), but has since gradually been implemented in other departments in Denmark. In 2015 the database was approved as a national clinical quality database with mandatory reporting of all fracture-related surgeries in Denmark[29]. It is however not yet implemented in all orthopedic departments in Denmark. As of 1st of March 2018 the database contains >85.000 registered procedures.

The validity and completeness of the database have been evaluated for report from the two instigating departments (Hvidovre and Odense) where a satisfactory completeness and validity of the data have been found[28]. However, the completeness of the database in other departments has not yet been estimated, and a system for continuous evaluation of this is currently under development.

For this thesis, the DFDB provided a platform of data available for further evaluation in effort to test our specific research hypotheses.

Specific topics evaluated in this thesis

Timing of the surgery

The length of the time period prior to the surgery – the surgical delay – is interesting, not only for the patient, but also in view of how to organize the treatment facility. Several studies have provided evidence for the notion that expeditious - rather than protracted - surgery has been associated with decreased risk of postoperative complications as well as shorter length of hospitalization[4,5,6,7]. The exact correlation with mortality is less clear: Some studies have shown surgical delay >24 or >48 hours to significantly increase mortality[8,9,10,11,12,13,14,15] while other studies found no correlation[4,16,17,6,18]. So far no association between a short surgical delay and adverse effects has been found[7]. Most studies have investigated the effect before and after watershed-lines of 24 or 48 hours, but whether an even lower delay is beneficial has not been well investigated. This raises the question: Should we prioritize to perform these surgeries as fast as possible, perhaps including during night time?

Another problem to remember is that if hip fractures are prioritized it may cause the surgical delay of other surgeries to increase. This may be relevant especially for other femoral fractures due to the similarities in patient population and practical impairment for both fracture types (frail elderly patients which are left bed-ridden by the fracture prior to surgery, with risk of peri-fracture bleeding, venous thromboembolism, infections etc.). However, the role of surgical timing of distal femoral fractures is sparsely elucidated[30–32] and as a result no general recommendation regarding timing of surgery in these fractures exists.

Choosing the best implant for the surgery

Current evidence suggests treatment of extracapsular fractures with either a sliding hip screw or a cephalomedullary nail, while screw/pin osteosynthesis or arthroplasty

is recommended for femoral neck fractures[33]. Several different versions of the implants are available with small variations in between. For introducing a new technology, regulations require some form of pre-marked testing both in vitro and in vivo testing. However, if the technology is similar to something already available on the market, the requirements of the premarket testing is less. As a consequence of this, roughly 90 % of all new techniques approved in the USA are implemented without pre-market clinical testing (via the PDA510(K) approval)[34]. Evaluation of implants is therefore primary conducted as clinical studies after implementation of the implant. Whether this system is sufficient to evaluate the performance of the implants can be debated[35].

Osteosynthesis of femoral neck fractures

When compared to arthroplasty, osteosynthesis of a femoral neck fracture with parallel implants is a relatively small surgical procedure with shorter duration of surgery, reduced bleeding and need for blood transfusions, smaller risk of deep wound infections, and a reduced length of hospitalization[36,37]. The hip joint and stabilising structures are left untouched, which insures the stability of the joint to remain unchanged. However, the rate of re-operation following osteosynthesis has been reported considerably higher than following arthroplasty[37–43], with mechanical failure as the most common cause[44]. Fracture displacement or angulation as well as high patient-age have been identified as risk-factors for reoperation[45,46], and as a consequence most national guidelines advocate for osteosynthesis with parallel implants for non-displaced fractures and displaced fractures in the younger patients, with arthroplasty replacement in the elderly patients with displaced fractures[22,33,47–49].

When performing an osteosynthesis, proper positioning of the implants has been proposed as an important risk factor for reoperation[50]. However, no clear definition of “proper positioning” is agreed upon. Biomechanical studies have indicated an importance of posterior and calcar support of the implants in the femoral neck[51,52].

This theory is confirmed in some clinical studies[53,54], while others do not find any association to reoperation[46,55]. Divergent findings exists as to the number of pins needed, some studies demonstrated an increased stability with 3 or 4 implants were used[56], other finding 2 to be adequate[57]. If 3 screws are used, it has been found to be most stable if placed in an inverted triangular configuration, with posterior screw close to the posterior cortex and the inferior close to the calcar[58,59].

The AO surgery reference guide for performing osteosynthesis of femoral neck fractures with cannulated screws advises the use of 3 parallel screws in an inverted triangular pattern with the inferior screw resting on the calcar[60].

Objectives

Purpose of the thesis

The overall objective of this thesis was to evaluate several niches in the treatment of hip fractures and to provide evidence to make a basis for further optimization of these fractures. Furthermore we wanted to explore the possibilities in using registry-based data in answering our research questions.

Objectives of the studies

Study I: The primary objective was to evaluate the possible effect of the time between the diagnosis and the surgery (the surgical delay) and the risk of early death in hip fracture patients. The secondary objective was to evaluate if the educational level of the surgeon was associated with this risk. The main hypothesis was that increased surgical delay increased the risk of death.

Study II: The primary objective was to evaluate the possible effect of the time between the diagnosis and the surgery (the surgical delay) and the risk of early death in distal femoral fracture patients. The secondary objective was to evaluate if the educational level of the surgeon was associated with this risk. The main hypothesis was that increased surgical delay increased the risk of death.

Study III: The objective was to evaluate the current literature for clinical evidence of implant 1-year performance for the implants used in pertrochanteric fractures in Denmark. The main hypothesis was that the amount literature available would be small.

Study IV: The objective was to investigate how the surgical details, including the positioning of the implants, in osteosynthesis of a femoral neck fracture with parallel implants influence the risk of reoperation within 1 year following surgery. The main hypothesis was that placement in accordance with current recommendations would be associated with a lower risk of reoperation.

Subjects and methods

Study design, subjects, methods and ethical considerations

For all studies a protocol with specified variables and outcome measures was written prior to onset of the study (see appendix). For detailed description please see these and the published or submitted manuscripts (appendix).

Studies I and II:

Study design

Studies I and II are retrospectively designed observational studies based on register data.

Subjects

All patients ≥50 years of age with a surgery for either a proximal (AO31) or a distal (AO33) low-energy femoral fracture reported to the DFDB up to the time of the study. Only surgeries performed at departments with more than 50 surgeries for a femoral fracture registered in the DFDB were included.

Method

Data on all surgeries for an AO31 or an AO33 type fracture was collected from the DFDB and sorted in accordance with the inclusion criteria. For included patients data on vitality status (alive/dead) and time of death was collected from the CRS.

The influence of the variables of interest on the outcome measure was evaluated using a univariate multivariable logistical regression.

Study III:

Study design

Study III is a systematic review of the literature.

Subjects

All papers written in English published in a PubMed indexed journal after 1st of January 1990 reporting implant performance of any implant for treatment of a trochanteric fracture which was in use in Denmark in November 2014. For inclusion the follow up time of the study had to be at least 12 months.

Method

All orthopedic departments performing hip fracture surgery in Denmark were contacted by either mail or phone and asked which specific implants (name and company) they used for treating trochanteric fractures. Based on this information two search lines (one for SHS and one for IMN) were constructed, with help from a librarian at The Royal Library of Copenhagen, and used to search PubMed. The search results were evaluated, first based on titles, then on abstracts of all maybe-relevant titles and, lastly, on texts of all maybe-relevant abstracts. For all reviews identified on the subject, the references were evaluated for relevant articles.

For articles which fulfilled the inclusion criteria the year of publication, type of study, specific type of implant(s), time-period of intervention, type of fracture, number of patients, age and gender distribution, follow-up time and outcomes were noted. Furthermore, the “Level of evidence” was estimated in accordance with OCEBM Levels of Evidence Working Group, "The Oxford 2011 Levels of Evidence," Oxford Centre for Evidence-Based Medicine[61].

When the review was concluded, a physical difference was noted between separate articles publishing results of the same implant. Therefore the manufactures of the

implants were contacted and asked if, and when, any changes had been made to the implants since introduction to the marked. This information was taken into account when presenting the data.

Data was presented as descriptive statistics.

Study IV:

Study design

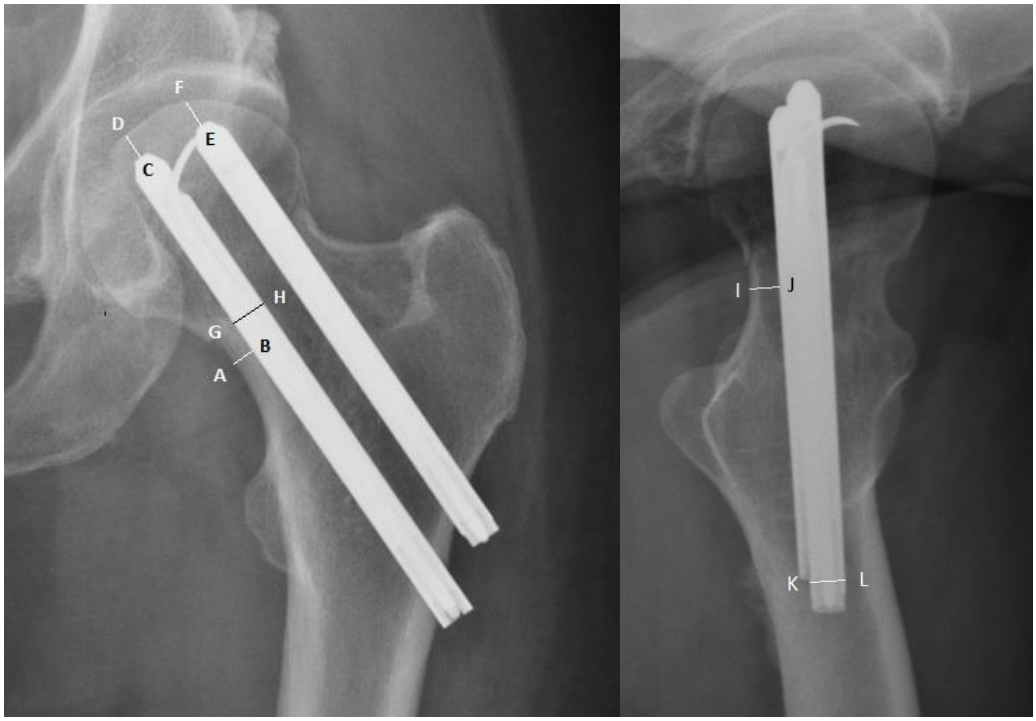
Study IV is a retrospectively designed observational study based on registry data and manual measurements of x-rays.

Subjects

All patients with a Danish Civil Personal Registration number and available pre- and postoperative X-rays, reported to the DFDB for a surgery for a femoral neck fracture (AO31B) with parallel implants (screws or pins) up to the time of the study.

Method

Data on all surgeries for an AO31B type fracture was collected from the DFDB and sorted in accordance with the inclusion criteria. X-rays of all patients were collected from the treating department and evaluated by the main author. Measurements included: “Fracture type” (preoperative displacement and angulation), “Reduction” (postoperative displacement and angulation), “Number of implants used”, “Angulation of implant”, “Calcar distance”, “Posterior distance”, “Tip-caput distance” and the diameter of the screws (figure 2).



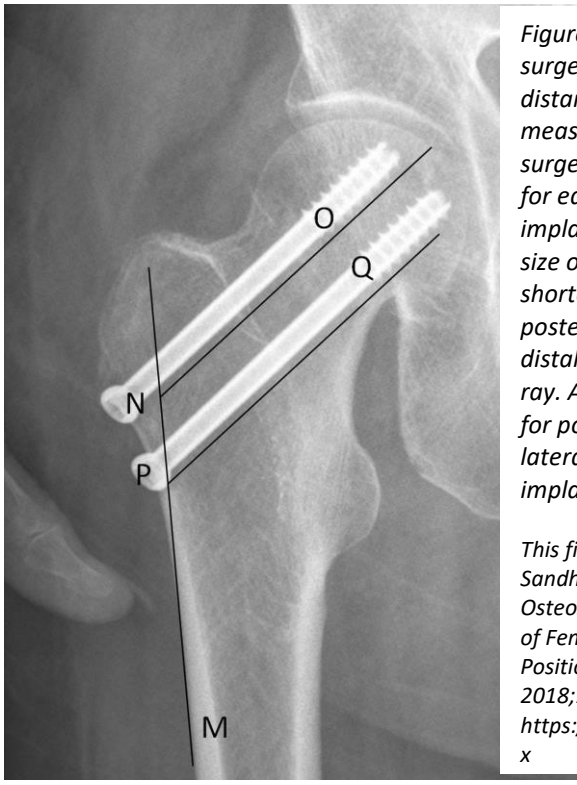


Figure 2 - Measurements of distances in the post-surgery x-rays. AB = Calcar distance: The shortest distance from the inferior implant to the calcar, measured distally to the fracture on the post-surgery AP x-ray. CD and EF = tip-caput distance for each implant: Distance from the tip of the implants to the surface of the caput. GH and KL = size of the implant, IJ = Posterior distance: The shortest distance from the posterior implant to the posterior cortex of the femoral neck, measured distally to the fracture on the post-surgery axial x-ray. Angles MNO and MPQ = implant-shaft angle for posterior and inferior implant: Angle between lateral cortex of the femoral diaphysis and the implant, measured on the AP x-ray.

This figure has been published in Nyholm AM, Palm H, Sandholdt H, Troelsen A, Gromov K, Collaborators D. Osteosynthesis with Parallel Implants in the Treatment of Femoral Neck Fractures - Minimal Effect of Implant Position on Risk of Reoperation. J Bone Jt Surg Am. 2018;100-A(19):1682-1690. https://journals.lww.com/jbjsjournal/pages/default.aspx

The intra- and interreader evaluation demonstrated a “Good” to “Excellent” reproducibility of the measurements (Please see appendix table 3 for study IV).

When evaluation of the X-rays was completed and follow-up was >12 months, data on any further hip-surgery performed since index surgery was collected from the LPR. Data on vitality status (alive/dead) and time of death was collected from the CRS.

The influence of the variables of interest on the outcome measures was evaluated using a univariate multivariable cox regression.

Statistics

Studies I, II and IV involved statistical calculations (table 1). Basic data was presented as table 1 demographics and basic diagrams. The possible effects of the variables of interest were evaluated using regression analysis. Since studies I and II had a fixed follow up times (30 and 90 days) and there were no competing outcomes, a logistical model was chosen. In study IV, several competing outcomes existed (death, infection, new fracture, etc.) and as a consequence the time at risk varied. To accommodate this setup, a cox-regression analysis was used. The variables included in the models were decided upon prior to the modeling. For variables with more than two levels, the overall effect of the variable in the model was estimated using a likelihood-ratio test. All statistical modelings have been conducted in collaboration with a statistician with knowledge of medical research principles.

