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# **Complications in Trochanteric and Subtrochanteric Femoral Fractures**

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To my beloved family

Luma, Lena and Samuel...



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# Abstract

The hip fracture is a major public health problem. The majority of hip fracture patients are elderly with comorbidities and there is a strong association with osteoporosis, especially for the extracapsular (trochanteric and subtrochanteric) types of fractures. The management of these patients is associated with a huge risk for medical and surgical complications. One of the most important risks is significant blood-loss and a subsequent need for blood transfusion. The treatment of choice for patients with extracapsular hip fracture is acute surgery with internal fixation, such as intramedullary nailing or plating with sliding hip screw. A hip arthroplasty is a salvage procedure and an option for the treatment of failures after internal fixation. In this doctoral project we study the complications, the epidemiology and the influence of early surgery in the management of this subgroup of hip fracture patients.

In *Study I*, a retrospective cohort study with a 5–11 years follow-up, 88 patients reoperated 1999 – 2006 at SÖS with a secondary hip arthroplasty due to healing complications after internal fixation of a trochanteric or a subtrochanteric fracture were analysed. The total reoperation rate was 16% (14/88). The most common reason for a reoperation was a periprosthetic fracture ( $n = 6$ ). Multivariable Cox regression analysis of reoperations using femoral stems with standard length, compared with long stems, showed a trend for increased risk with a hazard ratio (HR) of 4 ( $p = 0.06$ ). A recommendation for using long femoral stems may be one way to reduce the risk for reoperations.

In *Study II*, a retrospective cohort study, 987 patients operated with an intramedullary nail due to an unstable trochanteric or subtrochanteric hip fracture at SÖS, between January 1, 2011 and December 31, 2013 were analysed. Using the red blood cell transfusion rate and mortality as the main outcome measures, logistic regression analysis was used to adjust for anticoagulants, ASA class, fracture type, preoperative haemoglobin (Hb) value and time to surgery. It was found that anticoagulants (relative risk (RR) 2.0) and surgery delayed for more than 24 hours (RR 3.9) were significantly associated with an increased rate of preoperative transfusions.

In *Study III*, a retrospective case-control study of 198 patients: 99 warfarin patients and 99 patients without anticoagulants as a 1:1 ratio control group matched for age, gender and surgical implant were analysed. All patients were operated at SÖS within 24 hours with an intramedullary nail due to a trochanteric or subtrochanteric hip fracture after a low-energy trauma between January 1, 2011 and December 31, 2014. All patients on warfarin were reversed if necessary to  $INR \leq 1.5$  before surgery using vitamin K and/or four-factor prothrombin complex concentrate (PCC). There were no significant differences in the calculated blood-loss, in-house adverse events, mortality or pre- or perioperative transfusion rates between the groups. There was an increased rate of postoperative transfusions in the control group. The study demonstrated the safety of using vitamin K and/or PCC to be able to operate within 24 hours.

In *Study IV*, a descriptive epidemiological register study, a total of 10548 patients registered in the national Swedish Fracture Register from January 2014 to December 2016 were analysed. Individual patient data (age, gender, injury location, injury cause, fracture type, treatment and timing of surgery) were retrieved from the register database. Mortality data was obtained from the Swedish Death Register. The majority of the patients were elderly females (69%) who had sustained their fracture from a fall at the same level (83%) at the patients' residence (75%). The most commonly used implant was a short antegrade intramedullary nail (42%). With increasing fracture complexity, the proportion of intramedullary nails was increasing, and also the use of long versus short nails. Most of the patients were operated within 36 hours (90%). There was an increased mortality for males, and for all those who were delayed to surgery  $>36$  hours.

The major conclusions of this thesis were the epidemiological aspects, analyses showing the medical and surgical complexity of these fractures and the importance of optimising patients promptly before the surgery within 24 hours.





# List of Papers

This thesis is based on the following papers, which are indicated in the text by their Roman numerals (*Studies I-IV*):

- I.** Hip arthroplasty after failed fixation of trochanteric and subtrochanteric fractures. *Anders Enocson, Leif Mattisson, Carin Ottosson, Lasse J Lapidus. Acta Orthopaedica 2012; 83:5, 493-498.*
  
- II.** What is the influence of a delay to surgery >24 hours on the rate of red blood cell transfusion in elderly patients with intertrochanteric or subtrochanteric hip fractures treated with cephalomedullary nails? *Leif Mattisson, Lasse J. Lapidus, Anders Enocson. Journal of Orthopaedic Trauma Aug 2018; 32(8):403–407.*
  
- III.** Is fast reversal and early surgery (within 24 h) in patients on warfarin medication with trochanteric hip fractures safe? A case-control study. *Leif Mattisson, Lasse J. Lapidus, Anders Enocson. BMC Musculoskeletal Disorders June 2018; 19:203.*
  
- IV.** Epidemiology, treatment and mortality of trochanteric and subtrochanteric hip fractures: data from the Swedish Fracture Register. *Leif Mattisson, Alicja Bojan, Anders Enocson. BMC Musculoskeletal Disorders October 2018; 19:369.*



# List of Abbreviations

ASA class	American Society of Anesthesiologists classification
AO	Arbeitsgemeinschaft für Osteosynthesefragen
CCI	Charlson Comorbidity Index
CI	Confidence interval
DVT	Deep vein thrombosis
HB	Haemoglobin
HA	Hemiarthroplasty
HR	Hazard ratio
IF	Internal fixation
INR	International normalized ratio
LGN	Long gamma nail
MSP	Medoff sliding plate
NOACs	Novel oral anticoagulants
OTA	Orthopaedic Trauma Association
PCC	Prothrombin complex concentrate
RBC	Red blood cell
RR	Relative risk
SFR	Swedish Fracture Register
SGN	Short gamma nail
SHS	Sliding hip screw
SPSS	Statistical Package for the Social Sciences
SSP	Sliding screw plates
SÖS	Stockholm South General Hospital/Södersjukhuset
THA	Total hip arthroplasty
THR	Total hip replacement



# Introduction

Hip fractures in general are a serious health issue that can lead to impaired function, reduced quality of life and increased mortality. Globally hip fractures are affecting around 1.6 million people per year worldwide. Scandinavia has the highest incidence of hip fractures in the world (Thorngren et al. 1995, Johnell et al. 1992, Kanis et al. 2002, SBU report 2003) and about 18000 people incurs a hip fracture each year in Sweden. The number of hip fractures is likely to increase as the number of elderly people is increasing, and in the world it is estimated that the number of hip fractures will rise to 2.6 million by 2025, and 6.25 million in 2050 (Gullberg et al. 1997, Lofthus et al. 2001, Löfman et al. 2002, Johnell et al. 2004, Dennison et al. 2006, Cooper et al. 1992).

The absolute majority of hip fracture patients are elderly, and there is a strong association with osteoporosis. The prevalence of osteoporosis in women increases from 6.7% of the population in the 50-54 years old, to 47% in the 80-84 years old (Swedish Osteoporosis Society report, April 2014). Osteoporosis is the most important underlying factor and often only a mild trauma leads to the consequence of suffering a hip fracture. Women constitute about 70% of the sufferers. It is obviously clear from different hip fracture registers that there is a higher average age and a greater proportion of women among the patients who has trochanteric and subtrochanteric fractures compared to other types of hip fractures (Rikshöft 2016).

Suffering a hip fracture is a demanding issue, not just a serious physiological trauma for the patients but also a psychological trauma via the reduction in quality of life, increasing degree of dependence, chronic pain and reduced mobility (Keene et al. 1993, Salkeld et al. 2000).

## 1. Anatomy

The femur bone is the longest bone in the human body. It supports the whole body's weight during many activities. The proximal part of the femur bone consists of different parts (Figures 1-2);

**The femoral head** – Which is the proximal end of the femur, ball in its shape, with the cup-shaped acetabulum, forms the ball-and-socket hip joint in order to allow the rotational movement of the joint.

**The neck** – Which is the part of the femur that connects the head with the shaft. Depending on its angulations a significant range of movement is allowed at the hip joint.

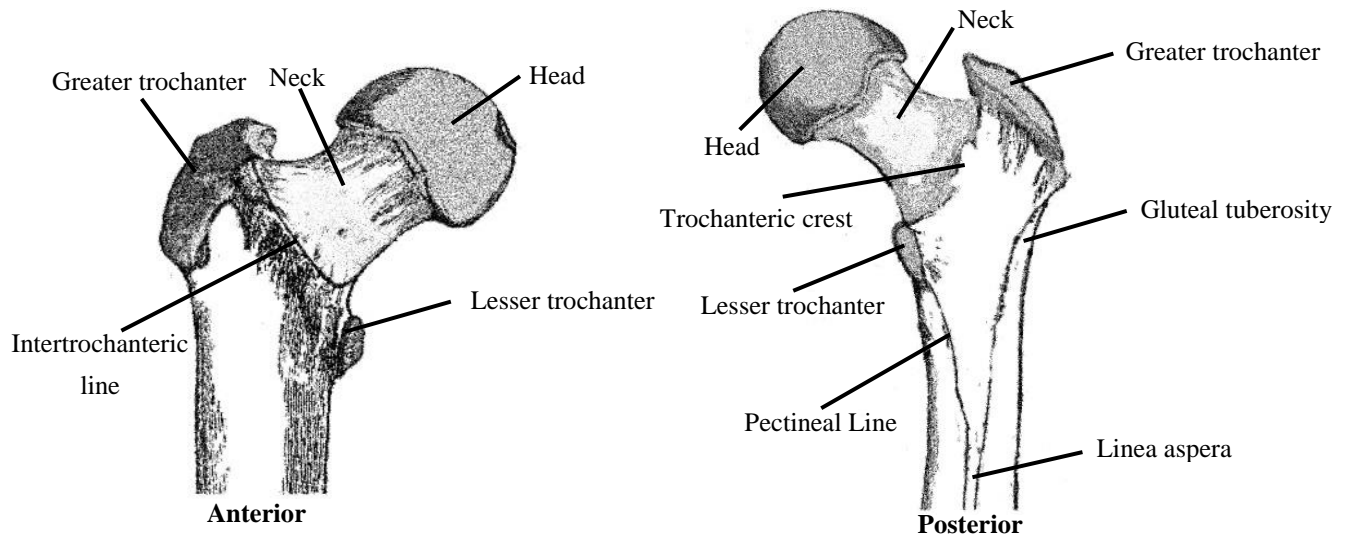
**The greater trochanter** – The bone projection that emerge from the anterior aspect of the proximal part, lateral to the neck with an angle superiorly and posteriorly. Several muscles in the gluteal region have a site of attachment at the greater trochanter, such as the gluteus medius, the gluteus minimus and the piriformis.

**The lesser trochanter** – The bone projection that emerge from the posteromedial side of the proximal part of the femur, inferior to the neck-shaft connection. Muscles such as the psoas major and the iliacus have this site of attachment.

**The intertrochanteric line** – A prominent bone at the anterior aspect of the proximal part of the femur that extend to an inferomedial direction, which connects the greater and lesser trochanters. The attachment site of the strong joint's ligament (iliofemoral ligament).

**The intertrochanteric crest** – The same as the intertrochanteric line, is a prominent bone that connects the two trochanters together, on the posterior aspect of the proximal part of the femur. Site of attachment for the quadratus femoris muscle.

**Figure 1. Posterior and anterior view of the proximal part of the femur.**



## 2. Types of hip fractures

Hip fractures are a common name for several different fracture types in the proximal part of the femur. Hip fractures are divided mainly into three types of fractures:

- **Cervical** (neck of the femur)
- **Trochanteric or intertrochanteric** (through the greater and lesser trochanter)
- **Subtrochanteric** (<5cm distal to the lesser trochanter)

In Sweden the cervical fractures account for 52%, the trochanteric fractures for 37% (of which 20% are so called unstable trochanteric fractures) and the subtrochanteric fractures for 8% of all hip fractures (Rikshöft 2016).

Furthermore, there is the **basocervical** fracture (through the base of femoral neck at the transition to the trochanteric region; uncommon fracture, represent only 3% of all hip fractures).

**Figure 2. Proximal femoral fractures.**



1. Femoral neck fractures  
(Intracapsular)
2. Trochanteric fractures  
(Extracapsular)
3. Subtrochanteric fractures  
(Extracapsular)

### 3. Fracture Classifications

For adequate management of fractures in general it is important to have a reliable classification. An effective fracture classification should be as simple as possible and provide a sufficient guideline for the clinical management. It should be appropriate, acceptable and widely-spread to be used in clinical studies (Burstein et al.1993, Martin et al.1997).

In the classifications of the trochanteric and subtrochanteric fractures several classification systems have been published. A large part of these classifications are based on description of the fracture pattern (Evans et al. 1949, Boyd et al. 1949) while others are based on description and providing prognostic information to achieve and maintain reduction (Tronzo et al. 1973) or are just based on the mechanism of the fracture (Ender et al.1970).

Two of the classification systems that are commonly used are the Jensen-Michaelsen (Jensen, Michaelsen et al. 1975) for trochanteric fractures and the Seinsheimer Classification for subtrochanteric fractures (Seinsheimer et al.1978).

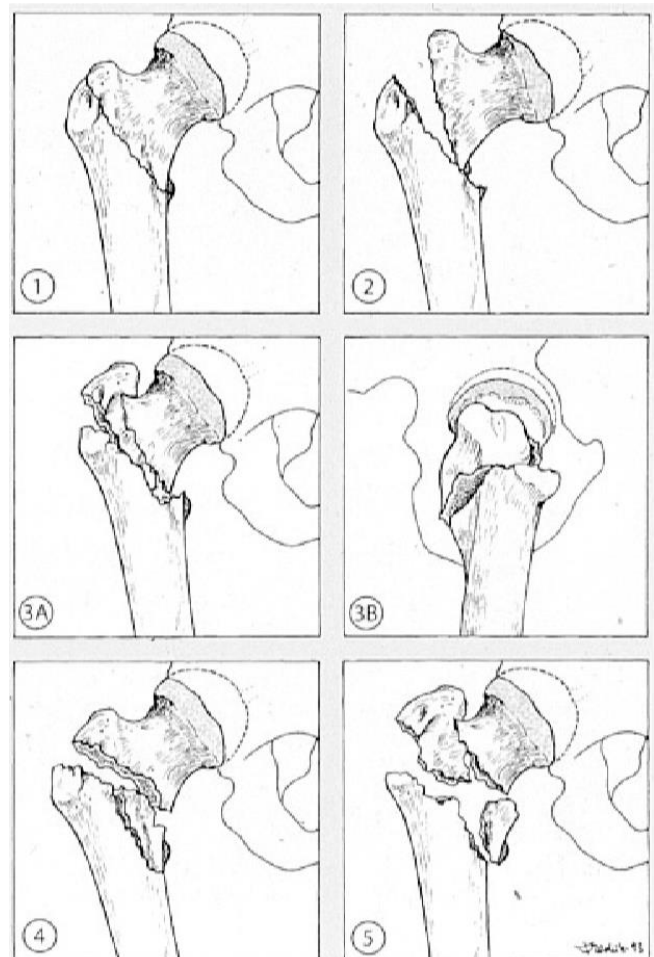
The Jensen-Michaelsen classification of trochanteric fractures divides the fractures in 5 different types (Jensen, Michaelsen et al. 1975):

1. (J.M. 1) undisplaced 2-part fracture.
2. (J.M. 2) displaced 2-part fracture.
3. (J.M. 3) 3-part fracture including a fracture of the greater trochanter.
4. (J.M. 4) 3-part fracture including a fracture of the lesser trochanter.
5. (J.M. 5) 4-part fracture including a fracture of both the greater and lesser trochanter.

