ASPECTS ON TREATMENT OF FEMORAL NECK FRACTURES

Studies on treatment methods, surgical approach and external validity

Sebastian Mukka
Aspects on treatment of femoral neck fractures

Studies on treatment methods, surgical approach and external validity

Thesis for doctoral degree

Sebastian Mukka

Main supervisor:
Associate professor Arkan Sayed-Noor
Umeå University
Department of surgical and perioperative sciences

Co-supervisor:
Associate professor Olof Sköldenberg
Karolinska Institutet
Department of clinical sciences at Danderyd hospital

Department of Surgical and Perioperative Sciences
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To my beloved family,

Continuous effort – not strength or intelligence – is the key to unlocking our potential

Winston Churchill
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Abstract

Femoral neck fracture (FNF) is a great challenge for today’s health care and is associated with high mortality and morbidity in the elderly. In the short term several studies in the literature have demonstrated improved hip function, quality of life and fewer re-operations in elderly patients treated with total hip arthroplasty (THA) instead of internal fixation (IF). There are few reports on the long-term outcome comparing IF and THA. The vast majority of orthopaedic departments in Sweden use the direct lateral (DL) or posterolateral (PL) approaches for hip arthroplasty. The PL approach has been linked to an increased risk of dislocation of the prosthesis and a higher rate of revision surgery in comparison to the DL approach. There are few reports focusing on radiological risk factors for prosthetic dislocation and patient reported hip function comparing the two surgical approaches for hip arthroplasty in FNF.

The randomized controlled trial (RCT) is the gold standard for evaluating medical or surgical interventions. An RCT of high quality has to be internally and externally valid. Internal validity refers to a correct study design to avoid bias skewing the results. External validity (EV) refers to whether the results will be clinically relevant to a definable group of patients and can be extrapolated to the general health care situation. There are only a few reports in the orthopaedic literature focusing on the EV of published studies and none in the field of hip fractures.

Study I: This is a RCT of 100 patients with a displaced FNF comparing THA and IF. Follow-up evaluations were performed at three months and 1, 2, 4, 11 and 17 years. It was found that the Harris hip score (HHS) was higher and the rate of reoperations lower for patients treated with THA.

Study II: This is a prospective cohort study of 185 hips, comparing the DL and the PL approaches in patients treated with a hemiarthroplasty (HA) for a displaced FNF. Follow-up was after 1 year. There was no difference in patient reported outcome between the groups measured with the HHS and WOMAC index. The PL approach resulted in a higher re-operation rate while the DL approach in a higher incidence of limping.

Study III: This is a retrospective cohort study of 373 patients with a cemented bipolar HA using a PL approach for a FNF with a follow-up ranging from 6 months to 7 years. Radiographs and all surgical records were reviewed regarding femoral offset (FO), leg length discrepancy (LLD) and Wiberg angle. Patients with recurrent dislocations had a decreased postoperative FO, LLD and shallower acetabulum on the operated side compared with their controls.
Study IV: This is a prospective cohort study of 840 hips comparing patients included in a RCT with those that did not give their informed consent (NC) or did not fulfill the criteria for participating in the trial (MS). Patients in the NC and MS groups had an increased mortality rate in comparison to those included in the study. We did not find any differences in hip function between these groups.

The main conclusions of this thesis are:

- Healthy and lucid elderly patients with good hip function preoperatively, should be treated with THA for a displaced FNF.
- The DL approach is favourable in treating displaced FNF with HA due to its decreased risk of reoperation but with an identical hip function outcome as the PL approach.
- Care should be taken to restore the LLD and FO otherwise this may increase the risk of recurrent dislocation of a HA.
- Our findings suggest that trial participants had a lower mortality rate than non-participants but the functional outcome of non-participants appeared to be satisfactory. This is important to take into consideration when extrapolating study results to a health care system.

Keywords
Hip fracture, femoral neck fracture, treatment, total hip arthroplasty, hemiarthroplasty, interal fixation, surgical approach, outcome, dislocation, femoral offset, leg length discrepancy, external validity.
Sammanfattning (Summary in Swedish)

Lårbenshalsfrakturer (FNF) är en utmaning för dagens sjukvård och förknippad med hög mortalitet i den äldre befolkningen. FNF orsakas främst av lågenergitrauma efter fall i samma plan hos patienter med benskörhet. Total höftledsprotes (THA) har visat sig ge en bättre höftfunktion, livskvalitet med färre omoperationer hos äldre patienter än slutten reposition samt fixering med skruvar (IF) under de första två-fyra åren efter operation. Få studier har publicerats med långtidsuppföljning av THA jämfört med IF.

Vid behandling av felställd FNF med halv höftledsplastik (HA) eller THA finns olika kirurgiska metoder (snittföring) för implantation av protesen. Majoriteten av ortopedkliniker i Sverige använder direkt lateral (DL) eller posteriolateral (PL) snittföring. PL har kopplats till en ökad risk för luxation av protesen (urledsvridning), vilket i sin tur genererat en högre risk för omoperation jämfört med DL. Få studier har utvärderat höftfunktion med avseende på snittföring. Detsamma gäller vilka radiologiska faktorer som påverkar risken för protesluxation.


**Studie I:** Prospektiv randomiserad studie av 100 patienter med en felställd FNF jämförs THA med IF med avseende på höftfunktion och reoperationer. Uppföljning gjordes efter tre månader samt 1, 2, 4, 11 och 17 år. HHS som mått på höftfunktion var högre och andelen reoperationer lägre för patienter som behandlades med THA.

**Studie II:** Prospektiv kohortstudie med 183 patienter med felställd FNF behandlade med HA och antingen DL eller PL. Vi fann ingen skillnad i patientrapporterad höftfunktion utvärderat med HHS och WOMAC efter 1 år men en ökad förekomst av hälta vid DL.

**Studie III:** Retrospektiv kohortstudie av 373 patienter opererade med en cementerad bipolär HA och PL. Postoperativa röntgenbilder granskades avseende femoral offset (FO), postoperativ benlägdsskillnad (LLD) samt acetabulär Wibergvinkel och relaterades till återkommande protesluxationer. Detta relaterades till återkommande luxationer.
Uppföljningstiden varierade mellan 6 månader och 7 år. Patienter med återkommande luxationer hade en minskad postoperativ global FO, förkortad LLD och grundare acetabulum på den opererade sidan jämfört med kontroller.

**Studie IV:** Prospektiv kohortstudie av 840 patienter med felställd FNF där patienter som ingick i en RCT jämförs med de som inte gav sitt samtycke för deltagande eller ej inkluderats i screeningprocessen. De patienterna som inte gav sitt samtycke hade ökad dödlighet, men ingen skillnad i höftfunktion jämfört med deltagare.

**Slutsatser**

- Friska och kognitivt vitala äldre patienter med god höftfunktion innan en felställd lårbenshalsfraktur bör behandlas med total höftledsprotes.
- DL snittföring ger ett lika bra patientrapporterad höftfunktion men en ökad förekomst av hälta jämfört med PL snitt vid behandling med halvprotes på grund av en felställd lårbenshalsfraktur.
- Ansträngning bör göras för att återställa benlängdsskillnad samt femoral offset och därigenom minska risken för återkommande luxation.
- Våra resultat tyder på att patienter som deltar i en randomiserad studie har lägre dödlighet än patienter som avböjt att delta samt de som missats i screeningprocessen. Det är viktigt att ta hänsyn till när extrapolera studieresultat till ett hälso- och sjukvårdssystem. Detta bör vägas in i värderingen av studieresultatens externa validitet.
List of publications

I. Total hip replacement versus Open Reduction and Internal Fixation of Displaced Femoral Neck Fractures: A Randomized Long-Term Follow-up Study.

Mukka S, Mahmood S, Sköldenberg O, Kadum B, Sayed-Noor A.
Submitted

III. Dislocation of bipolar hip hemiarthroplasty through a postero-lateral approach for femoral neck fractures: A cohort study.

IV. External validity of a randomized controlled trial in patients with femoral neck fractures.
Sebastian Mukka, Ghazi Chammout, Arkan Sayed-Noor, Olof Sköldenberg.
Manuscript

Permission to reprint article I has been given by The Journal of Bone and Joint Surgery, Inc.
Permission to reprint article III has been given by Springer.
# List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<tr>
<td>DL</td>
<td>Direct lateral surgical approach to the hip</td>
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<tr>
<td>EQ-5D</td>
<td>The European five-dimensional self-assessment instrument</td>
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<td>EV</td>
<td>External validity</td>
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<tr>
<td>FNF</td>
<td>Femoral neck fracture</td>
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<td>FO</td>
<td>Femoral offset</td>
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<td>HA</td>
<td>Hemiarthroplasty</td>
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<td>HHS</td>
<td>Harris hip score</td>
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<td>IF</td>
<td>Internal fixation</td>
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<tr>
<td>LLD</td>
<td>Leg length discrepancy</td>
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<td>MS</td>
<td>Missed screening</td>
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<tr>
<td>NC</td>
<td>Non-consenters</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<tr>
<td>PL</td>
<td>Posterolateral surgical approach to the hip</td>
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<tr>
<td>PNRS</td>
<td>Pain numerical rating scale</td>
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<td>PRO</td>
<td>Patient reported outcome</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SPMSQ</td>
<td>Short portable mental state questionnaire</td>
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<tr>
<td>THA</td>
<td>Total hip arthroplasty</td>
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<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster osteoarthritis index</td>
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Definitions

Bipolar hemiarthroplasty
Hemiarthroplasty that includes an articulation between the larger and the smaller implant head as well as against the acetabulum.

Direct lateral approach
Also known as the “anterolateral transgluteal approach”. A surgical approach to the hip where the ventral part of the gluteus medius and minimus are deflected to access the anterior joint capsule. Described by Hardinge and Gammer.

EQ-5D
A 5-dimensional standardized instrument used as a measure of health outcome.

Hemiarthroplasty
A surgical procedure for repair of a fractured femoral neck by replacement of the head of the femur with prosthesis and leaving the acetabulum intact.

Hip arthroplasty dislocation
Loss of contact between the femoral head and the acetabulum (hemiarthroplasty) or the acetabular component (total hip arthroplasty) that needs intervention to relocate the joint.

Posterolateral approach
Also known as the “posterior approach”. A surgical approach to the hip where the gluteus maximus is split in the direction of the fibers and external rotators (with or without sparing of m.piriformis) to access the posterior joint capsule. Described by Moore.

Re-operation
Any further surgery to the hip. In this thesis including closed reduction of a dislocated prosthesis.

Total hip arthroplasty
A surgical procedure for repair of a femoral neck fracture by replacement of the head of the femur and the acetabulum with an articulating prosthesis.

Unipolar hemiarthroplasty
Hemiarthroplasty with a solid head that articulates against the acetabulum.
Introduction

Background

Definition of hip fractures

Hip fractures are located in the proximal femur and can involve the femoral neck, trochanteric and subtrochanteric regions. The two most common types are trochanteric (intertrochanteric) and femoral neck (cervical) fractures (FNF). Fractures that extend from the trochanteric area and distally within 5 cm below the lesser trochanter are named subtrochanteric fractures. These fractures are a common sight at orthopaedic departments around the world and are a common cause of misery and mortality in the aging population (Bhandari et al. 2003, Ahlblom et al. 2010). The term “hip fracture” excludes fractures located at the acetabulum, femoral shaft or the femoral head due to their different clinical presentation, operative treatment and rehabilitation.

The FNF was first described by Sir Astley Cooper (1768-1841) in 1822. The definition of “femoral neck fracture” is most often used to describe an intracapsular fracture thereby excluding fractures through the lateral or basocervical region. The first to argue for operative treatment was a German surgeon Mr B. von Langenbeck (1810-1887) while the pioneer who first implemented surgical treatment was Professor J. Nicolaysen (1831-1911), at Rikshospitalet in Oslo, Norway. Nicolaysen published his novel technique and the results of closed nailing of FNF for his series of 21 patients (Dahl HK 1994).

Epidemiology

Worldwide the number of hip fractures has been estimated as 1.3-1.7 million annually and since life expectancy is increasing; the numbers of hip fractures is expected to rise to 6.3 million by 2050 (Gullberg et al. 2003, Dennison et al. 2006). The incidence of hip fractures has been reported to differ between different regions and countries in the world. The Scandinavian countries and the U.S report a high incidence in contrast to Turkey, Chile, Venezuela and Korea, which have a low incidence of hip fractures (Kanis et al. 2002). In Sweden there are approximately 18000 hip fractures annually (Löfman et al. 2002).

FNFs are mainly a fragility fracture in the elderly and frail, predominantly affecting women after menopause but recent reports have indicated an increased incidence in elderly men (Löfman et al. 2002, Finsen et al. 2004, Bergstrom et al. 2009). The average age of patients suffering a hip fracture has been increasing over the last decade and is around 80 years with an exponential increase of incidence with age (Cooper et al. 1992, Thorngren et al. 2002, Johnell and Kanis 2004, Chevalley et al. 2007, Karampampa et al. 2015). Women sustaining a hip fracture are generally older whereas males generally have poorer health and an increased mortality (von Friesendorff et al. 2008, von Friesendorff et al. 2011, Thorngren and Hommel

Classification

Different classification systems for FNFs have been proposed. The classification according to Pauwels (1935) was graded depending on the shearing angle of the fracture. However it has not been shown to predict the rate of non-union (Parker and Dynan 1998). The AO classification has been difficult to use due to poor intra and interobserver reliability and lack of predictive utility for the outcome of treatment (Blundell et al. 1998).

FNFs are also classified according to the degree of fracture displacement and the most widely used system is that of Garden (Garden 1961). As displacement increases, the risk of disruption to the blood supply to the femoral head increases. With a disrupted vascular supply the risk for healing disturbances, complications and reoperations increases when treated with IF. The Garden classification is based on the degree of fracture displacement on the anteroposterior radiographic images. Garden I and II represent a valgus impacted or a complete fracture without displacement and are considered as undisplaced types. Garden III and IV represent a partially displaced or fully displaced fracture and are considered as displaced fracture types, which represent two thirds of the FNFs (Figure 1). Garden’s classification system has been criticized for its poor interobserver reliability (Frandsen et al. 1988). The most reliable subdivision of FNFs, which corresponds well to secondary complications after IF such as non-union and avascular necrosis, are undisplaced and displaced FNFs (Alberts and Jervaeus 1990, Nilsson et al. 1993).

Figure 1.
Left a radiograph of an undisplaced FNF.
Right a radiograph of a displaced FNF.
Treatment of femoral neck fractures

Non-operative treatment

Nonoperative treatment of FNFs is used only in rare exceptions and mainly in frail or moribund patients where the risk of surgery outweighs the benefits. Nonoperative treatment is linked to poor functional outcome and is associated with a high risk of pain, fracture displacement and medical complications (Cserháti et al 1996, Handoll and Parker 2008).

Internal fixation

Internal fixation (IF) is a relatively short, atraumatic treatment due to being a minimally invasive surgical procedure. Closed (or rarely open) reduction is used and stabilized with IF, usually with two or more screws or nails (Figure 2). The most important factor for successful treatment, resulting in a stable and ultimately healed fracture, is the quality of reduction followed by preoperative displacement and the positioning of the hardware (Alberts and Jervaeus 1990). The reduction of the fracture in a valgus position has been shown to be more favorable than in anatomical or varus position (Niemin et al. 1981). There have been no reports of differences in outcome between the different types of implants, that is screws and pins or in combination with side-plates (Parker and Blundell 1998). The aim of the treatment is to fix the fracture to allow mobilization and fracture healing.


IF remains the treatment of choice for patients below 65 years of age with a displaced fracture because of its lower failure rate compared to that in elderly patients where there is a risk of long term prosthetic complications and need for revision surgery (Zetterberg et al. 1982, Gray and Parker 1994, Damany et al. 2005). IF was used as the primary treatment in Sweden also for displaced fractures in elderly patients (over 65 years old) until the end of the 1990’s, despite a high rate of complications and reoperations (Rogmark et al 2010). Failure rates of 35-50% have been reported in the literature and this method has been strongly questioned (Bhandari et al 2003, Rogmark and Johnell 2006, Heetveld et al 2009). The most frequent complications are avascular necrosis and pseudarthrosis due to disrupted vascular supply of the femoral head and mechanical failure due to inadequate fixation (Parker et al 2002, Rogmark et al 2002, Tidermark et al 2003, Kumar et al
IF has also been proposed as an alternative for the most elderly and frail due to the limited surgical trauma. It has been presumed that this would decrease the short-term postoperative mortality but the supporting evidence is limited (Parker et al. 2002, Davison et al. 2001). These differences have not been confirmed in a meta-analysis (Gao et al. 2012). The most consistent finding is a reoperation rate of around 10% for HA and 30-40% for IF. A number of studies indicating equivalent results or favoring IF in comparison to hip-arthroplasty have been published (Jensen et al. 1984, van Vugt et al. 1993, van Dortmont et al. 2000, Parker and Pryor 2000, Partanen et al. 2002, Heikkinen et al. 2002, El-Abed et al. 2005). However the present evidence was mainly based on RCTs with modern implants, indicating a superior PRO for hip arthroplasty, even in patients with uneventfully healed fractures treated with IF (Søreide et al. 1979, Sikorski and Barrington 1981, Jónsson et al. 1996, Bray et al. 1993, Ravikumar and Marsh 2000, Johansson et al. 2000, Puolakka et al. 2001, Röden et al. 2003, Bhandari et al. 2003, Tidermark et al. 2003, Parker and Gurusamy 2006, Frihagen et al. 2007, Gjertsen et al. 2008, Gjertsen et al. 2010b, Gao et al. 2012).