In study IV, the intra- and interreader reliability of the measurements were estimated using Lin's Concordance Coefficiency Coefficient[62], Bland Altman analyses[63], and coefficient of variation (within-subject standard deviation method)[64,65]. Lin's Concordance Coefficience Coefficient was chosen since it is superior to the traditional calculation of correlations by Pearson in that it takes into account that the proportionality coefficient between the raters ideally should be 1. Furthermore, Bland Altman analyses were performed and data presented as mean difference (95% CI) and 95% limits of agreement. The distribution of the standard deviations was visually assessed using standard Bland-Altman plots (not presented). The coefficient of variation, which is a measure of variability relative to the mean, was calculated to illustrate how large a percentage of the measurement value the measurements uncertainty presented. The measurements were calculated with help from a researcher with experience in intra- and interreader evaluations.

Statistical method	Study I and II	Study IV
Type of data		
- Categorical	X	X
- Continuous	X	X
Comparison between groups		
- Logistical regression analysis	X	
- Cox regression analysis		X
Intra- and inter-reader measurements		
- Lin's concordance correlation coefficient		X
- Mean difference		X
- Limits of agreement		X

Table 1 – Statistical analysis used in this thesis.

Ethical considerations

Study III is a review of the literature and does not involve any patient related data.

Studies I, II and IV are retrospective observational studies with no intervention. Patients and their relatives have not been contacted in relation to these studies. No further information has been collected than what is registered in the journals, in DFDB or in the CRS.

No ethical issues to consider were present in relation to the studies included in this thesis.

Permission to obtain and evaluate data for studies I, II and IV was obtained from the Danish Data Protection Agency prior to onset of the studies.

Summary of the results

Study I

3517 surgeries were included. Median patient age was 82.0 (range 51-107) and 2458 (70%) of the patients were female. 1720 (49%) surgeries were for a trochanteric fracture (AO31A) while 1807 (51%) were for a femoral neck fracture (AO31B). 722 (21%) patients were operated within 12 h, 2482 (71%) within 24 h, 3024 (86%) within 36 h, 3242 (92%) within 48 h and 3353 (95%) within 72 h. A surgeon with an education of "Attending or above" performed or supervised the surgery in 1710 (49%) of all cases.

Mortality was 10.8% at day 30 and 17.4% at day 90. The incidence of death increased with increasing surgical delay at both day 30 and day 90 (figure 3).

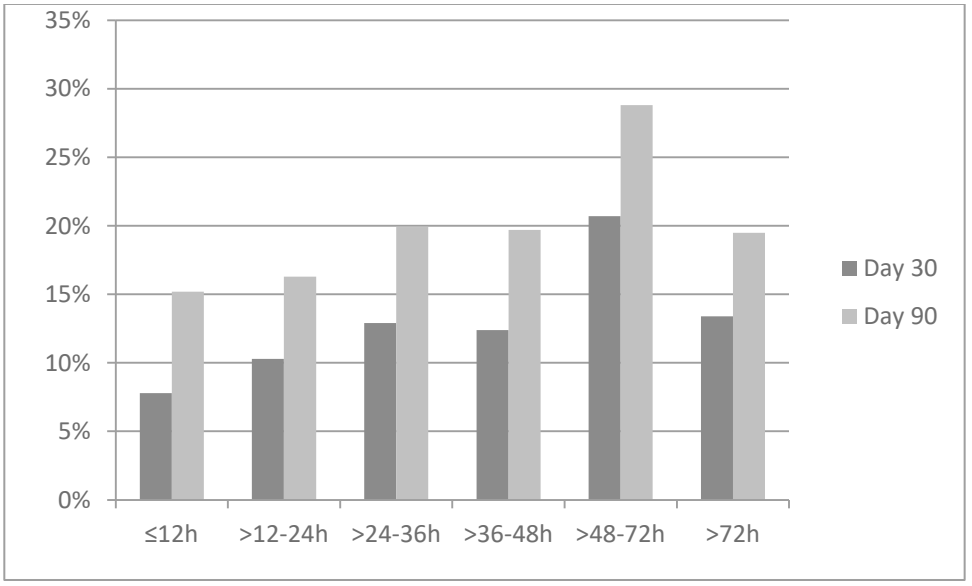


Figure 3 – Incidence of death stratified according to surgical delay

When comparing surgical delay of more or less than a given time period, an increased risk of both 30-day and 90-day mortality was estimated for all comparisons. For the

30-day mortality risk these estimates were significant only for surgical delay > 12h compared to ≤ 12h, surgical delay > 24h compared to ≤ 24 h and surgical delay > 48 h compared to ≤ 48 h. For the 90-days mortality risk only the estimate for surgical delay > 24 h compared to ≤ 24 h was significant (table 2).

Surgical delay	30-day mortality risk (OR (CI))	90-day mortality risk (OR (CI))
≥12 vs <12h	1.45 (1.06 - 1.99)	1.10 (0.86 - 1.40)
≥24 vs <24h	1.34 (1.06 - 1.70)	1.23 (1.00 - 1.50)
≥36 vs <36h	1.32 (0.98 - 1.78)	1.21 (0.93 - 1.56)
≥48 vs <48h	1.56 (1.07 - 2.26)	1.36 (0.98 - 1.89)
≥72 vs <72h	1.23 (0.74 - 2.02)	1.09 (0.71 - 1.68)

Table 2 - OR calculated using log-regression. Adjusted for age, gender, ASA score, fracture type, treatment, educational level of surgeon

Comparing the disjoint time intervals for surgical delay in-between, with the ≤12 h group as reference interval, an increased risk of mortality was found in all later groups for both 30 day and 90 day mortality. This was statistically significant for 30 day mortality at time intervals 24-36 h and 48-72 h, and for 90 day mortality only at 48-72 h (table 3).

Surgical delay	30-day mortality risk (OR (CI))	90-day mortality risk (OR (CI))
<12h	1	1
12-24h	1.33 (0.95 – 1.85)	1.02 (0.78 - 1.31)
24-36h	1.60 (1.08 – 2.37)	1.22 (0.89 - 1.67)
36-48h	1.37 (0.82 – 2.29)	1.08 (0.71 - 1.65)
48-72h	2.61 (1.45 – 4.70)	1.83 (1.10 – 3.05)
≥72h	1.67 (0.95 – 2.94)	1.18 (0.74 – 1.90)

Table 3 - OR calculated using log-regression. Adjusted for age, gender, ASA score, fracture type, treatment, educational level of surgeon

When the surgery was performed in the absence of an attending, or a more qualified, surgeon as primary surgeon or supervisor, the risk of both 30 day and 90 day mortality increased by approximately 25 % (OR 1.28, p = 0.035 and OR 1.26, p = 0.016).

Both 30- and 90-days mortality increased with increased ASA score, male gender and increasing age.

Study II

392 surgeries were included. Mean age was 76 years (range 50-101), 79% of patients were female and 65% had an extra-articular fracture (AO33A). 8% were operated within 12 h, 33% within 24 h, 67% within 48 h and 83% within 72 h. A surgeon with an educational level of "attending or above" performed the surgery in 56% of all cases and supervised in further 33%. Mortality was 7.1% at day 30 and 12.5% at day 90.

The logistical regression analysis did not demonstrate any association between surgical delay and mortality following surgery for a distal femoral fracture. Furthermore, no association between the educational level of the surgeon and mortality following surgery for a distal femoral fracture was found. It is however noted, that several of the confidence intervals are fairly wide (table 4).

Surgical delay	30-day mortality risk (OR (CI))	90-day mortality risk (OR (CI))
≥12 vs <12h	0.53 (0.07-4.34)	1.35 (0.33-5.60)
≥24 vs <24h	1.05 (0.42-2.64)	1.15 (0.27-4.95)
≥36 vs <36h	1.13 (0.49-2.60)	1.02 (0.21-4.86)
≥48 vs <48h	0.85 (0.36-2.00)	1.82 (0.43-7.80)
≥72 vs <72h	1.64 (0.51-5.27)	0.97 (0.22-4.32)

Table 4 - OR calculated using log-regression. Adjusted for age, gender, ASA score, fracture type, educational level of surgeon.

Study III

The search and screening identified 30 publications for SHS and 54 for IMN (figure 4 and table 5). All studies identified were evidence level II (prospective observational studies and small randomized clinical trials) or III (retrospective observational studies).

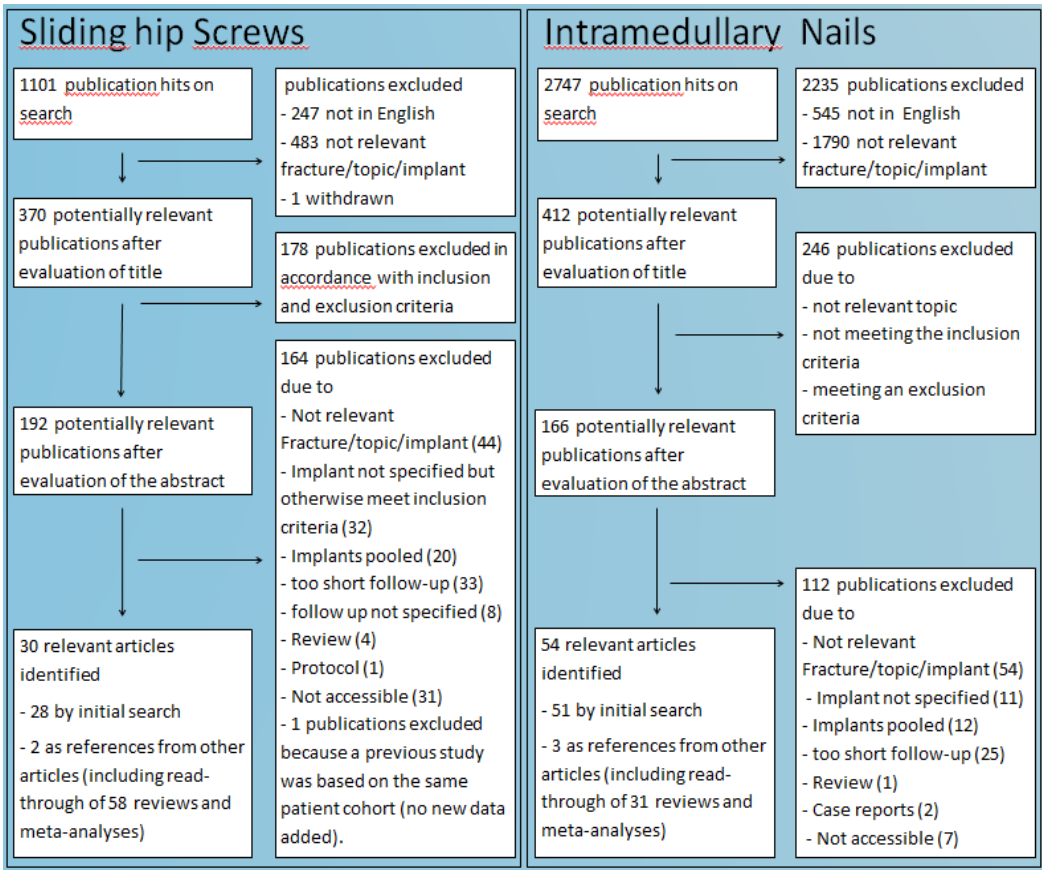


Figure 4 – Flowchart of the systematic search of the literature.

5 studies included more than 200 patients; 2 retrospectively investigating the DHS[66,67], one retrospective, study on IMHS[68], one prospective, randomised study of InterTan[69], and one prospective observational study of PFNA[70]. The follow up time for each implant varied from only studies with 12 months follow up to one study including 91 patients with the CHS followed for 13 years[71] and one study of the PFNA with follow up of 96 months[72]. The DHS was evaluated in most patients (2486, whereof 567 were evaluated prospectively) but PFNA was the implant where most patients were evaluated prospectively (1762 in total, 1018 prospectively). No studies evaluating the PTN were found.

Implant	N studies	NP followed pro-spectively	NP followed retro-spectively	NP Total	NP followed >12 months	Max follow up in months *
CHS	13	900	210	1110	642	13 years/91
DHS	15	567	1919	2486	1886	38 (16-60)/937
HipLoc	2	251	0	251	0	12 /251
Gamma3	13	829	259	1088	287	29 (12-63)/124
IMHS	7	210	1333	1543	1044	(12-72)/63
InterTan	5	585	10	595	167	(12-27)/100
PFN	10	557	159	716	65	20 (12-30)/45
PFNA	24	1018	744	1762	786	36 (24-96)/106
PTN	0	0	0	0	0	0

*Table 5 - Number of studies and patients investigating each implant. *[mean] (range)/[NP], N = Number, NP = Number of patients*

Changes/updates

The manufactures reported several updates (table 6).

Sliding hip screws	
Compression Hip Screw (CHS)	Not updated since 1980
Dynamic Hip Screw (DHS)	The Locking Compression Plate DHS (LCP-DHS) was introduced in 2006, replacing the previous version of the plate
HipLoc	No changes since introduction
Intramedullary nails	
Gamma3	No changes since introduction
Intramedullary Hip Screw (IMHS)	The IMHS-CP was introduced in 2004, replacing the older IMHS
InterTan	No changes since introduction
Proximal Femoral Nail (PFN)	In 1998 a collar was added to hinder migration
Proximal Femoral Nail Antirotation (PFNA)	The PFNA blade was updated in 2011 (perforated version allowing cement augmentation), replacing the older blade
PeriTrochanteric Nail (PTN)	No changes since introduction

Table 6 - Updates of implants reported from the manufacturers.

If only studies investigating patients that were operated after the latest implant update are considered, the number of publications for the implants which have been altered dropped considerably (table 7).

Implant	N studies	NP followed pro-spectively	NP followed retro-spectively	NP Total	NP followed >12 months	Max follow up in months *
CHS	13	900	210	1110	642	13 years/91
DHS	1	0	163	163	0	12/163
HipLoc	2	251	0	251	0	12 /251
Gamma3	13	829	259	1088	287	29 (12-63)/124
IMHS	1	110	0	110	0	12/110
InterTan	5	585	10	595	167	(12-27)/100
PFN	6	190	132	322	65	20 (12-30)/45
PFNA	0	0	0	0	0	0
PTN	0	0	0	0	0	0

*Table 7 - Number of studies and patients investigating each implant when only studies that might have been performed using the latest version were considered. *[mean] (range)/[NP], N = Number, NP = Number of patients*

None of the studies, in which patients were operated after the latest update of the implant was introduced, specifies whether the older or the updated version was used.

