

# **Timing of anticoagulation and surgery for hip fracture patients**

A search for factors influencing outcomes after surgery

Sunniva Leer-Salvesen



Thesis for the Degree of Philosophiae Doctor (PhD),

University of Bergen, Norway

2021

## Scientific environment

This PhD project took place in 2015-2019 in the Department of Orthopaedic Surgery of Haukeland University Hospital.

As a fresh medical student, I stumbled into the office of Professor Emeritus Lars B Engesæter in my search for a project for the research student programme at the University of Bergen. His engagement and knowledge convinced me to join the scientific environment of the Norwegian Arthroplasty Register in the Department of Orthopaedic Surgery, Haukeland University Hospital. This department had provided me with supervision from my time as a medical student to the end of this PhD, when I was working as an intern doctor. I have received funding in the years 2015-2019 from the University of Bergen.

My main supervisor has been Jan-Erik Gjertsen, head of the Norwegian Hip Fracture Register and Associate Professor in Orthopaedic Surgery in the Department of Clinical Medicine, University of Bergen. My co-supervisors have been Eva Dybvik, statistician at the Norwegian Hip Fracture Register and Lars B. Engesæter, Professor Emeritus in Orthopaedic Surgery.



---

## Acknowledgements

First of all, I would like to thank the *Department of Orthopaedic Surgery* for including me fully in clinical projects from my first day as a new research student, 21 years old and without any experience from the field of surgery. In my future work, I will make sure that I pass on to colleagues the trust and patience you have shown me.

The loyal reporting to the Norwegian Hip Fracture Register by *orthopaedic surgeons in Norway* deserves special acknowledgement for enabling such a strong register. Without the invaluable work from *the staff of the Norwegian Hip Fracture Register* in gathering and preparing data, this thesis would have been impossible.

I would like to thank *Professor Emeritus Lars B Engesæter* for introducing me to the world of orthopaedic surgery and the Norwegian Arthroplasty Register when I was a young medical student. I was fortunate enough to receive the preliminary work on timing of anticoagulation for hip fracture patients from Lars Birger in 2015. My curiosity leading to the formation of my thesis began in his office. His powerful hands-on engagement for the field of clinical medicine combined with his experience in the field of education supported me through the ups and downs of my first years of research.

I am greatly indebted to *Dr Jan-Erik Gjertsen* for his sharing of his consistently brilliant work and knowledge for the frail hip fracture population. Even as the leader of the Norwegian Hip Fracture Register and working actively as a chief physician, Jan-Erik always answers my inquiries day and night. He is a role model who always includes me in his hard-working atmosphere. I have grown a lot with Jan-Erik's thorough supervision. This thesis would not have existed without him.

My co-supervisor deserves a special thank you, *statistician Eva Dybvik*. Her patience with novice researchers combined with her understanding of the intricate paths of statistics made it possible to complete this PhD.

The brilliant *Professor Anne-Berit Guttormsen* deserves acknowledgement for her involvement in my research. As the leader of the research student programme in the Faculty

of Medicine, her guidance and trust in my endeavours has been of invaluable importance. I was struggling with ethical approval of my fourth project without any acceptable legal justification for the battle and delay. I will never forget the strong engagement of Anne-Berit when she summoned the regional ethics committee, lawyers, and co-professors to secure approval of my project without further unacceptable delay, far beyond what a medical student could achieve alone. In addition to the academic support from the research student programme, I am grateful for their scholarships, which have supported this PhD.

I have truly appreciated the scientific enthusiasm of co-author *Emeritus Research Director Ola Dahl*. His long career of exceptional efforts at the Thrombosis Research Institute (UK) and Innlandet Hospital Trust has given the PhD a vital depth.

I would like to thank co-authors *Professor Anette Hylene Ranhoff* and *Dr Bjørn Liljestrand Husebø* for their invaluable contributions and guidance from the fields of geriatric medicine and anaesthesiology, respectively. The perioperative treatment of hip fracture patients truly needs interdisciplinary cooperation. I am grateful to have learned from experienced clinicians.

*Dr Torbjørn Kristensen* and *Professor Ove Furnes* must also be mentioned. Their experience and welcoming approach have been of great importance both in the field of research and in the social arena, including clinical practice and conference attendances.

I am grateful for the love and support from my parents throughout my life, *Solvor and Kristian*. I would not be where I am today without the vital support from my friends, my exceptional *Bergen family*, both within and outside the world of research.

Finally, I would like to thank my *Thor*, who carries me through bright and dark days to remind me of what really matters in life.

---

## Contents

<b>Scientific environment.....</b>	<b>2</b>
<b>Acknowledgements.....</b>	<b>3</b>
<b>Contents.....</b>	<b>5</b>
<b>List of abbreviations.....</b>	<b>7</b>
<b>List of publications.....</b>	<b>8</b>
<b>Abstract.....</b>	<b>9</b>
<b>1. Introduction.....</b>	<b>11</b>
1.1 Background and importance of topic.....	11
1.2 Definition of hip fractures .....	12
1.3 Treatment of hip fractures .....	14
1.4 Surgery and complications.....	16
1.5 Thromboprophylaxis.....	19
1.6 Anticoagulation in relation to surgery and neuroaxial anaesthesia.....	24
<b>2. Aims of the study.....</b>	<b>26</b>
<b>3. Materials.....</b>	<b>27</b>
3.1 The Norwegian Patient Registry.....	27
3.2 The Norwegian Hip Fracture Register.....	28
3.3 Mortality, reoperations and complications.....	29
3.4 Medical records.....	30
<b>4. Statistics.....</b>	<b>33</b>
4.1 Survival analysis.....	33
4.2 Continuous variables.....	33
4.3 Categorical variables.....	34
4.4 Power analysis.....	34
<b>5. Summary of Papers I-IV.....</b>	<b>35</b>
5.1. Paper I.....	35
5.2. Paper II.....	37
5.3. Paper III.....	39
5.4. Paper IV.....	41