Recently published long-term follow-up studies have further emphasized the superiority of THA in comparison to IF in regard to hip function (Leonardsson et al. 2010, Johansson, 2014). The main treatment alternative for a failed IF is secondary HA or THA. However, a secondary procedure has been shown to result in a worse outcome in comparison to a primary arthroplasty (Nilsson et al. 1989, Blomfeldt et al. 2006, Leonardsson et al. 2009). In summary, IF remains as the treatment of choice for patients with undisplaced fractures, displaced fractures and below 65 years of age and patients considered too frail to undergo surgery with hip arthroplasty.

Figure 2. Hip arthroplasties:
Left a total hip arthroplasty.
Middle two screws for internal fixation of FNF.
Right a hemiarthroplasty.
Hip arthroplasty


In hip arthroplasty implants are fixed to the bone with or without the use of bone cement (polymethyl methacrylate). In Sweden cemented hip arthroplasties are most frequently used and are regarded as the gold standard for FNF patients. Uncemented fixation in FNF patients has been linked to an increased risk for periprosthetic femoral fractures (Leonardsson et al. 2012, Rogmark et al. 2014, Grammatopoulos et al. 2015).

Hemiarthroplasty

Hemiarthroplasty (HA) is the most commonly used treatment for patients with a displaced FNF (Miller et al. 2008, Rogmark et al. 2010). Treatment with HA involves the resection of the femoral head and the majority of the femoral neck. The acetabulum is left intact. There are three different types of HA prosthesis; monoblock, modular unipolar and modular bipolar.

The monoblock HA prosthesis is casted in one piece and the surgeon is unable to modify the length of the neck or the offset. This type has been used to a large extent but unfavorable results regarding the need for re-operation and PRO has made surgeons explore other options (Kofoed and Kofod 1983, Kuokkanen et al. 1990, Jalovaara and Virkkunen 1991, Emery et al. 1991, Ravikumar and Marsh 2000, Garellick et al. 2010, Rogmark et al. 2012).

Modular bipolar or unipolar heads are manufactured in pieces and assembled during surgery to fit the specific needs of each patient. The unipolar head is a solid metal head in the same size as the measured native femoral head. The bipolar head was developed to decrease acetabular erosion and involves an articulation between a small and a larger head that swivels during movement. However, studies regarding component motion have indicated that the interprosthetic movement decreases with time and the majority of bipolar heads function as a unipolar head, two to four years postoperatively (Phillips 1987, Bochner et al. 1988, Eiskjaer et al. 1989). Recent studies comparing the types of HA prosthesis have reported a higher rate of dislocation and risk for reoperation in patients operated using bipolar heads compared to their unipolar counterparts (Leonardsson et al. 2012, Rogmark et al. 2014). A recent meta-analysis found that unipolar and bipolar HA achieved similar clinical outcomes (Liu et al. 2014, Yang et al. 2015, Jia et al. 2015).
A long term follow-up of patients treated with bipolar HA emphasized a difference in reoperation rate between patients less than 75 years of age (38%) and those who were older (6%) (van den Bekerom et al, 2013). Thus HA remains a valid treatment for elderly patients with a displaced FNF.

The femoral component is designed to transmit torsional and axial load to the cement and bone and there are two main types of modular stems; the "loaded-taper" and the "composite-beam" (Scheerlinck et al. 2006, Garellick et al. 2014).

The loaded-taper is characterized by the straight, polished, tapered Exeter implant (Stryker, Mahwah, New Jersey) and forms a wedge in the cement mantle and during axial loading the stem is allowed to subside into a stable position. However, a high incidence of early periprosthetic fracture has been associated with two widely used cemented, polished tapered stems in elderly patients (Inngul and Enocson. 2014, Brodén et al. 2015).

The composite-beam model is built upon a rigid stem-cement interface fixation and mainly as an anatomical stem with anterioposterior curve to match the natural bow of the patient’s femur. This type of stem is characterized by the matte, anatomically shaped Lubinus SPII (Waldemar Link GmbH, Hamburg, Germany).

**Total hip arthroplasty**

A THA replaces the femoral head and the acetabulum by two separate articulating components. THA is a reliable option due to its ability to restore hip function and reduce the need for secondary surgery after a FNF (Squires and Bannister 1999, Ravikumar and Marsh 2000, Keating et al 2005, Blomfeldt et al. 2005, Baker et al. 2006, Blomfeldt et al. 2007, Leonardsson et al. 2010). However there are still only a few published reports with long-term follow-up (Ravikumar and Marsh 2000, Leonardsson et al. 2010, Johansson 2014). Long-term follow-up is important due to the increasing lifespan of patients with a FNF.

During the last decade a number of RCTs comparing THA and HA in the treatment of displaced FNFs have been published (Baker et al. 2006, Keating et al. 2006, Blomfeldt et al. 2007, Macaulay et al. 2008, van den Bekerom et al. 2010, Avery et al. 2011, Hedbeck et al. 2011, Cho et al. 2011). These studies have formed a core of the recent published reviews and meta-analyses that conclude that THA may produce better hip PRO despite a higher rate of dislocation compared with HA (Hopley et al. 2010, Carroll et al. 2011, Zi-Sheng et al. 2012, Burgers et al. 2012, Yu et al. 2012). However, due to heterogeneity in patient selection and the impact of subgroup effects, the authors were unable to make any definitive recommendations.
The most common complications of THA and HA are dislocation (0-22%) and infection (0-18%) (Bhandari et al. 2003, Hopley et al. 2010). In comparison to patients treated with THA for osteoarthritis, fracture patients are more prone to reoperations, mainly due to prosthetic dislocation (Berry et al. 2004, Hailer et al. 2012). Dislocation is a severe complication that affects the patient-reported quality of life and increases mortality (Blewitt and Mortimore 1992, Hedlundh and Fredin 1995, Petersen et al. 2006, Enocson et al. 2009). Patients suffering a dislocation have an increased incidence of up to 50-60% of recurrent instability of the prosthesis (Barnes et al. 1995, Pajarinen et al. 2003, Noon et al. 2005, Enocson et al. 2008, Enocson et al. 2009, Madanat et al. 2012, Wallner et al. 2014). There are factors affecting the stability of a hip arthroplasty. Patient related factors include age, female sex, cognitive dysfunction and the indication for surgery. Implant related factors include choice of head diameter, femoral offset (FO) and length of the neck, postoperative leg length discrepancy (LLD), femoral component rotation and anteversion, cup abduction angle in THA. Surgical related factors include the experience of the surgeon, surgical approach, pre-operative planning and frequency of component malposition (Hedlundh et al. 1996, Pajarinen et al. 2003, Masaoka et al 2006, Hailer et al. 2012, Brooks 2013, Wallner et al. 2014).

Several techniques have been designed to address the issue of prosthetic instability. Change of surgical approach from PL to DL, larger prosthetic heads, constrained liners, constrained and unconstrained dual mobility components are a few examples (Bourne and Mehin 2004). The unconstrained dual mobility cups have in recent research showed promising results in preventing dislocations in patients with FNF (Tarasevicius et al. 2010, Adam et al. 2012, Bensen et al. 2014). However, there is a lack of published long-term data on the dual mobility concept.
Considerations related to the treatment of a femoral neck fracture

Surgical approach in THA or HA

There are a number of different surgical approaches to the hip joint. In clinical practice, the four most commonly used are the anterior, anterolateral, DL and PL approaches.

Kevin Hardinge published a description of the “direct lateral approach” in 1982 (Hardinge 1982). The patient was positioned supine and a straight incision was made through the skin and fascia, along the midline of the trochanter. The anterior part of the gluteus medius was deflected anteriorly and the anterior capsule was visualized. After a capsulectomy the joint was accessed. The prosthesis was implanted and the tendinous complex was re-sutured to its origin. A modification of this approach was later published as “a modified approach” by Gammer (Gammer 1985). The modification includes the patient positioned in the lateral decubitus position and release of the gluteus medius by decortication of the insertion with an osteotome. These similar approaches are named “the direct lateral approach”.

The anterolateral approach (Watson-Jones) uses the interval between the tensor fascia lata and the anterior margin of the gluteus medius muscle and is similar to the direct lateral approach.

The anterior approach was originally developed by Smith-Petersen (1949). The anterior approach is performed with the patient in supine position and an incision is made following the lateral iliac crest to the anterior superior iliac spine, turning distally to follow the lateral side of the sartorius muscle. The lateral cutaneous branch of the femoral nerve is retracted medially. The tensor fasciae latae and the sartorius are separated. The rectus femoris is severed from the anterior inferior iliac spine and the capsule of the joint exposed. The direct anterior approach is a modification of the original anterior approach where only the distal portion incision is used (Matta et al. 2005, Lovell 2008). This approach is not as commonly used as the direct lateral approach and is regarded as being more technically demanding. Therefore it is not suitable for the general orthopaedic surgeon. There are few published studies evaluating the direct anterior approach on FNF patients (Auffarth et al. 2011, Schneider et al. 2012, Langlois et al. 2015).

Austin Moore developed “the southern exposure” or as it is more commonly known “the posterior approach”, alongside his classic Moore prosthesis (Moore 1952, Moore 1957). The patient was positioned in the lateral decubitus position and a curved incision was made behind the trochanter through the skin and fascia. The
gluteus maximus was bluntly dissected alongside the fibers. The short external rotators were released and the joint capsule identified. A capsulectomy was performed and the joint assessed. This approach has been modified in order to decrease the number of prosthetic dislocations by using a posterior repair of the short external rotators (Ko et al. 2001).

The use of different approaches varies among countries. The DL and PL approaches are the most frequently used approaches to the hip joint (Chechik et al. 2013, Hunt et al 2013, Havelin et al 2009, Jolles, Bogoch 2006). In Sweden 72% of hip fracture patients were operated using the DL approach during 2013 (Garellick et al 2014).

The question of optimal surgical approach and the suggestion that differences exist between the DL and the PL approaches in terms of type of complications is still debatable. An increased incidence of damage to the superior gluteal nerve, gluteus medius insufficiency and trochanteric tenderness have been linked to the DL approach. (Baker and Bitounis 1989, Ramesh et al. 1996, Masonis and Bourne 2002, Picado et al. 2007, Kiyama et al. 2010, Berstock et al. 2015). Others have not found any clinically relevant increase in these complications (Downing et al. 2001, Chomiak et al. 2015). The PL approach is linked to an increased risk of reoperation due to prosthetic dislocation in both patients treated for osteoarthritis and FNF (Lindgren et al. 2012, Hailer et al. 2012). Patients suffering a FNF are generally older and more fragile than patients with OA and thus more susceptible to complications and reoperations. The DL approach has been proven to reduce dislocation related reoperations (Bush and Wilson 2007, Enocson et al. 2008, Enocson et al. 2009, Sköldenberg et al 2010, Biber et al. 2012, Rogmark et al. 2014, Cebatorius et al. 2014).

Prosthesis-related complications are known to affect PRO measures and other scores of pain and function negatively (Edmunds et al 2011, Smith et al 2012). Two recent reports of large cohorts of patients from the Swedish and Norwegian hip arthroplasty registries have revealed better PRO in patients with OA treated with THA through a PL approach in comparison to the DL approach (Lindgren et al. 2014, Amlie et al. 2014). However, the functional outcome and quality of life in FNF patients in relation to the surgical approach has not been adequately studied in the literature.
Restoration of hip biomechanics

Malpositioning of the prosthetic components is a risk factor for dislocation and thus revision surgery, in patients with osteoarthritis treated with THA (Morrey et al. 1997, Biedermann et al. 2005, Lewinnek et al. 1978). Restoration of the biomechanical forces affecting the hip joint with appropriate FO and LLD is an important aim (Tanaka et al. 2010, Lecerf et al. 2009). The radiographic evaluation of these parameters requires—adequate validity, interobserver reliability and intraobserver reproducibility (Mahmood et al. 2014). Computed tomography and magnetic resonance imaging have been proven to be the gold standard in this respect (Olivecrona et al. 2004). However, high cost, radiation exposure and availability in relation to the huge number of hip arthroplasty procedures make their routine use impractical (Sabharwal et al. 2008, Pasquier et al. 2010). Therefore plain radiographs remain as the standard for clinical use. The criteria for evaluation of plain radiographs for this purpose rely on proper standardization and measurement techniques to minimize the shortcomings associated with their use.

Patients that receive a hip arthroplasty for FNF are at greater risk for postoperative dislocation and thus revision surgery compared to patients with OA (Garellick et al. 2014). Failure to achieve an adequate restoration of the FO, an excessive residual femoral neck and a smaller centre-edge angle of Wiberg may influence the dislocation rate in patients treated with HA for a FNF (Pajarinen et al. 2003, Ninh et al 2009, Madanat et al. 2012, Wallner et al. 2014).

The association between acetabular cup position and the risk for dislocation is a frequently discussed topic in several studies. A recommendation for an inclination angle between 30-50° and an antversion of 5-25° are based on research mainly on patients with degenerative joint disease (Lewinnek et al. 1978, Dorr and Wan, 1998, Biedermann et al. 2005). Studies by Enocson et al. (2010) and Biedermann et al. (2005) has indicated that the relative risk for anterior dislocation increases with the anteversion of the acetabular component. The inverse relationship was identified for posterior dislocation. However, other authors have not been able to replicate this finding (Pollard et al. 1995, Paterno et al. 1997).

The evaluation of femoral stem version and rotation is difficult on standard radiographs and the orientation of the stem is assumed to be of less importance than the acetabular component in the context of dislocation (Kristiansen et al. 1985, Daly and Morrey. 1992, Nishii et al. 2004). The influence of stem position in the coronal (varus-valgus) and sagittal (neutral or C-position) planes on implant survival is under debate; varus-positioned cemented stems have shown poor survival due to aseptic loosening (Manuera and Garcia-Cimbrello. 1992, Jaffe and Hawkins. 1999).
Patient related risk factors for revision surgery

Advanced age, male gender and cognitive impairment has been linked to an increased risk for dislocation and revision surgery (Johansson et al. 2000, Leonardsson et al. 2009, Garellick et al. 2013, Wallner et al. 2014). The reasons for this may be that men are biologically older than their female counterparts, cognitive impairment predisposes to failure to adhere to motion restrictions and advanced age often is linked to poor coordination and vision (Woolson and Rahimtoola 1999, Meek et al. 2006). The Swedish hip arthroplasty registry has identified a high BMI as a risk factor for reoperation in patients with FNF (Garellick et al. 2013, Garellick et al. 2014).
Generalizability of study results

External validity of RCTs

The practice of health care relies on evidence-based medicine and previous proven experience. In recent years there has been an increasing demand for evidence-based management and modalities (Evidence-Based Medicine Working Group, 1994). Well-designed and conducted RCTs are the most reliable way to evaluate the effect of treatments by comparing them to previously accepted treatment regimes. For study results to be converted into clinical practice, there is a need for ‘internal validity’ and ‘external validity’. High quality RCTs are ‘internally valid’, resulting in an appropriate comparison between the randomized groups thereby reducing possible bias and confounding factors to a minimum. However, even when a RCT reveals a positive result there is often a question as to whether the results can be extrapolated from the study environment to the general health care situation (Rothwell 2005). This phenomenon is called ‘external validity’ (EV). The EV depends on how representative the study population is compared to the whole population. However, the RCT relies on active participation and individuals who decline to participate affect its validity. There are numerous reasons for non-participation and this may vary between studied populations. If the baseline characteristics between non-participants differ substantially from participants, it may worsen the EV (Hartge 2006, Galea and Tracy 2007). How these factors are taken into account in the design and performance of an RCT and in the reporting of the results can affect the EV. Publications in other fields of medical research evaluating the EV indicated that non-participants had a lower socioeconomic status, poorer health status and higher mortality rates (Hoeymans et al. 1998, Hara et al. 2002, Kauppi et al. 2005, Steg et al. 2007, Travers et al. 2007, Travers et al. 2007b, Ethgen et al. 2009, Bjoernshave et al. 2010, Hutchinson-Jaffe et al. 2010, Suominen et al. 2012).