Study IV

1206 surgeries on 1198 patients were included. Median age was 73.3 (range 21-102) and 832 (69%) were female. 783 surgeries were for an AO31B1 fracture, 192 for an AO31B2 fracture and 231 for an AO31B3 fracture.

Two implants were used in 997 patients, while 3 were used in 209 patients. In 30 patients, an implant protruded into/through the cartilage on the femoral head, and in other 41 patients, an implant protruded through the cortex of the femoral neck.

157 (13%) of patients underwent a relevant reoperation within 1 year and 228 (19%) patients died. Mean and median time to reoperations was 140 and 116 days.

Of the patient-related variables younger age, female gender, high ASA score and displaced or angulated fracture were associated with increased risk of reoperation (table 8).

For surgical delay of 12-24h vs 0-12h only a borderline significant association was found in the multivariable analysis (table 8). When performing an identical multivariable analysis exclusively on the initially displaced fractures, a significant association between surgical delay of 12-24 h vs 0-12 h and risk of reoperation was found (HR 1.76, CI (1.05 ; 2.96), p=0.032). No association between surgical delay and risk of reoperation was found in the initially non-displaced fractures.

Of the variables investigating the osteosynthesis only an insufficient reduction of the fracture, placing the implants with an angle to the shaft of ≤125°, and perforating the caput with an implant were significantly associated with an increase in risk of reoperation in the multivariable analysis (table 8).

We found no association between reoperation and the number of implants used, posterior distance, calcar distance, tip-caput distance or whether the implants were parallel or not (table 8).

In analysis of the risk of death, none of the factors related to the osteosynthesis demonstrated any relationship with the risk of death.

Variable	HR	CI
Age	1.00	(0.98 ; 1.01)
Gender		
Female	1	
Male	0.62	(0.42 ; 0.91)
ASA Score		
"1-2"	1	
"3-4"	1.58	(1.11 ; 2.24)
Surgical delay		
0-12h	1	
12-24h	1.49	(0.997 ; 2.24)
24-36h	0.82	(0.44 ; 1.52)
>36	0.74	(0.35 ; 1.58)
Fracture type		
Non-displaced, <20°	1	
Displaced	2.33	(1.52 ; 3.57)
Reduction		
Non-displaced, <10°	1	
Non-displaced, >=10°	1.64	(1.00 ; 2.69)
Displaced	1.88	(1.28 ; 2.77)
Number of implants		
2	1	
3	1.21	(0.81 ; 1.81)
Angle of distal screw		
>125°	1	
<=125°	1.91	(1.06 ; 3.43)
Angle between screws		
<=3°	1	
>3°	0.96	(0.56 ; 1.64)
Post. Distance		
1-3mm	1	
<1 mm	0.81	(0.54 ; 1.23)
>3 mm	0.80	(0.53 ; 1.19)
Calcar distance		
0-5 mm	1	
>5 mm	0.83	(0.60 ; 1.16)
Tip distance		
0-10 mm	1	

Protruding	3.07	(1.54 ; 6.14)
>10 mm	1.18	(0.62 ; 2.26)

Table 8 – Hazard Ratios for the association between the variables and the risk of reoperation within 1 year. Data is adjusted for all included variables.

Methodological considerations and limitations of the studies

General considerations

Research in hip fracture populations

The amount of literature investigating hip fractures is quite large, but a very large part of this research is of low or intermediate quality, mostly of a retrospective, observational design and with few patients included. Performing studies in the hip fracture population is challenging due to several hindrances. The golden standard of obtaining evidence for a causal link between intervention and outcome with the randomized controlled trial may not be realistic in the hip fracture population.

In the ideal RCT subjects are divided into groups identical in all maters except for the intervention under investigation. If the outcome of interest happens at a rate of 20% per year and the assumption is made that the clinically relevant reduction is at least 50% (to a rate of 10%), to obtain a power of 90% and a two-sided confidence of 5% approximately 550 observations would be needed[73]. This is under the assumption that the groups are of equal size and that there is no plan to test for confounding variables. In cases where outcome of interest is not “Death”, the high mortality would also have to be taken into account, complicating the process as well.

This is a rather large amount of patients to include in a study, especially considering that all participants will have to give informed consent to participate, which can be a challenge when cognitive impairment and other comorbidities are present. This problem is illustrated in the FAITH trial where, although 1108 patients were included and assessed, >5000 patients were evaluated and excluded, of which 1110 patients were excluded on the basis of cognitive impairment[74,75]. This selection bias raises the

question as to if the study population is representative of the population of interest[76,77].

Other problems may hinder the conduct and relevance of RCTs. In a Danish setup, a very large number of people take part in the treatment of the hip fracture patients. For instance; surgeries for hip fractures are performed by all levels of surgeons, from the just-started resident in training (with proper supervision) to the traumatology-specialised surgeon. To eliminate possible confounding effects, such as learning curve for the surgeon, one might choose to narrow the number of surgeons performing surgery on included patients[78]. This may raise concerns as to whether the findings of the study are applicable in the general setup. Lastly, we do have to acknowledge the ethical aspect as well. For instance, we do have evidence for an increased risk of complications with increased surgical delay[79–81], and to determine whether delay in the individual patient increases the mortality risk with a randomized set-up of plus/minus delay is therefore not ethically acceptable. In these cases, observational studies are the best option in investigating the research questions.

The alternative, observational studies, allow inclusion of all patients available and give a fairly accurate picture of the situation as it is in a clinical setting. It does however have several limitations. Interventions will not be randomly assigned and may not follow strict indications, which introduces a selection bias in the populations with different treatments and makes it unlikely that the different groups will be directly comparable. As example, whether a patient undergoes surgery as soon as possible, or is delayed may be determined by the medical condition of the patient. If the patient is stable and with no grave comorbidities, there may be no second thoughts as to perform the surgery immediately. If however the patient is dehydrated, anemic, infected, with a degree of heart failure and in anticoagulant therapy it may be possible that the surgery is postponed to allow medical optimization prior to surgery. If the delayed group of patients then has a higher mortality rate, it will be hard to

determine if this is due to the delay or to a higher amount of comorbidities. To accommodate this confounding, information on comorbidities can be collected and taken into account with the help of statistical modelling. It is however unlikely that all relevant confounders are identified and included, especially if the setup is retrospective, which will leave some residual confounding.

Furthermore, it should always be acknowledged that an observational study in principle only evaluates the presence of associations. It might be somewhat logic that an association identified in an observational study is in fact due to a cause-effect relationship, but for certain confirmation, some sort of interventional study is needed. It is however a possibility that an association is either a coincidence or due to other factors not accounted for.

Using data from registers

An option in conducting observational research is to collect data from registries. The advantages of registry data is that larger, uniform dataset can be obtained. Furthermore, if the completeness of the database is high, the risk of selection bias for inclusion is minimal and conclusions are applicable of the entire cohort. The risk of erroneous or missing data can however be considerable and may not be controlled, and, unless continuous validation of the database are performed, may introduce a significant bias for interpretation of the data[82]. Furthermore, the number and types of variables available are restricted to those registered in the databases. A considerable amount of residual bias might therefore be present if no further collection of data is performed.

Studies I, II and IV

Studies I, II and IV aimed at investigating the effect of several smaller details in the treatment of patients with hip fractures. For all studies a retrospective, observational cohort design was chosen.

A problem in our studies is the fact that the DFDB is a database still in the implementing phase and does not yet cover all departments in Denmark. A preliminary evaluation of the completeness from two departments demonstrated a completeness of 88% completeness for primary fracture surgery[28]. The missing 12% of the primary procedures may introduce a selection bias and should be taken into account when interpreting the results. A wider validation of the DFDB is still warranted, including estimation of the completeness. Furthermore, in study IV, it was not possible to retrieve the x-rays from all departments, and therefore only patients from Zealand, Fyn, and the southern part of Jutland is included. This may introduce a residential bias, but for the purpose of investigating the effect of surgical delay and the position of the osteosynthesis we do not believe this to be of importance.

Statistical power of the studies

No power calculation was performed in any of the studies. This was due to the consideration that we included all patients available, thus the study populations are (in principle) identical to the source population. This strategy does however not eliminate the risk that the studies may have been under-powered. This is seen in study II where, although no apparent association between surgical delay or educational level of the surgeon, and the mortality is seen, the confidence intervals for the estimates are fairly wide (please see results section), indicating that an association could be present, but the power of our study is too weak to demonstrate this.

On the chosen variables and outcomes

When evaluating the effectiveness of an intervention the following guidelines for choosing appropriate outcome measurements have been suggested[83]: The chosen measure should be 1) quantifiable, 2) relatively easy to define and diagnose, 3) lend itself to standardization and validation, and 4) clinical relevant in the population at risk.

These recommendation could easily be argued as valid for choosing relevant variables of interest and co-variables as well, however a suspicion or knowledge of an influence on the chosen outcome measure(s) should also be present.

Studies I and II

Variables of interest were "Surgical delay" and "Educational level of surgeon". "Age", "Sex", "ASA score", "Type of fracture" and "Type of surgery" were included as relevant co-variables. The outcome measure was "Death" 30 and 90 days following index surgery.

Study IV

Variables of interest were "Number of implants used", "Posterior distance", "Calcar distance", "Tip-cartilage distance" and "Angulation of implants". "Age", "Sex", "ASA score", "Surgical delay", "Fracture displacement" and "Reduction" were included as relevant co-variables. The primary outcome measure was reoperation due to re-osteosynthesis, femoral head removal or arthroplasty replacement within 1 year of index surgery. Secondary outcomes were "Further major surgery" and "Death" within 1 year of index surgery.

Validity and reliability

"Age", "Sex", "ASA score", "Type of fracture", "Type of surgery", "Surgical delay" and "Educational level of surgeon" were all collected from the DFDB. A previous investigation of the validity and completeness of the database found that "*Patient- and trauma-related data were 82-100% valid. Surgery-related data included method of osteosynthesis and was valid in 89-99% of the cases*"[28]. For the variables included in this study, the validity varied from 87%-100%; however the validity of the ASA score was only 80%. This validation was conducted in only two departments and a larger-

scale validation has not been conducted yet. In this study we did not perform any further validation of the variables.

"Number of implants used", "Posterior distance", "Calcar distance", "Tip-cartilage distance", "Angulation of implants", "Fracture displacement" and "Reduction" are all measures of the pre- and postoperative x-rays for the primary surgery. The quality of the x-rays varied and we could not be sure if standard recommendations had been followed when they were taken. The Garden classification and the posterior tilt, which are combined to produce the variables "Fracture displacement" and "Reduction" are previously described measures with acceptable reproducibility and clinical relevance[84,85]. For the measurements "Posterior distance", "Calcar distance", "Tip-cartilage distance" and "Angulation of implants" we found no "Gold Standard" and they are therefore our own definitions. The intra- and inter-reader evaluation showed a high reproducibility of the measurements, but whether the measurement of the 2D X-rays is a valid measurement of the actual distance in the 3D bone is unknown. A previous study of the uncertainty of measurements of the femoral neck angle with regards to external rotation on the x ray demonstrated a variation of less than 5° between measured angle on standard AP and actual angle measured on a CT scan[86]. The validity of the measurements of the distances within the femoral head and neck has to our knowledge only been estimated in a biomechanical setting, showing an uncertainty of up to 6.5 mm on measured calcar and posterior distances, depending on the rotation[87]. It has however not been validated in a clinical setting. This should be taken into consideration when interpreting our findings.

Data on both "Reoperation" and "Further major surgery" were collected from the LPR. Since the reimbursement of the department is based on the reports of ICD-10 surgical procedures, the completeness and validity of the registry in this regard is very high[88] thus minimizing the risk of missing or erroneous data.

The outcome “Death” is specific, clinically relevant, easily assessed, and, in Denmark, available with great accuracy from the CRS[89].

Specific considerations regarding chosen variables and outcomes

“Surgical delay” was defined as the time from fracture diagnosis (time of the pre-surgery x-ray) until onset of the surgery. This definition could be challenged since it does not account for the time-interval from injury to x-ray, which may vary considerably and in itself represents a risk factor for mortality. The definition of “Surgical delay” was chosen since time from injury until admission often is uncertain and lies beyond the setup that can be controlled in a hospital setting. Furthermore, it allows the inclusion of the 7% of the patients which sustain their fracture under hospital admission[90]. For the question as to whether expeditious surgery of patients with femoral fractures influence the risk of mortality in a hospital setting, the time from injury to radiologic diagnosis is therefore an unaccounted co-variable and may influence our results of the effect of surgical delay. Furthermore, this definition makes the surgical delay shorter than if time from admission to surgery had been chosen, which should be taken into account when comparing our findings with other studies using another definition.

“Educational level of surgeon” is based on whether or not the surgeon or the supervisor has obtained the level of attending surgeon. This is a rather crude surrogate measure of the experience level and does not take into account how many times or how frequently the given surgeon has performed the specific technique prior to the registered surgery. Many “below attending” surgeons close to completing their training may have a rather extensive experience while an “attending or above” surgeon might not have performed this technique frequently up to the registered surgery. A previous study with a comparable definition found no effect of the different experience-level of the “below consultant” surgeons and the risk of

reoperation[91], suggesting this in-group variation is negligible, but an evaluation of our definition of “Educational level of surgeon” has not been performed.

“Age”, “Sex”, “ASA score”, “Type of fracture” and “Type of surgery” have all previously been confirmed as factors associated with risk of death in hip fracture patients[92–96] and are thus included as relevant risk-modifiers in effort to isolate the effect of the variables of interest.

The ASA score was chosen to evaluate the healthiness of the patient at the time of the surgery. This score evaluates the risk of complications in relation to the anesthesia based on details of comorbidities and the state of the patient at time of surgery[97]. It does not provide any information about the type of comorbidities and therefore does not allow for stratification in accordance with these. An alternative could have been to use the Charlson comorbidity index based on data collected from the LPR. It has previously been demonstrated that the presence in LPR of a ICD-10 diagnosis of a disease included in this index is highly correlated to the patient actually having the disease[98], but speculations remain as to if all patients with comorbidities are registered in the LPR, thus if the completeness of data is acceptable. The ASA score is attributed to the patient by the anesthetist immediately prior to surgery and is therefore the most fitting description available of the patient’s medical condition at the time of surgery.