In the Jensen-Michaelsen classification, JM 1-2 fractures are described as stable, whereas JM 3-5, which consists of more than two fragments, are referred to as unstable.

**Figure 3.**

**The Jensen-Michaelsen classification for trochanteric fractures.**



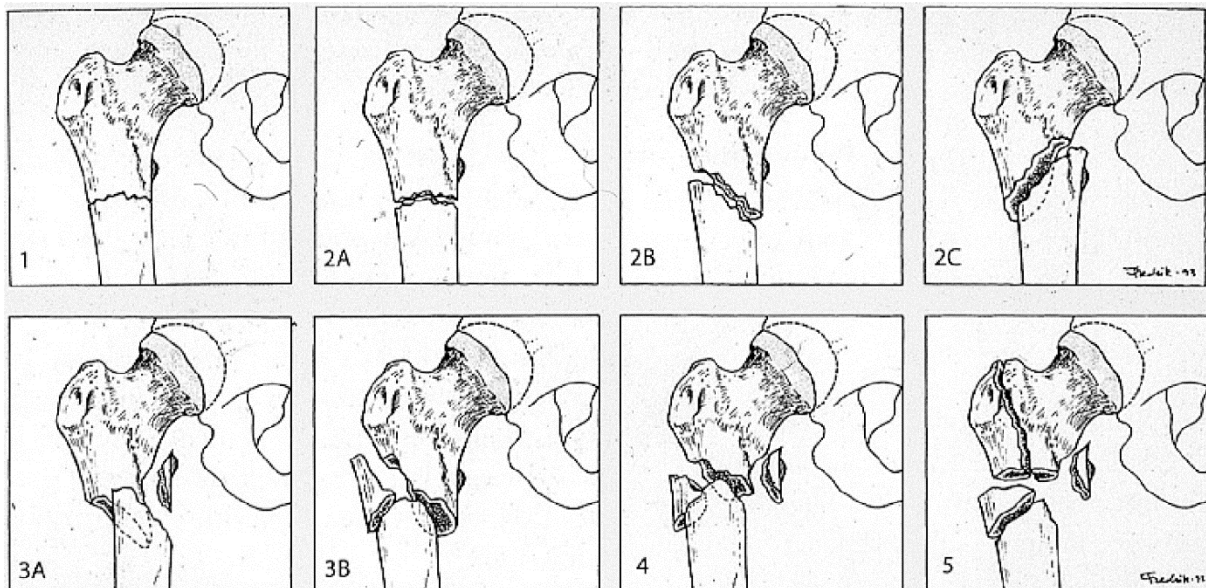
From: Ortopedi, U Lindgren, O Svensson, 3 ed, Liber Stockholm. With the permission of the authors.

For the subtrochanteric fractures, which is defined as a fracture in the region of the proximal part of the femur between the lesser trochanter and 5 cm distal to it, with or without extension to the trochanteric region, the Seinsheimer Classification (Seinsheimer et al. 1978) is one of the most widely used classifications:

1. Non-displaced fractures with less than 2 mm displacement.
2. Displaced 2-part fractures, which can be divided into the following subgroups:
  - 2A: 2-part transverse fractures.
  - 2B: 2-part spiral fractures with the lesser trochanter in the proximal fragment.
  - 2C: 2-part spiral fractures with the lesser trochanter in the distal fragment.
3. 3-part fractures, which can be divided into the following subgroups:
  - 3A: 3-part spiral fractures, the third fragment is the lesser trochanter.
  - 3B: 3-part spiral fractures, the third fragment is a butterfly fragment.
4. The comminuted fractures with four or more fragments.
5. The comminuted subtrochanteric fractures with an extension through the greater trochanter.

For the subtrochanteric fractures the two-part fractures (1-2C) are described as potentially stable, while the 3-part fractures and comminutes fractures (3A-5) are defined as unstable.

**Figure 4. The Seinsheimer classification for subtrochanteric fractures.**

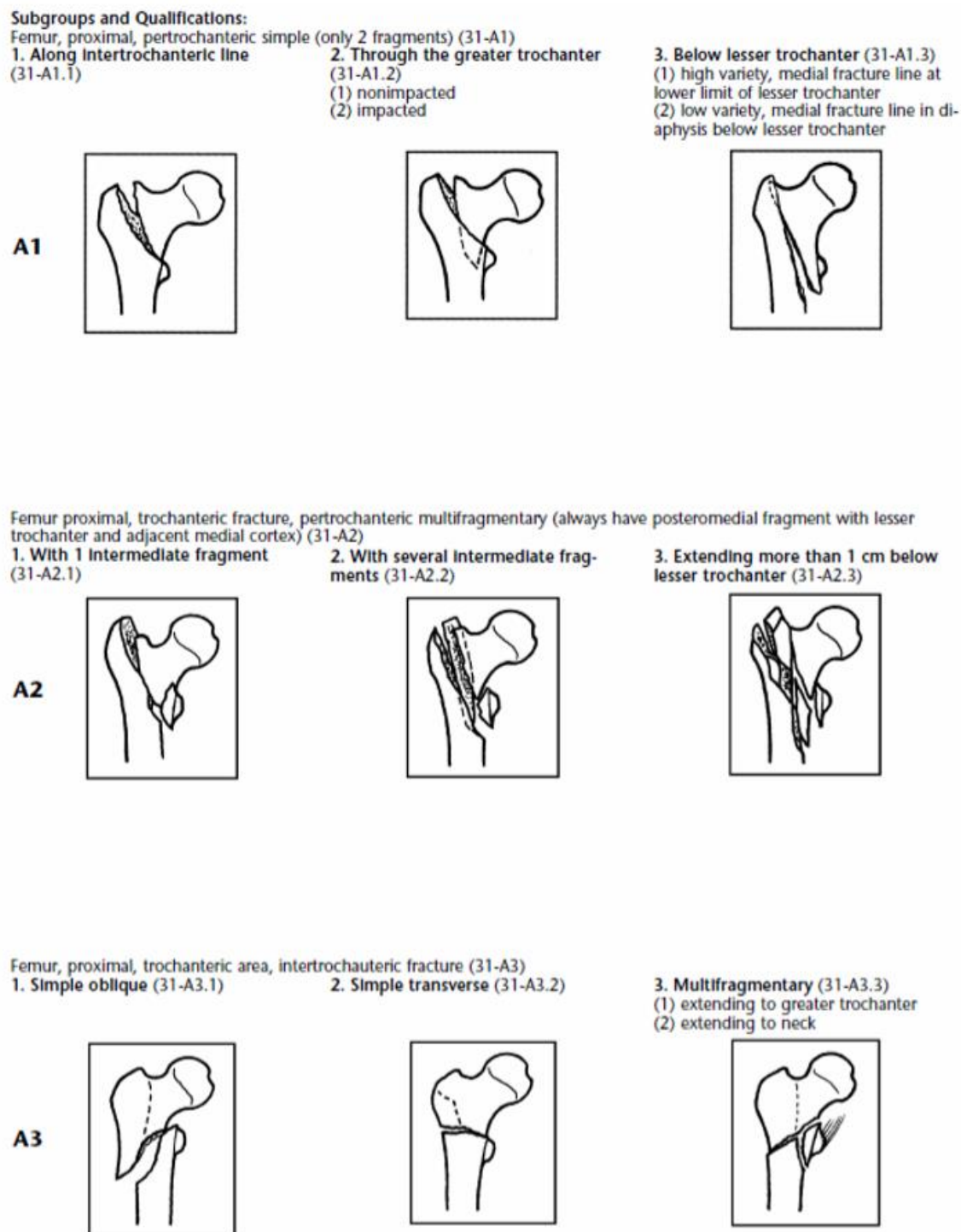


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Another system to classify both trochanteric and subtrochanteric fractures that is frequently used is the AO/OTA classification (Müller et al. 1990, Marsh et al. 2007) (Figure 5).

**Figure 5. The AO/OTA classification for trochanteric and subtrochanteric fractures.**



From [www.ota.org/compendium](http://www.ota.org/compendium).

## 4. The history of treatment

An intertrochanteric fracture was described in the early 1800's by Cooper (1822) who was the first that distinguished between the fractures of the proximal part of the femur as inside (intracapsular) and outside (extracapsular) the capsule. The intertrochanteric fractures were described by Cooper in his thesis 1851, and his recommended treatment was traction and steady support in natural position.

The diagnosis and care of intertrochanteric fractures were then studied by several other surgeons. Royal Whitman first reported a reduction procedure under anesthesia and immobilization with cast. In 1850 Langenbeck used an intramedullary nail to attempt an internal fixation of a reduced fracture. The nonsurgical managed fractures can heal with an acceptable rate but are associated with a high risk of deformity and a decreased function with unacceptable morbidity and mortality rates.

Therefore, the modern management of hip fractures involves surgical intervention.

## 5. Surgical treatment

Virtually all patients with a hip fracture needs acute surgery. The aim of the surgical management is to achieve adequate stabilisation of the hip fracture in order to tolerate mobilisation and early weight bearing. Furthermore, to enhance fracture healing and avoid complications due to prolonged bed rest. It is important that the elderly is not inactive and lose their previous level of function.

Operational management of trochanteric and subtrochanteric fractures consists of internal fixation. The choice of implant and technology depends on the fracture pattern. A variety of implants have been used in order to improve the surgical treatment of patients with trochanteric and subtrochanteric fractures. The most commonly used implants in Sweden today are sliding screw plates (SSP) and intramedullary nails. The treatment of stable trochanteric fractures (JM 1-2) are uncontroversial and good results can be expected with both SSP and intramedullary nail (Jensen et al. 1980, Bridle et al. 1991, Radford et al. 1993, Shaw et al. 1993, Bhandari et al. 2009). At the department of Ortopaedics at Södersjukhuset SSPs are used for these fractures, and in studies performed at the clinic with this method the proportion of healing complications was only 3% (Ekström et al. 2009), which is consistent with previous studies (Watson et al. 1998, Adams et al. 2001). For patients with unstable trochanteric (JM 3-5) and subtrochanteric fractures, the treatment is more controversial and the frequency of reoperations is significantly higher. The literature reports healing complications in 4-10% of the patients with unstable trochanteric fractures, and in 8-20% of the patients with subtrochanteric fractures (Watson et al. 1998, Madsen et al. 1998, Buciuto et al. 1998, Lunsjö et al. 1999, Adams et al. 2001, Harrington et al. 2002). At SÖS short intramedullary nails are used for unstable trochanteric fractures and long intramedullary nails for fixation of subtrochanteric fractures.

The proportion that undergoes surgery with intramedullary nail fixation increases while the fixation with SSP decreases in Sweden (Rikshöft rapport 2016).

### 5.1 Surgical complications

#### Fracture Collapse

- **Implant failure/Cutout** ; a common early complication which often occur within the first 3 months, usually when the internal fixation is not stable which lead to lossening from the bone and further collapse of the fracture, or when the sliding screw penetrates superiorly through the

femoral head and the hip joint (cut-out). This complication is more common in unstable trochanteric and subtrochanteric fractures (Figure 6).

- **Nonunion;** when the fracture fails to heal. Usually because of instability of the fracture or impaired blood supply to the fracture site. It is defined when there is no healing in a hip fracture for > 6 months. However, nonunions are relatively rare in intertrochanteric and subtrochanteric fractures (Figure 7).

- **Malunion;** when the fractures heals in an imperfect position. There is a number of muscles attachment at the proximal part of the femur, The gluteal and thigh muscles tend to pull in different directions on the bone fragments, leading to displacement or overlap and healing incorrectly. This can lead to limb shortening, medialisation of the femur shaft, varus or valgus deformity, rotational malunion, functional deficit and painful prominent hardware, usually because of fracture instability and collapse before the healing.

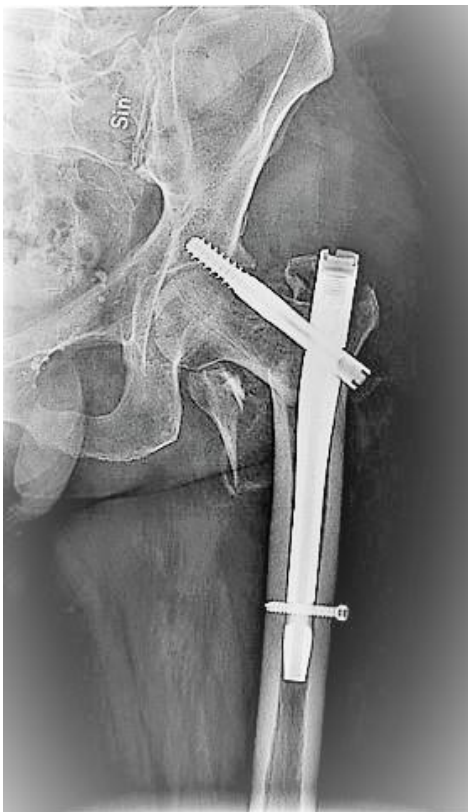
- **Anterior perforation of the distal femur;** following internal fixation with intramedullary nails, usually because of fracture instability.

- **Peri-implant fracture;** more common with nail than plate fixation (Osnes et al 2001).

- **Infection;** deep or superficial wound infections are often associated with excessive soft tissue damage, which lead to difficulties in the management and may demand long-term antibiotics treatment or reoperations. One of the theories of the advantages by using the intramedullary nailing technique is reduced incidence of infections as a result of less soft tissue damage.

In case of failure, a reoperation should be done by an alternative surgical method such as a reosteosynthesis or a hip prosthetic replacement (Mariani and Rand 1987, Sarathy et al. 1995, Said et al. 2006).

**Figure 6. Cut-out**



**Figure 7. Non-union**



## **5.2 Other complications**

Many patients are sick and have a pronounced comorbidity before they suffer from a hip fracture and it is common for the fall to occur due to impaired general conditions because of illness in these elderly patients. Furthermore, the stress and the damage of the operation increase the risk of medical complications such as myocardial infarction, stroke, confusion, pulmonary inflammation and infection, urinary tract infection and pressure sores.