In the orthopedic literature, the issue of EV has not received enough attention. Petersen et al evaluated the differences in baseline data in a RCT with patients treated with THA due to OA (Petersen et al. 2007). The authors concluded that significant differences in baseline data existed among those who gave consent and those who did not. In a systematic review, Pibouleu et al. (2009) analyzed RCTs and non-randomized comparative studies of total hip or knee arthroplasty carried out by a minimally invasive approach or computer-assisted navigation system. The authors found that the data needed to estimate the generalizability of these trials was not reported in sufficient detail in order to be able to evaluate their EV. Bhandari et al. (2004) conducted a meta-analysis comparing RCTs and non-RCTs in the treatment of FNF with THA and IF. The results indicated discrepancy between randomized and non-randomized studies in mortality and revision rates. A recent study that analyzed non-participants in comparison to participants in a cohort study of osteoporosis found a lower mortality rate for participants but no difference in the primary outcome variable and incidence of osteoporotic fractures (Wihlborg et al. 2014). When the work began with this thesis, there were, to our knowledge, no published reports concerning the EV of RCTs that included patients with a FNF.
Aims

The general aims of the studies were to guide surgeons in their choice of optimal treatment for displaced femoral neck fractures in the elderly.

The specific aims of these investigations were:

I. To compare the results of THA with IF over a long-term follow-up period of 17 years.

II. To compare reported hip function in patients treated with a HA using either a DL or PL approach.

III. To analyze postoperative global FO, leg length discrepancy (LLD) and Wiberg angle as risk factors for prosthetic dislocation after treatment with bipolar HA using a PL approach for FNF.

IV. To study the EV of an RCT in patients treated with hip arthroplasty for FNF.
Hypotheses of the studies

I. Primary THA will provide better hip function and significantly fewer re-operations than IF without increasing mortality in the long-term.

II. The DL approach gives patients an equivalent or better hip function and quality of life compared to the PL approach, despite an increased risk for postoperative limping.

III. A decreased postoperative global FO, LLD and Wiberg angle are associated with increased risk of recurrent dislocation of bipolar HA.

IV. Patients included in RCTs are healthier and have a better outcome than those that do not give their informed consent (NC) or are missed in the screening process (MS).
End points

Study I

The primary end point was hip function evaluated with the HHS (Harris 1969). Secondary end points included mortality, hip complications, reoperations, gait speed, pain in the involved hip (measured with the visual analogue scale (VAS), and the ability to carry out activities of daily living (Katz et al. 1963, Scott and Huskisson 1976, Olsson et al. 1986).

Study II

The primary end point was hip function evaluated using the HHS (Harris 1969). Secondary end points included WOMAC (Bellamy et al 1988), numerical rating scale for pain (PNRS), postoperative limp, mortality and re-operations (Brooks 1996, Rabin and Charro 2001).

Study III

The primary endpoints were global FO, LLD and Wiberg angle measured on postoperative radiographs. Secondary endpoints were mortality and mental status.

Study IV

The primary endpoint was hip function evaluated with the HHS (Harris 1969) at 1 year follow-up comparing patients included in a RCT to those that did not give their informed consent (NC) and those missed in the screening process (MS). Secondary outcome measures included quality-of-life evaluated with the EQ-5D (EuroQol group, 2010), mortality and reoperations.
Patients

Patients participating in studies I and IV were recruited from the Orthopaedic Department at Danderyd Hospital between 1990-1994 (Study I) and 2009-2015 (Study IV). For studies II and III, patients were recruited from the Orthopaedic Department at Sundsvall Hospital between 2012-2014 (Study II) and 2006-2013 (Study III).

The Orthopaedic Department of Danderyd Hospital, Stockholm, Sweden is an emergency regional teaching hospital affiliated with the Karolinska Institute and at the start of study I, had a catchment area of approximately 350,000 inhabitants. At the start of study IV the catchment area was approximately 500,000.

The Orthopaedic Department of Sundsvall Hospital, Sundsvall, Sweden is an emergency regional teaching hospital affiliated with Umeå University and has a catchment area of approximately 160,000 inhabitants.

Study I

All patients with a FNF who were admitted to the Orthopaedic Department of Danderyd Hospital between February 1990 and December 1994, were, during the inclusion period, screened for participation in the study.

We identified 1172 patients who were admitted due to a FNF. The inclusion criteria were:

- an acute displaced FNF (Garden stage III or IV) that had been sustained within the previous 36 hours
- age of 65 years or more
- admission from home with no concurrent joint disease or previous fracture involving the lower extremities
- a healthy status or only mild systemic disease [ASA (American Society of Anesthesiologists) grade 1 or 2]
- intact cognitive function (no diagnosis of dementia, with the patient being lucid and fully oriented)
- the ability to carry out all activities of daily living (Katz index A)

In addition, all patients had no hip dysfunction prior to the fracture, as measured by the HHS, with a score of 100 points. The preoperative HHS was obtained retrospectively when patients were admitted to the hospital. Patients with a pathological fracture and those who were deemed not suitable for a THA by the anaesthesiologist were excluded.
Those who agreed to participate gave their informed consent and were included and randomized according to the study protocol. Follow-up was performed at three months and at one, two, four, eleven, and seventeen years. The four-year results from this study were previously reported in a thesis but not in the peer-reviewed literature (Neander, 2000).

Study II

All patients with a FNF treated with a HA at the Orthopaedic Department at Sundsvall Hospital between February 2012 and June 2014 Hospital, were, during the inclusion period, screened for participation in a prospective cohort study. During the study period 345 patients were admitted with a FNF. Of these, 183 patients (185 hips) were treated with a HA due to a displaced FNF.

At our orthopaedic department, hip arthroplasty is performed on patients with a displaced femoral neck fracture above the age of 65 years. Patients 79 years and over are mainly treated with an HA but the final decision about whether to perform a HA or a THA is decided by the patient’s level of activity and surgeon’s preference.

The inclusion criteria were a non-pathological displaced FNF (Garden III or IV) and age ≥65 years. Patients with OA or rheumatoid arthritis with involvement of the fractured hip, non-walkers and non-Swedish speaking patients were excluded. Follow-up was performed at 12 months.

Study III

All patients with a FNF treated with HA at the Orthopaedic Department at Sundsvall Hospital between January 2006 and January 2013 were, during the inclusion period, identified for participation in a retrospective cohort study. Patients were treated with a cemented bipolar HA (Vario cup, Waldemar Link®, Germany) using a PL approach for a displaced FNF. Patients with pathological fractures were treated with a HA performed using a DL approach. Patients operated with a HA other than the bipolar Vario cup head and the Lubinus SPII stem were excluded. During the inclusion period, 541 hips with a FNF were operated on using HA. Of these patients 373 hips fulfilled the inclusion criteria and were included in the study. Of these, 45 hips were excluded due to inadequately documented postoperative radiographs. Therefore 328 hips were analyzed.
Study IV

All patients above 80 years old with an acute (<36 hours before admission) displaced FNF at Danderyds Hospital AB between October 2009 and April 2015 were screened and asked for their participation in a RCT comparing HA and THA. A total of 840 patients were screened. Inclusion criteria for the RCT were:

- patients with an acute (<36 hours) displaced FNF
- independent walker
- age above 80 years
- absence of cognitive impairment (Pfeiffer test >7 points)
- did not fulfill any exclusion criteria

Exclusion criteria were osteoarthritis or rheumatoid arthritis in the fractured hip, a pathological fracture, non-walker, cognitive impairment (Pfeiffer test <7 points), patients with comorbidities deemed not suitable for a THA by the anesthesiologist, coagulation disorder, and drug abuse.

Those who fulfilled the criteria for inclusion and gave their informed consent were enrolled in the RCT. Patients that did not give their informed consent and those missed in the screening process were enrolled in a prospective cohort study for evaluation of the EV.

Ethics

All studies were conducted in conformity with the principles of the Helsinki declaration (Association WM 2008). Studies I and IV were approved by the Ethics Committee of the Karolinska Institute and studies II and III were approved by the Ethics Committee of Umeå University.

The studies were initiated, designed and performed as academic investigations.

Registration

All studies were registered and publicly accessible at www.clinicaltrials.gov.
Study I: NCT01344772
Study II: NCT01486641
Study III: NCT02131987
Study IV: NCT02246335 and NCT02362971
Materials

Hip arthroplasty

In study I, all patients undergoing THA received a cemented, polished, tapered, collarless femoral stem manufactured from a titanium alloy (Ti-6Al-4V) (Bi-Metric; Biomet UK, Brigend, South Wales, United Kingdom) with a 28-mm chromium-cobalt head. The bone cement used was Optipac (Biomet, Malmö, Sweden).

In studies II and III, all patients received a cemented, matte, anatomical, collared femoral stem SP II® (The LINK®, Hamburg, Germany). For HA the unipolar head (Waldemar Link®, Hamburg, Germany) or the bipolar head (Vario cup, Waldemar Link®, Hamburg, Germany) was used. Bone cement was used for all patients Optipac (Biomet, Malmö, Sweden).

In study IV, patients treated with HA, the cemented CPT stem (Depuy, Warsaw, IN, USA) or cemented, matte, anatomical, collared femoral stem Lubinus SP II (Waldemar Link®, Hamburg, Germany) was used. CPT is a collarless, polished, tapered femoral stem made of chrome-cobalt alloy. The stem is double-tapered and has a rectangular proximal geometry. A modular 32-mm cobalt chrome femoral head was used in all THA patients and a modular unipolar head (Versys Endo (Zimmer)) or the Unipolar head (Waldemar Link®, Hamburg, Germany) was used for patients treated with an HA. Bone cement was used for all patients (Optipac; Biomet, Malmö, Sweden).

Acetabular Components

In study I, the acetabular component was a cemented polyethylene acetabular component (Müller; Biomet UK).

In studies II and III, we did not include patients treated with THA.

In study IV, patients treated with THA received a cemented highly crosslinked polyethylene acetabular component (Marathon Cup (DePuy)).
Methods

Study protocol

Study I was a prospective RCT carried out between February 1990 and June 2010 (inclusion period February 1990 to December 1994). The randomization process for the first 20 patients was conducted using sealed opaque envelopes. No stratification was used. Due to hospital economic and logistic reasons with lack of operating theatre staff with THA experience during weekends, a change in allocation routines was implemented during the study. Thus, the following 80 patients were allocated according to which weekday they were admitted. Patients admitted on Monday to Thursday were operated using THA, whereas from Friday to Sunday, IF was used. The patients, surgeons and staff were not blinded to choice of treatment. Follow-up at 3 months, 1, 2, 4, 11 and 17 years was done in the Orthopaedic Department at Danderyds Hospital, Sweden.

Study II was a prospective cohort study conducted between February 2012 and May 2015 (inclusion period was February 2012 to June 2014). Those patients deemed suitable for treatment with HA were included in the study. The routine at our department is to perform hip arthroplasty for displaced FNF in patients above 65 years of age. Total hip arthroplasty (THA) is used in the relatively young (65 to 79 years) and active patients while the HA is used in older (>79) less active patients and those with cognitive dysfunction.

Those deemed suitable for treatment with HA were included in the study. Cognitive dysfunction was not a contraindication for HA. The inclusion criteria were: a non-pathological displaced FNF (Garden III or IV evaluated by the treating surgeon) treated with a HA and age ≥65 years. Non-walkers, non-Swedish speaking and those with degenerative joint disease or rheumatoid arthritis of the fractured hip were excluded.

The decision as to whether to use the DL or the PL approach was according to surgeons’ preference. All patients were interviewed before surgery or before discharge from the ward regarding their preoperative mental status and hip function. Baseline data regarding date of surgery, surgical time, approach and ASA score were collected from medical records. An independent research nurse did a follow-up interview at 1 year postoperatively.

Study III was a retrospective cohort study conducted between January 2006 and September 2013. Three hundred and seventy three patients with a displaced FNF were treated with a cemented bipolar HA using the PL approach (Moore, 1957).
Patients treated using other approaches or implants as well as those with pathological fractures were excluded.

We conducted an analysis of this cohort and the number of single and recurrent dislocations was recorded. Standard antero-posterior (AP) and lateral radiographs were performed postoperatively. Patients with dislocation were compared to the cohort of patients without a dislocation. As a subgroup analysis, patients with dislocation were split into a group that experienced a single dislocation and a group with recurrent dislocations. Each of these groups was matched according to age and sex with patients without any dislocation from the same cohort. Fifteen patients with a single dislocation and 25 with recurrent dislocation were matched with 40 and 88 patients without dislocation respectively. Clinical data regarding patient demographics, medical comorbidities (ASA grade), mental status (as mentally healthy or mentally ill, without a standardized score) and one-year mortality were obtained from medical records.

*Study IV* was a prospective cohort study conducted between October 2009 and April 2015 (inclusion period was October 2009 to April 2015). All patients 80 years old and above with a displaced FNF admitted to Danderyd Hospital during the inclusion period were considered for participation in a clinical trial (“Hemiarthroplasty Compared to Total Hip Arthroplasty for Displaced Femoral Neck Fractures in the Elderly-elderly (HOPE)”). All were screened according to the inclusion and exclusion criteria. The inclusion criteria were an acute (<36h) displaced FNF in an elderly (>80 years old) patient without cognitive impairment (SPMSQ >7 points) and being an independent walker. Patients with OA and rheumatoid arthritis in the fractured hip, pathological fractures, non-walkers, patients with cognitive impairment (SPMSQ <7 points), drug abuse or severe coagulation disorder or by other reason deemed unsuitable for participation were excluded. Those that fulfilled the criteria for inclusion were allocated to the following groups:

1) those who gave their informed consent and were randomized (RCT group)
2) those that were asked to participate in the RCT but would not give their informed consent (non-consenters (NC) group)
3) all patients missed in the screening process (missed screening (MS) group)

Those who did not fulfil the inclusion criteria were excluded from the study since they were not part of the study population of interest. Follow-up was performed 1 year after surgery using a postal questionnaire that included the HHS and EQ-5D. All medical charts were screened for hip-related complications and reoperations. We used the unique Swedish civic registration number to verify mortality in the Swedish Death Register. We also used the Swedish Hip Arthroplasty Register to search for patients who had undergone reoperation elsewhere in Sweden but no cases were found.
Figure 3. Flow diagram of patients in studies I-IV.

Study I
- Screened (n=1172)
  - Included (n=100)
    - Allocated (n=100)
      - THA (n=43)
      - IF (n=57)
  - Included hips (n=185)
    - DL (n=102)
    - PL (n=83)

Study II
- Screened (n=346)
  - Included (n=183)
    - Incl. hips (n=185)
      - DL (n=102)
      - PL (n=83)

Study III
- Screened (n=373)
  - Included (n=328)
    - Incl. hips (n=328)
      - Dislocation (15)
      - Recurrent disl (25)
      - No dislocation (288)

Study IV
- Identified (n=840)
  - Included (n=267)
    - Incl. RCT (n=92)
      - Non-consent (n=54)
      - Missed screening (n=121)
Surgical technique

Internal Fixation

IF was used in study I, with the patient on a fracture table. The fracture was reduced closed, with the aid of an image intensifier, and was fixed with two cannulated screws (Olmed; DePuy/Johnson & Johnson, Sollentuna, Sweden). Capsulotomy or joint aspiration was not performed. In the anteroposterior projection, the distal screw was aimed to the level of the lesser trochanter to rest on the medial inferior cortex of the femoral neck. The proximal screw was positioned parallel to and at least 1 cm from the distal screw. The screws were parallel and were positioned in the central or posterior third of the femoral head and neck. All operations were performed on the day of admission or the following day. All patients were managed with dextran (Macrodex; Meda, Sweden) for thromboprophylaxis one hour preoperatively and postoperatively daily for four days. Antibiotic prophylaxis with cloxacillin (Ekvacillin; Meda, Sweden) was given on the day of surgery. Under the supervision of a physiotherapist, all patients were mobilized to full weight bearing on the first postoperative day.

Hip arthroplasty

The PL approach was used in Studies I-IV and the DL approach was used in Study II and IV.

The DL approach was performed via the abductor muscle “split” which was located in the anterior third or half of the gluteus medius and minimus tendons (Gammer, 1985). The capsule was incised T or H shaped or excised. At closure, the capsule, where possible, was reconstructed with Vicryl (Ethicon, Somerville, NJ). The gluteus medius and minimus tendons were repaired to the tendinous insertion by suture fixation with PDS II (Ethicon, Somerville, NJ) using either a number of double or continuous stitches.

A standard PL approach (Moore, 1957), with repair of the posterior capsule and external rotator muscles (Ko et al. 2001, Kwon et al. 2006) was used. The PL approach was performed via a blunt dissection along the fibers of the gluteus maximus. The external rotators were incised, if possible the piriformis tendon was spared and the posterior capsule was incised. At closure the posterior capsular flap was closed with PDS II using a number of double stitches if possible. The piriformis tendon and external rotators were reconstructed to the posterior proximal end of the greater trochanter mainly with or without osseus sutures with PDS II. The following
surgical technique and instrumentation used were identical regardless of type of arthroplasty or approach.