Whether “Death” is the optimal outcome measure to define the success of the treatment can be debated. Ideally other factors should be considered as well, such as re-admissions, ability to return to previous level of function and patient-related outcome measures. However, due to the composition of the general hip-fracture population, these measures can be quite difficult to obtain, and may not be representable for the entire population.

Regarding “Reoperation”, this was defined relatively narrow, including only arthroplasty replacement or femoral head removal, thereby excluding simple removal of the implants (healed fracture most likely), osteosynthesis for a new fracture (new trauma most likely), femoral amputation (hip fracture not likely cause) and revision due to infection, as those are not likely to be related to the technical aspects of the osteosynthesis of the primary fracture. It was assumed that replacement of the hip-joint or removal of the femoral head within 1 year following osteosynthesis was based on failure of the osteosynthesis and not due to primary osteoarthrosis. This theory was not validated. It is the authors’ experience that it is common practice to perform primary replacement if the patient has pre-fracture severe arthrosis, regardless of the type of fracture. It might be that some of the replacements might be unrelated to the osteosynthesis, but we believe this to be unlikely.

Study III

The study objective was to evaluate the evidence available for long-term performance of the implants used in trochanteric fractures. For this, a systematic review of the literature available in PubMed was conducted.

When investigating published literature it is important to remember the publication bias: Manuscripts with significant findings, controversial findings or from well-established research units are more likely to get published. It is therefore quite possible that the published results are not representative of “the truth”, which is to be kept in mind when interpreting the findings.

To narrow the search down, only implants used in Denmark was chosen. This may make the findings less relevant in other countries, but to our knowledge the review included all major implants available on the marked and it is therefore likely that a similar distribution of the types of implants used is found in other countries[6].

To identify the specific implants, surgeons or surgical nurses from each department were contacted by mail or by phone. Their answer was accepted without further need of proof, which may introduce the risk of a recall bias. We do however believe this to be a minor problem in our interpretation of the study findings, since all larger implant manufacturers were included anyway.

It could be argued that the majority of the failures occur within the first 6-12 months after surgery[99–101] and several studies have reported implant-related outcome with less than 12 months follow up. In the review a follow up time of at least 12 months was chosen. The main objective of the review was to evaluate the information available of long-term survival of the implants, and as such the publications with a shorter follow up time were not relevant.

Changes from the protocol

Initial plans may be altered during a study for several reasons. For the studies included in this thesis the following changes were made:

Study I and II

a) To reduce the number of included variables, the variables "time of the day", "Type of hospital" and "need for further surgeries/reoperations" were excluded. It is the authors' impression that femoral fracture surgery under normal circumstances do not occur during nighttime in Denmark. Although it has previously been demonstrated that the type of hospital may influence the risk of death following hip fracture surgery[102], we believe that this may be due to substantial difference in-between the different types of hospitals in the investigated population. It is the authors' impression that in Denmark, the differences between the different types of hospitals is small, and the close proximity of university hospitals allows for quick transfers if such are needed.
b) Since defined time-intervals were used and there were no competing outcomes, and therefore no censorship of time at risk, a logistical regression analysis was used instead of a cox regression.

Study III

a) The initial plan was to try and make a presentation of the implant-specific performance of the current published data, but this was not possible to do due to great variation between the study designs and the lack of data available. Therefore, the only summarized data presented are the amount of data available.

Study IV

a) With regards to data on reoperation, the original plan was to collect these from the DFDB, the DHR and the LPR. However, since all reoperations (in theory) are reported to the LPR and we did not plan to extract further information regarding these than that they had taken place, only LPR was consulted to identify further hip-related surgeries. Furthermore, the completeness of DFDB and DHR with regards to reoperations are somewhat lower than for the primary surgeries[28,103] and DHR only collects data only revision arthroplasty or explant of the hardware components[103].
b) An initial plan was to examine the x-rays and the medical charts of the reoperations in order to determine the cause of the reoperation. This was abandoned for this project, partly due to logistical difficulties and partly because we did not have any controls to determine if the findings were random or if a trend occurred.
c) We initially planned to investigate the possible effect of the x-ray measure "Spread", the distance between the screws in the axial x-ray. However, in the initial measurements of the x-rays it became apparent that the uncertainty of this measure was considerable and the measure was dropped.
d) The educational level of the surgeon was not included as a co-variable in the final analysis of the data, since this was considered a surrogate measurement of how well-performed the surgery was conducted. Based on the measurements of the position of the implants this aspect was already described.

Discussion

The objective of this PhD thesis was to evaluate a few small aspects in the treatment of proximal femoral fractures in hope to provide evidence to optimize the current treatment regimes.

Using mainly registry based data the following questions have been investigated: 1) Does the surgical delay influence the risk of mortality in the proximal femoral fractures? 2) Is the association present for distal femoral fractures? 3) Is the current post-marked evaluation of implants sufficient to monitor the performance of the implants? 4) How does the surgical technique influence the risk of reoperation in femoral neck fractures?

Surgical delay in fracture surgery

For hip fracture surgery, an agreement exists that surgical of >36-48 h increases the risk of complications (bedsores, infections and death) significantly, and guidelines advice to perform surgery within the day or the next following admission[20,22]. Whether efforts should be made to reduce this delay even further has been debated. To our knowledge the effect of surgical delay <12h has so far only been investigated in two previous studies: Uzoigwe et al found that surgical delay >12 h significantly increased for in-hospital mortality (OR 3,8, p = 0.046)[104], however Smektala et al found no significant adjusted effect on 1-year mortality[105]. In our study we demonstrated a significant association of surgical delay <12 hours only regarding 30 day mortality, with a less strong (and not significant) association with 90 day mortality. One explanation for the declining association between surgical delay and mortality over time could be that the effect of surgical delay <12 hours is only temporary and not lasting, as surgical delay <48 hours have been shown to be[24], but further research is needed to evaluate this possibility.

Another consideration is that to prioritize hip fracture surgery, surgery for other fractures (or other conditions) may have to be postponed. Whether surgical delay is associated with increased risk of complications and death in other fractures types has not been much investigated. Hip fractures are the most common fracture treated surgically[29], meaning other fractures are more rare and perhaps therefore less investigated. It is however possible that increased surgical delay in other fractures would result in worse outcomes. Delay of initial debridement of open tibia fractures has been associated with increasing risk of amputation[106] in one study, but not with increased risk of infection in another[107]. A short surgical delay has been associated with fewer early postoperative complications in closed ankle fractures[108,109]. A few studies have investigated the influence of surgical delay on mortality in distal femoral fractures. Streubel et al. investigated 92 patients over a period of 10 years (year 1999 to 2009)[30] and found that surgical delay of more than 48 hours significantly increased the mortality 6 months and 1 year after surgery, but demonstrated no relation to 30-day mortality. Brogan et al. evaluated 243 patients with osteoporotic non-proximal femoral fractures (including 80 naive distal fractures), operated between 2008-2014[32]. As in our current study they did not find any effect of surgical delay on 3-months-mortality and no effect on 1-year-mortality. They did however find that a longer surgical delay time was associated with fewer surgical complications, but had no obvious explanation for this[32]. Moloney et al. included 176 patients treated with plate osteosynthesis. In their study, surgical delay of more than 2 days was associated with increased 1-year mortality. Furthermore increasing delay was associated with increasing risk of postoperative pulmonary complications[31]. In our study of the effect of surgical delay in distal femoral fractures, we did not find any clear association to the risk of 30 day and 90 day mortality. Despite this being the largest study investigating this relationship, only 392 fractures were available for analysis, and as a consequence the study is underpowered to rule out the presence of an association. Further studies are therefore needed to evaluate this association.

If surgical delay should be reduced to a minimum, it might be relevant to consider after-hours surgery as an option. However, it could be speculated that surgery in this time interval might be with higher risk of peri- or postoperative complications and death, but so far this has not been demonstrated for hip fracture surgery[110–113]. A consideration in regards to including after-hours surgery to reduce the surgical delay is the economic aspect. The cost of performing surgery after-hours is higher than during daytime and if the effect of a very short surgical delay is minimal, it may not be cost-effectively reasonable to perform surgery in this time interval[114]. So far this has not been much investigated and further research is needed.

Experience level of the surgeon and risk of death

In our study of the hip fractures we found an increase in risk of death of 25% when resident in training performed the surgery unsupervised, which confirms previous findings[91,115–118]. Similar results have been found in the field of arthroplasty[119]. Distal femoral fractures are less common and can present a larger surgical challenge compared to proximal femoral fractures and it is quite likely that an effect is present for distal femoral fractures as well. Study II however did not demonstrate any association between the experience level and death following distal fractures. An explanation for this could be that only 11% of the surgeries were performed without and attending surgeon present. For proximal fractures, this happened in 51% of the surgeries. This could be due to awareness for the need for surgical experience to perform these surgeries which leads to patients receiving surgery by an adequately experienced surgeon. Furthermore, the study is underpowered to rule out an association.

To improve the treatment of hip fractures, guidelines now advocate for the supervision of “below-attending” surgeons[22] and in some countries it is now mandatory by law that an attending surgeon is present during the surgery (https://judicialis.de/Oberlandesgericht-M%C3%BCnchen_1-U-3145-

01_Urteil_31.01.2002.html). Furthermore, the possibility of improving surgical skills by virtual-reality simulation prior to proceeding to supervised surgeries on patients is a developing field, both in hip fracture surgery as well as other surgical procedures[120,121]. The results of these actions will have to be evaluated in the future.

Long term performance of implants

Study III demonstrated a lack of data available when relying on clinical research to evaluate the long-term performance of implants used for trochanteric hip fractures. Furthermore, these uncoordinated investigations results in studies with great diversity in setup and outcomes, and it is therefore not always possible to accumulate data from several studies[122]. Even though mortality following hip fractures is high, approximately 75% of patients will be alive after 1 year and will need the best possible implant for the optimal result and to avoid reoperations. However, with the lack of a clear evaluation of the implants available, the choice of specific implant will primarily be based on surgeons' personal experience or whatever deal the departments make with the different companies.

For arthroplasty implants it has been demonstrated that even small differences in design can have a substantial effect on long term survival of implants[123], and it is therefore reasonable to suspected that a difference in performance of the implants could exists. But since the current implants are not well evaluated and new implants can be introduced without pre-marked clinical testing, this notion is difficult to investigate[34]. This raises the question: What to do then?

In order to minimize the risk of submitting an unnecessary large numbers of patients to inferior implants it would be beneficial to accumulate data on the performance of implants[124]. Well-established continuous registration for all arthroplasties on specific implant level has existed for many years and has proven valuable in identifying implants with inferior survival rates[125,126]. A similar system with systematic

registration of primary surgeries and reoperation, including registrations of implants used, would be a valuable supplement to the clinical studies in trauma surgery[127].

The reoperation rate in femoral neck fractures is lower than previously reported.

Various incidences of reoperation have been reported following osteosynthesis with parallel implants, ranging from 10% (only non-displaced fractures) within 24 months[128], 13.3% within 12 months[101], 22.6% within 12 months[12], 23% within 6 months[46], 47% within 48 months[39] to 42% (only angulated or displaced fracture) within 24 months[40]. In our study, the overall reoperation rate was only 13%.

This may be due to variations in the definitions of a reoperation. Another explanation could be a more optimal patient selection. Based on the emerging literature, guidelines now advocate a wider use of arthroplasty primarily in high-risk patients (elderly patients with displaced femoral neck fractures)[33,129,130] and a following reduction in reoperations should be expected.

Osteosynthesis of femoral neck fractures

Apart from finding that implant cartilage perforation increased risk of reoperation, Study IV did not demonstrate any association between the position of the implants within the neck or the head of the femur and the risk of reoperation. These findings are in line with previous investigations by Hoelsbrekken et al. and Jordan et al. where the initial fracture displacement and insufficient fracture reduction increased the risk of failure, while implant positioning did not [46,55].

The effect of the implant positioning has been debated in previous studies, primarily based on a biomechanical set-up. Such studies have advocated the use of 3 or 4 parallel implants with calcar and posterior support[52,131]. A few clinical studies have found an effect of the calcar and posterior cortical support on the risk of non-union.

Lindequist investigated 82 femoral neck fractures treated with 2 parallel implants and found an effect, which was confirmed by Lagerby et al. in a prospective study of 268 patients[53,54].

Placing an implant so the tip reaches within 5 mm of the caput surface has been advised in guidelines[20], but to the best of our knowledge this has not been supported in any clinical studies. We found no association of a small tip-cartilage distance, confirming previous findings[53,59]. Barnes et al demonstrated an increased risk of failed union with protrusion into the hip joint, but no difference in incidence between a distance of 0-5 mm and 5-10 mm[132]. Jenkins et al demonstrated in a biomechanical study of osteoporotic femoral head from fracture patients that the strongest trabecular bone in the femoral head is in the centre at the epiphyseal scar with less dense and less strong bone in the apex of the femoral head[16]. It could therefore be that the main stability of the implants is obtained in the epiphyseal scar and a close contact to the cartilage therefore is less important and should not be obtained at any cost, including risking perforation of the cartilage.

In accordance with previous studies we did not find any effect of placing the implants in a parallel manner[133]. However, an angle between the implant and the corpus of the femur of at least 130° has been advocated as appropriate and cases of a “too flat” angle leading to fracture displacement have been described[134,135]. In this study, an angle of less than 125° between the lateral cortex and the inferior implant was significantly associated with increased risk of reoperation, thus supporting this theory. We found no upper limit to the angulation of the implants (data not shown).

Conclusions

The use of register data provided a large cohort with uniform data for further analysis and facilitated to evaluation of the research hypotheses. Based on the findings of the studies included in this thesis, the following can be concluded:

Increased surgical delay and a low educational level of the surgeon are associated with increased risk of death in proximal femoral fractures, but these associations are less clear in distal femoral fractures.

Using registry-based data an association between both surgical delay and educational level of the surgeon, and the risk of death has been demonstrated for proximal femoral fractures. In an identical setup this was not evident for distal femoral fractures. It should however be noted that due to the rarity of the distal femoral fracture, only 392 surgeries were available for evaluation and the power of the study is therefore not sufficient to determine that an association is not present.

The current system with sporadic evaluation by clinical studies is not sufficient to identify long term problems with the implants used in trochanteric fractures.

The review of the current available literature demonstrated that the amount of data available on long-term performance of the implants currently in use for proximal femoral fractures is small, especially considering the number of implants used worldwide.

Proper patient selection and sufficient fracture reduction are perhaps more important than focusing on an optimal osteosynthesis in femoral neck fractures.