The early postoperative period has a high risk for mortality with the 30-day mortality reaching up to 13 % (Hu et al. 2012).

Because of the injury and the conditions after surgery patients are not fully mobilised, and this may contribute to the formation of blood clots. Deep vein thrombosis (DVT) is a common complication after hip fractures due to impaired blood circulation and hypercoagulation of the blood because of the injury and the surgery. Pulmonary embolism (PE) may occur when coagulated blood detaches from a DVT in the leg veins and passes through up to the lungs. The circulation to parts of the lungs becomes affected and this can be fatal. Without prophylaxis, the prevalence of fatal PE within three months after hip fractures increases from 3.6 to 13 % (Geerts et al. 2001). Mortality is significantly higher after acute hip fracture surgery compared with elective hip and knee replacement surgery. This can be explained by the fact that hip fracture patients have higher age and are suffering from more medical problems (Borgström et al. 1965, Schröder et al. 1993, Perez et al. 1995, Geerts et al. 2001).

## **5.3 Blood loss and red blood cell (RBC) transfusion**

Major orthopedic surgery, such as the internal fixation of trochanteric and subtrochanteric fractures, is often associated with significant blood loss, and a subsequent need for blood transfusion. Before an operation it is important that a proper examination of the patient's blood and coagulation is performed. The causes of bleeding are multifactorial. Increased fibrinolytic activity is one of them (Sculco et al. 1998, Mannucci et al. 2007). Several methods (Keating et al. 2005) have been used to reduce perioperative blood loss, including hypotensive anesthesia (Pasch et al. 1986, Enlund et al. 1997). The use of allogeneic blood products can transmit infectious diseases, modulate the immune system and increases the risk of postoperative infections (Landers et al. 1996, Carson et al. 1999, Friedman et al. 2014, Annual SHOT Report 2017).

One of the alternative methods to reduce bleeding is administration of antifibrinolytic agents, such as tranexamic acid, before and/or during surgery to stabilise the multiple micro clots formed at the surgical site and thus reduce blood loss secondary to increased fibrinolysis (Verstraete et al. 1985, Dunn et al. 1999, Sadeghi et al. 2006, Molenaar et al. 2007, Zimmerman et al. 2007, Vijay et al. 2013, Mohib et al. 2015).

## **6. Time to surgery**

The consequence of waiting time for surgical intervention on the outcome in hip fractures is controversial. Some studies have shown that long waiting time for surgery of patients with hip fractures is associated with long hospital stay, increased mortality and/or morbidity and decreased functional outcome. Therefore, surgery is recommended for the majority of these

patients within 24 hours after arrival at hospital (Villar et al.1986, Perez et al. 1995, Orosz et al. 2004, Bottle et al. 2006, Novack et al.2007, Simmunovic et al. 2010).

The National American Guideline of the American Academy of Orthopaedic Surgeons mentioned (in September 2014) moderate evidence as support that hip fracture surgery within 48 hours of admission is associated with better outcomes.

On the other hand, it has been described in other studies that waiting time to surgery has no impact on the outcome, and other observational studies have found no association between time to surgery and mortality or morbidity and has concluded that further research is needed (Manninger et al. 1989, Rogers et al. 1995, Grimes et al. 2002, Bergeron et al. 2006).

It is probably important in hip fracture patients to start with a prophylaxis anticoagulant promptly, as in many cases, hip fracture patients do not go through surgery within 24 or 48 hours after arrival at the hospital, leaving them in risk for thromboembolic events during that time if they unprotected with a prophylaxis against thrombosis or DVT. Furthermore, most of the hip fracture patients are frail, elderly and associated excessive comorbidities and most of them require a special care preoperatively with accurate medical evaluation and stabilisation before starting the surgical management. After suffering a hip fracture, any postpone in the presentation to the hospital and the delay in time to surgery are associated with a significantly increased risk for thromboembolic events. A previous study showed that there was a significant difference in the prevalence of DVT in patients who had delayed admission to the hospital more than 48 hours after a hip fracture (55%), compared with those admitted to the hospital within 48 hours (6%) (Hefley et al. 1996).

## **7. Warfarin and hip fracture**

It is common in this elderly population with comorbidity such as atrial fibrillation, prosthetic heart valves and thromboembolic disorders that patients are treated with vitamin K antagonists (warfarin). This elderly group on warfarin therapy is prone to osteoporotic fractures, such as trochanteric and subtrochanteric hip fractures. Current recommendations state that surgery for hip fractures following patient optimisation should be undertaken early, ideally within 24–48 hours (Klein et al. 2006, Sircar et al. 2007). This can be a challenge for orthopaedic surgeons as warfarin therapy can cause significant delays in the surgical management of these patients (Tharmarajah et al. 2007).

Using a reversal antidote to prevent the risk of excessive bleeding at the time of hip surgery is required. This, however, can be associated with a risk of thromboembolism that is already affected by immobility and hip surgery itself (Dahl et al. 2000, Gallus et al. 2000). On the other hand, delaying surgery may result in increased morbidity and mortality (Shiga et al. 2008).



# **Aims of the Studies**

## **Study 1**

To analyse the reoperation rate and identify the risk factors for reoperations within the context of a cohort study with a 5 to 11 years follow-up of 88 consecutive patients with trochanteric or subtrochanteric hip fractures that have undergone a reoperation with a hip replacement due to failure after internal fixation.

## **Study 2**

To evaluate the influence of delay to surgery >24 hours on the rate of red blood cell transfusion within the context of a large retrospective cohort including a consecutive series of 987 patients operated with an intramedullary nail due to a trochanteric or subtrochanteric hip fracture.

## **Study 3**

Within the context of a case-control study including 198 patients evaluate if early surgery (within 24 hours) of trochanteric or subtrochanteric hip fractures using intramedullary nailing is safe in patients on warfarin treatment after fast reversal of the warfarin effect.

## **Study 4**

To describe the epidemiology, treatment and outcome in terms of mortality within the context of a large descriptive epidemiological register study including a total of 10548 patients with trochanteric or subtrochanteric hip fractures registered in the national Swedish Fracture Register from January 2014 to December 2016.





# Patients and Methods

## Ethics

All studies were conducted in conformity with the Helsinki Declaration and each protocol was approved by the local ethics committee (Regional Ethics Committee in Stockholm, Sweden).

## Age and Gender

The mean age in *Study I* at the primary operation was 83 years for females and 81 years for men, with 86% of the patients being females. The median time between the primary IF operation and the secondary prosthesis operation was 5 months.

In *Study II* the mean age was 86 years with 72% of the patients being females.

In *Study III* the mean age was 86 years for both the warfarin patients and the control group, with 69% of the patients being females in both groups.

In *Study IV* the mean age for all patients was 82 years and a majority of the patients were females (69%).

## Study I

We included a total of 88 patients operated with secondary hip arthroplasties performed after failure of the primary operation with internal fixation of a trochanteric (63 patients) or subtrochanteric (25 patients) femoral fracture (Table 1). No pathological fractures were included. All patients were operated at the Department of Orthopaedics at Stockholm South General Hospital between January 1, 1999 and December 31, 2006. The primary implant was a plate with a sliding hip screw (SHS) for stable 2-part trochanteric fractures (30 patients), unstable 3- to 4-part trochanteric fractures and subtrochanteric fractures were treated with a short Gamma nail (SGN) (40 patients), a long Gamma nail (LGN) (11 patients) or a Medoff sliding plate (3 patients). All registered individual patients' records were searched until August 31, 2011, or death, to find information about all reoperations, intraoperative blood loss, operating times, adverse events and mortality. In addition, the Swedish personal identification number was used to perform a search in the national registry of the National Board of Health and Welfare to find patients who had been treated elsewhere in Sweden for a reoperation up to August 31, 2011. No such cases were found. The median follow-up time was 4.0 (0–11) years for all cases, and 7.9 (4.9–11) years for those who were still alive on August 31, 2011.

A cut-out of the sliding screw due to a fracture nonunion or femoral head necrosis ( $n = 59$ ) was the most common indication for the secondary operation, followed by nonunion ( $n = 21$ ), femoral head necrosis ( $n = 6$ ), posttraumatic osteoarthritis ( $n = 1$ ) or an unacceptable implant position and fracture reduction ( $n = 1$ ). The prosthesis type used for the secondary operation was a THA in 63 patients and an HA in 25 patients. In the HA patients, the prosthesis used was a cemented Exeter HA with a unipolar Universal Head Replacement ( $n = 7$ ) or a bipolar Bicentric Head with a 28-mm head ( $n = 18$ ). Standard-length femoral stems were used in 47 of the hips and long femoral stems in 41. An anterolateral surgical approach (Hardinge et al. 1982)

with the patient in a lateral position was used in 53 patients and a posterolateral surgical approach (Moore et al. 1957) with the patient in a lateral position was used in 35 patients. The total number of surgeons was 29 (23 consultants and 6 registrars). The patients were mobilised on the day after surgery using crutches and allowed to bear weight as tolerated.

## Study II

We identified a consecutive series of 987 patients, 50 years of age and above, operated with an intramedullary nail due to a non-pathological unstable trochanteric or subtrochanteric femoral fracture between January 1, 2011 and December 31, 2013. All registered individual patients' records at the Stockholm South General Hospital were searched to find and collect information about patient characteristics, use of pharmacological agents affecting the hemostasis, timing of the surgery (time from admission to surgery in hours) and RBC transfusions given before, during, and after the surgery. Mortality data was obtained from the Swedish National Cause of Death Register. Follow-up time was 1 year.

## Study III

We identified and included 99 patients on warfarin medication operated at the Department of Orthopaedics at Stockholm South General Hospital with an intramedullary nail due to a trochanteric or subtrochanteric hip fracture from January 2011 to December 2014. The patients were >60 years of age, had sustained an acute non-pathological fracture due to a low-energy trauma without other injuries demanding acute surgery or causing major bleeding and without late presentation to the hospital (>24 hours from injury). All patients were operated within 24 hours, calculated from the hospital admission to the start of the surgery.

A 1:1 ratio control group (99 patients) which had no anticoagulation medication at all, matched for age, gender and surgical implant (long or short nail), operated within 24 hours, was identified. These patients were also operated at our institution during the same time period due to non-pathological trochanteric or subtrochanteric fractures after a low-energy trauma. Patients' records were searched in order to find information including demographic data, medication, pre- and postoperative data and adverse events occurring during the hospital stay. Mortality data was obtained from the Swedish National Cause of Death Register. Follow-up time was 1 year.

To compare the state of health of both groups we used the ASA class and the Charlson Comorbidity Index.

Before the operation all patients on warfarin with an INR >1.5 were reversed to  $\leq 1.5$  using vitamin K (Konakion®) or four-factor prothrombin complex concentrate (PCC) (Ocplex®), or both.

**Calculation of blood-loss** was based on the haemoglobin (Hb) level (g/dL) and the estimated blood volume (BV). The later was calculated according to gender, weight and height using the formulae (Gao F-Q et al. 2015):

$BV (l) = \text{height (m)}^3 \times 0.356 + \text{weight (kg)} \times 0.033 + 0.183$  for women.

$BV (l) = \text{height (m)}^3 \times 0.367 + \text{weight (kg)} \times 0.032 + 0.604$  for men.

In assumption that the BV on day 2–4 after surgery was the same as that before surgery and that all the red blood cell (RBC) transfusion units contained the same number of cells (a unit of RBC contains approximately 250 ml and 45 g Hb). The loss of Hb (in grams) was then estimated according to the formula:  $\text{Hb loss} = \text{BV} \times (\text{Hb adm} - \text{Hb fin}) + \text{Hb trans}$ .

The Hb loss is the calculated total Hb loss (g), Hb adm is the haemoglobin value (g/dL) on admission, Hb fin is the final recorded Hb value (g/dL) on day 2–4 after surgery, and Hb trans is the total amount of haemoglobin (g) in the transfused RBC units before the measurement of Hb fin. We finally estimated the Blood loss (BL) using the following formula:  $\text{BL (mL)} = 1000 \times (\text{Hb loss} / \text{Hb adm})$ .

### **Study II and III - RBC transfusion**

In *Study II and III* no strict transfusion protocol was used, but the patients were given RBC transfusion based on their current Hb level and a cut-off level of 10 g/dL was mostly used. One unit of RBC contained approximately 250 mL. However, the decision whether to transfuse was always made on an individual basis with consideration of several factors, such as ongoing cardiac disease and blood pressure and other factors were taken into consideration in addition to the Hb value.

### **Study II and III - Fracture type**

In *Study II* 736 patients had an unstable trochanteric fracture (Jensen-Michaelsen type III-V, OTA/AO type 31 A2, A3) and 251 patients had a subtrochanteric fracture (OTA/AO type 32A, 32B, 32C).

In *Study III* 68 warfarin patients and 66 patients in the control group had an unstable trochanteric fracture (Jensen-Michaelsen type III-V, OTA/AO type 31 A2, A3) and 31 warfarin patients and 33 control patients had a subtrochanteric fracture (OTA/AO type 32A, 32B, 32C) (Table 1).

### **Study II and III - Surgical procedures & Implant types**

In *Study II and III* all operations were performed on a radiolucent traction table and spinal anaesthesia was the standard method for anaesthesia. Implants used were a short Gamma3 nail (Stryker Howmedica, Kalamazoo, MI) for trochanteric fractures and for subtrochanteric fractures a long Gamma3 nail (Stryker Howmedica) was used (Table 1).

As antibiotic prophylactics Cloxacillin 2 g administered within 30 min before the operation was used.

As thromboprophylactics low-molecular weight heparin (5000 U dalteparin or 4500 U tinzaparin) given subcutaneously once daily with the first dose given in the evening of the day of admission or the evening after the operation with a minimum of 2 h after wound closure and then continued for 4 weeks, was used. In *Study III* thromboprophylactic therapy was continued until INR was on a therapeutic level for the warfarin patients and for 4 weeks for the control patients.

Postoperatively the patients were mobilised the day after the surgery using necessary walking aids and usually allowed full weight-bearing as tolerated.

## Study IV

Between January 2014 and December 2016 detailed epidemiologic data (patient age and gender), injury data (injury location, cause and date), fracture data (fracture type, treatment and timing of surgery) and mortality data about patients with trochanteric or subtrochanteric femoral fractures were collected from the database of the national Swedish Fracture Register (SFR). The inclusion criteria in this study were primary surgically treated traumatic non-pathological fractures in patients aged 18 years and above. A total of 10548 entries fulfilling the inclusion criteria were identified in the register and included in the study.