The femoral head was dislocated from the acetabulum and resection of the femoral neck was done. When performing a HA, the femoral head is measured and the head size is determined. When performing a THA, the acetabulum is prepared with reaming until cartilage and cortical bone are removed. The acetabular component was positioned and fixated with bone cement. The femoral canal was then prepared by reaming and thereafter with broaching with increasing sizes until adequate resistance was achieved. With the final broach in place, the calcare femorale was planed, the biomechanics were evaluated and the implant was inserted in a cement mantle.

Peri-operative care

All procedures were performed on the day of admission or the following day. Antibiotic prophylaxis was given as three doses of 2 grams of Cloxacillin (Ekvacillin®; Meda, Sweden) at 0.5 hours before and 1.5 and 9.5 hours after the start of surgery. Thrombo-prophylaxis with subcutaneous high molecular weight heparin (Fragmin® Pfizer AB, Sweden) was given to all patients in studies II-IV. Dextran (Macrodex; Meda, Sweden) was used for thromboprophylaxis one hour preoperatively and postoperatively daily for four days in study I.

Under the supervision of a physiotherapist, all patients in studies I-IV were mobilized to full weight bearing on the first postoperative day. Patients operated using the DL approach were not given any restrictions. Patients operated using the PL approach were given restrictions to avoid flexion beyond 90 degrees, adduction and internal rotation of the hip.
**Radiological parameters**

In studies I-III, anterioposterior and lateral radiographs were reviewed postoperatively and at follow-up visits. In Study I plain, and in Studies II-III, digital radiographs were used. Standard anterioposterior and lateral radiographs were performed postoperatively. All postoperative radiographs were made on a computerized radiography system (Siemens, Erlangen, Germany) and all measurements were performed on the anteroposterior radiographs of the pelvis and hip. The anteroposterior hip radiograph was made with the patient in supine position and both legs 15° internally rotated. The X-ray beam was centered on the pubic symphysis with a film focus distance of 115 cm. All images were digitally acquired using the Picture Archiving and Communication System (PACS, Impax: Agfa, Antwerp, Belgium).

In study I, the positioning of the prosthetic components were evaluated and classified as follows:

- **Good**
  - Minimum circumferential cement mantle around cup and stem of 2 mm
  - Abduction angle of the cup 35°-55°
  - Anteversion angle of the cup 10°-25°
  - Varus/Valgus angle of the stem below 3°
  - Postoperative limb-length difference below 10 mm.

- **Fair**
  - At least four of the five categories graded as good.

- **Poor**
  - Three categories or fewer graded as good.

In patients treated with internal fixation, the reduction and position of the screws was categorized, in accordance with the recommendations of Tidermark et al as:

- **Good** (displacement <2 mm; Garden angle 160° to 175°; posterior angulation <10°)
- **Fair** (displacement <5 mm; Garden angle 160° to 175°; posterior angulation <20°)
- **Poor** (displacement >5 mm; Garden angle <160° or >175°; posterior angulation >20°)

The position of the screws was good if the tips of the screws were <5 mm from the subchondral bone (Tidermark et al. 2003). To assess the stability of the implants, radiolucent lines between bone and cement were classified according to DeLee and
Charnley zones around the cups and by Gruen zones around the stems (DeLee, Charnley 1976, Gruen et al. 1979).

In study III, measurement of the global FO was carried out on anteroposterior view as follows: the addition of the distance between the longitudinal axis of the femur to the center of the femoral head plus the distance from the center of the femoral head to a perpendicular line passing through the medial edge of the ipsilateral teardrop point of the pelvis (Kjellberg et al. 2009). The measurement was repeated bilaterally to compare the global FO of the operated to the non-operated hip (Figure 4).

In studies II and III, the LLD was defined as the difference in perpendicular distance in millimeters between a line passing through the lower edge of the teardrop points to the corresponding tip of the lesser trochanter (Figure 4). The Wiberg angle was measured as the angle between the center of the prosthetic head and the lateral edge of the acetabulum on AP pelvis radiographs (Figure 4).

Figure 4. Radiographic measurements
Left: global offset. Middle: leg length discrepancy. Right: Wiberg angle.
Clinical outcome measurements

HHS

The most widely used hip-specific outcome score after THA is the HHS (Harris 1969). Originally developed for outcome measurements of mold arthroplasty after traumatic arthritis, it has been proven to be a valid and reliable score for hip function after THA (Söderman and Malchau 2001). The HHS was originally surgeon-assessed but has been validated for self-reporting and for outcome after FNF (Mahomed et al. 2001, Frihagen et al. 2008). The HHS has a range from 100 points (full function of the hip) to 0 (no function). It has 4 subgroups or domains: pain, function, deformity and range of motion. Pain and function are the two subgroups with major weighting (44 and 47 points, respectively). Function is further subclassified into activities of daily living (14 points) and gait (33 points). Range of motion, deformity and LLD receive 9 points. Limping is a subgroup and was used in study II and dichotomized into limping or no limping.

In this thesis, the assessment of the HHS was done by interview with grading of pain and function as a total of 91 points. The HHS was modified in this thesis to be used as a patient self-reported questionnaire by excluding the clinical examination domain. This modification has previously been evaluated and found to be in concordance with the surgeon assessed HHS (Mahomed et al. 2001). The modified HHS is used in Studies I, II and IV.

WOMAC

The WOMAC is a disease-specific twenty-four item questionnaire initially developed for patients with OA of the hip and knee (Bellamy 1988, Bellamy 1992). It has been validated for comparing clinical outcomes in patients with a FNF (Burgers et al. 2015). WOMAC has been used in studies of hip fracture patients (Jain et al. 2002, Macaulay et al. 2008, Sanz-Reig et al. 2012, Zielinski et al. 2013). WOMAC consist of 3 subgroups or domains: pain, stiffness and function. It has a range from 96 points (full function of the hip) to 0 (no function). Pain and stiffness are the two domains with least weighting (20 and 8 points respectively). Function is the most weighted subgroup (68 points). The minimal detectable clinical improvement has been suggested to be 14 points (Quintana et al. 2005, Hmamouchi et al. 2012). WOMAC is used in Study II.
**EQ-5D**

EQ-5D is a standardized, self-reported, non-disease-specific instrument for measurement of health-related quality of life (EuroQol-group 2010). EQ-5D is widely used and has been translated into most major languages including Swedish (Brooks 1996, Rabin, de Charro 2001, Burström et al. 2001). EQ-5D describes health status in 5 dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each dimension is divided into 3 levels: 1 - no problems, 2 - some problems and 3 - extreme problems. A unique health state is defined by combining 1 level from each of the 5 dimensions. This results in a possible 243 (3^5 = 243) different health states. The states can be expressed as index scores ranging from 0.59 (worse possible health state) to 1 (best possible health state).

EQ-5D has been used in clinical trials in many different fields of medicine including evaluation of quality of life after hip fracture surgery (Blomfeldt et al. 2007, Tidermark et al. 2003). The responsiveness has been found to be adequate in patients with FNF (Tidermark et al. 2003, Tidermark and Bergström 2007). EQ-5D is used in Study IV.

**Pain Numeric Rating Scale**

The Pain Numeric Rating Scale (PNRS) is a 10-point (1-10) numerical rating scale that is easy to administer (Downie et al. 1978). A score of 0 denotes no pain and 10 indicates the worst possible pain. The PNRS was used in Studies I, II and IV. Patients were asked to evaluate the level of pain they experienced in the operated hip during the previous week.

**The Short Portable Mental State Questionnaire (SPMSQ)**

The short portable mental state questionnaire (SPMSQ) is a 10-point (0-10) mental test that is easy to administer (Pfeiffer, 1975). A score of 0 to 2 indicates severe cognitive dysfunction, 3-5 points indicates a moderate cognitive dysfunction, 6-7 points indicates a mild cognitive dysfunction and 8-10 points indicates that no cognitive dysfunction exists. The SPMSQ has shown a good sensitivity and specificity in detecting cognitive dysfunction and has been validated for screening of cognitive dysfunction in the elderly population (Erkinjuntti et al. 1987, Smith et al. 1995). The SPMSQ was used in Studies I-II and IV during prefracture assessment and during follow-up.
Reoperations

In all studies information regarding frequency and occurrence of reoperations was collected on all patients. This was done prospectively at follow-up in Studies I, II and IV and retrospectively in Study III where it was obtained from medical records.

The decision as to whether to perform revision surgery because of dislocation was primarily done by a subspecialist hip arthroplasty surgeon. If the femoral component was in an acceptable position, closed reduction under general anesthesia was always done as a primary procedure. After successful closed reduction an abduction brace was used for six weeks. Two or up to three closed reductions are preferred before considering a revision procedure.

An orthopaedic consultant made the decision about revision surgery when there was suspicion of deep periprosthetic infection. At our department the definition of periprosthetic joint infection was determined according to Parvizi et al. (2011). We perform debridement, antibiotics and implant retention as the primary treatment for early infections (<3-6 weeks) in association with stable implants. Up to 2 to 3 debridements were performed due to treatment failure before an implant extraction or a two-stage revision was performed.
Statistical methods

In all studies the statistical software SPSS Statistics 18.0-22.0 for Windows or Mac was used. Sample size calculations were performed using the software SamplePower 2.0.

Sample size calculation

In Study I, at the time of initiation of the study, no formal power analysis had been performed. An interim analysis (two-sided, p = 0.05) was performed after one year on the primary end point, and we tested the null hypothesis that the mean Harris hip scores for the two groups would be equal. We assumed that a mean difference of 10 points (standard deviation, 15 points) in the HHS was the smallest effect that would be clinically relevant. Taking into consideration the difference in the number of patients included in the two groups, we calculated that a total of 90 patients with one year of follow-up (40 in the THA group and 50 in the IF group) would give a power of 87.5% to yield a significant result. A total of 100 patients (43 in the THA group and 57 in the IF group) were recruited to allow for any loss to follow-up.

In Study II, prior to the study, a power analysis was performed using G*Power software based on comparing the means of the HHS of each group. With a power of 0.80 and a significance level (alpha) of 0.05, a minimum of 52 patients at follow-up was needed in each group to detect a clinically significant 7-points difference (standard deviation (SD) 18) in HHS among the groups. We assumed that a 10-point difference in HHS is the smallest effect that would be clinically relevant. A total of 185 hips (183 patients) were recruited to allow for any loss to follow-up.

In Study III, no formal power analysis was performed. All patients were included in the analysis.

In Study IV, no formal power analysis was performed. All patients were included in the analysis.
Statistical analysis

Due to varying journal policies, the methods regarding parametric or nonparametric tests differ somewhat in the studies. We used the chi-square test to test for differences between distributions. In all studies, P-values ≤0.05 were considered significant.

In Study I, analyses of outcome were based on the intention-to-treat principle, and all patients remained in the group to which they had been randomized, regardless of any later surgical intervention. Patients with missing data at any of the follow-up evaluations were analyzed with the last observation carried forward. For the clinical outcome variables (HHS, gait velocity, and VAS), we used a one-way repeated measures analysis of covariance (ANCOVA) to detect an overall difference between the two treatment arms throughout the study period, with use of estimated marginal means to adjust for the difference between the two groups in terms of sample size. Age, sex, and surgeon (registrar or consultant) were included in the analysis. The Bonferroni correction was used to adjust for multiple comparisons. The Pearson chi-square test was used to compare categorical variables between the groups. Kaplan-Meier curves with the log-rank test were used for the analysis of patient and implant survival.

In Study II, The student’s t-test was used for normally distributed data and the Mann-Whitney U test for ordinal data. The chi-squared test or Fisher’s exact test were used for nominal data. All tests were two-sided.

For the clinical outcome variables (HHS, WOMAC), we used a linear regression analysis to detect a difference between the two groups. Possible predictor variables for inclusion in the model were determined using univariate tests and a multivariate model (ANCOVA) adjusted for surgical approach, age, sex, and surgeon (registrar or consultant) and ASA category (1-2 or 3-4).

Logistic regression analyses were performed in order to evaluate factors associated with postoperative limp, hip complications and reoperations. Surgical approach, age, sex, the surgeon’s experience, cognitive dysfunction and ASA category (1-2 or 3-4) were tested as independent variables in the model. Possible predictor variables for inclusion in the model were determined using univariate tests. The adjusted associations are presented as odds ratios (OR) with 95% confidence intervals (CI). Kaplan-Meier curves with the log-rank test were used for the analysis of patient survival.

In Study III, categorical data is presented as counts and percentages and continuous data as the mean and range. Student’s t-test for independent samples was used to compare radiological parameters and Fisher’s exact test to compare nonparametric data between groups.

In Study IV, for the clinical outcome variables (HHS, EQ-5D), one-way repeated measures analysis of covariance (ANCOVA) was used to detect a difference
between the three groups of patients. Age, sex, and ASA category (1-2 or 3-4) were included in the analysis. The Bonferroni correction was used to adjust for multiple comparisons. The Mann-Whitney U-test was used for scale variables in independent groups. Nominal variables were tested using the Chi-square test or Fisher’s exact test. All tests were two-sided. Logistic regression analyses were performed in order to evaluate factors associated with reoperation. The associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Cox-regression analyses with adjustment for age, sex and ASA category were used for analysis of mortality. The associations are presented as hazard ratios with 95% confidence intervals (CIs).
Results

Study I

Patient flow and baseline data
Eleven hundred and seventy two patients with a FNF were admitted to the Orthopaedic Department at Danderyd Hospital, Stockholm, Sweden (Flow of patients, figure 5). Of these, 100 patients met the inclusion criteria [mean age 78 years (range, 65-90 years), 79 females] and were recruited to participate in the study. All subjects received their allocated treatment. The two groups characteristics were similar at baseline (table 1).

Operative data
A total of 18 surgeons performed all the operations and a greater proportion of IF were performed by registrars (THA versus IF; consultants/registrars: 41/2 versus 47/10). Duration of surgery and blood loss was greater in the THA group. The THA was graded as good in 40 (93%) patients and fair in 3 (7%). In the IF group closed reduction was categorized as good in 51 (89%) and fair in 6 (11%). The positioning of the screws was considered good in 56 (98%) and fair in 1 (2%). We found no correlation between the incidence of failed fracture healing and the reduction and positioning of the screws.

Primary end point
The HHS was higher in the THA group with a mean difference throughout the study period of 14.7 points (95% CI 9.2 to 20.1; P<0.001, ANCOVA) with the greatest difference between the groups during the first 2 years.

Mortality
The mortality was high regardless of treatment. At 11 and 17 years, 25% and 13% respectively were still living. The mortality rate did not differ between the groups over the study period.

Hip complications and re-operations
During the study period 40 (40%) hips required re-operation at least once (Table 2). In the THA group 4 (9%) patients and 22 (39%) in the IF group had undergone a major re-operation (relative risk [RR] 0.24; 95% CI, 0.09 to 0.64; P=0.001) (Table 2). The overall re-operation rate was 23% (10/43) in the THA and 53% (30/57) in the IF group (RR 0.44; 95% CI 0.24 to 0.80; P=0.003) (Table 2). Median time to first re-operation was 33 (range, 0.5-114) months in the THA group and 10 (range, 0.5-47) months in the IF group. Twelve patients underwent more than 1 surgical procedure (range 1 - 4), 10 of these were in the IF group. The most frequent
complications in the THA group were dislocations (n=6), late presenting periprosthetic fractures (n=2) and aseptic loosening (n=2). In the IF group, avascular necrosis (n=17) and non-union/mechanical failure (n=14) were the two most common hip complications.

During the first two years after surgery a large number of IF failed and 20 of the initial 57 patients recruited received a secondary THA. Patients receiving primary THA went through fewer reoperations (4 of 43 patients) and these were performed in later years (4 to 12 years after primary surgery) (table 2, figure 7).

**Gait speed, pain and activities of daily living**

Gait speed was significantly faster in the THA group at 3 months (THA vs IF; 37 vs 50 seconds to walk 30 metres, P= 0.005) but did not differ between groups at the later follow-ups.

Patients in the THA group had less pain in the operated hip throughout the study period. The mean difference was 1.2 (95% CI 0.4 to 2.0; P<0.001, ANCOVA) points out of 10 on the VAS. A greater proportion of patients in the THA group were fully independent in ADL during the 1st year of the study. At the later follow-up visits there was no difference between the groups (table 3).
Figure 5: Flow of patients study I.