13 % of patients underwent reoperation within 1 year. Initial fracture displacement, insufficient reduction, angle between the implants and the femoral shaft ≤125° and protrusion of an implant-tip in the joint significantly increased the risk of reoperation within 1 year. No effect of the number of implants, the distance of the implants to the calcar, the distance of the implants to the posterior cortex of the femoral neck or the angle between the implants was found. This may indicate a relatively low importance of the exact location of the implants within the femoral head and neck, compared to proper patient selection for osteosynthesis.

Perspectives and future research

The treatment of hip fracture patients has improved much over the last decades, but with the high incidence and devastating consequences for the patients, as well as the financial burden on society, further research to improve outcomes is still needed.

Although the diversity, high morbidity and high mortality of the population makes it difficult to perform proper interventional studies, RCTs are vital to confirm or deny causal relationship, but should aim at including all relevant participants to provide evidence concerning the entire fracture-population.

In the discussion about delay to surgery, some aspects are still not well investigated. The causes of the delay may be many, and for some subgroups of the population, e.g. patients in anticoagulant treatment or with systemic infections, some delay to allow optimization may be beneficial to reduce risk of complications. This will have to be evaluated in future studies.

The possible effect of the educational level of the surgeon on mortality is a relevant topic for future research. Not much evidence exists as to how to educate aspiring surgeons most efficiently. New developments to improve the qualification of the surgeons with computer simulation prior to performing surgery on patients is an interesting topic and should be evaluated further.

As evidence supporting more expeditious surgery and more extensive postoperative rehabilitation emerges, an evaluation of the resources needed to meet these demands, as well as the expected reductions in treatment cost with improved treatment, is warranted, and it might be necessary to discuss if implementing new treatment routines is cost-effectively justifiable.

As study III demonstrates, no proper post-marked evaluation of hip fracture related implants exists, and a continuous performance monitoring of properly registered

implants would be of value in optimizing treatment. Furthermore this could be expanded to other types of traumatology procedures and a systematic registration of all implants used in traumatology surgery should be considered.

Endpoints of the research of hip fractures have to a large degree been well-defined hard outcomes such as death, re-admission and reoperation. As these outcomes hopefully improve, a further emphasis of functional and patient-reported outcomes is needed.

Many of the aspects found the hip fractures may be relevant for other fractures, but lack evaluation due to a lower frequency of the fractures, and therefore, to less data available for evaluation. By performing continuous data-collection of all fracture-related surgeries, we might be able to obtain the quantity needed to evaluate these.

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Appendix

Protocol for studies

Papers I-IV*

***The papers are not included in the electronic version available from the Danish Orthopaedic Society. The papers can be found in the publishing journals.**

Protocol for studies I and II

Projektbeskrivelse

Projekttitel

Sammenhæng imellem ventetiden på operation og dødeligheden hos patienter med lårbensbrud

Introduktion

Lårbensbrud kan inddeles I 3 grupper jvf et klassifikationssystem udviklet af Müller og AO Foundation: (1) Hoftenære brud (AO31), (2) skaftbrud (AO32) og (3) knænære brud (AO33). Disse kan igen inddeles i undergrupper alt efter den specifikke placering og type af brud. Fælles for patienter med lårbensbrud er den efterfølgende immobilisering pga. smerter og manglende funktion af benet.

Den mest almindelige form for lårbensbrud er de hoftenære brud,(AO31)[1]. De forekommer hyppigst hos ældre patienter med knogleskørhed, som falder og slår sig direkte på hofteregionen [2, 3]. Hovedformålet med at behandle disse brud er at opnå et stabilt og smertefrit ben så hurtigt som muligt. Den optimale behandling for disse skader er operation, da konservativ behandling (dvs behandling uden operation) med stræk og bandagering er forbundet med en længere indlæggelse, større risiko for manglende heling og en mindre sandsynlighed for at kunne vende tilbage til det tidligere funktionsniveau [4, 5]

Der har været en del debat om, hvorvidt man skal operere patienter med hoftenære brud så snart der var personale og operationsstuer klar, eller om patienterne ville have gavn af at vente og blive optimeret mhp deres øvrige konkurrerende lidelser mest muligt inden operation. Forskning har vist, at en længere ventetid på operationen (delay of surgery, DOS) fører til en længere indlæggelse [6-10] og en højere risiko for at udvikle liggesår og andre komplikationer efter operationen [6, 7, 9, 11-13]. Hvorvidt der er en sammenhæng imellem DOS og dødeligheden efter et hoftebrud er mindre klart. Trods omfattende forskning på området, har der indtil nu været meget varierende resultater. Nogle studier har vist, at en kort DOS nedsætter dødeligheden efter at have pådraget sig et hoftenært brud [13-29], mens andre ikke har kunnet finde nogen effekt af kort DOS [6, 7, 10-12, 30-34]. Der lader dog ikke til at være nogen komplikationer forbundet med kort DOS. [35] Dette har alt i alt ført til at "Det Danske Referenceprogram for Hoftenære Frakturer" anbefaler, at patienter med hoftenære brud bliver opereret indenfor 24 timer fra indlæggelsen[36].

Grænsen på de 24 timer er diskuteret en del. Enkelte studier har vist, at dødeligheden er lavere i den gruppe af patienter, der opereres indenfor 12 timer, og at dødeligheden stiger med stigende DOS.[19, 21]

Andre faktorer, så som mandligt køn [37, 38], alder [37, 38], ASA score (en angivelse af patientens overordnede helbredstilstand) [37], operatørens erfaring[39], funktionsniveauet før skaden [25, 37, 38, 40], typen af hospital (universitetshospital vs. Distriktshospital) [13] og typen af brud [40-42], er også blevet identificeret som havende indvirkning på dødeligheden efter et hoftenært brud. Det per-operative blodtabs betydning for dødeligheden i forbindelse med hoftenær fraktur er ikke tidligere blevet undersøgt i større studier.

Indtil nu er det kun nogle få studier der har undersøgt effekten af DOS på andre typer af lårbensbrud så som skaftbrud(AO32) og knænærebrud (AO33). På grund af de kliniske ligheder med immobilisering efter skaden er det nærliggende at forvente en lignende sammenhæng mellem DOS og dødeligheden i disse grupper. Streubel et al. har fundet, at operation indenfor 48 timer efter indlæggelse sammenlignet med operation efter 4 dage signifikant nedsætter dødeligheden efter et knænært lårbensbrud (AO33) [43].

Der er i dag ingen rekommandationer i forhold til tidlig kirurgi af skaftbrud (AO32) eller knænære brud (AO33). Vi tror at patienter, der har pådraget sig disse brud, på linje med patienter med hoftenære brud vil have gavn af tidlig kirurgi.

Dansk Frakturdatabase (DFDB) [1] blev opstartet i sin nuværende webbaserede form i november 2011 med det primære formål at udføre systematisk registrering og kvalitetssikring af alt frakturrelateret kirurgi. DFDB er siden blevet implementeret på i alt 16 afdelinger og dækker aktuelt (januar 2014) et estimeret optageområde på 3,7 millioner borgere. Indrapportering til DFDB foretages af operatøren efter den kirurgiske behandling af et brud og indeholder patient-, brud- og kirurgi-relaterede data. Databasen er godkendt af datatilsynet med journalnr. 2007-58-0015.

DFDB blev valideret i marts 2013, hvor man fandt en tilfredsstillende komplethedsgrad og høj datavaliditet [44]. Alle typer brud, inkl lårbensbrud bliver registreret i DFDB sammen med relevante oplysninger om tidspunktet for diagnosen, tidspunktet for operationen, brudtype, operationsmetode, operatørens uddannelses niveau samt patientens overordnede heldbredstilstand.

Formål

Målet med dette studie er at undersøge: a) hvilken effekt DOS har på dødeligheden efter lårbensbrud (herunder hoftenærebrud, skaftbrud og knænære brud) i en dansk population; b) hvorvidt der er en nedre grænse for, hvor hurtigt man ideelt set skal operere patienterne med lårbensbrud; c) om sammenhæng mellem DOS og dødelighed er ens for alle typer lårbensbrud (herunder hoftenærebrud, skaftbrud og knænære brud) og; d) som et sidestudie til dette studie, ønsker vi at undersøge betydningen af det per-operative blodtabs betydning for dødeligheden efter hoftenære frakturer.

Projektet problemstilling

- Er der en sammenhæng imellem ventetiden til operation og dødeligheden efter et hoftenært brud i en dansk population?
- Er der en sammenhæng imellem ventetiden til operation og dødeligheden efter et andet brud på lårbenet i en dansk population?
- Er der en sammenhæng mellem det per-operative blodtabs størrelse og dødeligheden efter et hoftenært brud i en dansk population?

Data og Metode

Vi vil gerne undersøge sammenhængen imellem den tid, der går fra vi har konstateret at patienten har et behandlings krævende brud på lårbenet og operationen (delay of surgery (DOS)) og efterfølgende dødelighed for disse patienter,.

DOS bliver indirekte registret i DFDB i form af tidspunktet for at bruddet er blevet bekræftet (i form at et rtg. billede) og et tidspunkt for start på operation.

Fra DFDB vil vi lave et udtræk på alle indtastede AO31, AO32 og AO33 brud og udvælge egnede patienter til analysen ud fra nedenstående inklusion og eksklusionskriterier.

For den udvalgte patientgruppe vil vi undersøge sammenhængen mellem DOS og dødeligheden ved at sammenkøre data om operationen fra DFDB med data om dødelighed fra CPR registret.

Dødelighed vil blive opdelt i grupper som dødelighed inden for 30 dage, inden for 90 dage og inden for 365 dage.

DOS vil blive opdelt i undergrupper efter varigheden: 0-12 timer, 12-24 timer, 24-36 timer, 36-48 timer, 48-72 timer samt >72 timer. Vi vil herefter sammenligne dødeligheden inden for 30, 90 og 365 dage undergrupperne imellem. Efterfølgende vil vi sammenligne dødeligheden imellem de 3 forskellige typer lårbensbrud.

Det er tidligere vist, at en række andre faktorer har betydning for dødeligheden efter et brud på lårbenet, som vi vil korrigere for i den statistiske analyse af data.

Sammenhængen mellem per-operativt blodtab og dødeligheden er aldrig undersøgt i større studier.

Disse inkluderer: Køn, en samlet vurdering af patienternes helbred (ASA score), tidspunkt på døgnet for operation, brudtype, operationsmetode, operatørerfaring/supervision, hospitalstype (universitet/distrikts) og behov for gentagne operationer.

Da det per-operative blodtabs betydning for dødeligheden ikke er klarlagt, ønsker vi at klarlægge dette i et sidestudie. Til dette studie sammenkører vi data om per-operativt blodtab fra den lokale operationsdatabase (ORBIT) med data om dødelighed fra CPR registret. Dødelighed vil blive opdelt i grupper som dødelighed inden for 30 dage, inden for 90 dage og inden for 365 dage.

Inklusionskriterer

Alle brud på lårbenet inkluderet i DFDB: (1) Hoftenære brud (AO31), (2) skaftbrud (AO32) og (3) knænære brud (AO33).

Eksklusionskriterer

- Højenergitraumer, dvs. hvis der har været traumekald på pt.
- Alder <50 år.
- Hvis pt. Ikke er registreret i CPR regitret.
- Opereret på et hospital, hvorfra der er <50 indberetninger om AO31, AO32 og AO33 frakturer.

Statistiske metoder

Cox regressions analyse vil blive brugt til at sammenligne dødelighed mellem de forskellige grupper ved beregning af risk ratio (RR). Overlevelsen vil desuden blive estimeret vha Kaplan Meier kurver.

En redegørelse for etiske overvejelser

Det er tale om en retrospektiv observations studie uden intervention. Patienterne eller pårørende vil ikke blive kontaktet i forbindelse med studiet. Det vil ikke blive undersøgt for yderligere helbredsoplysninger end dem der allerede er registreret i patient journalerne samt i DFDB. Der er således ingen etiske problemstillinger i forbindelse med dette studie.

Perspektivering

Hoftenære brud er de hyppigste type brud der bliver opereret på ortopædkirurgiske afdelinger og som samtidigt har en meget høj dødelighed – op til 25% af patienterne er døde inden for et år. Vores studie vil undersøge sammenhæng mellem tidspunkt for kirurgi og overlevelse, ikke kun for hoftenære brud, men også andre typer brud på lårbenet, som rammer en lignende patient gruppe og er ligeledes forbundet med høj dødelighed. Ved at undersøge den rolle som forsinkelsen af operationen spiller for dødeligheden blandt disse patienter, vil vi danne en grundlag for optimering af behandlingen af lårbensbrud som på længere sigt kan føre til nedsat dødelighed hos denne patientgruppe.

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Protocol for study III

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Evidence for performance of implants used for proximal femoral fractures in Denmark

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review.

Give the date when the systematic review commenced, or is expected to commence.

20/11/2014

4 Anticipated completion date

Give the date by which the review is expected to be completed.

19/06/2015

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Anne Marie Nyholm

7 Named contact email

Enter the electronic mail address of the named contact.

rienyholm@gmail.com

8 Named contact address

Enter the full postal address for the named contact.

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Clinical Orthopedic Research Hvidovre, University Hospital Copenhagen, Denmark

Website address:
CORH.dk

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mrs	Anne Marie	Nyholm	Clinical Orthopedic Research Hvidovre
Dr	Kirill	Gromov	Clinical Orthopedic Research Hvidovre
Mr	Henrik	Palm	Department of Orthopedics, Copenhagen University Hopsital Hvidovre, Denmark
Professor	Anders	Troelsen	Clinical Orthopedic Research Hvidovre
Mr	Henrik	Malchau	Department of Orthopedics, Sahlgrenska University Hospital, Sweden

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
No funding has been received.

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
What is the current evidence of implant survival for implants used in treatment of proximal femoral fractures in Denmark?

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
PubMed search using search lines (sliding hip screw OR SHS OR (dynamic hip screw) OR DHS OR (compression hip screw) OR CHS OR HipLock) AND (hip fracture OR cephalo medullary fracture OR trochanteric fracture OR femoral fracture OR "Hip Fractures"[Mesh]) (Intramedullary nail OR IMHS OR (intramedullary hip screw) OR PFN OR (proximal femoral nail) OR PTN OR (Peritrochanteric Nail) OR Gamma 3 OR PFNa OR (Proximal femoral nail antirotation)) AND (hip fracture OR cephalo medullary fracture OR trochanteric fracture OR femoral fracture OR "Hip Fractures"[Mesh])

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Proximal femoral fractures. Implant performance.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: Patients treated for a primary proximal femoral fracture. Exclusion: not written in English published before 1990 Patients with subtrochanteric fractures Patients with pathological fractures

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Inclusion: Implants used in the treatment of proximal femoral fractures in Denmark, specifically: IMHS (Smith&Nephew) PTN (Biomet) Gamma 3 (Stryker) PFNa (Synthes) PFN (Synthes) InterTan (Smith&Nephew) DHS (Synthes) CHS (Smith&Nephew) HipLock (Biomet) Exclusion: Other implants Implants not specified. Follow up less than 12 months

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

We are aiming to present the type and amount of evidence for each implant, not to compare implants.