The variables were categorised as; 1. Injury location: at the patients' residence or accommodation, in a public place, in a street/road or in an unspecified place. 2. Cause of injury: a fall at the same level, an unspecified fall, a fall from height, a traffic injury or any other cause. There is no strict guideline for classification of the energy level in the SFR and it is up to the registering doctor to distinguish between high- and low-energy trauma mechanism. Fractures were classified according to the AO/OTA classification and the ICD-10 code. Surgical implants were categorised as: a short or long antegrade intramedullary nail, a retrograde intramedullary nail, a plate with sliding hip screw, any other type of plate fixation, a hip arthroplasty or any other type of implant (Table 1). The experience of the main surgeon was divided into: a specialist in orthopaedic surgery, an orthopaedic registrar or any other surgeon. Starting in early 2015, the time of the radiograph confirming the fracture and the time for the start of the operation was included in the register. From these variables, the time (in hours) from the radiograph to the start of the surgery was calculated. Patient mortality was presented as 30-day and 1-year mortality.

At the start of this study in January 2014 the number of affiliated departments that register data was 24, and end of the study in December 2016 the number of affiliated departments was 39. The total number of departments in Sweden that are treating fractures is estimated to 54. Data on patient mortality is obtained to the register via linkage to the national Swedish Death Register.

**Table 1. Patients fracture- and implant types for all studies**

Study I n = 88				Study II n = 987				Study III n = 198				Study IV n = 10548					
Primary fracture type				Primary fracture type				Warfarin group n = 99		Control group n = 99		Fx type according to AO/OTA class					
Trochanteric fx		Subtrochanteric fx		Trochanteric fx		Subtrochanteric fx		Troch. fx	Subtroch. fx	Troch. fx	Subtroch. fx	31-A1	31-A2	31-A3			
63		25		736		251		68	31	66	33	3067	5191	2288			
Primary implant type				Primary implant type				Primary implant type				Primary implant type					
SGN	SHS	LGN	MSP	Op ≤24h	Op >24h	Op ≤24h	Op >24h	SGN	LGN	SGN	LGN	SGN	LGN	SHS	Other		
44	30	11	3	648	88	221	30	66	33	66	33	4411	1903	3935	299		
Secondary prosthesis type				Secondary prosthesis type				Secondary prosthesis type				Secondary prosthesis type					
THA		Bipolar HA		Unipolar HA		THA		Bipolar HA		Unipolar HA		THA		Bipolar HA		Unipolar HA	
63		18		7		735		252		735		252		735		252	
Op ≤24h		Op >24h		Op ≤24h		Op >24h		Op ≤24h		Op >24h		Op ≤24h		Op >24h		Op ≤24h	
646		89		223		29		646		89		223		29		646	

## ASA Classification and CCI

The general physical health prior the surgery was assessed according to the ASA (American Society of Anesthesiologists) classification (Owens et al. 1978) which is an effective mortality predictor in hip fracture patients (Söderqvist et al. 2009). This assessment was used in *Study II* and *III* and was made by the attending anaesthetist before the surgery. ASA 1 indicates a normal healthy patient, ASA 2 is a patient with mild systemic disease, ASA 3 is a patient with severe systemic disease, ASA 4 is a patient with severe systemic disease that is a constant threat to life and ASA 5 is a moribund patient who is not expected to survive without the operation. There was no ASA 5 patient in the studies. For analysis, the ASA results were further dichotomised into ASA 1-2 and 3-4.

In addition, the Charlson comorbidity index (CCI) (Charlson et al. 1987) was used. The CCI has been shown valid as a prognostic indicator and a measure of 1-year mortality by classifying comorbidity conditions (17 comorbidities) (De Groot et al. 2003). A higher CCI score indicates increasingly severe systemic diseases and increased mortality risk. In *Study III*, in order to compare the state of health of both groups, we preferred the use of CCI to address the confounding influence of comorbidities and to standardise collection of the comorbidity data from the patient's record.

## Statistical Methods

In *Study I* and *II* the nominal variables were tested by the Fisher's exact test, and in *Study II* the Mann-Whitney U test was used for scale variables in independent groups. All tests were two-sided.

Cox regression was used to test and evaluate factors associated with reoperation risk in *Study I* and logistic regression was used to test increased incidence of transfusion in *Study II*. First, crude associations for each variable were studied in univariable models. Secondly, a multivariable model with all independent factors was used to study the adjusted associations.

In *Study III* the nominal variables were tested by the Chi-square test or the Fisher's exact test. The Mann-Whitney U-test was used for comparisons of nonparametric variables in independent groups. The Student's t-test was used for comparisons of normally distributed variables in independent groups. Normality was tested with the Kolmogorov-Smirnov test. All tests were two-sided.

In *Study IV* statistical testing of the variables was not performed because of the descriptive nature of the study. Variables are presented as proportions of all registered fractures, meaning the available number of inputs in the register excluding any missing values. For scale variables mean  $\pm$  standard deviations (SDs) are presented.

In all studies the results were considered significant at  $p < 0.05$ . The statistical software used in *Study I* was SPSS Statistics 18 for Windows and the statistical software used in *Studies II-IV* was IBM SPSS Statistics, version 23 for Windows (SPSS Inc., Chicago, USA).

## Radiological Analysis

In *Study I-III* the radiological analysis of the fracture type and implant type were performed by the authors through an individual analyse of the radiographs which were saved in the patient's record for every patient included in the studies.

## Arthroplasties and Implants for Internal Fixation

Types of prosthesis and IF implants used in *Study I-III* are shown in Figure 8.

**Figure 8**

**Radiographs of the prostheses and IF implants used in the studies**



**Cemented THA**



**Cemented Unipolar HA**



**Cemented Bipolar HA**



**Sliding Hip Screw  
DHS**



**Short Gamma Nail  
SGN**



**Medoff Sliding Plate  
MSP**



**Long Gamma Nail  
LGN**

## Results

### Study I

The mean operative time for the prosthesis surgery was 153 (75–355) min, and the mean intraoperative blood loss was 1.1 (0.3–3.9) L. Of 88 included hips 14 were reoperated, giving a reoperation rate of 16%. The causes for reoperations were:

**Periprosthetic femoral fractures** (Figure 9) in 6 patients, 4 patients of those were reoperated with open reduction and internal fixation with plate osteosynthesis and 2 patients were reoperated with a revision to a longer femoral stem (1 of whom also had a plate osteosynthesis performed). Of the 6 patients who sustained a periprosthetic fracture, 5 were primary operated using standard-length stems and 1 patient had a long stem.

**Deep prosthetic infections** in 5 patients, 4 of those were successfully treated with debridements (1 to 3 times) plus antibiotics. In 1 patient, the prosthesis was extracted permanently due to persistent infection despite debridement and antibiotic treatment.

**Dislocation of the prosthesis** in 3 patients, 2 underwent a successful closed reduction and had no recurrent dislocations. In the third patient, a closed reduction failed. In the subsequent open procedure, the stem was found to be loose and was therefore revised using cement-in-cement fixation. No further dislocations occurred in this patient. (Table 2).

The periprosthetic fractures occurred late (2–59 months) after surgery, in contrast to dislocations and deep infections which all occurred within the first 2 months of the prosthesis operation.

A primary analysis indicated an increased risk for reoperation when using standard-length femoral stems (11/47), compared to long stems (3/41) ( $p = 0.05$ ). There was no statistically significant differences in the reoperation rate of the prosthesis between primary trochanteric and subtrochanteric fractures, or between the primary implant types: intramedullary nails (SGN and LGN) and plates (SHS and Medoff plate), between THAs and HAs, between the anterolateral and the posterolateral surgical approaches or operations performed by consultants and those performed by registrars. Multivariable Cox regression analysis was performed adjusting for fracture type, primary implant type, prosthesis type and surgical approach: HR = 4 (1.0–13) ( $p = 0.06$ ) (Table 3).

**Figure 9**  
Periprosthetic femoral fracture



**Table 2. Patients with reoperations of the secondary prosthesis (n = 14)**

A	B	C	D	E	F	G	H	I
1	70	Male	T	SHS	Post traumatic osteoarthritis	THA	Deep infection	7 weeks. Debridement x 1. Later extraction of prosthesis
2	78	Male	T	SGN	Cut out	Bipolar HA	Deep infection	2 weeks. Debridement x 1
3	85	Female	S	LGN	Cutout	Bipolar HA	Deep infection	3 weeks. Debridement x 1
4	85	Female	T	SGN	Cutout	THA	Deep infection	3 weeks. Debridement x 3
5	87	Female	S	LGN	Nonunion	Unipolar HA	Deep infection	2 weeks. Debridement x 2
6	72	Female	T	SHS	Femoral head necrosis	THA	Periprosthetic fracture	253 weeks. Revision of femoral stem + plate osteosynthesis
7	80	Female	T	SGN	Cutout	THA	Periprosthetic fracture	63 weeks. Revision of femoral stem
8	80	Female	S	LGN	Nonunion	THA	Periprosthetic fracture	21 weeks. Plate osteosynthesis
9	81	Female	S	SGN	Cutout	THA	Periprosthetic fracture	56 weeks. Plate osteosynthesis
10	93	Female	T	SGN	Cutout	Unipolar HA	Periprosthetic fracture	8 weeks. Plate osteosynthesis
11	95	Female	T	SGN	Cutout	Bipolar HA	Periprosthetic fracture	23 weeks. Plate osteosynthesis
12	77	Female	T	SGN	Cutout	THA	Dislocation	3 weeks. Revision of femoral stem
13	84	Female	T	SGN	Nonunion	THA	Dislocation	3 weeks. Closed reduction x 1
14	86	Male	T	SHS	Nonunion	THA	Dislocation	5 weeks. Closed reduction x 1

A Patient  
 B Age  
 C Sex  
 D Primary fracture type  
   S: Subtrochanteric  
   T: Trochanteric  
 E Primary implant  
   SHS: sliding hip screw;  
   SGN: short Gamma nail;  
   LGN: long Gamma nail;  
 F Indication for secondary prosthesis  
 G Secondary prosthesis type  
   THA: total hip arthroplasty;  
   HA: hemiarthroplasty.  
 H Indication for reoperation of secondary prosthesis  
 I Time to reoperation and history

**Table 3. Baseline data in relation to the occurrence of reoperation**

	No reoperation (n = 74)	Reoperation (n = 14)	p-value	Cox regression HR (95% CI)	p-value
Primary fracture type					
Trochanteric	53	10		1 <sup>c</sup>	
Subtrochanteric	21	4	1.0	1.2 (0.3–4.5)	0.8
Primary implant type					
Intramedullary nail <sup>a</sup>	44	11		1 <sup>c</sup>	
Plate <sup>b</sup>	30	3	0.2	0.4 (0.1–1.4)	0.1
Secondary prosthesis type					
THA	54	9		1 <sup>c</sup>	
HA	20	5	0.5	1.7 (0.5–5.2)	0.4
Femoral stem length					
Long stem	38	3		1 <sup>c</sup>	
Standard length	36	11	0.05	3.6 (1.0–13)	0.06
Surgical approach					
Anterolateral	44	9		1 <sup>c</sup>	
Posterolateral	30	5	1.0	0.8 (0.3–2.7)	0.8

<sup>a</sup> includes short and long Gamma nails.  
<sup>b</sup> includes sliding hip screw and Medoff plates.  
<sup>c</sup> reference.



## Study II

In *Study II* most of the patients (n = 869; 88%) were operated upon within 24 hours after hospital admission. Approximately half of the patients (510/987; 52%) were on anticoagulant medication, with low-dose ( $\leq 75$  mg) ASA being the most commonly used drug.

**Transfusions:** A total number of 701 patients (71%) had an RBC transfusion pre-, peri-, or postoperatively. There was an increased preoperative transfusion rate among patients delayed for more than 24 hours to surgery (26/118; 22%), compared with those operated within 24 hours (53/869; 6.1%) ( $p < 0.001$ ). No differences were found in peri- or postoperative transfusion rates.

Logistic regression analysis was performed to evaluate factors influencing the incidence for preoperative transfusions. Univariate logistic regression indicated a more than 3-fold risk of transfusion if surgery was delayed more than 24 hours (relative risk (RR), 3.6; 95% confidence interval (CI), 2.4–5.3). Multivariate logistic regression, adjusting for all covariates, indicated a roughly 4-fold increased risk of transfusion if surgery was delayed greater than 24 hours (RR, 3.9; 95% CI, 2.3–6.1). In addition, anticoagulation therapy (other than low-dose ASA) was associated with an increased risk of transfusion (RR, 2.0; 95% CI, 1.1–3.5), and an increasing preoperative Hb value (analysed as a continuous variable) was associated with a decreased risk for transfusion (RR, 0.3; 95% CI, 0.2–0.4) (Table 4).

Patients without anticoagulant medication, or on low-dose ASA, had less preoperative but more postoperative transfusions compared with patients on more potent anticoagulants (Table 5).

In patients who received preoperative transfusions, the number of units was greater in the group delayed to surgery compared with those operated within 24 hours ( $p = 0.01$ ). No such difference was demonstrated for patients receiving peri- or postoperative transfusions (Table 6).

**Table 4.**

**Logistic Regression to evaluate factors associated with increased preoperative transfusion rate**

	All	Preoperative Transfusion	Univariable		Multivariable	
	n	n (%)	RR (95% CI)	P	RR (95% CI)	P
Anticoagulants						
None or low-dose ASA	847	61 (7.2)	1 (reference)		1 (reference)	
All other	140	18 (13)	1.8 (1.1–2.8)	<b>0.02</b>	2.0 (1.1–3.5)	<b>0.03</b>
ASA class						
1–2	273	10 (3.7)	1 (reference)		1 (reference)	
3–4	714	69 (9.7)	2.6 (1.4–4.7)	<b>0.003</b>	1.7 (0.7–3.6)	0.2
Fracture type						
Intertrochanteric	736	50 (6.8)	1 (reference)		1 (reference)	
Subtrochanteric	251	29 (12)	1.7 (1.1–2.6)	<b>0.02</b>	1.5 (0.8–2.6)	0.2
Time to surgery						
$\leq 24$ h	869	53 (6.1)	1 (reference)		1 (reference)	
$> 24$ h	118	26 (22)	3.6 (2.4–5.3)	<b>&lt;0.001</b>	3.9 (2.3–6.1)	<b>&lt;0.001</b>
Preoperative Hb*	987	79 (8.0)	0.3 (0.2–0.4)	<b>&lt;0.001</b>	0.3 (0.2–0.4)	<b>&lt;0.001</b>

**Table 5. Number of patients given RBC Transfusion, in relation to anticoagulants therapy**

	<b>None or Low-Dose ASA (n = 847)</b>	<b>More Potent Anticoagulants (n = 140)</b>	<b><i>P</i></b>
Preoperative transfusion, n (%)	61 (7.2)	18 (13)	0.03
Perioperative transfusion, n (%)	65 (7.7)	11 (7.9)	0.9
Postoperative transfusion, n (%)	596 (70)	83 (59)	0.01

**Table 6. Number of RBC Units given in transfused patients, in relation to timing of surgery**

	<b>≤24 h</b>	<b>&gt;24 h</b>	<b><i>P</i></b>
Preoperative transfusion	1.7, 2 (1–4)	2.3, 2 (1–6)	0.01
Perioperative transfusion	1.4, 1 (1–3)	1.6, 1 (1–4)	1.0
Postoperative transfusion	2.7, 2 (1–17)	2.5, 1 (1–9)	0.2

Mean and Median (Range)

### Study III

A total of 198 patients divided into two matched groups were included in the study. In the warfarin patients (n=99) the most common indications for warfarin treatment were: atrial fibrillation (n=55/99), atrial fibrillation with previous stroke (n=21/99) or previous embolism (n=7/99). One warfarin patient was treated with low-dose ASA (75 mg) and one patient with dipyridamol in addition. No other anticoagulants were used by the warfarin patients. The initial mean ( $\pm$ SD, range) INR of the warfarin patients was 2.5 ( $\pm$ 0.6, 1.2–4.4). Before the surgery patients with INR >1.5 were reversed to  $\leq$ 1.5 using vitamin K (n=33/99), PCC (n=14/99) or both (n=45/99), no plasma was used for reversing the warfarin effect (Table 7).