---

<b>6. Discussion.....</b>	<b>43</b>
6.1 Observational studies versus randomized controlled trials .....	43
6.1.1 Strengths of register studies.....	44
6.1.2 Limitations of register studies.....	45
6.2 Discussion of results.....	48
6.2.1 Preoperative versus postoperative start of thromboprophylaxis...	48
6.2.2 Delay to hip fracture surgery.....	52
6.2.3 Direct oral anticoagulant when the hip fracture occurs .....	55
<b>7. Conclusions.....</b>	<b>58</b>
<b>8. Future research.....</b>	<b>60</b>
8.1 Timing and duration of thromboprophylaxis.....	60
8.2 Fast track algorithms for hip fracture treatment to reduce mortality and complications.....	61
<b>9. References.....</b>	<b>62</b>
<b>9. Appendices.....</b>	<b>83</b>
Appendix I: Operation form from the Norwegian Hip Fracture Register (in Norwegian)	
Appendix II: Correspondence in Acta Orthopaedica: Letter from Dr. Ye and Dr. Huilin regarding Paper I	
Appendix III: Correction to Paper IV	
<b>Papers I-IV</b>	

---

## List of abbreviations

ASA	American Society of Anaesthesiologists
BCIS	Bone Cement Implantation Syndrome
CI	Confidence Interval
CT	Computed Tomography
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
FNF	Femoral Neck Fracture
HA	Hemiarthroplasty
INR	International Normalized Ratio
IPCD	Intermittent Pneumatic Compression Device
IU	International Units
ICD-10	International Classification of Diseases (version 10)
LMWH	Low-Molecular-Weight Heparin
LOS	Length Of (hospital) Stay
MRI	Magnetic Resonance Imaging
NHFR	Norwegian Hip Fracture Register
NICE	National Institute for Health and Care Excellence
NPR	Norwegian Patient Registry
NNH	Numbers Needed to Harm
OR	Odds Ratio
PE	Pulmonary Embolism
PJI	Periprosthetic Joint Infection
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
RCT	Randomized Controlled Trial
RR	Relative Risk
SAG	Concentrate of erythrocytes in a standardized storage unit (SAGMAN)
VKA	Vitamin K-Antagonists
VTE	Venous Thromboembolism

## List of publications

1. Leer-Salvesen S, Dybvik E, Dahl OE, Gjertsen JE, Engesæter LB. Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures. *Acta Orthop*. 2017 Feb;88(1):48-54.
2. Leer-Salvesen S, Dybvik E, Engesaeter LB, Dahl OE, Gjertsen JE. Low-molecular-weight heparin for hip fracture patients treated with osteosynthesis: should thromboprophylaxis start before or after surgery? An observational study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register. *Acta Orthop*. 2018 Dec;89(6):615-621.
3. Leer-Salvesen S, Engesæter LB, Dybvik E, Furnes O, Kristensen TB, Gjertsen J-E. Does time from fracture to surgery affect mortality and intraoperative medical complications for hip fracture patients? An observational study of 73 557 patients reported to the Norwegian Hip Fracture Register. *Bone Joint J* 2019;101-B(9):1129-1137. Reproduced with permission and copyright © of the British Editorial Society of Bone & Joint Surgery.
4. Leer-Salvesen S, Dybvik E, Ranhoff AH, Husebø BL, Dahl OE, Engesæter LB, Gjertsen JE. Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay, and poorer outcome for hip fracture patients? *Eur Geriatr Med*. 2020 Aug;11(4):563-9.

*The articles are reprinted with permission from the publishers.*



---

## Abstract

Suffering a fracture has been ranked among the world's ten most incapacitating conditions when measuring disability-adjusted life years. Each year, 9,000 hip fractures occur in Norway. Frail elderly hip fracture patients have a high mortality compared to their non-fractured counterparts. One in four will not survive the first year following the fracture. Evidence-based treatment of hip fracture patients includes both surgical interventions and perioperative care, yet neither have reached international consensus with systematic guidelines. The overall intention of this thesis was to focus on the perioperative care of hip fractures with special emphasis on anticoagulation and time to surgery. In *Papers I-III*, we used data from the Norwegian Hip Fracture Register, which includes information from all hospitals performing hip fracture surgery in Norway. In *Paper IV*, we studied detailed information from medical records from a large trauma centre, Haukeland University Hospital.

In *Paper I*, we aimed to compare preoperative with postoperative start of thromboprophylaxis for femoral neck fracture (FNF) patients operated with hemiarthroplasty. We included 20,241 patients operated between 2005-2014 receiving low-molecular-weight heparin (LMWH) either before surgery (52%) or after surgery (48%). Postoperative start of LMWH was associated with increased mortality and risk of reoperation in the first six months postoperatively. No differences in the risk of bleeding complications or reoperation due to haematoma could be detected whether LMWH was started before or after surgery.

In *Paper II*, we continued the work from *Paper I* by comparing preoperative with postoperative start of LMWH in hip fracture patients operated with osteosynthesis. We included 45,913 patients operated between 2005-2016 with LMWH started before surgery (45%) or after surgery (55%). In contrast to *Paper I*, the start of LMWH did not change mortality or risk of reoperation the first six months after osteosynthesis. However, more intraoperative bleeding complications were reported when LMWH was started preoperatively compared to postoperatively.