22 Types of study to be included initially

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

We plan to include retrospective, prospective and interventional studies wich describe implant survival, failure-rate and reoperationrate for a relevant implant. Studies with a follow up of less than 12 months will be excluded.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Studies will be included no matter the setting.

24 Primary outcome(s)

Give the most important outcomes.

Implant performance/survival

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

None

Give information on timing and effect measures, as appropriate.

26 Data extraction, (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer. A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: Study period, study method (retrospective, prospective, interventional), type of fracture, type of implant, number, gender and age of patients, time to follow up. One review author will extract data, uncertainties will be identified and resolved through discussion (with a third author where necessary).

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Level of evidence will be evaluated for each study in accordance with OCEBM Levels of Evidence Working Group, "The Oxford 2011 Levels of Evidence," Oxford Centre for Evidence-Based Medicine, http://www.cebm.net/ocebm-levels-of-evidence/

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

We will, for each implant, provide a presentation of the included studies, structured around the type of study, target population characteristics, type of outcome and length of follow-up. We anticipate that there will be limited scope for meta-analysis because of the small number of existing trials and the limited number of relevant events in each trial.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

None planned

Review general information

30 Type of review

Select the type of review from the drop down list.

Intervention

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Denmark

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

We hope to present our review both as a congress presentation and as an article in a relevant journal.

Do you intend to publish the review on completion?

Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

Proximal femoral fracture

Sliding hip screw

Intramedullary Nail

implant performance

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.

Completed but not published

39 Any additional information

Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Protocol for study IV

Research Protocol for an Observational Study

Title

Full title: Surgical delay, quality of osteosynthesis, and rate of reoperation after osteosynthesis of femoral neck fractures with parallel implants – A retrospective study based on data from the Danish Fracture Database

Running title: Factors influencing reoperation in femoral neck fractures

Names, roles and contact details

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Henrik Palm, Department of Orthopaedics, Copenhagen University Hospital Hvidovre, Copenhagen, Denmark, principal superviser

Kirill Gromov, Department of Orthopaedics, Copenhagen University Hospital Hvidovre, Copenhagen, Denmark, principal co-supervisor

Thomas Kallemose, Clinical Research Centre, Copenhagen University Hospital Hvidovre, Denmark, Statistical advisor

Anders Troelsen, Department of Orthopaedics, Copenhagen University Hospital Hvidovre, Copenhagen, Denmark, Principal Supervisor on project.

Table of Contents

1 Summary

1.1 Objective

a) To estimate the incidence of re-operation following osteosynthesis with parallel implants of a femoral neck fracture within the first 12- and 24 months in the Danish population older than 18 years of age.
b) To estimate the association between surgical delay and quality of the osteosynthesis, and risk of re-operation and death within 12 months and 24 months following osteosynthesis with parallel implants of a femoral neck fracture.

1.2 Target and study population

Our target population will be patients in Denmark with femoral neck fractures. All consecutive surgeries of patients with a primary femoral neck fracture reported to the Danish Fracture Database, which covers the entire Danish population, will be included. Each surgery will be evaluated as a separate case.

1.3 Methods

1.3.1 Study design

A retrospective cohort study on data from several registers.

1.3.2 Exposures and outcomes of interest

Primary outcome is re-operation due to any cause. Secondary outcomes are death to any cause and re-operation due to specific causes.

As exposure, the surgical delay and several technical surgical details will be measured.

The known confounding variables age, gender, ASA-score and surgical expertise will be registered and adjusted for in our analysis.

1.3.3 Sampling methods

All surgeries with complete data will be included for analysis.

1.3.4 Statistical analyses

A power calculation has demonstrated that at least 1100 surgeries are needed to demonstrate a 25% reduction in re-operation. We are including approximately 1550 surgeries.

Descriptive presentation will be used to estimate the rate, type and distribution of re-operation following surgery. To estimate the influence of surgical delay and the surgical details investigated, data will be analysed using a logistical or cox regression analysis. Results will be presented in OR or HR with respective confidence intervals.

1.4 Expected results

We expect a re-operation rate of approximately 30% within 2 years following surgery with parallel implants for a femoral neck fracture. Furthermore, we expect to estimate the influence of the quality of the osteosynthesis as well as the surgical delay on this rate of re-operation.

1.5 Discussion

Our main concern is control of potential confounding factor. We do not have data on several potentially confounders, which might influence the risk of re-operation. By including as many patients as possible, we hope that due to random stratification of these factors, the estimates will be valid, however with greater uncertainty.

2 Background

2.1 Literature review

2.1.1 Literature search

A PubMed search done using the following key words and combinations:

(Femoral neck fracture OR hip fracture OR proximal femoral fracture OR medial femoral fracture) AND (parallel implants OR cannulated screws OR Hansson hook pin OR Hansson pin) AND (reoperation OR implant failure OR caput necrosis OR pseudoarthrosis OR malunion OR avascular necrosis)

(Femoral neck fracture OR hip fracture OR proximal femoral fracture OR medial femoral fracture) AND (parallel implants OR cannulated screws OR hansson hook pin) AND (positioning OR biomechanics OR)

2.1.2 Literature summary

Fracture of the hip (OTA/AO31) is the most common fracture treated with surgery in Denmark and is associated with increased risk of morbidity, mortality and decreased level of function (1). Femoral neck fractures (OTA/AO31B) account for 51% of these fractures (2). Two main treatment options exists for this type of fracture: Either retain the femoral head and perform an osteosynthesis with parallel implants (screws or pins), or replace the femoral head with a hip prosthesis (3). For non-displaced fractures (Garden 1 and 2) and displaced fractures in patients younger than 70 years of age, retaining the femoral head is preferred (3,4). Osteosynthesis is a smaller surgical procedure with shorter duration of surgery, less bleeding, less need for blood transfusions and a smaller risk of deep wound infections compared to prosthetic replacement (5). Furthermore, when this treatment is successful, no further major surgery is needed, which is to be expected with prosthetic replacement due to wear of the components. However, the rate of re-operation within 2 years following osteosynthesis is considerably higher than following prosthetic replacement (40% versus 11%) (5–11).

To reduce the risk of re-operation, several factors have been investigated as potential risk factors. Initial fracture displacement and sub-optimal quality of the fracture reduction have both been demonstrated as important risk fractures for re-operation (12,13). However, other (potentially modifiable) factors, such as the influence of the time until surgery (surgical delay) and the experience level of the surgeon have not been much investigated, with several published studies conducted in small samples (<100 patients included), finding conflicting results (14–18). With regards to the optimal placement of the implants, studies have indicated the need for calcar- and posterior-cortex-support, the need for a wide distance between implants and the need to minimise penetration of the surface of the caput during procedure (19,20) (ref), but further details are still not known and several differences in treatment occur between surgeons within Denmark.

2.2 Justification

An expected rate of re-operation of 40% within 2 years is high. Many of the patients selected for this procedure are young, mobile and independent, and re-operation has been shown to prolong and impair functional recovery (21). This is of inconvenience to the patient and an economic burden to the society in terms of increased hospital cost and, in the younger patients, lost earnings. The influence of specific technical surgical details has not been well investigated and further research is needed to diminish the risk of re-operation if possible.

2.3 Relevance

The influence of many variables in the treatment of patients with femoral neck fractures is unknown and the treatment choices is widely based on tradition and logical deduction from general assumptions. With our study we aim to clarify the influence of several surgery-related variable to help surgeons, other care-givers related to these patients and decision-makers optimise the treatment for the benefit of the patients and reduce the cost of complications following treatment.

2.4 Feasibility

All data are available in different databases.

To perform this study, data will need to be collected from the relevant databases, including retaining permission to do so. Furthermore, all patient x-rays will have to be evaluated by at least one investigator. We estimate this is possible to conduct by one investigator within 12 months. We will be limited by time from application for permission and data transmission from external sources and perhaps also by the extend of the analysis of the x-rays.

We do not expect any financial difficulties in relation to this study.

3 Purpose, Objectives and Hypothesis

3.1 Purpose of the study

The purpose of the study is to estimate the rate of re-operations following treatment with parallel implants of femoral neck fractures in the Danish population, and to evaluate if and how possible modifiable factors influences this rate. By this we hope to give an impression of the magnitude of the problem and to provide new knowledge in order to reduce the risk of re-operation, if possible.

3.2 Objectives

c) to estimate the incidence of re-operation following osteosynthesis with parallel implants of a femoral neck fracture within the first 12- and 24 months in the Danish population older than 18 years of age.
d) To estimate the association between surgical delay, quality of the osteosynthesis, and risk of re-operation and death within 12 months and 24 months following osteosynthesis with parallel implants of a femoral neck fracture.

3.3 Hypothesis

We hypothesise that a surgical delay of less than 6, 12 and 24 hours, and placing the osteosynthesis with the distal pin within 5 mm of calcar, the posterior pin within 5 mm of posterior cortex of the femoral neck, the tip of the pins within 10 mm of the capitular cortex, and when a third implant is used, with the anterior pin as anterior as possible, so as to increase the distance between the posterior and anterior pin as much as possible, will reduce the risk of re-operation in intra-capsular proximal femoral fractures.

4 Populations

4.1 Study unit

The study unit is the patient treated surgically with parallel implants for a femoral neck fracture.

4.2 Target population

We aim at making an inference about the influence of surgical delay and several technical surgical details on re-operation and mortality rates following surgery with parallel implants for femoral neck fractures in the Danish population. We believe that if a clear association is found, this association would also be present in patients treated in a perioperative regime similar to the Danish (3), such as several other industrialised countries.

4.3 Study population

The study population consists of all patients with surgeries reported to the Danish Fracture Database (DFDB) since the establishment of the database (2011-2015).

5 Study design

This study is a register based retrospective cohort study with a cohort of approximately 1550 consecutive patients treated for a primary femoral neck fracture with parallel implants between 2011 and 2015 with a

follow-up period of minimum 12 months. Data will be partly collected from several registers, from patient records, and from analysis of x-rays.

6 Sampling

6.1 Sampling procedure

6.1.1 Source of study units – Study population

The study population consists of all patients with surgeries reported to the Danish Fracture Database (DFDB) from December 2011 to December 2015.

The DFDB was established as a web-based database in November 2011 (22). Its primary purpose is prospective, systematic data collection and quality-assessment of fracture-related surgery. In 2015, the DFDB was approved as a national database with compulsory reports for all fracture-related surgeries, including re-operations. Data are entered into the DFDB by the surgeon immediately after end of the surgical procedure and consists of patient, fracture and surgery related data. In marts 2013, a part of the database was validated, finding an acceptable completeness and a high data validity (23). Further validation has been undertaken, but is not yet completed.

All pre- and post-operative x-rays will be evaluated to ensure fracture diagnosis and collect data by performing several measurements.

Furthermore, data on re-operation and mortality will be collected from the DFDB, Danish Hip Register (DHR) and the Civil Registrational System (CRS). All registers collect data in a continuous manner.

The DHR was established in 1995 with the purpose of prospective, systematic data collection and quality-assessment of total hip arthroplasty surgery. It is continuously validated against the CRS. We expect these registers have a very high completeness and do not expect missing data.

In this manner we hope to secure a large and representative study population.

6.1.2 Inclusion/exclusion criteria for sampling

All fracture-related surgery (nothing excluded) is (in principle) reported to the DFDB.

In this study:

Inclusion criteria:

All patients reported to the Danish fracture database (DFDB) with:

- a Danish social security number
- the diagnosis “femoral neck fracture” (AO31B)
- treatment with parallel implants or screws
- correct fracture diagnosis (evaluated on pre-operative x-rays)
- no missing post-surgery x-rays
- no new fracture due to new trauma before post-operative x-rays.

will be included as study units.

With these criteria we hope to include as many patients with relevant fracture and treatment as possible and to be able to make assumptions about the Danish population in general.

6.1.3 Sampling method

All patients suitable for inclusion will be included.

7 Data management

7.1 Variables

7.1.1 Outcome variables

Our primary outcome will be

- First re-operation of any cause, reported to either DFDB, DHR or CRS (dichotomous variable, either a re-operation occurs or it do not)

Our secondary outcomes will be:

a) Death of any cause, reported to the CRS (dichotomous variable, either death occurs or it do not).

b) Secondary fractures of the same hip due to new trauma, defined as fracture requiring surgical removal or replacement of the implants, reported to either the DFDB, the DHR or the CRS (dichotomous variable, either fracture occurs or it do not).

c) Re-operation due to specific causes (categorical variable with 6 levels):

   a. Infection, stated as the reason for re-operation in the CRS or in the patient's medical record.

   b. Secondary displacement of fracture and/or cut out (implants erode out of the caput), determined by comparison of post-surgery and pre-re-operation x-rays.

   c. Avascular necrosis of the head, determined by comparison of post-surgery and pre-re-operation x-rays, which will be evaluated in accordance with the Steinberg classification (24).

   d. Non-union defined as absence of formation of callus and persistent pain in the hip more than 6 months following surgery, determined by comparison of post-surgery and pre-re-operation x-rays.

   e. Discomfort or pain due to the implant (Tractus irritation (a condition, where the ends of the implants is mechanically irritating the tractus iliotibialis, resulting in pain on the lateral side of the thigh when moving the leg) or entrapment of the skin when lying on the side), described in the medical journal. Can only be considered in patients where the fracture is clinically and radiologically healed. Stated as the reason of re-operation in the medical journal of the patient. X-rays will be evaluated to rule out b, c and d.

   f. Other, defined as anything else, with exclusion of secondary fracture due to new trauma.

   The reasons for re-operation given above is in prioritized order, meaning that if several reasons is given, e.g. infection and discomfort due to the implant, the re-operation will be considered as due to infection.

d) The time from surgery to any outcome (quantitative, continuous variable, measured in days).

7.1.2 Other variables

Primary exposure/risk factors.