The warfarin patients in general had an impaired state of health compared with the control patients, displayed as a lower number of patients with ASA class 1–2 (n=5 versus 18, p=0.007) and a higher mean ( $\pm$ SD) Charlson comorbidity index (5.4 $\pm$ 1.3 versus 5.0 $\pm$ 1.2, p=0.1). The warfarin patients also had a higher mean ( $\pm$ SD) weight (69 $\pm$ 14 versus 64  $\pm$ 12 kg, p=0.02), but similar height.

All patients were operated within 24 h after admission, but the mean ( $\pm$ SD) time to surgery was shorter for the control group (14 $\pm$ 5.6 h) compared to the warfarin patients (16 $\pm$ 4.8 h) (p=0.04). There was no difference in the time of the surgery between the groups. The mean ( $\pm$ SD, range) length of stay was 4.9 ( $\pm$ 2.6, 1–15) days for the warfarin patients and 4.9 ( $\pm$ 2.6, 1–16) days for the control group (p=0.9). There was no difference in number of re-admissions within 30 days between the warfarin patients (9.1%, n=9/99) and the control group (16%, n=16/99) (p=0.2).

**Transfusions and blood-loss:** The total rate of patients given any RBC transfusion was 65% (n=128/198). The mean ( $\pm$ SD) preoperative (on arrival) Hb was lower in the control group (12.3 $\pm$ 1.5 g/dL) compared to the warfarin group (12.8 $\pm$ 1.6 g/dL) (p=0.03) as was the mean ( $\pm$ SD) postoperative Hb (9.9 $\pm$ 1.4 g/dL) compared to (10.4 $\pm$ 1.2 g/dL) (p=0.01). There were no differences in the late (day 2–4) Hb or the calculated blood-loss between the groups (Table 8).

There was a greater proportion of control group patients who received postoperative transfusions (71%, n=70/99) compared to warfarin patients (54%, n=53/99) (p=0.02). There were no differences in the pre- or intraoperative transfusion rates, or the mean total number of units given between the groups. Four patients, 3 in the warfarin and 1 in the control group, were given plasma postoperatively.

**Table 7. Details on warfarin patients**

<b>Indication for warfarin</b>	<b>n (%)</b>
Atrial fibrillation	55 (56)
Atrial fibrillation with previous stroke	21 (21)
Previous embolism	7 (7.1)
Mechanical valve replacement	6 (6.1)
Atrial fibrillation with biological valve replacement	4 (4.0)
Atrial fibrillation with ischemic heart disease	3 (3.0)
Previous stroke	3 (3.0)
<b>Methods for reversing warfarin preoperative</b>	<b>n (%)</b>
Vitamin K + PCC	45 (46)
Vitamin K	33 (3.0)
PCC	14 (14)
None	7 (7.1)
PCC = four-factor prothrombin complex concentrate	

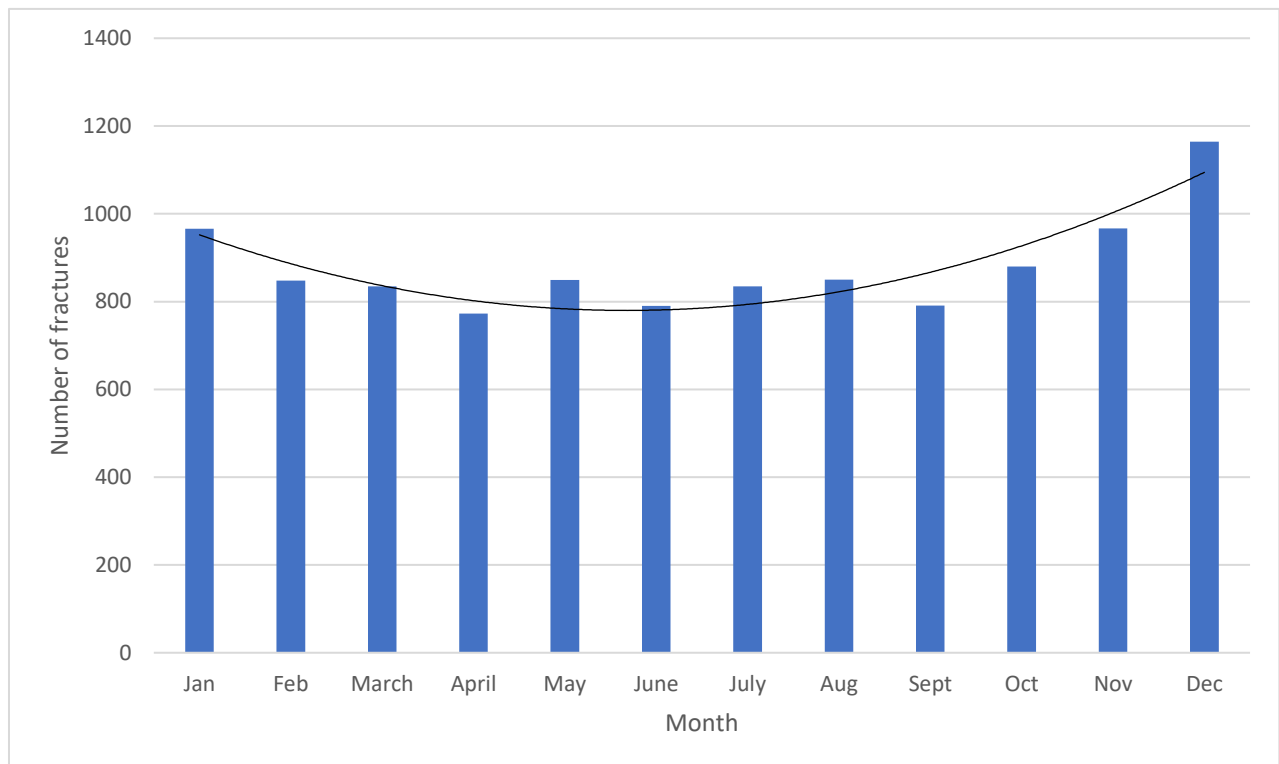
**Table 8. Blood-loss and transfusions for all patients**

	<b>Warfarin patients (n = 99)</b>	<b>Control group (n = 99)</b>	<b>p- value</b>
Preoperative Hb (g/dL), mean ( $\pm$ SD)	12.8 (1.6)	12.3 (1.5)	0.03
Postoperative Hb (g/dL), mean ( $\pm$ SD)	10.4 (1.2)	9.9 (1.4)	0.01
Day 2-4 Hb (g/dL), mean ( $\pm$ SD)	10.7 (1.1)	10.7 (1.0)	0.7
Calculated blood loss (ml), mean ( $\pm$ SD)	1306 (960)	1285 (588)	0.5
Patients given preoperative transfusion, n (%)	5 (5.1)	1 (1.0)	0.2
Patients given intraoperative transfusion, n (%)	8 (8.1)	12 (12)	0.5
Patients given postoperative transfusion, n (%)	53 (54)	70 (71)	0.02
Patients given any <sup>1</sup> transfusion, n (%)	56 (57)	72 (73)	0.03
Transfusions per transfused patient, mean ( $\pm$ SD, range)	2.8 (2.8, 1-19)	2.8 (1.4, 1-8)	0.2
<sup>1</sup> Patients given transfusion pre- and/or intra- and/or postoperative.			

## Study IV

**Fracture epidemiology:** The location for the trauma was most commonly at the patients' current residence or accommodation (75%, n=7631/10249) and the most common cause of the injury was a fall at the same level (83%, n=8796/10548). Patient and injury epidemiology data in relation to fracture type are presented in Table 10. The fractured side was equally distributed with 50% (n=5253/10548) involving the right side and 50% (n=5295/10548) involving the left side. Fourteen patients (out of 10548, 0.1%) had an open fracture and 1.6% (n=169/10246) of the fractures were due to a high-energy trauma (Table 9). Fractures were most common during the winter months of January and December (Figure 10).

**Figure 9. Monthly distribution of trochanteric and subtrochanteric femoral fractures**



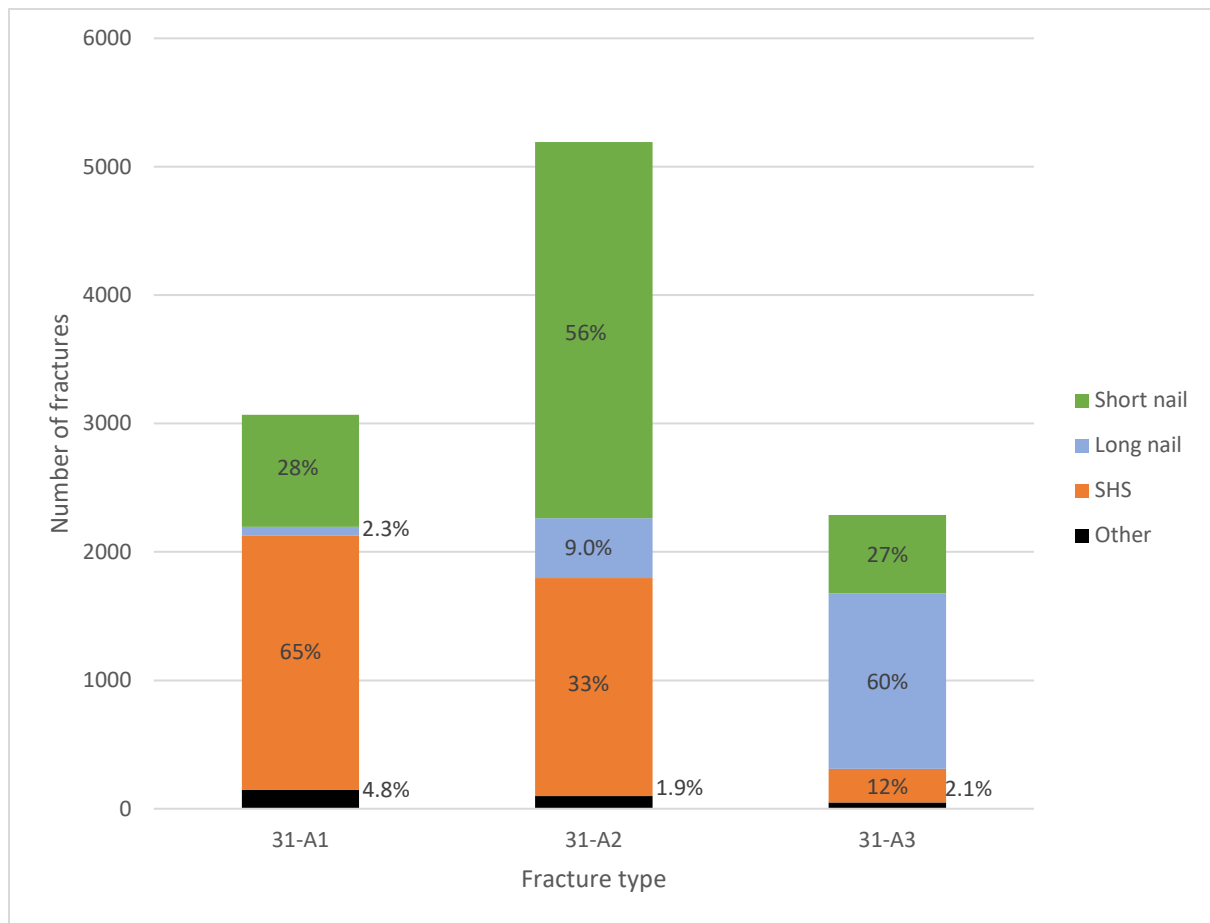
**Classifications:** The fractures were classified according to the ICD-10 code system as trochanteric (S72.1) in 78% (n=8260/10548) and as subtrochanteric (S72.2) in 22% (n=2288/10548) of the cases. In addition, fractures were classified using the AO/OTA classification as 31-A1 in 29% (n=3067/10546), as 31-A2 in 49% (n=5191/10546) and as 31-A3 in 22% (n=2288/10546) of the cases (Figure 5) (Table 9).

**Surgical results:** The majority of the patients were operated within 24 hours (75%, n=4471/5928), or 36 hours (90%, n=5354/5928) from time of the radiograph verifying the fracture to the start of the operation. The operations were performed during night time (22-08 hours) in 8.5% (n=522/6126) of the cases. The operations were performed by a specialist in orthopaedic surgery in 62% (n=6348/10186), an orthopaedic registrar in 37% (n=3759/10186) or by any other surgeon in 0.8% (n=79/10186) of the cases. Implants used were: a short antegrade intramedullary nail (42%, n=4411/10548), a plate with sliding hip screw (37%, n=3935/10548), a long antegrade intramedullary nail (18%, n=1903/10548), any other type of plate fixation (1.6%, n=167/10548), a retrograde intramedullary nail (0.6%, n=63/10548), a hip arthroplasty (0.5%, n=58/10548) or other implants (0.1%, n=11/10548). Implants used in relation to fracture type are presented in Figure 11. The distribution of the fractures by age and gender is presented in Figure 12.