In *Paper III*, we studied whether time to surgery influenced outcomes for hip fracture patients. Both the total delay (time from fracture to surgery, 38,754 patients) and hospital delay (time from admission to surgery, 73,557 patients) were investigated. Time of admission was obtained from the Norwegian Patient Registry and time of fracture from the Norwegian Hip Fracture Register. From 2008 to 2017, the mean time from fracture to admission was 6.2 hours while the mean time from admission to surgery was 21.7 hours. Both total delay and hospital delay exceeding 48 hours were associated with increased mortality for hip fracture patients in the first postoperative year. In addition, more intraoperative medical complications were reported when the hospital delay exceeded only 24 hours. Our study supports early surgical intervention within 48 hours of the fracture to reduce mortality and complications for the frail hip fracture patients.

In *Paper IV*, we regained focus on anticoagulation. While studying surgical prophylaxis in *Papers I-II*, we now aimed to investigate the consequences of long-term use of direct oral anticoagulants (DOACs) when the hip fracture occurs. DOACs have only been on the market since 2010, thus we lack experience and guidelines for their use in semi-urgent surgery, such as hip fracture surgery. The number of DOAC prescription users has increased by 150% from 2014 to 2018 and their prevalence in Norway has surpassed Warfarin. 314 hip fracture patients operated in 2016-2017 were studied by using medical records in a single large trauma centre (Haukeland University Hospital). 47 patients (15%) were using DOACs before the hip fracture. In contrast to earlier studies, we did not find any difference in time from admission to surgery, length of hospital stay, blood loss, transfusion rate, and bleeding complications in patients who took DOACs before the fracture, compared to non-users. DOAC users were more often operated under general anaesthesia than non-users. Delay to surgery was on average 13 hours longer if the DOAC users were given neuroaxial anaesthesia compared to general anaesthesia. The conclusion was that the use of DOACs did not result in more bleeding complications for hip fracture patients compared to non-users. Thus, early surgery should also be prioritized in DOAC users to reduce mortality and complications, as studied in *Paper III*.

# 1 Introduction

## 1.1 Background and importance of topic

It is estimated that 1.6 million patients worldwide fracture their hip each year (1). Countries in Northern Europe, and in particular Norway, have some of the highest incidences of hip fractures in the world (2, 3). Around 9,000 patients fracture their hip annually in Norway. Current estimates tell us that one in four women will suffer a hip fracture and 25-27% of hip fracture patients will not survive the first year following the fracture (4, 5). A hip fracture will often bring substantial changes in the lives of elderly patients, resulting in reduced quality of life and increasing need for assistance and care (6-8). A hip fracture has been rated among the top ten most incapacitating conditions in terms of disability-adjusted life years (9).

For several decades of the last millennium, the incidence of hip fractures seemed to be increasing (10-13). Later studies have demonstrated that age-specific incidences have stabilized (14-17). However, as the population is ageing rapidly, the total number of hip fractures is still growing. By the year 2050, more than 6 million hip fractures are estimated to occur each year worldwide (18). Most hip fractures occur due to low-energy trauma combined with osteoporosis (19, 20). Thus, hip fracture incidence can mark the prevalence of osteoporosis and frailty. The incidence of hip fractures increases with age (14). Elderly victims of the injury have a higher one-year mortality than their non-fractured counterparts. Such an excess mortality following a hip fracture may partly be caused by impaired health and frailty before the fracture (21). Male gender, high age, and admission from nursing homes have all been identified as predictors of short-term mortality (22).

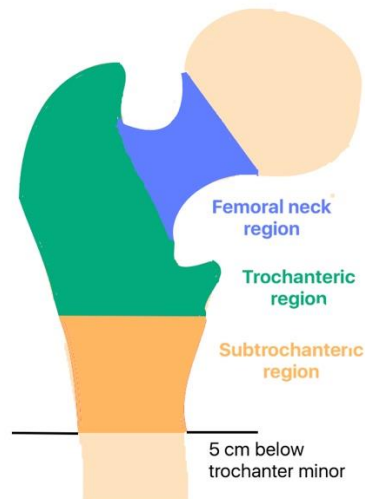
For many patient groups, long-term results are of great importance as they will impact their many years to come. For example, elective joint replacements need to provide joints that last for decades to improve function and quality of life. Studies on joint replacements therefore focus on long-term results after 10 and 20 years (23-25). In contrast, many hip fracture patients are vulnerable in their need for short - and

intermediate - term results. The precious months up to one year following surgery need to be medically and surgically optimized to allow early mobilization, gain of self-care, and improvement of quality of life to ensure a fast recovery. The median survival time after a hip fracture has been estimated to be 2.6 years for men and 4.2 years for women (26). After 20 years, the chosen treatment will only have implications for a minority of hip fracture patients due to the limited life expectancy. The average cost in the first year after a hip fracture in Norway has recently been estimated to be NOK 660,000, and the total cost may be close to one million if the following first years are included (27). There is an evident need to optimize the treatment of hip fracture patients to reduce mortality, complications and costs in the coming years.