Assessed for eligibility (n=1172)

Enrollment

Randomized (n=100)

Excluded (n=1072)

Allocation

Allocated to total hip replacement (n=43)
♦ Received allocated intervention (n=43)

Allocated to internal fixation (n=57)
♦ Received allocated intervention (n=57)

Analysis

Analysed (n=43)
♦ Excluded from analysis (n=0)

Analysed (n=57)
♦ Excluded from analysis (n=0)

Follow-Up

3 months (n=39)
Lost to follow-up (n=2) Deceased (n=2)
1 year (n=40)
Lost to follow-up (n=1) Deceased (n=2)
2 year (n=48)
Lost to follow-up (n=2) Deceased (n=3)
4 year (n=34)
Lost to follow-up (n=1) Deceased (n=8)
11 year (n=17)
Lost to follow-up (n=3) Deceased (n=23)
17 year (n=5)
Lost to follow-up (n=1) Deceased (n=37)

3 months (n=52)
Lost to follow-up (n=4) Deceased (n=1)
1 year (n=50)
Lost to follow-up (n=4) Deceased (n=3)
2 year (n=45)
Lost to follow-up (n=5) Deceased (n=7)
4 year (n=41)
Lost to follow-up (n=1) Deceased (n=15)
11 year (n=14)
Lost to follow-up (n=2) Deceased (n=41)
17 year (n=7)
Lost to follow-up (n=1) Deceased (n=49)
Table 1: Study population characteristics. Values given as number of patients or the mean, with percentages or range in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>THA No. 43</th>
<th>IF No. 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>78 (65 to 90)</td>
<td>79 (66 to 90)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (12%)</td>
<td>16 (28%)</td>
</tr>
<tr>
<td>Female</td>
<td>38 (88%)</td>
<td>41 (72%)</td>
</tr>
<tr>
<td>Side (No. patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>23 (53%)</td>
<td>26 (46%)</td>
</tr>
<tr>
<td>Left</td>
<td>20 (47%)</td>
<td>31 (54%)</td>
</tr>
</tbody>
</table>

Figure 6: Line graph illustrating the mean Harris hip score during the study period according to treatment.
Table 2: Number of reoperations.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Total hip arthroplasty</th>
<th>Internal fixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed reduction*</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Screw extraction</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Excision arthroplasty</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Secondary arthroplasty</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Periprosthetic fracture</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Aseptic loosening</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Deep infection</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Total number reoperations 13               40
Major hip reoperation* 4 (9%) 22 (39%)
Any hip reoperationb 10 (23%) 30 (53%)

All reoperations counted, more than one event may be counted for each hip.
*One patient dislocated 4 times and five patients dislocated once.
a Defined as revision of THA components, open reduction and osteosynthesis due to periprosthetic fracture, THA as a secondary or tertiary procedure, and excision arthroplasty.
b Including all reoperations, all major reoperations, closed reduction, screw removal and surgical debridement.

Figure 7: Line graph of cumulative reoperation rate during the study period.
Table 3: Proportion of patients fully independent in activities of daily living according to treatment.

<table>
<thead>
<tr>
<th></th>
<th>THA No. 43</th>
<th>IF No. 57</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100% (43 of 43)</td>
<td>100% (57 of 57%)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>85% (33 of 39)</td>
<td>64% (33 of 52)</td>
<td>0.03</td>
</tr>
<tr>
<td>1 year</td>
<td>88% (33 of 40)</td>
<td>70% (35 of 50)</td>
<td>0.05</td>
</tr>
<tr>
<td>2 years</td>
<td>87% (33 of 38)</td>
<td>78% (35 of 45)</td>
<td>0.3</td>
</tr>
<tr>
<td>4 years</td>
<td>82% (28 of 34)</td>
<td>73% (33 of 45)</td>
<td>0.3</td>
</tr>
<tr>
<td>11 years</td>
<td>82% (14 of 17)</td>
<td>79% (11 of 14)</td>
<td>0.8</td>
</tr>
<tr>
<td>17 years</td>
<td>80% (4 of 5)</td>
<td>71% (5 of 7)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Study II

Patient flow and baseline data
Between February 2012 and June 2014, 346 patients with a FNF were admitted to the Orthopaedic Department at Sundsvall Hospital, Sweden. Of these, 185 hips (183 patients) met the inclusion criteria [mean age 84.4 years (range, 66-99 years), 128 female, 55 men] and were recruited into the study (Figure 8). The group characteristics were similar at baseline (table 4).

Operative data
Fifteen consultants and 7 registrars performed the DL approach while 16 consultants and 6 registrars performed the PL approach (DL versus PL; consultants/registrars: 42.2% versus 19.3%). The DL and PL group characteristics were similar at baseline (Table 1). Duration of surgery and blood loss was greater in the DL group (table 4).

Patient outcome measurements
We did not find any difference between the groups regarding WOMAC, HHS and PNRS, also when adjusting for confounders (Table 5 and 6). The only factor affecting HHS, WOMAC and PNRS was present cognitive dysfunction (Table 6). We found a significant increased risk for postoperative limp in the DL group (adjusted OR; 2.97, 95% CI 1.32 to 6.67, p=0.008) (table 7).

Mortality
The mortality was high regardless of surgical approach. Seventy-two (39.3%) of the patients died during the study period with no statistically significant difference between the groups (log rank test, p=0.43).

Hip complications and re-operations
Twenty four (12.9%) hips required re-operation at least once including closed reduction due to dislocation. The rate of reoperation was lower in the DL group compared to the PL group (9 hips (8.8%) vs. 15 (18.1%)). This difference did not reach statistical significance when adjusted for confounders; (Adjusted OR 0.42; 95% CI, 0.16 to 1.11; p=0.08) (Table 7). In the DL group 7 patients (6.9%) and 11 patients (13.3%) in the PL group had undergone a major re-operation (Adjusted OR 0.51; 95% CI, 0.18 to 2.07; p=0.23) (Table 8). The most frequent complications in the DL group were infection (n=5) and dislocation (n=3, recurrent dislocation n=1). In the PL group, infection (n=6) and dislocation (n=7, recurrent dislocation n=5) were the two most common hip complications.
Assessed for eligibility (n=346)

Undisplaced FNF treated with internal fixation (n=79)

Displaced FNF (n=267)

Other treatment (n=48)
- Internal fixation (n=44)
  - Medical condition (n=41)
  - Wound (n=3)
- Excision arthroplasty (n=4)
  - Medical condition (n=4)

Total number of Hip replacement (n=219)

Total hip arthroplasty (n=29)
- Tripolar cup (n=3)
- Pathological fracture (n=2)

Included (n=185)

Enrollment

Direct lateral approach (n=102)
- Number of patients (n=101)

Posterolateral approach (n=83)
- Number of patients (n=82)

Follow-Up

Direct lateral approach (n=76)
- Deceased (n=26)
- Lost to follow-up (n=0)

Posterolateral approach (n=58)
- Deceased (n=24)
- Lost to follow-up (n=1)

Figure 8. Flow of patients in study 2.
Table 4: Study population characteristics. Continuous variables are presented as mean and standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Direct lateral</th>
<th>Posterolateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. 102</td>
<td>No. 83</td>
</tr>
<tr>
<td>Age</td>
<td>83.5 (±6.4)</td>
<td>85.51 (±6.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (33.3%)</td>
<td>22 (26.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (66.7%)</td>
<td>61 (73.5%)</td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>55 (46.1%)</td>
<td>36 (43.4%)</td>
</tr>
<tr>
<td>Left</td>
<td>47 (53.9%)</td>
<td>47 (56.6%)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>45 (44.1%)</td>
<td>41 (49.4%)</td>
</tr>
<tr>
<td>3-4</td>
<td>57 (55.9%)</td>
<td>42 (50.6%)</td>
</tr>
<tr>
<td>SPMSQ</td>
<td>6.22 (±3.64)</td>
<td>6.18 (±3.36)</td>
</tr>
<tr>
<td>WOMAC</td>
<td>90.0 (±13.9)</td>
<td>89.9 (±12.3)</td>
</tr>
<tr>
<td>Harris Hip score</td>
<td>81.5 (±13.1)</td>
<td>82.1 (±11.2)</td>
</tr>
<tr>
<td>PNRS</td>
<td>1.37 (±1.12)</td>
<td>1.44 (±1.09)</td>
</tr>
</tbody>
</table>

Table 5: Outcome variables. Presented as mean and standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Direct lateral</th>
<th>Posterolateral</th>
<th>Mean dif.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. 76</td>
<td>No. 58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris hip score</td>
<td>71 (±18)</td>
<td>72 (±17)</td>
<td>0.85</td>
<td>-5.3 to 6.9</td>
</tr>
<tr>
<td>WOMAC total</td>
<td>79 (±22)</td>
<td>79 (±24.0)</td>
<td>-0.16</td>
<td>-8.2 to 7.8</td>
</tr>
<tr>
<td>PNRS</td>
<td>2.1 (±2.2)</td>
<td>2.0 (±1.7)</td>
<td>-0.15</td>
<td>-0.8 to 0.5</td>
</tr>
<tr>
<td>Bloodloss</td>
<td>254 (±141)</td>
<td>239 (±186)</td>
<td>-14.7</td>
<td>-63 to 33</td>
</tr>
<tr>
<td>Surgical time</td>
<td>90 (±21)</td>
<td>66 (±18)</td>
<td>-23</td>
<td>-29 to -18</td>
</tr>
</tbody>
</table>
Table 6: Outcome variables. Linear regression including adjusted variables for HHS and WOMAC.

<table>
<thead>
<tr>
<th>Variable</th>
<th>WOMAC Coef</th>
<th>2.5 % to 97.5 %</th>
<th>HHS Coef</th>
<th>2.5 % to 97.5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterolateral</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Direct lateral</td>
<td>-1.25</td>
<td>-9.02 to 6.53</td>
<td>N.S</td>
<td>-1.67</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Resident</td>
<td>-0.569</td>
<td>-8.89 to 7.75</td>
<td>N.S</td>
<td>0.68</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Yes</td>
<td>-12.68</td>
<td>-20.47 to -4.90</td>
<td>p=0.002</td>
<td>-7.89</td>
</tr>
<tr>
<td>Age</td>
<td>-0.51</td>
<td>-1.13 to 0.11</td>
<td>N.S</td>
<td>-0.07</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Female</td>
<td>5.45</td>
<td>-3.09 to 13.99</td>
<td>N.S</td>
<td>2.19</td>
</tr>
<tr>
<td>ASA 1-2</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>ASA 3-4</td>
<td>-3.63</td>
<td>-11.43 to 4.18</td>
<td>N.S</td>
<td>-2.12</td>
</tr>
</tbody>
</table>

Table 7: Postoperative limp. Logistic regression presenting adjusted odds ratio.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Limp Coef</th>
<th>2.5 % to 97.5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterolateral</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Direct lateral</td>
<td>3.07</td>
<td>1.35 to 6.99</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Resident</td>
<td>0.73</td>
<td>0.31 to 1.69</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.88</td>
<td>0.87 to 4.10</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.95 to 1.01</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Female</td>
<td>0.73</td>
<td>0.30 to 1.73</td>
</tr>
<tr>
<td>ASA 1-2</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>ASA 3-4</td>
<td>0.56</td>
<td>0.27 to 1.31</td>
</tr>
<tr>
<td>Leg length discrepancy</td>
<td>0.98</td>
<td>0.92 to 1.01</td>
</tr>
</tbody>
</table>
Table 8: Hip complication and reoperation.

<table>
<thead>
<tr>
<th>hip complications</th>
<th>Direct lateral (n=102)</th>
<th>Posterolateral (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dislocation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent dislocation</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Deep infection</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Acetabular erosion</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wound rupture</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Periprosthetic fracture</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Number of hips with any complication</strong></td>
<td><strong>9 (8.8%)</strong></td>
<td><strong>15 (18.1%)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hip re-operations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed reduction due to dislocation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>THA with dual mobility cup or excision arthroplasty due to dislocation</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Surgical debridement due to deep infection</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Excision arthroplasty due to deep infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Open reduction and internal fixation of periprosthetic fracture</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Secondary total hip arthroplasty due to acetabular erosion</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Secondary suture due to wound rupture</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Number of hips with any major re-operation</strong></td>
<td><strong>7 (6.9%)</strong></td>
<td><strong>11 (13.3%)</strong></td>
</tr>
<tr>
<td><strong>Number of hips with any re-operation</strong></td>
<td><strong>9 (8.8%)</strong></td>
<td><strong>15 (18.1%)</strong></td>
</tr>
</tbody>
</table>

No. (%) are presented.

a Adjusted OR 0.42; 95% CI, 0.16 to 1.11; p=0.08.

b Adjusted OR 0.51; 95% CI, 0.18 to 2.07; p=0.23.

c Adjusted OR 0.42; 95% CI, 0.16 to 1.11; p=0.08.
Study III

Patient flow and baseline data
Between January 2006 and December 2013, 511 hips with a FNF were admitted to the Orthopaedic Department at Sundsvall Hospital, Sweden. Of these, 49 hips were excluded due to low-quality postoperative radiographs. Three hundred and twenty eight hips met the inclusion criteria [mean age 84 years (SD 6)] and were recruited into the study (Table 9). There were no differences between the single and recurrent dislocation groups and their controls regarding one-year mortality, ASA classes or altered mental status.

Hip complications and re-operations
During the study period 40 (10.7%) hips dislocated at least once. The incidence of dislocation was 10.7% (40/373), 18 men and 22 women with mean age of 82 years (SD 6). The mean time from surgery to the first dislocation was 3.9 months (range 0-47 months). Dislocations occurred within the first six months of surgery, except for four late dislocations that occurred at between one to four years postoperatively. Of the dislocated hips, 37.5% (n=15) experienced one dislocation and 62.5% (n=25) had recurrent dislocations.

Outcome
In comparison with the remaining cohort, patients with dislocation had smaller postoperative global FO, shorter operated leg, and lower Wiberg angle (Table 8). Patients with dislocation had a higher one-year mortality (30 % vs. 16 %, p=0.04) and were more prone to have altered mental status (33 % vs. 21 %, p=0.04). There were no differences regarding age, sex or ASA classes between the two groups (Table 9). In comparison with age and sex-matched controls, patients with single dislocations had no differences in postoperative global FO, LLD and Wiberg angle (Table 10). To the contrary, patients with recurrent dislocations had a significantly smaller global FO, shorter operated leg and lower Wiberg angle on the operated side compared with age and sex-matched controls (Table 11).
Table 9: Study population characteristics. Continuous variables are presented as mean and standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Cohort No. 288</th>
<th>Dislocation No. 40</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>84 (±6)</td>
<td>82 (±6)</td>
<td>0.18</td>
</tr>
<tr>
<td>1 year mortality</td>
<td>16 %</td>
<td>30 %</td>
<td>0.04</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>21 %</td>
<td>33 %</td>
<td>0.04</td>
</tr>
<tr>
<td>Global FO (mm)</td>
<td>-2.8 (11)</td>
<td>-6.4 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>LLD (mm)</td>
<td>1.5 (8)</td>
<td>-2.0 (7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Wiberg angle (°)</td>
<td>46 (7)</td>
<td>40 (6)</td>
<td>0.01</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>55 %</td>
<td>52 %</td>
<td>0.80</td>
</tr>
<tr>
<td>3-4</td>
<td>45 %</td>
<td>48 %</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Comparison of the study findings between the single dislocation group and their age and sex matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Controls No. 40</th>
<th>Dislocation No. 15</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year mortality</td>
<td>16 %</td>
<td>35 %</td>
<td>0.10</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>33 %</td>
<td>35 %</td>
<td>0.80</td>
</tr>
<tr>
<td>Global FO (mm)</td>
<td>-4.5 (10)</td>
<td>-3.8 (12)</td>
<td>0.80</td>
</tr>
<tr>
<td>LLD (mm)</td>
<td>0.8 (8)</td>
<td>-0.5 (7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Wiberg angle (°)</td>
<td>45.5 (8)</td>
<td>42.8 (6)</td>
<td>0.20</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>60 %</td>
<td>43 %</td>
<td>0.15</td>
</tr>
<tr>
<td>3-4</td>
<td>40 %</td>
<td>57 %</td>
<td></td>
</tr>
</tbody>
</table>

Controls=age and sex-matched controls
Table 11: Comparison of the study findings between the single dislocation group and their age and sex matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Controls No. 88</th>
<th>Recurrent No. 25</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year mortality</td>
<td>21 %</td>
<td>32 %</td>
<td>0.02</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>25 %</td>
<td>40 %</td>
<td>0.03</td>
</tr>
<tr>
<td>Global FO (mm)</td>
<td>-3 (9)</td>
<td>-8 (9)</td>
<td>0.04</td>
</tr>
<tr>
<td>LLD (mm)</td>
<td>1.75 (7)</td>
<td>-2.12 (6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Wiberg angle (°)</td>
<td>46.2 (7)</td>
<td>38.8 (5)</td>
<td>0.01</td>
</tr>
<tr>
<td>ASA 1-2</td>
<td>57 %</td>
<td>60 %</td>
<td>0.7</td>
</tr>
<tr>
<td>ASA 3-4</td>
<td>43 %</td>
<td>40 %</td>
<td></td>
</tr>
</tbody>
</table>

Controls=age and sex-matched controls


**Study IV**

**Patient flow and baseline data**
Between October 2009 and May 2015, 840 patients, 80 years and above, with a displaced FNF were admitted to the Orthopaedic Department at Danderyd Hospital, Stockholm, Sweden. Of these, 267 patients [76% females, mean age 87 (SD 4.7)] met the inclusion criteria and were included in the study (Figure 9). The group characteristics at baseline were similar but the NC and MS group were slightly older and had a higher proportion of patients in ASA grade 3-4 (Table 12).