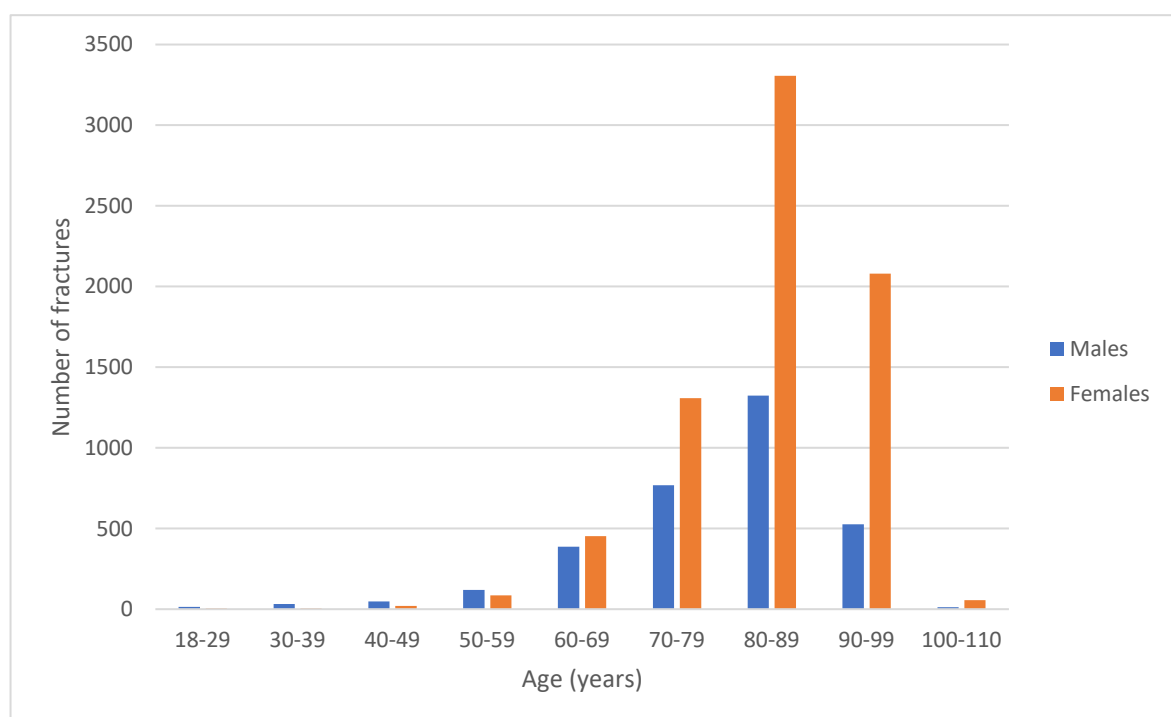
**Table 9. Overview of patient and injury epidemiology in relation to fracture type<sup>1</sup>**

		31-A1 (n=3067)	31-A2 (n=5191)	31-A3 (n=2288)
Age years, mean ( $\pm$ SD)		82.2 (10.3)	83.2 (9.8)	81.0 (12.0)
<b>% (n=)</b>				
Female gender		65 (1981/3067)	72 (3725/5191)	70 (1610/2288)
Injury location	At residence	74 (2202/2960)	75 (3816/5069)	73 (1611/2218)
	Public place	4.8 (143/2960)	4.6 (233/5069)	4.4 (97/2218)
	Street/road	3.5 (103/2960)	3.6 (183/5069)	4.1 (92/2218)
	Other	17 (512/2960)	17 (837/5069)	19 (418/2218)
Injury mechanism				
	Fall at same level	84 (2561/3067)	84 (4363/5191)	82 (1870/2288)
	Unspecified fall	9.7 (299/3067)	10 (532/5191)	8.9 (203/2288)
	Fall from height	3.6 (111/3067)	3.4 (179/5191)	5.7 (130/2288)
	Traffic	2.4 (74/3067)	1.7 (87/5191)	2.2 (51/2288)
	Other	0.7 (22/3067)	0.6 (30/5191)	1.5 (34/2288)
High energy trauma	Yes	1.4 (43/2971)	1.1 (55/5045)	3.2 (71/2229)
	No	97 (2890/2971)	98 (4924/5045)	96 (2134/2229)
	Unknown	1.3 (38/2971)	1.3 (66/5045)	1.1 (24/2229)
Open fracture		0 (0)	0.1 (5/5191)	0.4 (9/2288)
Data is presented in relation to the number of available inputs in the register				
<sup>1</sup> Fracture type according to the AO/OTA classification				

**Figure 11. Fracture type according to the AO/OTA classification in relation to treatment**



**Figure 12. Distribution of trochanteric and subtrochanteric femoral fractures by age and gender**



## **Mortality & Adverse Events (*Study I-IV*)**

In *Study I* the 6-month mortality was 8% and the 1-year mortality was 16%. The adverse events occurring within 6 weeks included a stroke in 3 patients (1 fatal), a cardiac infarction in 2 patients (1 fatal), and pneumonia, deep vein thrombosis, peroneal nerve palsy and extensive decubital ulcers in 1 patient each.

In *Study II* there were no statistically significant differences in 30-day or 1-year mortality for patients operated within or after 24 hours. The 30-day mortality was 77/869 (9%) and 11/118 (9%) ( $p = 0.9$ ) for patients operated within or after 24 hours, respectively. The corresponding numbers for the 1-year mortality was 237/869 (27%) and 39/118 (33%) ( $p = 0.2$ ) for patients operated within or after 24 hours, respectively.

There was an increased 1-year mortality among patients who had a transfusion (217/701; 31%) compared with those who did not have a transfusion (59/286; 21%) ( $p = 0.001$ ). No such difference was seen for the 30-day mortality: 65/701 (9%) and 23/286 (8%) ( $p = 0.6$ ) for patients who had and did not have transfusion, respectively.

In *Study III* the total in-house mortality was 3.5% ( $n=7/198$ ), the total 30-day mortality 8.1% ( $n=16/198$ ) and the total 1-year mortality 26% ( $n=52/198$ ). There were no statistically significance differences between the groups when comparing in-house, 30-day or 1-year mortality (Table10).

The total number of adverse events was 58: 27 in the warfarin group and 31 in the control group ( $p=0.6$ ). The most common adverse event was a urinary tract infection ( $n=28$ ), followed by a pressure ulcer ( $n= 20$ ), a pneumonia ( $n=16$ ), a myocardial infarction ( $n=1$ ) in the warfarin group and a stroke ( $n=1$ ) in the control group, no other thromboembolic disorders, such as pulmonary embolism or deep venous thrombosis were reported in any group. There were no statistically significance differences in the numbers of the different types of adverse events between the groups.



**Table 10. Mortality and adverse events for all patients**

	Warfarin patients (n = 99)	Control group (n = 99)	p-value
Myocardial infarction, n (%)	1 (1.0)	0	1.0
Stroke, n (%)	0	1 (1.0)	1.0
Pulmonary embolism, n (%)	0	0	
Deep venous thrombosis, n (%)	0	0	
Sepsis, n (%)	0	1 (1.0)	1.0
Pneumonia, n (%)	6 (6.1)	10 (10)	0.4
Urinary tract infection, n (%)	14 (14)	14 (14)	1.0
Pressure ulcer, n (%)	10 (10)	10 (10)	1.0
Any adverse event, n (%)	27 (27)	31 (31)	0.6
In-house mortality, n (%)	5 (5.1)	2 (2.0)	0.4
30-day mortality, n (%)	9 (9.1)	7 (7.1)	0.8
1-year mortality, n (%)	26 (26)	26 (26)	1.0

In **Study IV** the overall 30-day mortality was 7.7% (n=811/10548) and the 1-year mortality was 26% (n=2731/10548).

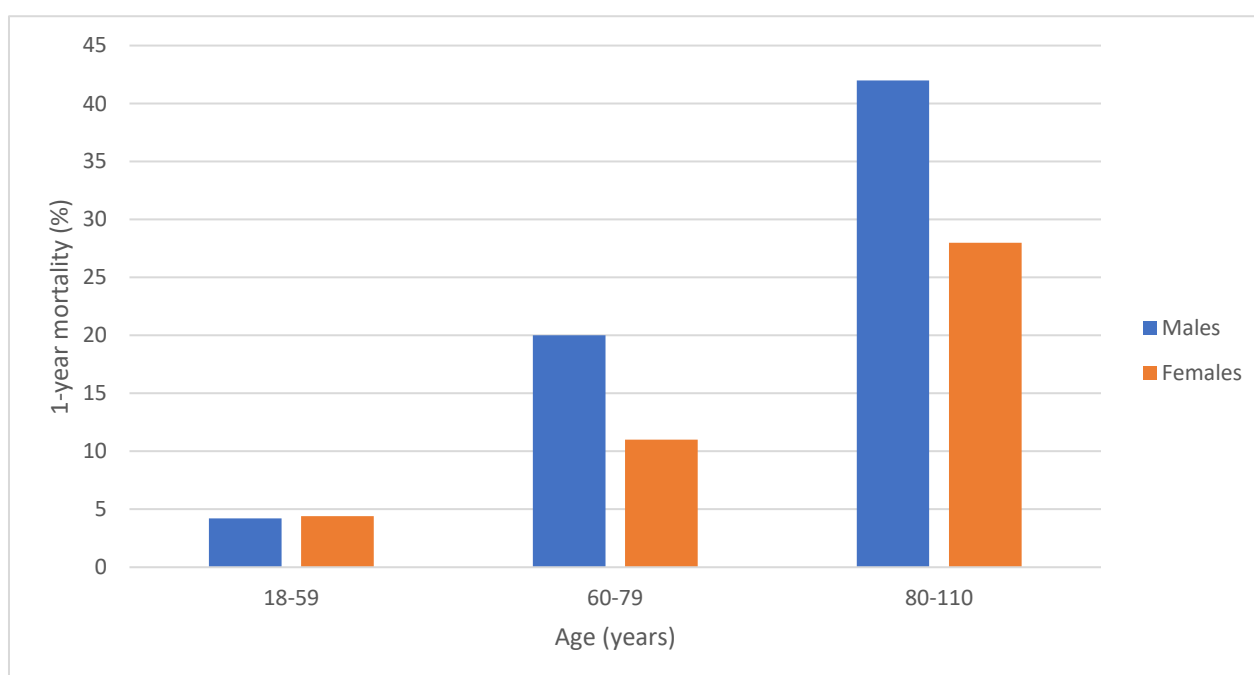
There was a higher 30-day and 1-year mortality for males compared to females. The 30-day mortality for males was (11%, n=355/3231) compared to females (6.2%, n=456/7317), and the 1-year mortality for males was (32%, n=1026/3231) compared to females (23%, n=1705/7317). There was a higher 30-day and 1-year mortality for patients operated >36 hours compared to patients operated ≤24 hours or ≤36 hours. The 30-day mortality for patients operated >36 hours was 9.8% (n=56/574) compared to patients operated ≤24 hours (7.8%, n=349/4471) or ≤36 hours (8.0%, n=429/5354). The 1-year mortality was 31% (n=179/574) for patients operated >36 hours, compared to patients with operations performed ≤24 hours (25%, n=1118/4471) or ≤36 hours (26%, n=1370/5354) (Table 11) (Figure 13).

**Table 11. Mortality in relation to gender, fracture type and surgical factors**

		30-day mortality % (n=)	1-year mortality % (n=)
All		7.7 (811/10548)	26 (2731/10548)
Gender	Female	6.2 (456/7317)	23 (1705/7317)
	Male	11 (355/3231)	32 (1026/3231)
Fracture type <sup>1</sup>	31-A1	7.2 (222/3067)	26 (793/3067)
	31-A2	8.2 (427/5191)	27 (1389/5191)
	31-A3	7.1 (162/228)	24 (548/2288)
Time to surgery	≤24 hours	7.8 (349/4471)	25 (1118/4471)
	≤36 hours	8.0 (429/5354)	26 (1370/5354)
	>36 hours	9.8 (56/574)	31 (179/574)
Time of surgery start	08-22	8.2 (460/5604)	26 (1476/5604)
	22-08	8.0 (42/522)	24 (126/522)
Implant	Short intramedullary nail	8.2 (362/4411)	27 (1167/4411)
	Long intramedullary nail	6.8 (130/1903)	24 (450/1903)
	Plate with sliding hip screw	7.6 (298/3935)	26 (1030/3935)
	Other	7.0 (21/299)	28 (84/299)

Data is presented in relation to the number of available inputs in the register  
<sup>1</sup> Fracture type according to the AO/OTA classification

**Figure 13. One-year mortality for different age-groups**



# General Discussion

The overall aim of this thesis was to study the surgical and medical complications that are associated with treatment of extracapsular proximal femoral fractures. The aim of *Study I* was to analyse the reoperation rate and identify the risk factors for reoperations in hip replacement which was done as a salvage procedure for the treatment of failure after internal fixation. In *Study II* the aim was to evaluate the influence of delay to surgery >24 hours on the rate of red blood cell transfusion. In *Study III* we have studied patients on warfarin to evaluate safety of early surgery (within 24 hours) after fast reversal of the warfarin effect. In *Study IV* we described the epidemiology, treatment and outcome in terms of mortality in trochanteric and subtrochanteric hip fracture patients in a large register study.

## 1. Surgical Complications

A prosthesis operation after a failed internal fixation of a trochanteric or subtrochanteric fracture is a challenge for the surgeon. Despite this, few authors have described the surgical outcome in these patients and the studies have usually only involved a few patients.

In *Study I*, the main finding was a reoperation rate of 16%, which highlights the complexity of the treatment. As a comparison, Bonneville et al. (2011) reported a reoperation rate of 3% in a prospective study of 106 patients followed for at least 6 months after an arthroplasty performed as a primary procedure due to a trochanteric fracture. We can also compare these figures to a previously published study from our department on patients with femoral neck fractures, where the reoperation rate was 13% in 154 secondary HAs after failed IF, as compared to 5% for 676 primary HAs (Enocson et al. 2012). All these results confirm the high reoperation rate after secondary hip arthroplasty.

### 1.1 The influence of standard-length femoral stem on the risk for a periprosthetic fracture

The surgery of a secondary hip arthroplasty as a salvage procedure after failure of internal fixation in trochanteric and subtrochanteric fractures is associated with difficulties regarding several factors such as: altered anatomy due to the primary fracture, nonunion, malunion, bone loss, holes from previous implant and poor bone quality. The periprosthetic fractures are obviously a major problem for these patients, and we believe that it is of vital importance to bridge previous defects and holes in the femur to reduce the risk.

One finding in *Study I*, was that standard-length femoral stems were associated with a higher risk (although statistically non-significant) of reoperation compared to long stems. A periprosthetic fracture was the most common reason for reoperation (6/88 patients), and this is probably associated with stem length, as 5 of these 6 patients were operated with standard-length stems compared to 47/88 for the whole cohort.

We can compare our results with those of Haidukewych and Berry (2003), who reported on 44 patients who were followed for 2–15 years after a secondary arthroplasty due to failed trochanteric fractures. Their total reoperation rate was 5/44, but this included only 1 patient with a postoperative periprosthetic fracture. It is possible that the fact that they used standard femoral stems in only 9 of their patients reduced the risk of periprosthetic fractures. In contrast, Zhang et al. (2004) reported no postoperative periprosthetic fractures, but 6 intraoperative

fractures in 19 patients who were operated using standard-length stems. Furthermore, Exaltacion et al. (2012) described 20 patients with secondary arthroplasties who were primarily treated with intramedullary nails. During 12 months follow-up they found 9 patients with a fracture of the greater trochanter and 2 patients who were reoperated with exchange of the acetabular component due to loosening and dislocations, respectively.