- Time of diagnosis, defined by when the diagnostic x-ray was taken (date and time, with precision in minutes)
- Time of onset of surgery, defined as when the surgical procedure is started/the cutting of the skin (date and time, with precision in minutes)
- Post-surgery displacement AP, measured in accordance with the Garden classification (25) (figure X, please see end of document) measured on the post-surgery x-rays. Garden III is defined as a step-off in the calcar of more than 2 mm (after adjustment of magnification) measured on the AP x-ray (ordinal variable, with 4 levels)

- Post-surgery posterior tilt of the caput-fragment, measured by the method suggested by Palm et al. (26) (figure Y) on the post-surgery x-rays (quantitative, continuous variable, measured in degrees)
- Calcar distance: The shortest distance from the inferior implant to the calcar, measured distally to the fracture on the post-surgery AP x-ray (figure E) (quantitative, continuous variable, measured in millimeters)
- Posterior distance: The shortest distance from the posterior implant to the posterior cortex of the femoral neck, measured distally to the fracture on the post-surgery lateral x-ray (figure E) (quantitative, continuous variable, measured in millimeters)
- Spread (only in patients where 3 implants are used): The distance between the anterior and the posterior implant, measured at the level of the fracture on the post-surgery lateral x-ray (figure F) (quantitative, continuous variable, measured in millimeters)
- Tip-caput distance: Distance from the tip of the implants to the surface of the caput. Will be measured for the inferior and the posterior implant (figure E) (quantitative, continuous variable, measured in millimeters)
- For all measurements on post-surgery x-rays, the size of the implant will be measured in order to scale the magnification of the x-ray and calculate the "actual" distances (figure E) (we know the size of the implant).

Secondary risk factors

- Fracture displacement AP, measured in accordance with the Garden classification (25) (figure X) on the pre-surgery x-rays. Garden III is defined as a step-off in the calcar of more than 2 mm measured on the AP x-ray (ordinal variable, with 4 levels)
- Fracture posterior tilt of the caput-fragment, measured by the method suggested by Palm et al. (26) (figure Y) on the pre-surgery x-rays (quantitative, continuous variable, measured in degrees)
- Educational level of surgeon, defined by the level of education of the most senior surgeon present during the surgery, either as primary surgeon or supervisor (ordinal variable with 9 levels: præ-KBU, KBU, intro, præ-kursist, kursist fase 1, kursist fase 2, kursist fase 3, speciallæge, traumatolog)
- Date of birth of the patient (date and time, with precision in days)
- American Society of Anaesthesiologists score (ASA-score) (a score evaluating the medically fitness of the patient to predict how hazardous anaesthesia of the patient is) determined at the time of surgery by the anaesthetist assisting the surgery (ordinal variable, with 6 levels; ASA I-VI)

Stratifying factors

- Number of implants used (dichotomous variable, either 2 or 3 implants is used)

Possible confounders not considered as risk factors with respective to the objective of the study.

- Gender (dichotomous variable, either male or female)

7.2 Data collection

The data will be obtained in part by collecting data from databases, by evaluating/measuring x-rays for each patient and by looking through medical records. Permissions to collect and evaluate the data will be obtained by the primary investigator prior to data collection.

The flow of the data concerning patients treated with parallel implants for a femoral neck fracture is shown in figure 1.

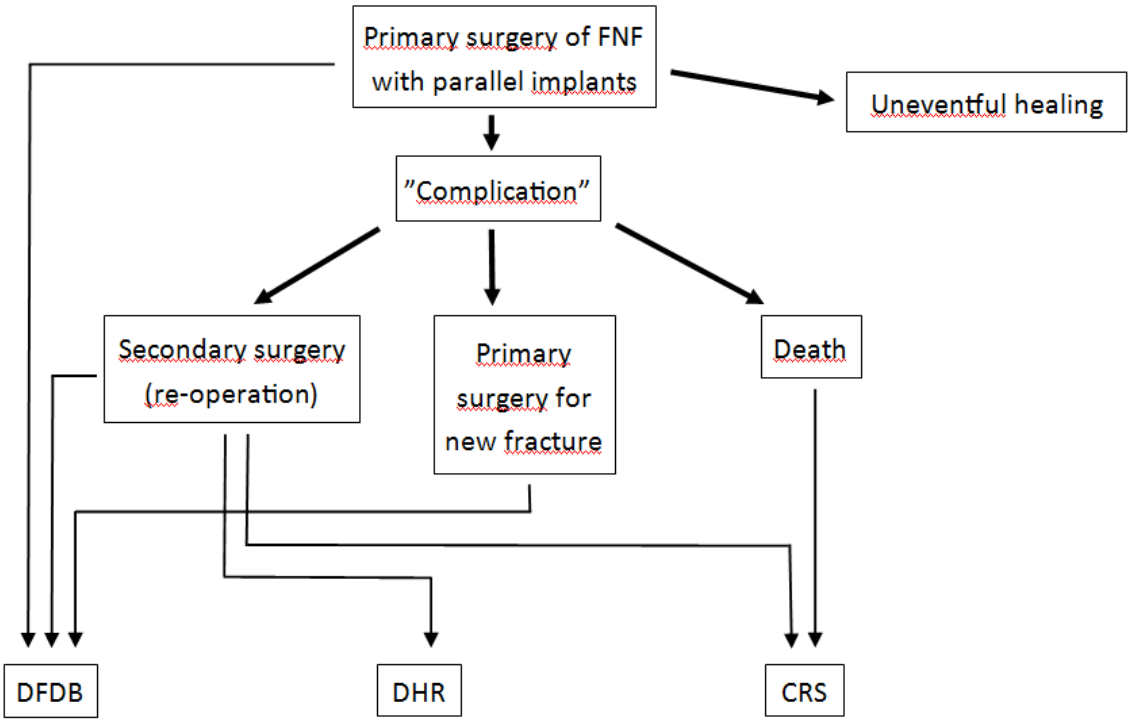


Figure 1: Outcomes following primary surgery of a femoral neck fracture with parallel implants. The surgery can be followed by two main outcomes: uneventful healing or a complication. In this study, we are concerned with three main complications: Re-operation, surgery for a new fracture or death. When a patient undergoes surgery, the details of the patient and the surgery is reported to the DFDB. Pre- and post-surgery x-rays are kept in the patient's medical record at the hospital for at least 10 years. If a patient undergoes a re-operation with some form of osteosynthesis, a hemiarthroplasty, or removal of the implants, this procedure is reported to the DFDB. If a patient undergoes a re-operation with a total hip replacement, this procedure is reported to the Danish Hip Register. The event of re-operation, subsequent surgery in the same hip or death is reported to the CRS. CRS = Civil Registrational System, DFDB = Danish Fracture Database, DHR = Danish Hip Register, FNF = Femoral neck fracture.

To evaluate candidates for inclusion, data on all surgeries for a femoral neck fracture (AO31B) treated with either "screws", "Gevind-pind", "LIH-pins" or "other" reported to the DFDB from December 2011 to December 2015 is collected by our local head of database. Data which do not fulfil the inclusion criteria will be excluded.

From this, the primary investigator will receive a table with CPR-numbers as well as patient age, gender, ASA-score, time of diagnosis, time of onset of surgery, educational level of the surgeon and the department where the surgery was performed.

The primary investigator will then contact each department and arrange for all pre- and post-surgery x-rays to be send electronically to the department at Copenhagen University Hospital Hvidovre, where the investigation is performed.

When the pre- and post-surgery x-rays are available, the primary investigator will perform the evaluation of these in accordance with pre-defined guidelines. If doubt arises as to how to measure the x-rays, a senior investigator will be consulted as to how to perform the measurement, or if the measurement is not possible. To estimate the precision of the measurements, a sample of x-rays will be evaluated by another researcher and the results compared.

When all x-rays have been evaluated, data on the occurrence of re-operation, other operations in the same hip and/or death will be obtained from the DFDB and the DHR and the CRS. The reason to search both the CRS as well as the DFDB/DHR is that the completeness of CRS is believed to be higher (please see section 9), thus increasing the completeness of our data. The data from DFDB and DHR is rather detailed, giving some information about the reason for re-operation. The data from CRS is not as detailed, and will most probably not give the reason for re-operation. For re-operation registered as due to infection or fracture displacement occurring within 3 months following primary surgery, the reason will not be investigated further. For all other

re-operations, the medical file of the patient and pre-re-operational x-rays will be obtained electronically by contacting the department where the re-operation has been performed. They will be evaluated to determine the cause of re-operation. This will be done independently by the primary investigator and a senior supervisor. If discrepancies exists, the x-ray will be evaluated by a second senior investigator and a decision will be made by discussion.

Data from other databases will be obtained in the form of a table and added to the study database.

Data from the X-ray evaluation will be collected and entered directly into the x-ray table of the study database by the primary investigator. If measurement is not possible, the data will be recorded as "missing".

Data from the medical records and evaluation of the pre-re-operation x-rays will be collected separately by the primary investigator and a senior investigator, with data being added to a designated table in the study database, and then compared. If a clear reason for re-operation is not found, the data will be recorded as "other".

7.3 Database construction and handling

The database will be constructed in Excel (Microsoft Office Professionel Plus 2010). One table will contain the details from the primary surgery, one table will contain the measurements of the pre- and post-surgical x-rays, one table will contain the date of death if a patient has died and one table will contain information on re-operations. In all databases, the study unit will be identified by the patient's CPR number.

The database will be located on a computer at the department. This computer is protected by approved firewall and password. When data collection has finished, the database will be anonymised and a conversion key as well as a non-anonymised database will transferred to the "Dansk Data Arkiv". Our local database manager will take care of the transfer.

I do not know the procedure for backup of the database, but I am aware that one exists.

7.4 Data control and editing

Data control will be conducted in R (version 3.2.2) by the statistician in collaboration with the primary investigator.

- For data collected manually during the study, the data will be controlled for outliers and these will be controlled for measuring errors by re-evaluation.
    - Outliers will be defined as:
        - For qualitative variables with defined levels: all levels other than those pre-defined (ex. entries of ex. "1", "4" or "6" for number of implants, which has 2 levels, either "2" or "3").
        - For quantitative variables:
            - Posterior tilt (either fracture or post-surgery): Measurements of less than -10^{o} and more than 30^{o}.
            - Calcar and post distance: Measures of more than 20 mm.
            - Spread: Measures of more than 50 mm.
            - Tip-caput distance: Measures of more than 20 mm.
            - Size of implants: Measures below 7 mm. and above 11 mm.

      When outliers have been identified, a new version of the database will be made with the new measurements, and the "original" database along with the R-code used for data controlling will be stored for documentation purpose.

- For data collected from databases:
    - Dates will be evaluated for the chronological order (birth, diagnosis, surgery, reoperation/death) during the processing of the data for analysis (please see section 7.5). Entries where the chronological order of the dates is not correct (thus yielding negative results in the processing) will be excluded.
    - For educational level of surgeon, ASA score and patient gender, the DFDB is constructed in such a way, that reporting cannot be done without these variables, and they have to be chosen, so no values are expected as "missing" or "outliers".

7.5 Data processing for statistical analysis

Data processing will be conducted in R (version 3.2.2) by the statistician in collaboration with the primary investigator.

From the original variables, the following new variables will be made:

- "Surgical delay", calculated as the time-interval between "time from diagnosis" and "time of surgery" (quantitative, continuous variable, measured in minutes)
- "Fracture displacement", defined by combining the "Fracture displacement AP" with the "Fracture posterior tilt" (ordinal variable, with 3 levels: Non-displaced (Garden I and II) with post tilt <20 degrees, non-displaced (Garden I or II) with post tilt ≥20 degrees, displaced (Garden III or IV))
- "Post-surgery reduction", defined by combining the "Post-surgery displacement AP" with the "Post-surgery posterior tilt" (ordinal variable, with 3 levels Non-displaced (Garden I and II) with post tilt <20 degrees, non-displaced (Garden I or II) with post tilt ≥20 degrees, displaced (Garden III or IV))
- "Age at diagnosis", calculated as the time-interval between "time of birth" and "time from diagnosis" (quantitative, continuous variable, measured in years)
- "Surgeon experience", a simplification of "educational level of surgeon", where one group will consist of "præ-KBU"-"kursist fase 3" and another of "speciallæge" and "traumatology" (ordinal variable, with 2 levels: Below attending, attending or above)
- "Time to re-operation", calculated as the time-interval between "time of surgery" and "time of re-operation" (quantitative, continuous variable, measured in days)
- "Time to death", calculated as the time-interval between "time of surgery" and "time of death" (quantitative, continuous variable, measured in days)

8 Statistical analysis

8.1 Sample size calculations

It has previously been demonstrated that the risk of re-operation following surgery for a femoral neck fracture with parallel implants is approximately 40%. In our study, we consider a risk reduction of 25% as clinically significant.

With regards to surgical delay:

In Denmark, approximately 20% of patients with hip fractures undergo surgery within 12 hours, and 70% within 24 hours (2). If we divide the patients into two groups with surgical delay of more or less than 24 hours, we have two groups of "almost" the same size.

If we do not consider testing for confounding variables and make the assumptions, that we want to show a difference in risk of re-operation of 25% with a power of 90% and a confidence of 5%, we can use the method

for categorical outcomes by Altman (ref til bog) for calculating the standardized difference = 0,21 and a required sample size of approximately 1100 observations.

Since we want to consider testing for confounding, we plan to make a simulation to estimate the sample size needed and estimate the smallest detectable difference.

With regards to the measures of the placement of the implants, no data on distribution variation in measurements have been found, so for this we plan to do a pilot study on 200 patients and use data from these to estimate the sample size needed and the smallest detectable difference.