**Operative data**
Duration of surgery was longer and a greater number of THA were performed in the RCT group.

**Primary end point**
We did not find any difference between the groups regarding HHS and EQ-5D, also when adjusting for confounders (Table 13). There was complete follow-up for 61 patients in the RCT group, 19 in the NC group and 41 in the MS.

**Mortality**
The mortality was high regardless of the group they belonged to and 84 (31.5%) of the patients died during the study period. There was a statistically significant difference between the three groups (p=0.047) as the non-consenter group had a higher risk of death than those included (HR 2.06, 95% CI 1.13 to 3.75) (Figure 10, Table 14).

**Hip complications and re-operations**
Seventeen (6.4%) hips required re-operation at least once including closed reduction due to dislocation. The rate of reoperation was lower in the MS group compared to the RCT and NC groups (4.1% vs 7.6% vs 9.3% respectively). This difference did not reach statistical significance when adjusting for confounders; (adjusted OR 1 vs 1.9 vs 2.4, total p=0.38, MS vs NC p=0.18, MS vs RCT p=0.29).
Figure 9: Flow of patients in Study IV.

Total population of patients with a displaced femoral neck fracture 80 years and above (n=840)

Did not fulfill the inclusion criteria (n=427)
- Osteoarthritis (n=13)
- Rheumatoid arthritis (n=2)
- Poor medical condition (n=142)
- Pathologic fracture (n=9)
- Non-swedish speaking (n=17)
- Non-walker (n=16)
- Fracture >36h (n=31)
- Psychiatric disorder (n=11)
- Cognitive dysfunction (n=288)
- By other reasons not suitable for inclusion (n=44)

Allocation (n=267)

Asked for informed consent (n=146)
- Included (n=92)
  - Follow-up (61)
- Non-consenters (n=54)
  - Follow-up (19)

Missed in screening (n=121)
- Follow-up (n=41)
Table 12: Study population characteristics. Continuous variables presented as mean and standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Included No. 92</th>
<th>Non-Consenters No. 54</th>
<th>Missed in screening No. 121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>85.6 (±3.6)</td>
<td>87.4 (±4.5)</td>
<td>87.9 (±4.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (23%)</td>
<td>12 (22%)</td>
<td>30 (25%)</td>
</tr>
<tr>
<td>Female</td>
<td>71 (77%)</td>
<td>42 (78%)</td>
<td>91 (75%)</td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>37 (40%)</td>
<td>22 (41%)</td>
<td>46 (38%)</td>
</tr>
<tr>
<td>Left</td>
<td>55 (60%)</td>
<td>32 (59%)</td>
<td>75 (62%)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>40 (44%)</td>
<td>18 (33%)</td>
<td>33 (27%)</td>
</tr>
<tr>
<td>3-4</td>
<td>52 (56%)</td>
<td>36 (67%)</td>
<td>88 (73%)</td>
</tr>
<tr>
<td>THA</td>
<td>40 (44%)</td>
<td>5 (9%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>HA</td>
<td>52 (56%)</td>
<td>47 (87%)</td>
<td>113 (93%)</td>
</tr>
<tr>
<td>IF</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>1 (%)</td>
</tr>
<tr>
<td>Surgical time</td>
<td>88 (SD 26)</td>
<td>84 (SD 23)</td>
<td>81 (SD 24)</td>
</tr>
</tbody>
</table>

Table 13: ANCOVA analysis of patient reported outcome variables. Adjusted means and 95% CI (adjusted for age, sex and ASA category 1-2 or 3-4) for HHS and EQ-5D

<table>
<thead>
<tr>
<th></th>
<th>Included No. 61</th>
<th>Non-consenter No.19</th>
<th>Missed No.41</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS at 1 year</td>
<td>65 (SD 14.4)</td>
<td>65 (SD 16.6)</td>
<td>64 (SD 64.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>EQ-5D at 1 year</td>
<td>0.66 (SD 0.29)</td>
<td>0.71 (SD 0.18)</td>
<td>0.58 (SD 0.34)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Table 14: Mortality. Cox proportional Hazard including adjusted variables and presented as hazard ratio.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (267)</th>
<th>Mortality rate (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT group</td>
<td>92</td>
<td>22</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Non-consenter</td>
<td>54</td>
<td>46</td>
<td>2.1 (1.2 – 3.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>Missed</td>
<td>121</td>
<td>32</td>
<td>1.5 (0.9 – 2.7)</td>
<td>0.133</td>
</tr>
<tr>
<td>Age</td>
<td>267</td>
<td>n.a</td>
<td>1.1 (1.0 – 1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>44</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>204</td>
<td>28</td>
<td>0.53 (0.5 – 0.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>ASA 1–2</td>
<td>91</td>
<td>19</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>ASA 3–4</td>
<td>176</td>
<td>38</td>
<td>2.2 (1.3 – 3.8)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Figure 10: Cox proportional hazards regression for survival in the different groups adjusted for age, sex and ASA category.
Discussion

Discussion of methods

Study design

Study I was conducted as an RCT, which is the main strength of the study along with the long-term follow-up of seventeen years and the use of intention-to-treat analysis. When the long-term follow-ups were initiated there were few publications analyzing a comparison between IF and THA over one to two decades. This continuing follow-up is important because of the increasing lifespan of patients with a FNF.

Patients were initially randomized using sealed opaque envelopes. However, due to difficulties with hospital logistics related to the lack of theatre staff with THA experience at the weekends, a change in allocation routines was implemented. The first 20 patients were randomized according to the initial protocol. The following eighty patients were allocated to treatment according to which weekday they were admitted. Patients who were admitted on Monday to Thursday were managed with THA and those who were admitted from Friday to Sunday were managed with IF. This flaw in the randomization process is a limitation of this study. When the study was designed in the beginning of the 1990’s, this type of allocation was accepted as a randomization procedure. However, currently this would be considered as stratification rather than a RCT.

This methodological flaw could have introduced inequalities between the groups and resulted in fewer patients receiving THA. It also resulted in a greater proportion of patients being allocated to IF performed by registrars. However, we analyzed our primary end point with ANCOVA and included covariates (age, sex and surgeon experience) to adjust for these inequalities. In addition, the radiographic results in the IF group were no worse following operations performed by registrars as compared with consultants.

It is also important to note that our trial focused on a very select group of healthy, cognitively intact patients with a FNF. More than eleven patients were screened for each patient who was included in the study. The reason for these strict inclusion criteria was to study only the function of the intervention; we therefore excluded all patients who had diminished walking ability due to comorbidities or other degenerative joint disease before the fracture. Due to this selection of patients, the generalizability of this study to the general population with FNF will be modest.
At the time of initiation of the study, no formal power analysis had been performed and the power analysis relied on an interim analysis that was performed at the one-year follow-up based on the HHS. This limitation may have underpowered the long-term results of this study. However, the differences between the groups were significant according to our statistical analysis.

During the course of the study, results from a number of RCTs with long-term follow-up were published comparing IF and THA in FNF patients (Leonardsson et al. 2010, Johansson 2014).

Study II was conducted as a prospective cohort study. When this study was initiated, there were no publications in a modern setting focusing on hip function after FNF with the regard to surgical approach. Our hypothesis was that there would be no clinically relevant difference between the DL and the PL approach.

We did not randomize the patients and the surgeon-on-call decided the approach he/she preferred. We chose this method to minimize the bias caused by the fact that few general orthopaedic surgeons serving on-call have the experience and perform the volume of procedures to be equally familiar with the two main approaches for hip arthroplasty. The allocation to the treatment arms by using surgeons’ preference inevitably risks selection bias and systematic differences in outcomes that are not due to the intervention. These could either under or overestimate the impact of surgical approach on the primary outcome variable. These differences may not be detected in the baseline data even though we did not find any difference between the groups.

The effect of type of surgical approach is difficult to access in a RCT. The optimal design for this is probably an RCT with randomization by surgeon. However, an RCT with randomization by surgeon may result in high cost because FNF is an acute procedure performed by surgeons on call. To avoid selection bias during the study, we included all patients consecutively regardless of surgical approach despite including different numbers of patients in each group. We did not find any differences in baseline data between the groups. The sample size was calculated but it is underpowered to detect any smaller difference than 10 points (SD 18) in HHS. The wide inclusion criteria may diminish the difference between the surgical approaches, and may be more pronounced in subgroups of patients.

The follow-up time of 1-year is relatively short. However, the short-term follow up is the most important in FNF patients owing to their high complication rate and mortality during the first postoperative year. To avoid loss to follow-up that may have occurred if a postal questionnaire had been used we performed a telephone interview at 1-year follow-up (Leonardsson et al. 2013). An independent nurse, blinded to the surgical approach used, conducted the follow-up in all patients.
thereby minimizing potential bias. These factors improve the generalizability of the results together with the prospective observational cohort design with consecutive patients, adequate sample size and minimal dropout.

During the course of Study II, results from a RCT with FNF patients and two registry studies had been published comparing the DL and the PL approaches in OA patients (Lindgren et al. 2014, Amlie et al. 2014, Parker 2015).

Study III was conducted as a retrospective cohort study. A consecutive series of patients treated with bipolar HA were included and a case-control sub-analysis of patients with single and recurrent dislocation was performed. This study was initiated on the basis of the results published by Ninh et al (2009) and Madanat et al. (2012). The retrospective design is flawed by inherited bias and confounding factors. But this study served as a hypothesis finding study and our results remain to be scrutinized in larger prospective cohort studies as published by Wallner et al. (2014).

Studies based on radiographic outcomes are not possible to perform in a RCT and up to this date are not feasible in a registry based setting. Due to the general condition of the included patients we could not standardize the postoperative radiographs in all patients. Therefore we had a small group of patients with low-quality radiographs that were excluded.

The main strength of this study was the inclusion of a consecutive series of an homogenous cohort of patients, with consistent follow-up using the unique Swedish 10 digits civil ID number. This allowed us to identify all cases and detect all complications and reoperations during the follow-up time. Due to the fact that all patients between 2006 and September 2013 were included consecutively in the study, the generalizability of the results to emergency hospitals with similar case volume is valid. Large studies based on registries are fundamental for studying risk factors for dislocation regarding patient characteristics, but radiological studies are not feasible in large registry studies.

Study IV was conducted as a prospective cohort study. When this study was initiated there were no publications on EV in the field of FNF. The study design had several advantages. It was based on a large well defined prospective RCT. Data was added from the Swedish Death Register and the Swedish Hip Arthroplasty Register, which are regarded as being complete. The design included three groups differentiated by their status in the RCT (RCT, NC, MS). A similar study design was used in a previously published study (Petersen et al. 2007). Patients in the NC and MS groups are important to evaluate due to the fact that the results in the RCT study are extrapolated to these patients. If the results in these groups differ from those included, one could question the EV of the study.
A prospective cohort study is, in the opinion of the author, the best possible design to address the EV of an RCT. The limitations of this study include the relatively low number of patients due to the high number of deceased patients and patients lost to follow-up. However, to detect a difference between the groups in the HHS would require a very large sample size and would not be feasible in the present setting.

During the course of Study IV, there were no publications regarding EV of a RCT including patients with FNF. This is the main strength of this study.

Outcome measurements

In Studies I and IV the primary outcome measure was the widely used HHS, which has been validated for patients with a FNF (Frihagen et al. 2008). The HHS has been reported to have good construct validity when used for evaluation of THA in the treatment of patients with OA (Söderman and Malchau, 2001, Shi et al. 2009). However, there are 5 important psychometric features in the evaluation of a questionnaire. Alongside construct validity, reliability, internal consistency, content validity, responsiveness and internal consistency are also important (Terwee et al. 2007). The HHS has been found to have a poor content validity due to ceiling and floor effects in patients with OA (Wamper et al. 2010). Therefore a high number of patients with high or low scores may limit the usefulness of the HHS. The ability of an outcome measure to detect clinically relevant improvements between studied treatments is important. Ceiling effects may hide or erase clinically relevant differences when patients already score the maximum or minimum possible score and are not able to change the score. The Oxford 12-item questionnaire and the HOOS (Hip disability and Osteoarthritis Outcome Score) have been reported to have good properties in this respect (Ostendorf et al. 2004, De Groot et al. 2009). When study I was initiated, other patient reported scoring systems such as the WOMAC or the HOOS were not available or not in clinical use at this department (Bellamy et al. 1988, Klässbo et al. 2003).

Secondary end points included mortality, reoperations, gait speed, and activities of daily living. These parameters were chosen to give a diversity of PRO beside the hard outcomes of complications and mortality. To assess the influence of their injury and to recover baseline data regarding hip function and cognitive function (WOMAC, HHS, PNRS and SPMSQ), patients were asked to report their pre-fracture status when they were included in studies I and II. The patients’ ability to correctly evaluate this in the aftermath of acute surgery is questionable. Due to the impossibility of data collection in a prospective manner, this method is generally used in studies of hip fracture patients (Rogmark et al. 2002, Tidermark et al. 2003, Blomfeldt et al. 2005).
In study II the primary outcome measure was HHS modified HHS is a well-known and used PRO (Mahomed 2001, Rogmark and Johnell 2006, Frihagen 2008). The secondary outcome measure was WOMAC, which recently has been validated for FNF patients (Burgers 2015). WOMAC has been used in a number of trials with hip fracture patients (Macaulay et al. 2008, Sanz-Reig et al. 2012, Zielinski et al. 2014). At present, no gold standard exists for functional evaluation of FNF patients and WOMAC was chosen because of its common use in different hip disease populations (Nilsdotter and Bremander 2011). Secondary end points included postoperative limping, residual hip pain measured with a PNRS, mortality and reoperations. These parameters were chosen to give a diversity of widely used PRO beside the hard outcomes of complications and mortality.

In study III the primary outcome measures were global FO, LLD and Wiberg angle. These radiological measurements have not been previously validated in FNF patients. However, in the evaluation of FO and LLD, the same landmarks and the same measurements have been validated on patients with THA due to OA (Kjellberg et al. 2009, Mahmood et al. 2014). Wallner et al. (2014) used these measurements in a recent study including FNF patients. We were not able to collect a complete set of baseline data to mount a trustworthy regression analysis of possible confounding factors.
Discussion of results

Study I

In a RCT of 100 healthy, cognitively normal patients sixty-five years and older with a displaced FNF and good pre-injury hip function, in the long term, primary THA provided better hip function and significantly fewer reoperations than IF, without increasing mortality.

The short term results of our study are consistent with the results of previous published studies in which patients who were allocated to THA had lower reductions of both hip function and quality of life as compared with those who were allocated to IF (Johansson et al. 2000, Davison et al 2001, Rogmark et al 2002, Tidermark et al. 2003, Blomfeldt et al. 2005, Keating et al 2005, Rogmark and Johnell 2006, Heetveld et al. 2009)(Table 15).

Between four and seventeen years the differences between the groups was less pronounced, probably because of the aging of the cohort and because a large proportion of those who received IF underwent conversion to a THA. To our knowledge, there have been only three published long-term follow-up studies comparing THA and IF (Ravikumar, Marsh 2000, Leonardsson et al. 2010, Johansson 2014). These studies included a greater number of patients than our study. Ravikumar and Marsh evaluated hip function using the HHS and found that THA yielded a superior result over IF at thirteen years. Leonardsson et al., in their ten-year follow-up study, did not use a standardized form to evaluate function but drew the conclusion that there was no significant long-term difference between the groups in terms of hip pain, reduction of mobility, the need for walking aids, and the ability to return to or remain in their pre-fracture accommodation. Johansson did not use any PRO.

In terms of complications and revision surgery, Ravikumar and Marsh, Leonardsson et al. and Johansson reported revision rates of 6.8%, 8.8% and 5.0%, respectively for THA and 33%, 46.6% and 55%, respectively for IF. These results are consistent with our findings. The secondary outcome measurements favored the group treated with THA except that there was no difference in mortality between the groups. Patients who were managed with THA also had less pain in the involved hip over the long term.