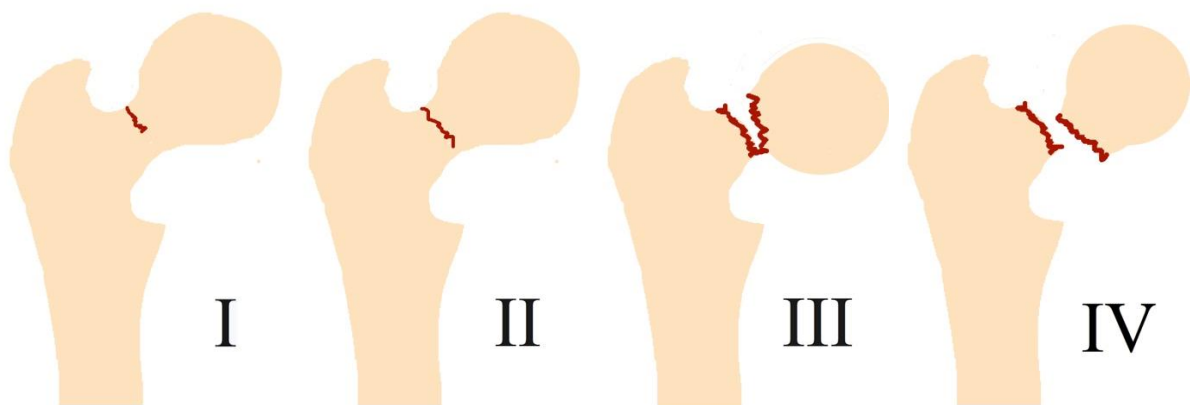
## **1.2 Definition of hip fractures**

A hip fracture involves a fracture of the proximal part of the femur. Hip fractures can be divided into FNFs (60%), trochanteric fractures (35%) and subtrochanteric fractures (5%) (Figure 1). Several classification systems exist for FNFs. The Garden classification is most commonly used (28). It describes four subgroups of hip fractures based on the displacement on an anteroposterior radiograph (Figure 2). In clinical practice, this classification is often simplified into undisplaced FNFs (Garden I-II) and displaced FNFs (Garden III-IV), which influences the choice of treatment.

Trochanteric fractures include both intertrochanteric and pertrochanteric fractures and are most often classified according to the AO/OTA system, based on numbers and localization of fragments and degree of stability (29). Hip fractures with the line of fracture located between the lesser trochanter and the proximal 5 cm of the femoral shaft are classified as subtrochanteric fractures.



**Figure 1.** Demonstration of the areas in the proximal femur used to classify hip fractures



**Figure 2.** Demonstration of the Garden classification of femoral neck fractures (I-IV). Garden I includes undisplaced incomplete fractures. Garden II includes undisplaced complete fractures. Garden III includes complete fractures that are incompletely displaced. Garden IV includes fully displaced complete fractures.

### 1.3 Treatment of hip fractures

In a historical perspective, modern hip fracture treatment began after the invention of x-rays by Wilhelm Konrad Röntgen in 1895 (30). Before orthopaedic surgeons were able to identify the fracture with sufficient quality of the radiographs, patients were often treated with conservative suboptimal solutions such as bed rest, cast systems and traction. Bed rest was a common form of treatment in the first part of the 20th century (31). Unfortunately, many patients did not survive due to medical complications, which may have been related to immobilization, for example venous thromboembolism and pulmonary infections. FNFs often resulted in non-union and were associated with high mortality. In 1934, Dr Kellogg Speed discussed FNFs using the title "the unsolved fracture" (32). He was referring to 100 years of controversy regarding optimal treatment for these fractures.

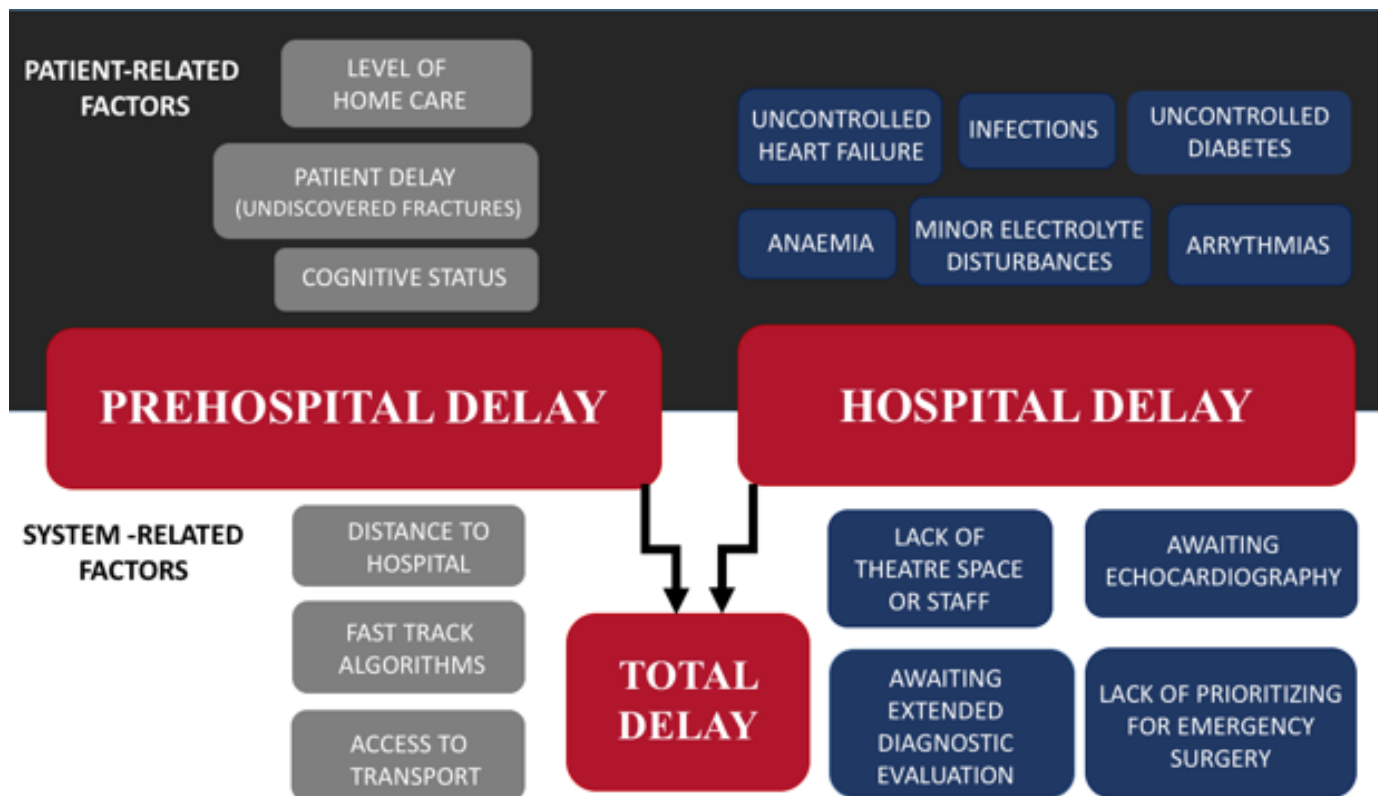
Today, there is a collegial agreement that all proximal fractures of the femur should be treated surgically in elderly patients, as long as they are expected to survive surgery. Research has shown a striking increase in mortality when hip fractures are treated conservatively compared to surgically (33, 34). Untreated displaced hip fractures can produce unacceptable pain and may impede mobilization and personal care for life (35). Surgery is performed to relieve pain and allow early mobilization following the fracture. Thus, complications can be devastating for the patient's morbidity and mortality.