8.2 Descriptive analysis

The descriptive analysis of the data will be presented as a table of patient demographics:

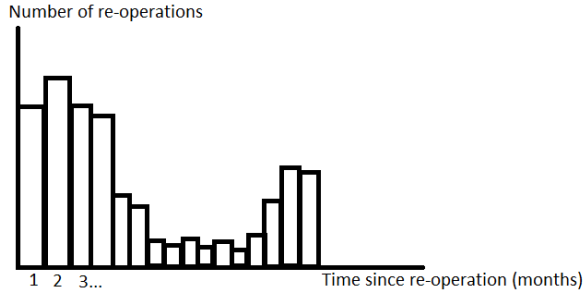
	No re-operation	*Re-operation*	*Total (%)*
*N**	x (%)	x (%)	N
Age			
50-60	x (%)	x (%)	x (%)
60-70	x (%)	x (%)	x (%)
70-80	x (%)	x (%)	x (%)
80-90	x (%)	x (%)	x (%)
90-100	x (%)	x (%)	x (%)
>100	x (%)	x (%)	x (%)
Sex			
Female	x (%)	x (%)	x (%)
Male	x (%)	x (%)	x (%)
ASA score			
1	x (%)	x (%)	x (%)
2	x (%)	x (%)	x (%)
3	x (%)	x (%)	x (%)
4	x (%)	x (%)	x (%)
5	x (%)	x (%)	x (%)
Educational level of surgeon			
AA	x (%)	x (%)	x (%)
BA	x (%)	x (%)	x (%)
Surgical delay			
0-<12h	x (%)	x (%)	x (%)
12-<24	x (%)	x (%)	x (%)
24-<36	x (%)	x (%)	x (%)
36-<48	x (%)	x (%)	x (%)
48-<72	x (%)	x (%)	x (%)
72-	x (%)	x (%)	x (%)
Fracture displacement			
Non-displaced, post tilt <20^{o}	x (%)	x (%)	x (%)
Non-displaced, post tilt ≥20^{o}	x (%)	x (%)	x (%)
Displaced	x (%)	x (%)	x (%)
Number of implants			
2	x (%)	x (%)	x (%)
3	x (%)	x (%)	x (%)
Post-surgery reduction			
Non-displaced, post tilt <20^{o}	x (%)	x (%)	x (%)
Non-displaced, post tilt ≥20^{o}	x (%)	x (%)	x (%)
Displaced	x (%)	x (%)	x (%)
Calcar distance	Mean (CI)	Mean (CI)	Mean (CI)
Posterior distance	Mean (CI)	Mean (CI)	Mean (CI)
Spread¥	Mean (CI)	Mean (CI)	Mean (CI)
Tip-caput distance			
Inferior	Mean (CI)	Mean (CI)	Mean (CI)
Posterior	Mean (CI)	Mean (CI)	Mean (CI)
Mortality			
12 months	x (%)	x (%)	x (%)
24 months	x (%)	x (%)	x (%)

*Table 1: Patient demographics stratified according to re-operation or not. AA = Above attending, ASA = American society of Anaestesiology, BA = Below attending, N = Number of patients in each group, * Percentage values in row 1 are in relation with the total number of patients. All other percentage values are related to the allocated delay group, ¥ only measured on surgeries with 3 implants.*

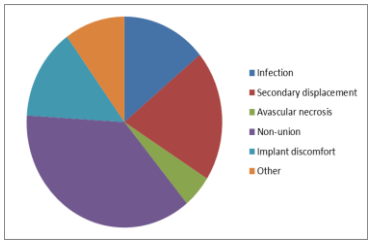
The distribution of the measurements marked with “mean (CI)” in the table will be checked, and if the data is not normally distributed, proper transformation will be used for calculating mean and CI.

8.3 Statistical analysis

To estimate the incidence of re-operation following osteosynthesis with parallel implants of a femoral neck fracture within the first 12- and 24 months in the Danish population older than 18 years of age (objective a), the number of patients undergoing re-operation will be presented as raw data in the descriptive analysis, along with number of patients who have died at 12- and 24 months after surgery. The incidence will be reported as part of the patients which undergoes re-operation (in percent) both with and without censuring the patients who have died. We would like to demonstrate at what time after surgery, the re-operations occur. This could be done by making f.ex. a histogram of time to re-operation following the surgery:



The distribution of the reasons for re-operation will be presented for the period 0-12 months and 12-24 months following surgery, either by a table or by histograms or circle diagrams, like this:



To estimate the association between quality of osteosynthesis and risk of re-operation (objective b), two separate logistical or cox regression analyses will be performed for the surgeries with two and three implants. The association of the post-surgery reduction, the posterior tilt, the calcar distance, the posterior distance, the tip-caput distances and, for the surgeries with three implants, the spread will be estimated, adjusting for the initial fracture displacement, educational level of surgeon, age, gender and ASA score.
If the evaluation of the surgical detail demonstrates that several factors do not interfere with re-operation rates, these factors will be excluded in the following analysis.

To estimate the association between surgical delay and the educational level of surgeon, and risk of re-operation and death within 12 months and 24 months following osteosynthesis with parallel implants of a femoral neck fracture (objective b), we plan to do either a logistical or a cox regression analysis for each variable. In this analysis, we will adjust for the other variable as well as the surgical details which we have found relevant, the initial fracture displacement, age, gender and ASA score.

Results from the regression models will be reported in tables as OR or HR with 95% confidence intervals.

By using regression models, we hope to estimate the influence of confounding factors and adjust our estimate of the association for this confounding.

9 Validity and bias

9.1 Data sources

Data from CRS covers the entire population and are considered to have very high completeness and validity. To the best of our knowledge, no full validation of this database exists, but a college of mine is currently validating the completeness and correctness of the data from several orthopaedic departments, so far finding the reports sufficiently valid in more than 90% of all cases (study almost finished and results not yet published). The DHR is yearly evaluated against CRS with a completeness of 97,8% (27). Therefore we do not expect any significant systematic errors in reports to these databases.

The DFDB however, was first established with reports from only two of the major traumatology departments. From 2011 to 2015, the rest of the departments in Denmark have started reporting to the database, with national coverage only from 2015. As a result we have a selectional bias in our source population, where regions Hovedstaden, Sjælland and Syd are well represented, but almost no patients from region Midt and only some from region Nord are included. However, due to the homogeneity of the Danish population in general and the nationwide use of guidelines in treatment of femoral neck fractures, we believe the study population to be representable of the entire Danish population.

9.2 Sampling methods

Since all patients fulfilling the inclusion criteria will be included, we do not expect any bias regarding this procedure.

9.3 Confounding variables

Other variables have been theorized, and some partly confirmed, as potential risk factors for mortality and re-operations, such as functional impairment (28,29), actual diagnosis of comorbidities (such as osteoporosis, treatments with high-dose prednisolone), mental health (30), admission in weekend/holidays, cause of delay, hospital-size (31), early mobilization, multi-disciplinary multimodal standardized approach and type of anaesthesia. By including all eligible surgeries we believe our estimates will be accurate for the Danish population, but the estimates of the effect of surgical delay and technical details should be interpreted with caution and a wider variation and hence confidence intervals are expected.

9.4 Other biases

Evaluation of the x-rays will be performed mainly by one investigator (primary investigator) and therefore a bias may be introduced due to misclassification.

Surgical delay is defined as from diagnosis of fracture and not from time of injury.

Patients may have left the country and had a reoperation in another country.

10 Limitations of the study

Firstly, the coverage of the population by DFDB is not complete during the entire study period, thereby introducing the risk of a selection bias in the source population and thus in the study population. We might therefore find that our population is not perfectly representable for the Danish population, however, we believe that due to the homogeneity of the Danish population, the use of national guidelines and the equal availability of the health service throughout Denmark, the treatments of patients with femoral neck fractures will be reasonably similar to allow inference from the study population to the Danish population.

Secondly, this study has limitations attributable to the nature of data collected in a registry. The registry only includes some of the factors hypothetically influencing mortality and risk of re-operation after surgery; thus functional impairment, actual diagnosis of comorbidities, mental health, admission in weekend/holidays, cause of delay, hospital-size, early mobilization, multi-disciplinary multimodal standardized approach and type of anaesthesia are not taken into account. By including a large and representable study population, we hope that

due to random stratification, the effects of these factors on our estimates will be minimal, but they will contribute to the random variation, thus causing the confidence intervals of the estimates to widen.

It might, however, be possible that the abovementioned factors have an effect on surgical delay and thus may not be randomly distributed with regards to surgical delay. Studies have demonstrated that increased surgical delay may be related to the presence of co-morbidities (32,33), which may make the effect of surgical delay seem more profound than it is. By adjusting for the ASA score (how "fit" the patient is to receive anaesthesia, which is determined based on the medical state of the patient at the time of surgery), we hope to reduce this confounding. With regards to the presence of dementia, it has been debated whether cognitive impaired patients are more often postponed than cognitive intact patients. Since dementia has been shown to increase mortality following hip fracture, an uneven distribution of cognitive intact and –impaired patients with regards to surgical delay will affect the estimate of the effect of surgical delay. To the best of our knowledge, the co-existence of surgical delay and mental health have only been evaluated in two studies, showing that a slightly larger proportion of the cognitive impaired patients receive treatment within a short delay time (34,35). We therefore do not believe the effect of dementia on surgical delay is significant, but further studies of this relation in the Danish population is needed. With regards to type of anaesthesia and surgical delay, a frequent reason for postponing the surgery, and thus increasing the surgical delay, is due to the patient receiving anti-coagulantia. Since this is a contra-indication for spinal anaesthesia, we would expect a more frequent use of general anaesthesia in the later delay groups. However, so far no difference in mortality between types of anaesthesia in hip fracture surgery has been found and we do therefore not believe this to influence our results with regards to mortality. The influence on re-operation has not been investigated but is not likely.

To our knowledge, no study has evaluated the relation between the above-mentioned factors and the quality of osteosynthesis, but we find it unlikely that the technical details of the surgery would be significantly affected by them and thus expect the factors to be randomly stratified with regards these.

We therefore believe that our study will be able to estimate the effect of surgical delay and quality of osteosynthesis on re-operation and mortality.

Thirdly, surgical delay is defined as time from radiographic diagnosis to onset of surgery, which should be taken into account when comparing with previous studies. This definition is used in the DFDB since time of injury is often difficult to identify and we want to evaluate modifiable factors, of which, in our hospital setting, we do not consider time from injury to diagnosis to be. It also allows the in-hospital sustained fractures to be included, which in Denmark accounts for 7% of all proximal femoral fractures (36). The lack of information about the time period between injury and diagnosis may cause the effect of surgical delay to be less clear and, if an effect is present, we expect it to be estimated as lower than if we had the entire time from injury to onset of surgery.

Fourthly, evaluation of the x-rays in this study will be carried out by one or two investigators, thus introducing the risk of systematic misclassification. We aim to evaluate this risk by making an inter-observer evaluation on a random sample from our study population.

And fifthly and last, patients may have moved to other countries and have had a re-operation done here, which will not have been registered in DFDB, DHR or CRS. When collecting follow-up data, we will be able to see if patients have left the country (residency is registered in the CRS). In such case, they will be censured in the analysis at time of departure. We do however not expect this to be a frequent event in this patient population and do not believe this to influence our result.

11 Ethical considerations

This is a retrospective observational study with no intervention. Patients and their relatives will not be contacted in relation to this study. No further information will be collected than what is registered in the journals, in DFDB, DHR or in the Danish Civil Register (CRS). Therefore we have no ethical issues to consider in relation to this study.

11.1 Project approval

11.1.1 Confidentiality and anonymity

Based on a protocol with defined hypothesis and outcome measures, the study has been approved by the Danish Data Protection Agency (j.nr.: 2007-58-0015).

During database construction, the patient will be identifiable in the database by the CPR number. When data collection has been completed, the database will be anonymized as described in section 7.3. No non-anonymised data will be made publicly available.

11.2 Authorship and publication rights

Anne Marie Nyholm, Kirill Gromov, Henrik Palm, Thomas Kallemose and Anders Troelsen will be authors on all articles from this study, because they have contributed in accordance with the International Committee of Medical Journal Editors (ICMJE) criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; and Drafting the work or revising it critically for important intellectual content; and Final approval of the version to be published; and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Anne Marie Nyholm is going to be the first mentioned author of all published articles from this study. Anders Troelsen or Kirill Gromov is going to be the last mentioned author of all published articles from this study. Anne Marie Nyholm is going to be the corresponding author.

Due to the large work behind the DFDB, and thus substantial contribution to our database, the local database managers will be listed as “one” author, the DFDB collaboration.

The database will be owned by Clinical Orthopaedic Research Hvidovre.

12 Project management

12.1 Project group

- Principal Investigator - Anne Marie Nyholm
- Secondary investigator - Kirill Gromov
- Supervisors – Anders Troelsen, Henrik Palm and Kirill Gromov
- Statistical advisor/manager – Thomas Kallemose
- Sponsor – Clinical Orthopaedic Research Hvidovre, Department of Orthopaedics, Copenhagen University Hospital Hvidovre, Denmark
- Database managers – Anne Marie Nyholm and Thomas Kallemose

13 Timeline and milestones

13.1 Project organization

The project was planned in spring 2015 and approval for the study was obtained from “Datatilsynet”. Collection of relevant subject from the DFDB and selection based on the inclusion criteria was conducted in April 2015. Collection of pre- and post-surgery x-ray was initiated and the evaluation of the x-rays started during November 2015.

The time plan for the future is:

August 2016: at least half of the initial x-ray analysis should be completed.

December 2016: Evaluation of x-rays related to primary surgery should be complete. Data on re-operation should be collected at this point and collection and evaluation of pre-re-operation x-rays and medical records should commence.

August 2017: Construction of the database should be finished.

September 2017: Statistical analysis should be finished.

October 2017: Manuscript should be ready for submission.

The supervisors are regularly updated, but we have no strict plan for meetings apart from the status required from the PhD office.

13.2 Budget

No costs is expected, but should any arise, it will be covered by the research department.

14 Deliverables – Reporting and dissemination

We plan to present our study results both as a congress presentation and as an article in a relevant journal.

15 References

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Figures:

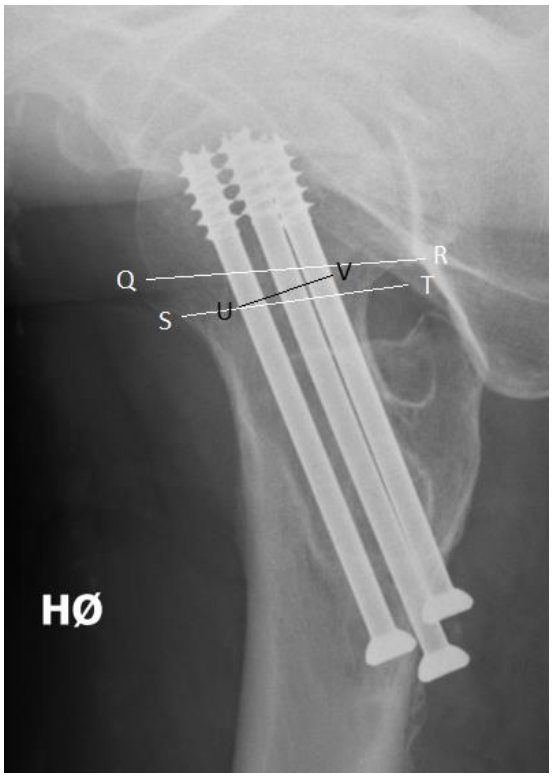

Figure F: Measurements of distances in the post-surgery x-rays. The fracture area lies between QR and ST. In this area, the spread of the implants is measured as UV.