Since the early 1990s when this study was initiated, there have been many improvements in THA that have increased implant life span and reduced the risk of complications and need for revision surgery. In this study the PL approach without capsular repair and a polished tapered titanium stem with 22mm head was used.
The PL approach has been linked to an increased risk for dislocation and revision surgery in comparison to the DL approach (Enocson et al. 2008, Sköldenberg et al. 2010, Haider et al. 2012). The dislocation rate has been similar to ours and was reduced by a change in routine from the PL to the DL approach (Enocson et al 2008, Sköldenberg et al. 2010). The use of larger femoral head sizes (32-36mm) has been shown to reduce the need for revision surgery due to dislocation (Haider et al. 2012). The cemented, straight, collarless, polished and tapered femoral stem of titanium alloy used in this study is a less than optimal cemented femoral component. Studies have shown superior results with less incidence of aseptic loosening for cobalt-chromium as opposed to titanium-alloy stems when used with bone cement (Maurer et al. 2001, Kovac et al. 2006). Two recent studies have indicated an increased risk of periprosthetic fractures in elderly patients treated with two similar cemented polished, straight, tapered and collarless femoral stems used in our study (Inngul and Enocson. 2014, Brodén et al. 2015). This femoral stem is no longer used at our institution. However, in the present study, the incidence of aseptic loosening of the prosthesis or periprosthetic fracture after primary THA was not greater than the rates in previously reported long-term studies of patients with OA (Lucht 2000, Malchau et al. 2002). The above-mentioned improvements have most certainly increased the differences in PRO and reoperation rates between primary THA and IF.

Table 15: Randomized controlled trials comparing hip arthroplasty and IF. Study I in the bottom for comparison.

<table>
<thead>
<tr>
<th>Authors</th>
<th>year</th>
<th>n</th>
<th>age</th>
<th>FU (yr)</th>
<th>Op</th>
<th>Outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson et al.</td>
<td>2000</td>
<td>100</td>
<td>84</td>
<td>2</td>
<td>THA/IF</td>
<td>PROM, Reop</td>
<td>THA</td>
</tr>
<tr>
<td>Parker et al.</td>
<td>2000</td>
<td>208</td>
<td>81</td>
<td>3</td>
<td>HA/IF</td>
<td>PROM, Reop</td>
<td>HA</td>
</tr>
<tr>
<td>Ravikumar, Marsch</td>
<td>2000</td>
<td>290</td>
<td>X</td>
<td>13</td>
<td>THA/HA/IF</td>
<td>PROM, Reop</td>
<td>THA</td>
</tr>
<tr>
<td>Davidson</td>
<td>2001</td>
<td>280</td>
<td>X</td>
<td>3</td>
<td>HA/IF</td>
<td>PROM, Reop</td>
<td>ND</td>
</tr>
<tr>
<td>Parker et al.</td>
<td>2002</td>
<td>455</td>
<td>X</td>
<td>3</td>
<td>HA/IF</td>
<td>PROM, Reop</td>
<td>HA</td>
</tr>
<tr>
<td>Rödén et al.</td>
<td>2003</td>
<td>96</td>
<td>81</td>
<td>5</td>
<td>HA/IF</td>
<td>Reop</td>
<td>HA</td>
</tr>
<tr>
<td>Blomfeld et al.</td>
<td>2005</td>
<td>102</td>
<td>80</td>
<td>4</td>
<td>THA/IF</td>
<td>PROM, Reop</td>
<td>THA</td>
</tr>
<tr>
<td>Keating et al.</td>
<td>2006</td>
<td>207</td>
<td>75</td>
<td>2</td>
<td>THA/HA/IF</td>
<td>PROM, Reop</td>
<td>THA/HA</td>
</tr>
<tr>
<td>Leonardsson et al.</td>
<td>2010</td>
<td>450</td>
<td>X</td>
<td>10</td>
<td>THA/IF</td>
<td>PROM, Reop</td>
<td>THA</td>
</tr>
<tr>
<td>Støen et al.</td>
<td>2014</td>
<td>222</td>
<td>83</td>
<td>6</td>
<td>HA/IF</td>
<td>PROM, Reop</td>
<td>HA</td>
</tr>
<tr>
<td>Johansson</td>
<td>2014</td>
<td>146</td>
<td>84</td>
<td>15</td>
<td>THA/IF</td>
<td>Reop</td>
<td>THA</td>
</tr>
<tr>
<td><strong>Chammout et al.</strong></td>
<td><strong>2012</strong></td>
<td><strong>100</strong></td>
<td><strong>78</strong></td>
<td><strong>17</strong></td>
<td><strong>THA/IF</strong></td>
<td><strong>PROM, Reop</strong></td>
<td><strong>THA</strong></td>
</tr>
</tbody>
</table>

n : number of patients  
age : mean age at surgery  
FU: mean follow-up time in years  
Outcome: PROM (Patient Reported Outcome Measurement), Reoperations  
ND: No difference
Study II

In this prospective cohort study, patients treated with HA for FNF using either the DL or PL approaches had comparable PRO after 1 year. The PL approach had a higher re-operation rate while the DL approach resulted in a higher incidence of limping.

The short-term results of our study are one of the first comparing PRO between the DL and PL approach in patients with FNF treated with HA (Mukka and Sayed-Noor 2014, Parker 2015). The insignificant differences in the primary outcome variable are small and most likely not clinically relevant. This may reflect the fact that surgical approach is just one factor affecting the overall outcome in this frail and elderly population with a high general burden of disease. However, prospective trials comparing surgical approaches in patients with OA, with comparable sample sizes to this study, have failed to show any difference. Larger registry studies may show that differences exist (Downing et al. 2001, Jolles and Bogoch. 2006, Palan et al. 2009, Lindgren et al. 2014, Amlie et al. 2014, Jameson et al. 2014). The incidence and factors affecting complications, reoperations and the need for revision surgery for patients with FNF treated with HA are well documented in the literature (van den Bekerom et al. 2013, Rogmark et al. 2014)(Table 16).

There are two RCTs that compared functional outcome between the two approaches in FNF patients (Sikorski and Barrington 1981, Parker 2015). Sikorski and Barrington (1981) performed a study comparing internal fixation with HA either through the DL or PL approach. This study randomised 114 patients to either a DL or PL approach using a cemented Thompson prosthesis. There was a tendency towards better functional results in the PL approach. However, there was a difference in the postoperative mobilization and medical complications between the two groups and the authors recommended the DL approach due to a decreased mortality. More recently, Parker (2015), published a study in patients treated with a HA after FNF. Patients were randomized to the DL or PL approach and the author did not find any difference in functional outcome or complications. However, the author either performed or supervised all procedures and patients that were operated on by others were excluded. This might introduce a performance bias that limits the generalizability of the obtained results.

A subgroup analysis was performed comparing the frequency of patient-reported limping at the one year follow-up and found a significant increased risk for those operated using the DL approach. This is a well-known complication due to severing of the gluteus medius muscle and the resulting abductor weakness with Trendelenburg gait. However, this gait disturbance did not affect the overall functional outcome of the DL approach. This may be linked with the relatively low functional demands of this specific category of elderly patients. Younger and more active patients, in Sweden primarily treated with THA may be more affected by this deficit.
The cohort studies by Enocson et al. (2008), Sköldenberg et al. (2010) and Biber et al. (2012) included a greater number of patients than our study did (table 14). However, the study by Enocson et al. included a mix of HA, monoblock, bipolar and unipolar prosthesis. Sköldenberg et al. included both HA and THA as primary and secondary procedures. The retrospective analysis published by Biber et al. included a record of complications. In these studies, no evaluation of functional outcome or quality of life was included. Keene and Parker (1993) reported an increased risk for thrombosis via the PL approach and an increased blood loss, surgical time and rate of postoperative infection linked to the DL approach. In our study, we had comparable blood loss and postoperative infection rate in the two approaches, while the surgical time was longer in the DL approach.

There was a tendency towards a higher risk of major reoperation in the PL group and a contributing factor was the higher rate of reoperation due to recurrent dislocation (1 DL vs. 6 PL hips). This difference might be related to the mechanism of dislocation in the two approaches. In the DL approach, dislocation is provoked by excessive extension and external rotation which is more difficult to achieve in comparison to dislocation after the PL approach which usually occurs with increased flexion and internal rotation associated with sitting or leaning forward.

Table 16: Studies comparing direct lateral and posterolateral approach for FNF treated with hip arthroplasty. Study II in the bottom for comparison.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Type of study</th>
<th>Arthroplasty</th>
<th>DL*</th>
<th>PL*</th>
<th>Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keene and Parker</td>
<td>1993</td>
<td>531</td>
<td>Prospective cohort</td>
<td>HA</td>
<td>1.7%</td>
<td>4.4%</td>
<td>DL</td>
</tr>
<tr>
<td>Enocson et al.</td>
<td>2008</td>
<td>739</td>
<td>Prospective cohort</td>
<td>HA</td>
<td>3.9%</td>
<td>8.5%</td>
<td>DL</td>
</tr>
<tr>
<td>Enocson et al.</td>
<td>2009</td>
<td>713</td>
<td>Prospective cohort</td>
<td>THA</td>
<td>2%</td>
<td>12%</td>
<td>DL</td>
</tr>
<tr>
<td>Sköldenberg et al.</td>
<td>2010</td>
<td>372</td>
<td>Prospective cohort</td>
<td>HA/THA</td>
<td>1%</td>
<td>9%</td>
<td>DL</td>
</tr>
<tr>
<td>Biber et al.</td>
<td>2012</td>
<td>704</td>
<td>Retrospective cohort</td>
<td>HA</td>
<td>0.5%</td>
<td>3.9%</td>
<td>ND</td>
</tr>
<tr>
<td>Leonardsson et al.</td>
<td>2012</td>
<td>23509</td>
<td>Registry</td>
<td>HA</td>
<td>0.7°</td>
<td>1.0°</td>
<td>DL</td>
</tr>
<tr>
<td>Rogmark et al.</td>
<td>2014</td>
<td>33205</td>
<td>Registry</td>
<td>HA</td>
<td>1.0°</td>
<td>1.4°</td>
<td>DL</td>
</tr>
<tr>
<td>Cebatorius et al.</td>
<td>2014</td>
<td>1412</td>
<td>Registry</td>
<td>THA</td>
<td>3.1%</td>
<td>6.8%</td>
<td>DL</td>
</tr>
<tr>
<td>Parker</td>
<td>2015</td>
<td>216</td>
<td>RCT</td>
<td>HA</td>
<td>1.9%</td>
<td>0.9%</td>
<td>ND</td>
</tr>
</tbody>
</table>

Mukkat et al. 2015 185 Prospective cohort HA 3.9% 8.4% DL

n: number of patients
age: mean age at surgery
DL: Direct lateral surgical approach.
PL: Posterolateral surgical approach
*: Dislocation rates.
°: Hazard ratio
ND: No difference.
Study III

In patients with FNF treated with a bipolar HA using the PL approach, patients with recurrent dislocations had a decreased postoperative global FO, shorter leg and shallower acetabulum on the operated side compared with their controls. These factors might decrease the soft-tissue tension around the operated hip and predispose to dislocation.

In the present study, the dislocation rate was 10.7% with 62.5% recurrence. These rates agree with previously published reports (Barnes et al. 1995, Noon et al. 2005, Enocson et al. 2008, Madanat et al. 2012, Wallner et al. 2014, Salem et al. 2014) (Table 17). Wallner et al. (2014) found that a combination of postoperative discrepancies in FO and LLD resulted in an increased risk for dislocation. Two other studies also found that a decreased postoperative FO increased the risk for dislocation (Pajarinen et al. 2003, Ninh et al. 2009, Wallner et al. 2014). We found no differences in age, sex or ASA classes between the dislocation group and the remaining cohort. The incidence of altered mental status and the risk of one-year mortality were significantly higher in the dislocation group compared to the remaining cohort.

When the groups of single and recurrent dislocations were compared to their controls, these differences did not meet statistical significance possibly due to the small sample size. However, the assessment of mental status was based on medical records on admission without the use of a standardized questionnaire. Our results are in agreement with earlier cohort studies and confirm that cognitive dysfunction or postoperative radiological discrepancy are risk factors for dislocation and recurrent instability (Hedlundh et al. 1995, Hedlundh et al. 1996).

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>n</th>
<th>Stem</th>
<th>Dislocation</th>
<th>Predisposing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pajarinen et al.</td>
<td>2003</td>
<td>338</td>
<td>Thompson</td>
<td>7%</td>
<td>FO, SA</td>
</tr>
<tr>
<td>Ninh et al.</td>
<td>2009</td>
<td>217</td>
<td>Conquest FX Hip</td>
<td>6%</td>
<td>FO, Sex, CF, WA</td>
</tr>
<tr>
<td>Madanat et al.</td>
<td>2012</td>
<td>602</td>
<td>LPP-EcoFit</td>
<td>5.6%</td>
<td>WA</td>
</tr>
<tr>
<td>Wallner et al.</td>
<td>2014</td>
<td>2093</td>
<td>CPT</td>
<td>2.4%</td>
<td>CF, LLD, FO</td>
</tr>
<tr>
<td>Mukka et al.</td>
<td>2015</td>
<td>373</td>
<td>Lubinus SPII</td>
<td>10.7%</td>
<td>FO, LLD, WA</td>
</tr>
</tbody>
</table>

n = sample size
Outcome = FO=Femoral Offset, LLD= Leg length difference, Wiberg angle=Centre-edge angle of acetabulum, RN=Residual femoral neck, SA=Surgica approach, Sex, CF=Cognitive alteration.
Study IV

In this prospective, observational cohort study we found a higher mortality rate but comparable hip function and quality-of-life among eligible NC compared to eligible consenters when evaluating the EV of an RCT of patients with FNF age 80 and above.

We hypothesized that patients included in the RCT would have favourable hip function and health status in comparison to NC and excluded patients. Our results show no difference in hip function among the groups despite higher prevalence of THA in patients included in the RCT. One explanation for this is the high mortality in the NC group, leaving those with the best possible outcome for follow-up at 1 year. The discrepancy between RCTs and non-RCTs has been addressed previously in a meta-analysis by Bhandari et al. (2004). They compared the pooled results of RCTs and non-RCTs in patients treated either with arthroplasty or IF for a displaced FNF. The authors concluded that non-RCTs underestimated the relative benefit of arthroplasty by indicating higher mortality and revision rates than in their randomized counterparts. However, this conclusion could be the result of selection bias, caused by healthier patients being included in the RCT. Petersen et al evaluated the differences in baseline data in an RCT in patients with OA treated with THA (Petersen et al. 2007). The authors reported a significant difference in baseline data among those who gave consent and those who did not. Also, a recent study that analyzed non-participants in comparison to participants in a cohort study of osteoporosis found a lower mortality rate for participants but no difference in the incidence of osteoporotic fractures between the groups (Wihlborg et al. 2014).

Studies from other fields of medicine have also indicated that NC and non-participation are associated with both inferior health status and higher mortality. This suggests that a large proportion of the population are excluded from participating in an RCT (Table 18). In a recently published study analyzing the EV of an RCT in patients treated for breast cancer, the EV was questioned (van de Water et al. 2014). Patients who participated in the RCT had fewer comorbid diseases, a higher socioeconomic status and smaller tumors. A subgroup analysis of patients aged 75 years or above indicated that those who participated in the RCT had a lower overall mortality than patients in the general population. In contrary, two RCTs in the field of general surgery, between interrupted and continuous slowly absorbable sutures for closure of midline abdominal incisions and laparoscopic or open resection in colon cancer, have shown good EV according to baseline data and demographics (Janson et al. 2009, Fisher et al. 2012). The reporting of data related to EV in RCTs varies, thereby putting the burden on the reader to address the question of generalizability (Ahmad et al. 2009, Pibouleau et al. 2009). Our results and those previously published indicate that study participants might be a generally
healthier group than non-participants. Furthermore, this finding has been shown in other settings such as a preventive trial (Wilhelmsen et al. 1976) and population-based surveys (Goldberg et al. 2001, Hasserius et al. 2002). On the basis of the present evidence, care should be taken in the screening and recruitment processes. Less restrictive inclusion criteria in RCTs may increase generalizability relative to the whole population with a specific disease. However the issue of NC is difficult to address and may only be adjusted for by involving patients in follow-up. The NC should be addressed and presented in order to further facilitate the interpretation of the EV of study results.