#### *Time from fracture to surgery*

A hip fracture represents a trauma which induces hormonal and catabolic stress responses (36). The patient is also susceptible to immobilization, pain, and loss of life control. Most trials study the hospital treatment, while prehospital factors influencing hip fracture patients are less known. Transfer between hospitals predisposes patients for delayed surgery (37). Hospital transfers have also been associated with increased mortality compared to direct admission to the final treatment facility (38). After

---

admission, most fractures are diagnosed with a simple x-ray in two levels. Studies have shown a sensitivity of more than 90% to detect hip fractures using x-ray images (39-41). The remaining patients with occult hip fractures need extended diagnostic evaluations, most commonly using CT or MRI scans (42), which can prolong delay from diagnosis to surgery. However, delay to hip fracture surgery can be further prolonged even after diagnosis for a variety of reasons. Time from fracture to surgery can be crucial to optimize the medical condition of the patient and potentially reduce the risk of complications during and after surgery (43, 44). Delays from admission to surgery for more than 24, 36 or 48 hours have been associated with increased risk of mortality and complications in some studies (45-48), while other studies have not found such negative effects of delay to surgery (49-52). Therefore, efforts have been made to differentiate between acceptable and unacceptable reasons for surgical delay: anaemia (haemoglobin below 8 g/dl), correctable arrhythmias, uncontrolled diabetes, chest infections with sepsis, and uncontrolled heart failure are listed as acceptable reasons for delayed surgery. Minor electrolyte disturbances, awaiting echocardiography, and lack of surgical competence, facilities and theatre space have all been stated as unacceptable reasons (44).



**Figure 3.** Reasons for delay to hip fracture surgery

## 1.4 Surgery and complications

After diagnostic verification, hip fractures are treated with either osteosynthesis or arthroplasty, depending on type of fracture, displacement of the fracture, bone mineral density and both the chronological and physiological age of the patient, including activity level and comorbidity (53-56). Undisplaced FNFs are primarily treated with internal fixation with percutaneous screws (57-59). Elderly patients with displaced FNFs are mainly treated with hemiarthroplasty (HA) while subtrochanteric fractures are most often treated with an intramedullary nail (57-59). However, for the remaining subgroups of hip fracture patients, no consensus on surgical treatment exists. Due to the high risk of avascular necrosis following an FNF, since the blood supply to the femoral head is limited (60), prostheses are being increasingly used, especially for displaced FNF in elderly patients (5, 61, 62). In Norway, trochanteric fractures are most often operated with sliding hip screws (63). Intertrochanteric nails are a mini-invasive procedure frequently used for both trochanteric and sub-trochanteric fractures (63). The choice of osteosynthesis versus HA leads to different risk profiles for the hip fracture patient, which will be further discussed in the next section.



---

### Osteosynthesis

An osteosynthesis may represent the optimal choice of reconstruction if fracture anatomy, bone mineral density, and compliance are satisfactory. Complications following osteosynthesis include non-union or malunion, avascular necrosis of the femoral head, osteosynthesis failure, infections, and local pain due to the osteosynthesis material (55, 64, 65). In recent years, intramedullary nails have gained popularity in treatment for trochanteric fractures (66, 67). The use of intramedullary nails can cause peri-implant fractures (68), but with better implant design and improved learning curves with intramedullary nails, the problem of peri-implant fractures has been reduced. When comparing sliding hip screws and intramedullary nails, a large randomized controlled trial (RCT) reported similar rates of complications for trochanteric and subtrochanteric fractures (69). However, observational studies have found increased risk of reoperation when sliding hip screws are used compared to nails for trochanteric fractures with a detached greater trochanter (70), and also for trochanteric and subtrochanteric fractures (69). One cause of this increased revision rate may be postoperative femoral medialization, which seems to occur more often after the insertion of sliding hip screws than with intramedullary nails (71). In contrast, two-part trochanteric fractures seem to have more reoperations when intramedullary nails are used than sliding hip screws (72). A cost-effectiveness analysis supports these findings (73). For FNFs, more reoperations are performed following osteosynthesis than HA, especially for displaced fractures (5, 65, 74, 75).