## **1.2 The influence of surgical approach on the risk for prosthetic dislocations**

There might be different reasons to choose a surgical approach for a secondary hip arthroplasty. One may prefer the posterolateral approach for less tissue dissection and less gait problem, in comparison to the anterolateral approach which might provide better access to the acetabulum, lower risk to sciatic nerve injury and a lower risk for dislocations. The low incidence of prosthetic dislocations in our study (3/88) is probably explained by the fact that more than half of the patients were operated through an anterolateral approach. It has previously been reported that the posterolateral surgical approach is associated with a higher risk of dislocations after femoral neck fractures, when compared to the anterolateral approach (Enocson et al. 2008, Enocson et al. 2009). The current results correspond well with previous findings, where there was a dislocation rate of 2-3% for both HA patients (Enocson et al. 2008) and THA patients (Enocson et al. 2009) in large series when using the anterolateral approach on hip fracture patients.

## **1.3 Periprosthetic joint infection**

There are a lot of factors that increase the risk of periprosthetic infection; high age, high ASA class and high BMI. The incidence of infections after primary hip arthroplasty is 1-2%, while a secondary hip arthroplasty after a fracture complication has a 3 times higher risk compared to a primary arthroplasty (The Swedish Hip Arthroplasty Register, 2016).

In *Study I*, a deep infection occurred in 5 patients. This is in line with a study by Exaltacion et al. (2011) on arthroplasty patients after failed trochanteric fractures, and also studies on patients with femoral neck fractures (Calder et al. 1996, Baker et al. 2006, Frihagen et al. 2007). In contrast, other authors such as Mehlhoff et al. (1991) and Laffosse et al. (2007) reported no deep infections in arthroplasty patients after failed trochanteric fractures. The wide range of the reported incidence of infections after hip arthroplasty may be explained at least in part by different definitions of a postoperative infection.

## **2. Medical Complications & Influence of Time to Surgery**

Several studies have reported on different adverse events, blood loss, the need of blood transfusion and increased mortality because of delayed surgery for hip fracture patients in general. There is an obvious need to operate them promptly if possible within 24 hours in order to achieve early mobilisation, reduce the medical complications and decrease the mortality. However the majority of the studies on timing of surgery in hip fracture patients do not differentiate between different type of fractures and different type of operations performed.

## 2.1 Blood Transfusion & Blood Loss

We believe that intracapsular (femoral neck) and extracapsular (trochanteric- and subtrochanteric) hip fractures should be analysed separately due to their inherent differences in bleeding tendency due to the tamponade effect of the articular capsule on intracapsular fractures and more excessive soft tissue injury and bleeding tendency for comminuted extracapsular fractures. This is supported by 2 studies from 2011, Smith et al. and Kumar et al., both of which reported lower preoperative Hb in patients with extracapsular hip fractures compared to those with intracapsular. In addition, other studies found that intramedullary nailing compared with other surgical techniques was associated with an increased rate of RBC transfusions (Foss et al. 2006, Desai et al. 2014).

In a recent study by Neufeldt et al. (2016) on 26,000 hip fracture patients they found that delayed surgery was associated with an increased rate of transfusions. In contrast, Hagino et al. (2015) reported no difference in transfusion rates comparing early surgery (up to 1 day after admission) and late surgery in hip fracture patients. However, in both the above-mentioned studies, the study population consisted of a mixture of different fracture types and operations performed.

We found in *Study I* that the mean intraoperative blood loss was 1.1L. In *Study II*, there was a total number of 701 patients (71%) that had an RBC transfusion pre-, peri-, or postoperatively. Also, in *Study III* we found a high total transfusion rate (65%) for patients given any RBC transfusion and a calculated blood loss of about 1.3L in both the warfarin and control cohorts.

This explain a part of the complexity of the operations regarding the excessive blood loss and that the unstable trochanteric and subtrochanteric fractures are considered to be those fractures with the most pronounced blood loss.

Our findings were in line with the previously published literature such as Desai et al. (2014) who found that 52% of intertrochanteric fractures treated with an intramedullary nail were transfused. In addition, Fazal et al. (2018) recently reported a transfusion rate of 53% in 79 patients who underwent nailing surgery and among those the transfusion rate was 72% for the 32 patients that were treated with a long nail. Finally, Boone et al. (2014) reported a transfusion rate of 57% and 40% for long and short nails respectively.

In *Study II* we found an increased preoperative transfusions rate (RR 3.9 in a multivariable logistic regression analysis) and a greater number of given blood units preoperative (p= 0.01) among patients delayed for more than 24 hours to surgery compared with those operated within 24 hours.

The Hb value is often the single most important factor when deciding whether to transfuse these patients. It is therefore not surprising that in *Study II* patients found with a low preoperative Hb value had more preoperative transfusions, and another finding that an increasing preoperative Hb value was associated with a decreasing risk for transfusion (RR 0.3).

It is also described in *Study III* that patients with lower preoperative Hb did need pre- or intraoperative transfusions, but patients in the control group with lower postoperative Hb had more postoperative transfusions (71%) compared to warfarin patients (54%) (p=0.02).

## 2.2 The influence of anticoagulants

Often, the hip fracture patients are elderly with comorbidities that may need treatment with anticoagulations, such as warfarin or NOACs, creating another challenge in the surgical treatment as it is recommended that these patients should be operated without delay to reduce postoperative complications and mortality. Lawrence et al. in 2017, showed an association between warfarin therapy and prolonged time to surgery (mean 46 h versus 24 h for the control group).

In *Study II* our finding was a slight overweight of patients with more potent anticoagulants in the group delayed for surgery and among those who had preoperative transfusions. This is expected because the use of these drugs sometimes is the reason itself for delaying the surgery. Whereas warfarin can be quickly pharmacologically reversed, other potent anticoagulants (NOACs and antiplatelet drugs) often lacks established and easy methods for reversing the effect. Some orthopedic surgeons, and anesthetists, believe that the effect of these drugs should just be waited out before the surgery can be performed. This opinion is however nowadays questioned and patients on these medications can most likely be operated upon without delay in a similar way as those without potent anticoagulation therapy as long as spinal anesthesia can be avoided, and the patient is fit enough for general anesthesia.

In relation to anticoagulation therapy (other than low-dose ASA) the patients on potent anticoagulants were associated with an increased risk of preoperative transfusion (13%) and less postoperative transfusion (59%) compared with those on no anticoagulants or only low-dose ASA medication (7.2% and 70% respectively). A logistic regression used to evaluate factors associated with increased preoperative transfusion rate showed 2 times (RR 2.0) risk for transfusion in patients with potent anticoagulant.

In *Study III* we have especially studied patients on warfarin in this subgroup of hip fracture patients. Obviously, the choice of the way to overcome the anticoagulation effect of the warfarin will influence and sometimes delay the time to surgery. Bhatia et al. in 2010, described that using intravenous vitamin K is a safe and effective treatment to avoid delay in the treatment in this group of patients. Despite this statement they still reported at least 2 days (mean 38 h) delay to surgery in the warfarin group. Similarly, Moores et al. in 2015, described that using vitamin K is a safe method but they still had a time to surgery of 36–48 h in their study. Another option is administration of PCC which shows an effect within 30 min and that lasts for at least 6 h. The co-administration of vitamin K will give a stable and rapid reversal of anticoagulation and prevent rebound increases in INR. In our study, almost all the warfarin patients were actively reversed preoperatively, and the combination of vitamin K and PCC was the most commonly used method (46%). As we found no statistically difference in the calculated blood loss, no increase in transfusion rate and no decrease in Hb level in the warfarin group we conclude that using vitamin K and/or PCC as mentioned above minimize bleeding.

Similar, in a recent study by Cohn et al. in 2017 they found significantly lower preoperative Hb in patients undergoing intramedullary nailing (of extracapsular fractures) and a greater blood loss in the warfarin group compared with a control group (1.22 L versus 1.19 L), but it was not statistically significant. In contrast we found no difference in the calculated blood-loss when comparing warfarin patients with control patients. One reason could be that we used a more active approach when reversing the warfarin effect that resulted in a pronounced shorter time to surgery in comparison with Cohn et al. (mean 16 versus 47 h). Cohn et al. furthermore reported that their warfarin patients had a longer hospital stay (mean 5.6 versus 8.6 days) when

comparing control patients with warfarin patients. This indicates the superiority of using vitamin K and/or PCC to reduce the INR level to  $\leq 1.5$  and operate these patients without delay within 24 h.

Another finding in *Study III* was a lower postoperative RBC transfusion rate in the warfarin group. We speculate that this is because a prolonged effect of the reversing agents administered preoperatively.

## 2.3 Fracture Epidemiology

In *Study IV*, an observational study of trochanteric and subtrochanteric hip fracture patients, our finding that the majority of the fracture patients were females, is in line with most of the previous studies and has an association with high prevalence of osteoporosis in this population. The high age of the patients reflects that there is an increased risk to fall with advanced age, and as these patients often are frail with poor bone-quality there is an increased risk for suffering from a hip fracture even after a low-energy fall. Mangram et al. (2014) described that 73% of their trochanteric fracture patients fell at home. Similarly, Hagino et al. (2017) reported that an indoors simple fall was the trauma mechanism in 80% of their hip fracture patients, and 85% of them were  $\geq 90$  years old. Interestingly we found that fractures were slightly more common during the winter months of January and December, despite that the majority of them occurred indoors at the patients' accommodation. But this finding is in line with previous studies. Pueyo-Sanchez et al. (2017) reported that in Catalonia, Spain, a seasonal variation was observed with more cases in the winter. Similarly, Gronskog et al. (2010) found a seasonal variation in hip fracture incidence among elderly women in Norway which was characterised by higher fracture rates during the winter months. Finally, Hagino et al. (2017) reported a monthly variation where January had the highest number of patients per month during the observation period.

Another finding was that the AO/OTA type 31-A1 and 31-A2 fractures, which are sometimes referred to as stable, were most common (78%). This finding is similar to Chehade et al. who in 2015 published a prospective consecutive cohort of 743 patients where the majority (60%) were classified as stable trochanteric and only 40% as unstable trochanteric or subtrochanteric fractures. We found that with increasing fracture complexity the proportion of intramedullary nails, compared to plating with sliding hip screw, was increasing and also the use of long versus short nails. Previous literature has advocated the superiority of intramedullary nails, compared to plate with sliding hip screw, and proposed advantages in the management of unstable trochanteric and subtrochanteric fractures in providing biomechanical stability and improved functional outcome. Furthermore, a long nail can offer protection all along the femur, in comparison to a short nail. The "plate versus nail" debate is probably not yet over as the latest Cochrane report (Parker et al. 2010) comparing intramedullary nails with plate and sliding hip screw concluded that "sliding hip screw appears superior for trochanteric fractures". In our observational study we found that although intramedullary nailing was the most commonly used implant overall, the plate with sliding hip screw was commonly used as well, especially for the stable fractures.

## 2.4 Comorbidity & Adverse Events

As this subgroup of hip fracture patients are elderly and are associated with comorbidities they may suffer of serious adverse events postoperatively.

In *Study I* there was a high incidence of severe adverse events (10%) occurring within 6 weeks, including fatal events of stroke and cardiac infarction. This not only reflects the complexity of the surgery but also the general risks that are associated with this condition.

In *Study II* we have not collect data on adverse events, however there was a high incidence of high ASA class (ASA class 3-4) (72%) patients in the cohort. One hypothetic explanation for increased preoperative transfusion among patients delayed for surgery could be that these patients do in fact have more comorbidity. Although significant in the univariable analyses, multivariable analysis revealed no significant associations between the ASA class and the risk for transfusion. However, we cannot know if this finding is due to too small sample sizes or other confounding factors. This finding highlights that these patients are already sick and should be medically optimized with care.

In *Study III* we have used the Charlson comorbidity index in addition to ASA class. The warfarin patients in general had an impaired state of health compared with the control patients, displayed as a lower number of patients with ASA class 1–2 and a higher mean Charlson comorbidity index. We found no difference in the frequency of adverse events.

## 2.5 Mortality

**Table 12. Patients mortality data for all studies**

Study I n = 88		Study II n = 987				Study III n = 198			Study IV n =10548					
		Op<24h		Op>24h										
6- months	1- year	30- day	1- year	30- day	1- year	In house	30- day	1- year	30-day		1-year			
8%	16%	9%	27%	9%	33%	3.5%	8.1%	26%	7.7%		26%			
		Transfusion		No transfusion					Male	Female	Male	Female		
		30- day	1- year	30- day	1- year				11%	6.2%	32%	23%		
		9%	31%	8%	21%				30-day		1-year			
									≤24h	≤36h	>36h	≤24h	≤36h	>36h
									7.8%	8%	9.8%	25%	26%	31%

We think that it is important to differentiate between the different types of hip fractures. The need to analyse intra- and extracapsular hip fractures separately is furthermore supported by the results from Steinberg et al. (2014) who, somewhat surprisingly, reported increased 1-year mortality in patients with intracapsular, but not in patients with extracapsular, hip fractures delayed for surgery more than 48 hours.

Obviously, several factors can affect the postoperative mortality but the time to surgery is one of the most debated ones. Moja et al. (2012) described in a meta-analysis that a delay to surgery was associated with a significant increase in the risk of death and pressure sores and recommended that most patients with a hip fracture should be operated within one or two days.



In addition, early fracture fixation and mobilisation of these patients decreases the economic burden as it might reduce the overall length of stay, and thus the total cost (Siegmeth et al. 2005). On the contrary, a recent prospective cohort study from Lizaur-Utrilla et al. (2018) including 1234 patients who underwent hip fracture surgery suggested that waiting time for the surgery of more than two days to stabilise patients with active comorbidities at admission was not associated with higher complication or mortality rate. However, the patients who were delayed to surgery due to organisational reasons had a significantly higher rate of postoperative complications and 1-year mortality.

Table 12 summarises the postoperative mortality data for the patients in all *Studies I-IV*, and highlights the high mortality rate in this subgroup of patients.

In *Study II* we found a high 30-day and 1-year mortality rate in general, although there were no statistically significant differences for patients operated within or after 24 hours. There was an increased 1-year mortality rate among patients who had an RBC transfusion compared with those who did not have a transfusion. However, because there was no difference in the 30-day mortality, we believe that this result must be interpreted with care. Usually mortality analyses demand larger study populations than the current one.

In *Study III* we found a high mortality rate up to 1 year despite that there was no difference in the rate of mortality between warfarin patients and the control group. This was in line with a recently published study by Cohn et al. 2017.