<p>| Table 18: Studies on external validity. Study IV in the bottom for comparison. |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Field</th>
<th>Year</th>
<th>Disease/Intervention</th>
<th>Design</th>
<th>N</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersen et al.</td>
<td>Orthopaedic</td>
<td>2008</td>
<td>Arthroplasty</td>
<td>RCT</td>
<td>130</td>
<td>Non-consenters were older and less healthy in comparison to included patients.</td>
</tr>
<tr>
<td>Wihlborg et al.</td>
<td>Orthopaedic</td>
<td>2014</td>
<td>Osteoporosis</td>
<td>PSC</td>
<td>1,604</td>
<td>Non-consenters had an increased mortality in comparison to included patients.</td>
</tr>
<tr>
<td>Bjornshave et al.</td>
<td>Medicine</td>
<td>2010</td>
<td>COPD</td>
<td>RCT</td>
<td>n.r</td>
<td>75% of patients in general population did not meet inclusion criteria.</td>
</tr>
<tr>
<td>Hutchinson-Jaffe et al.</td>
<td>Medicine</td>
<td>2010</td>
<td>NSTEMI</td>
<td>RCT</td>
<td>13,556</td>
<td>Significant differences persist in baseline characteristics, treatment and outcomes between patients enrolled and those not enrolled in clinical trials.</td>
</tr>
<tr>
<td>Steg et al.</td>
<td>Medicine</td>
<td>2007</td>
<td>AMI</td>
<td>RCT</td>
<td>8469</td>
<td>Patients with AMI participating in RCTs have a lower baseline risk and experience lower mortality than non-enrolled patients, even when they are trial eligible.</td>
</tr>
<tr>
<td>Koeth et al.</td>
<td>Medicine</td>
<td>2009</td>
<td>AMI</td>
<td>RCT</td>
<td>20,175</td>
<td>In conclusion, about 50% of patients with ST-elevation myocardial infarction seen in clinical practice are usually excluded from RCTs. Hospital mortality in those patients is very high.</td>
</tr>
<tr>
<td>Travers et al.</td>
<td>Medicine</td>
<td>2007</td>
<td>COPD</td>
<td>RCT</td>
<td>3500</td>
<td>Major COPD RCTs on which the GOLD treatment guidelines are based may have limited external validity. Over 90% of the COPD subjects in the community who were taking medication, would not have been eligible.</td>
</tr>
<tr>
<td>Van de Water et al.</td>
<td>Oncology</td>
<td>2014</td>
<td>Breast cancer</td>
<td>RCT</td>
<td>1325</td>
<td>Participants in the trial had fewer comorbid diseases, a higher socioeconomic status, smaller tumors and lower mortality.</td>
</tr>
<tr>
<td>Mukka et al.</td>
<td>Orthopaedic</td>
<td>2015</td>
<td>Femoral neck fracture</td>
<td>RCT</td>
<td>267</td>
<td>Participants had a lower mortality rate than non-participants. The functional outcome and the external validity for the RCT appeared to be satisfactory.</td>
</tr>
</tbody>
</table>

COPD: Chronic obstructive pulmonary disease. AMI: acute myocardial infarction
NSTEMI: non-ST-segment elevation myocardial infarction. PSC=prospective single cohort, RSC=retrospective single cohort,
General discussion

The optimal treatment for an elderly patient with a FNF

New implants, treatments, surgical methods and strategies are essential for the continuing development of human health. However, there is a need for scepticism and a balanced attitude towards implementation of new techniques especially in the context of the present health care system. Complex treatments such as surgical procedures or very different health care settings may diminish the efficacy of the obtained study results as presented by Flather et al. (2006). The concepts of generalizability and EV are vital when interpreting the results of a RCT. NC consist of a subgroup of the screened population to whom study results are generalized. However, this group seems to have an increased burden of disease and mortality. One can speculate whether this subgroup may benefit less from more complex and extensive surgical treatment. These results, which we present, are consistent with reports from other fields of medicine and raise questions about the generalizability of previously published RCTs in the field of orthopaedic surgery. We propose an improved reporting of patients excluded from participation, missed in the screening process or did not give their consent to participate in an RCT. It is highly important that the readers and researcher can understand which patients are eligible for the study, what proportion of the total population the actual study is focusing on, what proportion and which patients are actually enrolled and how many are potentially missed in one way or another.

The present evidence including study I, strongly imply that THA is superior to IF in the treatment of displaced FNF in elderly patients (Jiang et al. 2015). The previously published reports have used a variety of stem types, femoral head dimensions and surgical approaches which all affect the rate of complications. Probably in a modern setting with recent retrieved knowledge, the THA has an increased longevity and a lower risk for revision surgery. In the elderly patients above 80 years of age and those with cognitive dysfunction, a cemented HA is the preferred treatment in the majority of Swedish hospitals. The potential benefit of improved PRO for THA in a mobile and cognitively intact elderly patient may be counteracted by the fact that HA is a less technically advanced surgical procedure, and may be more feasible for the general orthopaedic surgeon on call.

The costs for medical attention include hospital treatment, rehabilitation, and an increased level of care postoperatively and change in living situation. Comparative analyses between hip arthroplasty and IF has been investigated both in international (Iorio et al. 2001) and Scandinavian settings (Rogmark et al. 2003, Frihagen et al. 2010, Waaler Bjørnelv et al. 2012). These analyses pointed out that the initial surgery and hospitalization is less costly in those treated with IF, but that due to
subsequent readmissions and reoperations IF is the most costly option for society. Adopting recent advances in hip arthroplasty surgery may further increase this difference in costs.

One frequently asked question in the orthopaedic community is the preferred surgical approach in hip prosthesis surgery. Many surgeons state that the most important factor in order to avoid dislocation is to use the approach, which a surgeon feels most comfortable and familiar with. The direct anterior approach has a disadvantage due to its technically advanced nature especially in this group of patients when treated by general orthopaedic surgeons. During the last decade, due to the evidence presented, orthopaedic departments in Sweden are implementing the DL approach when treating displaced FNF with a hip arthroplasty (Garellick et al. 2014). The present evidence for the effect of surgical approach on PRO is sparse and may vary between the different subgroups that receive a hip prosthesis. Our results obtained are obviously not generalizable to younger patients treated with THA for a FNF.

Recent registry reports by Lindgren et al. (2014) and Amlie et al (2014) have indicated that the PL approach has a superior PRO in comparison to the DL approach in patients with OA. The obvious difference between the populations with FNF and OA include the general demographics and also possible differences in the biomechanics. FNF patients are generally older and weaker with a higher incidence of cognitive deficit than OA patients. Pre-fracture hip range of motion is mostly well preserved in fracture patients in comparison to OA patients where arthritic hip changes limits motion. This combination increases the risk for dislocation and subsequent revision surgery, but may also affect the risk for postoperative limp and trochanteric tenderness in FNF patients.

Promising results have been reported in FNF patients treated with dual mobility acetabular components (Tarasevicius et al. 2010, Adam et al. 2012, Bensen et al. 2014). There are few reports of long-term survival of these cups and mainly from France (Stroh et al. 2012). The first generation dual mobility cups used in primary arthroplasty for OA reported a 84-97% survival rate, when considering revision for any reason, in a large cohort study with follow-up of up to 16 years (Philippot et al. 2009, Vielpeau et al. 2011, Combes et al. 2013). The bearing surfaces include a soft-on-hard articulation, which have created some concerns regarding polyethylene wear in experimental studies (Schmalzried and Callaghan. 1999, Adam et al. 2005). The long-term survival of the new generation of dual mobility cups with highly cross-linked polyethylene in active patients remains to be investigated (Grazioli et al. 2012).

The increased stability of the DL approach may be counteracted by an increase of postoperative limp in the younger and more active population receiving a THA for a
FNF. There are no published RCTs focusing on PRO and complications of the PL versus the DL approach in combination with a dual mobility cup. A dual mobility component could be a feasible solution in low volume hospitals when surgeons do not feel comfortable with both the DL and the PL approach.

Recent studies has pointed out that straight, polished, tapered stems may be associated with a higher risk for periprosthetic femoral fractures, especially in elderly patients treated with a hip prosthesis for a FNF (Inngul and Enocson 2014, Brodén et al. 2015). Using an anatomic stem seems to counteract this increased risk for periprosthetic fractures (Lindahl et al. 2005).

The present evidence suggest that elderly patients with a displaced FNF should be treated with a THA or a HA using a DL approach with a cemented composite-beam stem. Care should be taken to restore the biomechanical aspects of the hip.
Conclusions

Study I

Over a period of seventeen years in a group of healthy, elderly patients with a displaced FNF, THA provided better hip function and significantly fewer reoperations compared with IF without increasing mortality.

Study II

The DL and PL approaches have a comparable functional outcome 1 year postoperatively. Despite an increased risk for limping, we recommend the DL approach due to a decreased rate of re-operation.

Study III

Patients with recurrent dislocations had decreased postoperative global FO, shorter leg and shallower acetabulum on the operated side compared with their controls. These factors might decrease the soft-tissue tension around the operated hip and predispose it to dislocation.

Study IV

Our findings suggest that participants had a lower mortality rate than non-participants. The functional outcome and the external validity for the present RCT appeared to be satisfactory.
Implications for future research

- There are few reports investigating hip function in patients treated with THA for displaced FNF with regard to surgical approach. In this thesis, elderly patients treated with HA did not show any difference in hip function between the two surgical approaches used. In theory, younger and more active patients may suffer more from postoperative limping after the DL approach and therefore report lower PRO.

- A number of published studies have suggested that THA may produce better hip PRO compared with HA. However, the majority of studies conducted are made for a subgroup of patients that are active and living in their own homes. A RCT is needed to evaluate if THA results in better hip function in comparison to HA in healthy and cognitively aware patients aged above 80 years. This may also answer the question of whether or not to replace a healthy acetabulum.

- Dual mobility cups have shown promising results in decreasing the frequency of dislocation. A RCT or large cohort study comparing the DL and PL approaches using dual mobility cups with regard to hip function and complications with long term follow-up may answer this question.

- The radiological risk factors for dislocation in HA for FNF are to be further investigated. A shallow acetabulum is a well-known clinical consideration for the surgeon. A low preoperative Wiberg angle may be a radiographic sign and thus an important feature in the preoperative planning. This question has rarely been studied.

- The EV of published RCTs in the orthopaedic literature is seldom reported. This important factor needs to be further investigated to improve the conclusions and the implementation of future research. Especially, the role of NC and the difference between this eligible group and those enrolled in an RCT remains to be investigated.
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Appendix

Harris Hip Score

1. Beskriv om du har någon smärta i den opererade höften?
A. Ingen
B. Lätt smärta, ingen begränsning i aktivitet, känner av höften vid enstaka tillfällen
C. Lindrig, ej påverkan i dagliga aktiviteter, smärta vid större ansträngning, ibland smärtstillande läkemedel
D. Måttlig smärta, begränsad i dagliga aktiviteter, regelbundet smärtstillande läkemedel
E. Uttalad smärta, stark begränsning i dagliga aktiviteter, regelbundet starka smärtstillande läkemedel.
F. Invalidiserande smärta, vilosmärter

2. Använder du något gånhjälpmiddel?
A. Inget
B. Käpp vid långa promenader
C. Nästan alltid käpp
D. 1 Krycka eller rollator
E. 2 Käppar
F. 2 Kryckor eller gångbord
G. Går inte alls
3. Har du hälta på den opererade sidan efter promenad med det gånghjälpmedel du använder?

A. Ingen hälta  
B. Lätt hälta  
C. Måttlig hälta  
D. Uttalad hälta  

4. Hur långt kan du gå med det gånghjälpmedel du använder?

A. Över 2 kilometer  
B. 1-2 kilometer  
C. 0,5 – 1 kilometer  
D. Mindre än 0,5 kilometer eller endast inomhus  
E. Kan inte gå  

5. Trappor

A. Jag går i trappa utan stöd  
B. Jag använder ledstång eller räcke vid trappgång  
C. Jag går i trappa med stora svårigheter  
E. Jag kan inte gå i trappa  

6. Ta på skor och strumpor på opererade sidan

A. Utan svårighet  
B. Med svårighet  
C. Jag kan inte ta på mig skor och strumpor själv
7. Sitta

A. Jag kan sitta bekvämt på en vanlig stol

B. Jag sitter endast bekvämt i en hög stol, jag kan endast sitta bekvämt i en halvtimme

C. Jag kan inte sitta bekvämt i en halvtimme på grund av höftsmärta

8. Tunnelbana/Buss

A. Jag kan åka tunnelbana eller buss

B. Jag kan inte åka tunnelbana eller buss

9. Smärt nummereringsskala (NRS)

Ringa in det nummer som bäst motsvarar din GENOMSNITTLIGA nivå för din höft/bensmärta i den opererade benet under de sju senaste dagarna

1 – Ingen smärta

2

3

4

5

6

7

8

9

10 – Värsta tänkbara smärta
Formulär EQ-5D

Rörlighet

1. Jag går utan svårigheter
2. Jag kan gå men med viss svårighet
3. Jag är sängliggande

Hygien

1. Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning
2. Jag har vissa problem att tvätta eller klä mig själv
3. Jag kan inte tvätta eller klä mig själv

Huvudsakliga aktiviteter (t ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

1. Jag klarar av mina huvudsakliga aktiviteter
2. Jag har vissa problem med att klara av mina huvudsakliga aktiviteter
3. Jag klarar inte av mina huvudsakliga aktiviteter

Smärtor/besvär

1. Jag har varken smärtor eller besvär
2. Jag har måttliga smärtor eller besvär
3. Jag har svåra smärtor eller besvär

Oro/nedstämdhet

1. Jag är inte orolig eller nedstämd
2. Jag är orolig eller nedstämd i viss utsträckning
3. Jag är i högsta grad orolig eller nedstämd

**Generellt hälsotillstånd**

Ditt bästa tänkbara hälsotillstånd markerats med 100 och Ditt sämsta tänkbara hälsotillstånd med 0.

Vi vill att Du på denna skala markerar hur bra eller dåligt Ditt hälsotillstånd är, som Du själv bedömer det. Gör detta genom att dra en linje från nedanstående ruta till den punkt på skalan som markerar hur bra eller dåligt Ditt nuvarande hälsotillstånd är.

0-----------------------------------------------------------50-----------------------------------------------------100
SPMSQ - the Short Portable Mental State Questionnaire

Fråga:

1. Vad är det för datum i dag? Rätt/Fel

2. Vilken veckodag är det? Rätt/Fel

3. Vad heter detta sjukhus? Rätt/Fel

4. Vilken adress har du? Rätt/Fel

5. Hur gammal är du? Rätt/Fel

6. När föddes Du (år, månad, dag)? Rätt/Fel

7. Vad heter nuvarande statsminister? Rätt/Fel

8. Vad hette den förre statsministern? Rätt/Fel

9. Vad var din mors flicknamn? Rätt/Fel

10. Dra 3 från 20 och fortsätt hela vägen ner. Antal rätta svar. Rätt/Fel
Smärta

Följande frågor rör den höftsmarta du eventuellt upplevt den senaste veckan. Ange graden av smarta du har kant i följande situationer.

1. Gå på jämnt underlag

   Ingen  Lätt  Måttlig  Svår  Mycket svår

2. Gå upp eller ner för trappor

   Ingen  Lätt  Måttlig  Svår  Mycket svår

3. Under natten i sängläge (smärta som stör sömnen)

   Ingen  Lätt  Måttlig  Svår  Mycket svår

4. Sittande eller liggande

   Ingen  Lätt  Måttlig  Svår  Mycket svår

5. Stående

   Ingen  Lätt  Måttlig  Svår  Mycket svår

Stelhet

Följande frågor rör ledstelhet (inte smärta). Stelhet innebar svårighet att komma igång eller ökat motstånd vid rörelser i höftleden. Ange graden av stelhet du har upplevt i din höft den senaste veckan.

1. Hur stel har din höft varit när du just har vaknat på morgonen?

   Ingen  Lätt  Måttlig  Svår  Mycket svår

2. Hur stel har din höft varit efter att du suttit eller legat och vilat

   Ingen  Lätt  Måttlig  Svår  Mycket svår
**Fysisk funktion**

Följande frågor rör din fysiska funktion. Ange graden av svårighet du har upplevt den senaste veckan vid följande aktiviteter på grund av dina höftbesvär.

1. Gå nerför trappor
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

2. Gå uppför trappor
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

3. Resa dig upp från sittande
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

4. Stå stilla
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

5. Böja dig, tex för att plocka upp ett föremål från golvet
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

6. Gå på jämt underlag
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

7. Stiga i och ur bil
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

8. Handla/göra inköp
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår

9. Ta av strumpor
   - Ingen
   - Lätt
   - Måttlig
   - Svår
   - Mycket svår
10. Stiga ur sängen

Ingen  Lätt  Måttlig  Svår  Mycket svår

11. Ta av strumpor

Ingen  Lätt  Måttlig  Svår  Mycket svår

12. Ligga i sängen (vända dig, hålla höften i samma läge under lång tid)

Ingen  Lätt  Måttlig  Svår  Mycket svår

13. Stiga i och ur badkar/dusch

Ingen  Lätt  Måttlig  Svår  Mycket svår

14. Sitta

Ingen  Lätt  Måttlig  Svår  Mycket svår

15. Sätta dig och resa dig från toalettstol

Ingen  Lätt  Måttlig  Svår  Mycket svår

16. Utföra tungt hushållsarbete (snöskottning, golvtvätt, damsugning etc)

Ingen  Lätt  Måttlig  Svår  Mycket svår

17. Utföra lätt hushållsarbete (matlagning, damning etc)

Ingen  Lätt  Måttlig  Svår  Mycket svår