### Hemiarthroplasty

HA involves the replacement of the femoral head while the acetabulum remains intact. The prosthesis stem may be fixated with or without cement. For uncemented procedures, the prosthesis coating facilitates bone anchoring over time. Hemiprostheses can be of a unipolar or bipolar design. Bipolar hemiprostheses have traditionally been used in Norway (99.2% of HA for hip fracture patients) (63).

The routines for follow-up care after discharge following HA vary among hospitals, and the rates and diversity of complications are therefore difficult to assess. One retrospective study found a complication rate of 12% following HA (76). A large multicentre RCT found a rate of reoperations of 8.3% while serious adverse events occurred in 36.3% of patients during the first two years after HA for displaced FNFs (77). A review of RCTs reported failure rates of 3-23%, while reoperations were reported among 0-24% of patients with HA used in treatment for displaced femoral fractures (78). Complications following HA include periprosthetic joint infections, dislocations, periprosthetic fractures, and aseptic loosening (55, 65, 74, 78, 79).

Younger, more active patients also seem to be at risk of acetabular erosions (80). One of the most feared complications after HA is periprosthetic joint infection (PJI), which seems to occur in 1.7-7.3% of cases (81). PJIs require large resources, long hospital stays, and most often a need for reoperation. One prospective study has shown significantly higher 30-day mortality for patients with a PJI than for patients without infection (82). These findings are supported by a retrospective study, which found increased one-year mortality when PJI treatment failed (83).

The insertion of a prosthesis in the femoral canal has been shown to increase intramedullary pressure (84-86). Sudden deaths occurring during cementation in arthroplasty surgery have led to the term "bone cement implantation syndrome" (BCIS) (85, 87, 88). Over the years, BCIS has caught the attention of both orthopaedic surgeons and anaesthesiologists. In 2009, Donaldson et al. proposed a definition of BCIS (89). Several theories have been advanced to explain the systemic effects of cement, and clinical, pathological and experimental studies have been performed to investigate BCIS. Postmortem studies have demonstrated pulmonary fat embolism in patients dying during cementation (90). Blood aspirated from the right atrium during cementation have raised suspicion of granular bone dust particles (91). Histamine-mediated hypersensitivity and complement activation have also been investigated for causing cardiorespiratory reactions following cementation (92-94). Transoesophageal echocardiography demonstrates embolization during cemented total hip arthroplasty (THA) (95, 96), and embolization seems to be inferior in uncemented THAs (95). Such embolic consequences can increase pulmonary vascular tone, leading to mild to

---

devastating haemodynamic effects including hypotension, hypoxia and arrhythmias, which may in turn result in cardiac arrest (89, 97). Transportation of procoagulant cell fragments, fat, microparticles and cement particles from the bone marrow to the systemic circulation have been blamed for the haemodynamic effects. Hypotheses have diverged into a cement monomer model and an embolic model. However, the pathophysiology and clinical impact of BCIS are still not fully understood. BCIS is feared to be underreported, and the risk seems to be higher among patients undergoing hip arthroplasties than knee and shoulder arthroplasties (98). A recent retrospective study identified BCIS in 31% of cemented HAs, and severe BCIS was associated with increased 30-day mortality (98). BCIS has been associated with renal impairment, ASA class III to IV, and age above 75 years (98). Thus, comorbid hip fracture patients may be at risk. Importantly, large observational studies report similar long-term mortality rates for uncemented and cemented hip arthroplasties (99-101).

To summarize, after the initial trauma of a hip fracture, an arthroplasty seems to be a greater trauma for the patient than osteosynthesis, thus leading to different pathophysiological effects.

## **1.5 Thromboprophylaxis**

In Norway, with a population of about 5.3 million inhabitants, 220,000 patients were prescribed anticoagulants in 2019 (102). The most common cause of death in Norway is cardiovascular disease. Therefore, long-term use of thromboprophylaxis is common among elderly patients. In addition, anticoagulation plays a key role in hip fracture treatment as systemic thromboembolic events are common and feared complications (103). 98% of hip fracture patients operated in Norway from 2005 to 2019 received thromboprophylaxis (104). The use of perioperative heparin significantly reduces the risk of deep vein thrombosis and fatal pulmonary embolism in major orthopaedic surgery (105). On the other hand, bleeding-related complications following major orthopaedic surgery can increase length of stay and hospital expenses (106). Major bleeding is a strong predictor for mortality in hospitalized patients (107). Therefore,

the use of thromboprophylaxis needs to be balanced against the risk of both thromboembolic and bleeding-related complications following the hip fracture trauma and subsequent surgery.

Compared to the average user, both long-term and temporary anticoagulant drugs can offer additional challenges in the elderly hip fracture population due to organ frailty, reduced kidney function, altered drug distribution, and drug interactions. Many clinical drug trials conducted by the industry exclude elderly patients (108). However, elderly people may need treatment optimization the most.