In *Study IV* we have studied the mortality of this group of fracture patients within the context of a national register study. This provides a unique opportunity to integrate epidemiologic data with a relevant outcome measurement (mortality). The high overall 30-day and 1-year mortality was in line with the other studies. We found an increased mortality in males, despite younger mean age. In 2010 Kannegaard et al. observed in a nationwide register-based cohort study including more than 41,000 Danish hip fracture patients, increased 1-year mortality in men. Furthermore, the mean survival time was slightly shorter after trochanteric and subtrochanteric fracture (3.3-3.4 years) compared with other types of hip fractures (3.5-3.8 years). Haentjens et al. (2010) performed time-to-event meta-analyses and showed that the relative hazard for all-cause mortality in the first three months after a hip fracture was 5.75 in women and 7.95 in men. The majority of our population was operated within 24 hours (75%) or 36 hours (90%) calculated from the time of the radiograph verifying the fracture to the start of the operation, and this is consistent with the current recommendations for the management of hip fractures in many settings.

To be able to operate patients within 24 or 36 hours one might need to operate also at night-time (22:00-8:00 hours). We found no relation between mortality and the starting time of the surgery, whether it was performed during day-time or night-time. Although other studies have defined the night-time slightly different (16:00-07:00 hours) they showed similar results (Rashid et al. 2013, Switzer et al. 2013).



# Strengths & Limitations

## Study I

The *strengths* of this study were the large number of consecutively included patients, the relatively long follow-up period and the validation of reoperation and dislocation data via the nationwide registry of the Swedish National Board of Health and Welfare.

One *limitation* of the study was the lack of postoperative assessment of functional outcomes.

## Study II

One *strength* of this study was the large population of patients with similar fractures and operations performed. This makes our results easy to interpret and apply in a clinical setting. Another *strength* was the unique Swedish personal identification number used in follow-up and mortality control enables high-quality data and follow-up of patients.

One *limitation* of this study was that a strict protocol for transfusions was not used. The decision whether to transfuse was usually based on a cutoff Hb level of 10 g/dL in combination with an assessment of the individual patient's physiological status. However, we think that this approach is a pragmatic one that reflects the clinical situation in many settings around the world. Another *limitation* of this study was its retrospective design, which could mean that there are other confounding factors that we are not aware of. Using a more detailed score such as the Charlson Comorbidity Index might have added important additional information about the patient's comorbidities

## Study III

The major *strengths* of the study were the large and homogenous groups, both the study group and the control group. This limits the influence of confounding factors on the results. The accurate mortality data up to 1 year after surgery to some extent compensate for the lack of information on late complications (after hospital discharge).

One obvious *limitation* of this study was its retrospective design. Ideally this topic should be investigated within the context of a randomised controlled trial. However, the current knowledge and opinion would hardly ethically allow a study that compare early and late surgery in these fragile patients. Most of the patients in our cohort had relatively benign indications for warfarin, such as atrial fibrillation. Therefore, the safety of active warfarin reversal in patients on warfarin for reasons other than atrial fibrillation remain unaddressed in this study.

## Study IV

The major *strength* of the last study was the large number of included fractures. The data from the well validated SFR provides prospective data on a national level regardless of local differences in epidemiology, socio-demographics and treatment traditions. The mortality data was another *strength* that provides a unique opportunity to integrate epidemiologic data with a relevant outcome measurement.

A *limitation* in this study was that the SFRs coverage during the study period (January 2014 to December 2016) included, with increasing number of participating departments, by the end of 2016 approximately only 72% of Sweden's orthopaedic departments. However, the remaining clinics that have not yet signed up are mostly smaller units, so in reality the national proportion

of excluded fractures is most likely small, but still the incomplete coverage of the SFR is a *limitation*. Registration of the time for the radiograph confirming the fracture and the start of the operation did not start until 2015. The number of valid inputs in the register on this topic is therefore somewhat limited, but since the total number of valid inputs is large, we still think that the results regarding delay to surgery and timing of the operations are valid indicators and represents true national trends. Another *limitation* was that due to the descriptive nature of this register study all the results were unadjusted regarding different reasons for delay to surgery, implant choice or co-morbidities of the patients.

## Clinical Implications

Performing a salvage reoperation after failed fixation of trochanteric and subtrochanteric fractures is challenging and associated with major complications. With respect to the difficulties, we recommend in *Study I* that this surgical procedure should be performed only by experienced surgeons and long femoral stems that bridge previous holes and defects should be used to reduce the risk for reoperation.

Timing and delay to surgery is one of the important ongoing debates on how to best treat patients with hip fractures. Several studies have reported different adverse effects, including increased mortality because of delayed surgery for hip fracture patients in general, but it is important to describe this particular issue in this subgroup of hip fracture patients (operated upon with an intramedullary nail due to an unstable trochanteric or subtrochanteric hip fracture) separately. The main finding of *Study II* was that prolonged waiting for surgery was associated with an increased rate of preoperative RBC transfusions. A potent anticoagulants medication may be one of the reasons to delay the surgery and was associated with a higher risk for preoperative transfusions.

In *Study III* we showed that patients on warfarin medication can be safely operated within 24 hours by reversing the effect of warfarin to  $INR \leq 1.5$  using vitamin K and/or PCC.

An up-to-date of the epidemiology of trochanteric and subtrochanteric hip fracture patients was performed with *Study IV*. As these fractures were more common among elderly females and a fall at the same level at the patients' residence was the dominating injury mechanism, measurements should be taken to avoid patients fall at home. Furthermore, special care and optimisation of the medical status for all fracture patients in general, and especially for patients at risk (males) to operate them without delay to decrease the risk for mortality. A suitable fixation method should be chosen depending on the fracture classification and complexity.

# Conclusions

## Study I

In patients undergoing a reoperation with a secondary hip arthroplasty after a failed primary internal fixation of trochanteric and subtrochanteric fractures, a high rate of reoperations, postoperative medical complications and mortality reflects and demonstrates the difficulties and complexity of the surgery. A surgical option which may reduce the risk for reoperation due to a periprosthetic fracture is the use of long femoral stems that bridge previous defects and holes.

## Study II

In patients operated upon with an intramedullary nail due to an unstable trochanteric or subtrochanteric hip fracture that were delayed for surgery more than 24 hours, we found an increased rate of preoperative RBC transfusions. A potent anticoagulant medication may be one of the reasons to delay the surgery and was associated with a higher risk for preoperative transfusions.

## Study III

In patients on warfarin medication, surgical treatment with intramedullary nailing within 24 hours due to an unstable trochanteric or subtrochanteric hip fracture, after reversing the warfarin effect to  $INR \leq 1.5$  using vitamin K and/or PCC was safe. We found no significant differences in the calculated blood-loss, in-house adverse events, mortality (in-house, 30-day or 1-year), pre- or peroperative transfusion rates, re-admissions within 30 days or hospital length of stay compared with a control group. A lower postoperative RBC-transfusion rate in the warfarin group can be explained by the prolonged effect of the reversing agents administered preoperatively

## Study IV

Trochanteric and subtrochanteric hip fractures were more common among females and most of the patients were elderly. A fall at the same level, at the patients' residence was the dominating injury mechanism and location. With increasing fracture complexity, the proportion of intramedullary nails was increasing, and also the use of long versus short nails. Male gender and delay to surgery were associated with increased mortality.

## Overall conclusion

In conclusion we add important information to the ongoing debate on how to best treat patients with hip fractures, especially those with trochanteric and subtrochanteric fractures. Using a long femoral stem in secondary hip arthroplasty after failed internal fixation can be an important factor to reduce the reoperation rate. Delay to surgery more than 24 hours was associated with an increased rate of preoperative RBC transfusions. Operating patients on warfarin medication within 24 hours can be safely done by reversing the warfarin effect to  $INR \leq 1.5$  using vitamin K and/or PCC. Finally, we add an up-to-date epidemiological overview of the trochanteric and subtrochanteric hip fracture patients and treatment.



## Implications for Future Research

- The consequence of waiting time for surgical intervention and the effectiveness of RBC transfusions at different time points in the surgical pathway and the outcome in hip fracture patients, especially in those with trochanteric and subtrochanteric fractures is controversial. Future research in form of randomised controlled trails are still needed to address this correlation.
- In *Study III*, we found that it is safe to operate patients with trochanteric or subtrochanteric hip fractures on warfarin medication within 24 hours after fast reversing its effect to  $INR \leq 1.5$  by using vitamin K and/or PCC. This important subject should be scoped out and further research should be considered in the form of a high quality randomised controlled trial. However, according to the ethical aspects and the existing knowledge it would be difficult to permit such a study in these frail patients





## Abstract in Swedish

Höftfrakturer är ett betydande folkhälsoproblem. Majoriteten av höftfrakturpatienterna är äldre och lider av andra sjukdomar. Det finns en stark association med osteoporos, speciellt för de extra-kapsulära (trokantära och subtrokantära) frakturerna. Behandlingen av dessa patienter är förknippad med stor risk för medicinska och kirurgiska komplikationer. En av de viktigaste riskerna är blodförlust och ett efterföljande behov av blodtransfusion. Behandlingen av extra-kapsulära höftfrakturer är i första hand akut operation med intern fixation, såsom intramedullär märgspikning eller plattfixation med glidande höftskruv. En höftprotes är ett alternativ för behandling av misslyckanden efter intern fixation. I detta doktorandprojekt beskriver vi epidemiologin, studerar komplikationerna och påverkan av tidig operation vid hanteringen av denna grupp av höftfrakturpatienter.

I *Studie I*, analyserade vi i en retrospektiv kohortstudie, 88 patienter med en 5–11 års uppföljning som reopererades mellan 1999 - 2006 vid SÖS med en sekundär höftprotes på grund av läkningskomplikationer efter intern fixation av en trokantär eller subtrokantär höftfraktur. Den totala reoperationsfrekvensen var 16% (14/88), vilket återspeglar den kirurgiska komplexiteten. Den vanligaste orsaken till reoperation var en protesnära fraktur (n = 6). Multivariabel Cox-regressionsanalys av reoperationer för patienter med femurstammar av standardlängd jämfört med långa stammar visade en trend för ökad risk med en riskfrekvens (HR) på 4 (p = 0,06). En rekommendation att använda långa femurstammar kan vara ett sätt att minska risken för reoperationer.

I *Studie II*, analyserade vi i en retrospektiv kohortstudie, 987 patienter opererade med en intramedullär märgspik på grund av en instabil trokantär eller subtrokantär höftfraktur vid SÖS, mellan 1:a januari 2011 och 31:a december 2013. Förekomst av blodtransfusioner var det primära utfallsmåttet. Logistisk regressionsanalys användes för att justera för antikoagulantia, ASA-klass, frakturtyp, preoperativt hemoglobinvärde (Hb) och tid till operation. Det visade sig att antikoagulantia (relativ risk (RR) 2,0) och operation som fördröjdes i mer än 24 timmar (RR 3,9) var signifikant associerad med en ökad frekvens av preoperativa transfusioner.

I *Studie III*, analyserade vi i en retrospektiv fall-kontrollstudie, 198 patienter: 99 warfarin patienter och 99 patienter utan antikoagulantia med en 1: 1 ratio. Kontrollgruppen matchades för ålder, kön och kirurgiskt implantat. Alla patienter opererades inom 24 timmar med en intramedullär märgspik på grund av en trokantär eller subtrokantär höftfraktur vid SÖS efter ett lågenergitrauma mellan 1:a januari 2011 och 31:a december 2014. Alla patienter som stod på warfarin reverserades om nödvändigt till INR  $\leq 1,5$  före operationen med K-vitamin och/eller fyr-faktors-protrombin komplexkoncentrat (PCC). Det fanns inga signifikanta skillnader i beräknad blodförlust, tidiga biverkningar, pre- eller peroperativa blodtransfusionsfrekvenser eller mortalitet mellan grupperna, men det var en ökad frekvens av postoperativa transfusioner i kontrollgruppen. Konklusionen var att det är säkert att använda vitamin K och/eller PCC för att kunna operera dessa patienter inom 24 timmar.

I *Studie IV*, analyserade vi i en beskrivande epidemiologisk registerstudie, totalt 10.548 patienter registrerade i det nationella svenska frakturregistret från januari 2014 till december 2016. Individuella patientdata (ålder, kön, skadeplats, skadeorsak, frakturtyp, behandling och tidpunkt för operation) hämtades från registerdatabasen. Mortalitetsdata erhöles från det svenska dödsregistret. Majoriteten av patienterna var äldre kvinnor (69%) som drabbades av sin fraktur efter ett fall i samma plan (83%) vid patientens boende (75%). Det vanligaste implantatet var en kort antegrad intramedullär märgspik (42%). Med ökande frakturkomplexitet ökade andelen intramedullära märgspikar, och även användningen av långa versus korta märgspikar. De flesta patienterna opererades inom 36 timmar (90%). Det var en ökad mortalitet för män, och för alla som var försenade till operation > 36 timmar.

De viktigaste slutsatserna i denna avhandling var de epidemiologiska aspekterna, analyser som visar den medicinska och kirurgiska komplexiteten hos dessa höftfrakturpatienter och vikten av att optimera patienterna omgående före operationen inom 24 timmar



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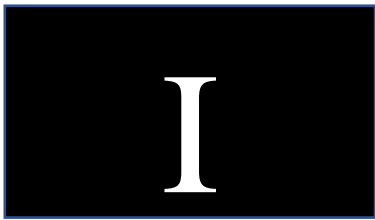
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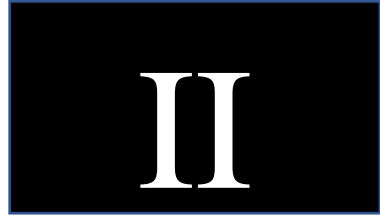
## Original Papers I - IV

- I. Hip arthroplasty after failed fixation of trochanteric and subtrochanteric fractures. *Anders Enocson, Leif Mattisson, Carin Ottosson, Lasse J Lapidus. Acta Orthopaedica 2012; 83:5, 493-498.*
- II. What is the influence of a delay to surgery >24 hours on the rate of red blood cell transfusion in elderly patients with intertrochanteric or subtrochanteric hip fractures treated with cephalomedullary nails? *Leif Mattisson, Lasse J. Lapidus, Anders Enocson. Journal of Orthopaedic Trauma Aug 2018; 32(8):403–407.*
- III. Is fast reversal and early surgery (within 24 h) in patients on warfarin medication with trochanteric hip fractures safe? A case-control study. *Leif Mattisson, Lasse J. Lapidus, Anders Enocson. BMC Musculoskeletal Disorders June 2018; 19:203.*
- IV. Epidemiology, treatment and mortality of trochanteric and subtrochanteric hip fractures: data from the Swedish Fracture Register. *Leif Mattisson, Alicja Bojan, Anders Enocson. BMC Musculoskeletal Disorders October 2018; 19:369.*

















IV