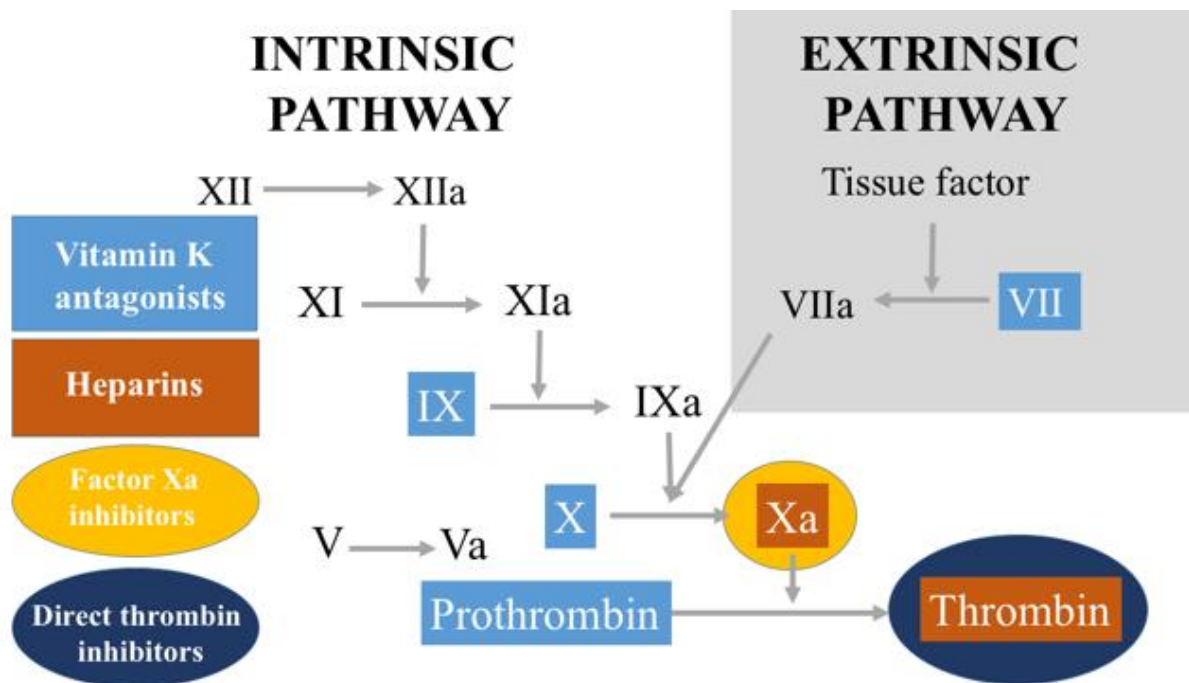
### Classification of anticoagulants

Several anticoagulants exist, some with competing functions, others with parallel functions, and their preference is mostly determined by the need for monitoring and route of administration.

**Heparin** potentiates the effect of antithrombin III and releases tissue factor pathway inhibitors from the vessel walls. The drugs are given intravenously as unfractionated heparin or subcutaneously as LMWH. Due to the routes of administration, heparin is mostly used as temporary anticoagulation during or after hospital stays. The effects of heparin can be reversed fully (or partly, in the case of LMWH) by administration of protamine sulphate.

Oral anticoagulants include **vitamin K antagonists (VKAs)** and **direct oral anticoagulants (DOACs)** which directly inhibit factor Xa or thrombin. Oral anticoagulants have revolutionized the possibility of easy and safe drug administration at home. Consequently, they are now often preferred for long-term treatment. The main indications for oral anticoagulants include venous thromboembolism (VTE), stroke prevention (DOACs and VKA) and post-heart valve replacement prophylaxis (VKA) (109). DOACs are administered in fixed doses with generally predictable anticoagulant effects; they therefore do not require routine monitoring, unlike VKAs. As of 2020, the newly arrived DOACs have limited reversal opportunities available. One specific immediate reversal agent for the thrombin inhibitor dabigatran has been

on the market since 2015 (Idarucizumab, Praxbind™) (110). Less than three years ago (2018), the American Federal Drug Agency approved a reversal agent for factor Xa inhibitors as rivaroxaban and apixaban (andexanet alpha, AnedexXa™) (111). However, these reversal agents are expensive with a short time of experience. In Norway, their use is restricted to patients suffering from uncontrolled haemorrhage or needing emergency surgery. Norwegian guidelines also suggest the use of prothrombin complex concentrate to partially reverse DOACs (112). Routine reversal of DOACs preoperatively is not advised in Norwegian guidelines for hip fracture treatment (113).

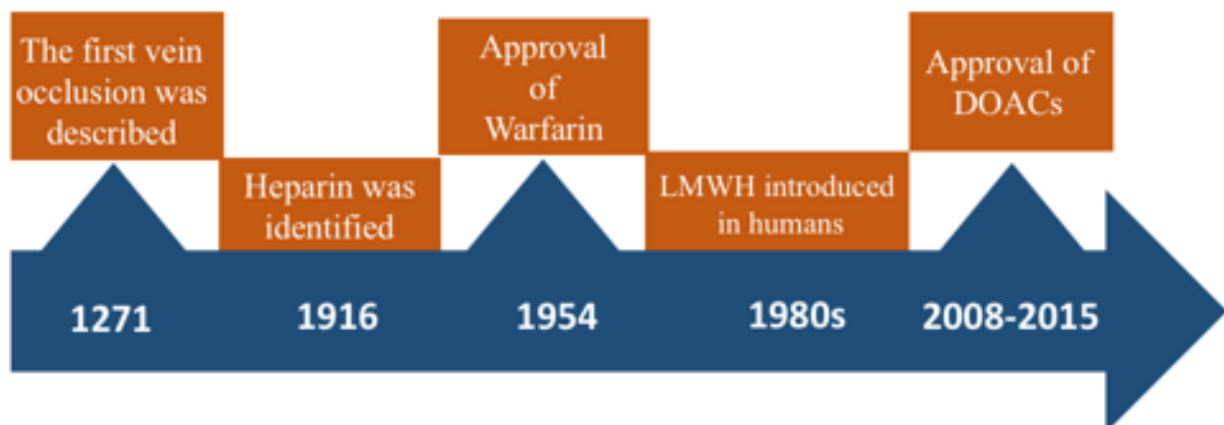


**Figure 4.** Illustration of the main mechanisms of action of anticoagulants using colour orientation. The figure does not show either the coagulation cascade or the mechanism of actions of the medication in a complete manner.

#### Development of modern VTE prevention

The first known identification of a deep vein thrombosis (DVT) was described in the Middle Ages, in 1271 (114). Many forms of treatment for DVT have been attempted through history, including bloodletting, cold baths, application of heat, vein ligation,

antibiotics, and the use of lumbar spinal blocks (115, 116). Strict bed rest was common practice to prevent thrombus migration until the 19th century (114, 117). Splints were often used to secure immobilization. In 1793, occlusion of veins due to blood clots were hypothesized to cause DVTs by Dr John Hunter (118). The relationship between deep vein thrombosis and pulmonary embolism was discovered by Rudolph Virchow in the mid-1850s. Still to this day, the three main factors contributing to thrombosis are recognized as Virchow's triad (stasis, endothelial damage and hypercoagulability) (119). The anticoagulant era began when the first effective medicine, heparin, was identified in 1916 and introduced in humans in 1935-37 (120-123). Even though RCTs did not exist at the time, heparin was already being widely used in the 1940s due to steep reductions in mortality following symptomatic VTE (124). Surgical thromboprophylaxis was among the first established indications for using heparins (125). LMWH was introduced in the 1980s, thus abandoning the need for drug monitoring and allowing home care.



**Figure 5.** Timeline of the development of modern anticoagulation

In 1954, the first oral drugs, VKAs, were approved for the prevention of VTE by the US Food and Drug Administration, thereby allowing for long-term anticoagulant treatment. While VKAs have been on the market since 1954, the first DOACs were approved in 2008-2010. In large trials, DOACs have been equivalent to or better than warfarin in the prevention of arterial embolism and cerebral infarction due to atrial fibrillation (126-128). The risk of cerebral bleeding also seems to be lower with

---

DOACs than with warfarin (126, 128, 129). Due to encouraging study results, active marketing, and decreased monitoring requirements, the numbers of DOAC users increased by 150% in Norway from 2014 to 2018 and DOACs as a group have surpassed VKAs (102).

Controlled trials have investigated the use of anticoagulation versus placebo for hip fracture at least as far back as 1959 (130). However, baseline risk of VTE and bleeding for hip fracture surgery are difficult to study as there have been major changes in surgical techniques and time to ambulation, which influence the risk of bleeding and VTE-related complications. A Norwegian study reported an average length of stay for hip fracture patients of 35 days in the 1960s (131). In comparison, length of stay for hip fracture patients in seven European countries was recently compared with a Norwegian average of 10 days (132). The estimated risk of complications related to VTE following hip fracture surgery has fallen from 15-46% without anticoagulation, as reported from RCTs before the 1980s (133-135)), to 1-2% reported from observational studies using LMWH in the early 2000s (136, 137).

Internationally, guidelines now strongly recommend the use of thromboprophylaxis for hip fracture surgery. However, consensus has not been reached regarding the choice of medication, time of initiation, and duration of use. American guidelines recommend anticoagulation for at least 10 to 14 days (138); Grade 1B evidence supports the use of LMWH, fondaparinux, adjusted doses of unfractionated heparins or VKAs, and aspirin. LMWH is stated to be the preferred drug of choice, partly due to good efficacy-to-safety profiles (139). The guidelines of the UK National Institute for Health and Care Excellence (NICE) recommend one month of thromboprophylaxis with LMWH or fondaparinux for fragility fractures of the femur (provided that there is a low risk of bleeding) (140). In Norway, 98% of hip fracture patients have received LMWH as thromboprophylaxis since 2005 (104). Similar predominance of LMWH has also been reported from Denmark and the Netherlands (141, 142). For other types of major surgery of the hip and knee, such as total hip or total knee replacements, guidelines from Norway, the UK and the US also support the use of DOACs as thromboprophylaxis (138, 140, 143). However, DOACs have only been in use for a

short time and have limited opportunities for surveillance and reversal. They are therefore still not recommended for perioperative thromboprophylaxis in the elderly hip fracture population.

Complimentary non-pharmacological treatments have also been suggested to prevent VTE complications following major orthopaedic surgery with varying success. Intermittent pneumatic compression devices (IPCDs) are recommended in the UK if pharmacological interventions are contraindicated or denied due to patient compliance (140), or as a supplement to a pharmacological intervention in the US (138). The placement of inferior vena cava filters is not recommended for primary prophylaxis today. Filters and IPCD solutions are currently either not approved or not used for orthopaedic surgery in Norway. They have therefore been excluded from recent national thromboprophylaxis guidelines (143). Mechanical non-pharmacological interventions will not be further discussed in the thesis. Early mobilization after the hip fracture is thought to reduce the risk of VTE. However, the evidence concerning benefits of early ambulation is sparse.

## **1.6 Anticoagulation in relation to surgery and neuroaxial anaesthesia**

The benefits of anticoagulants must be balanced against the risks in order to perform safe surgical and neuroaxial anaesthesia procedures. RCTs aiming to find the optimal timing of anticoagulation before anaesthesia are problematic due to few neuroaxial bleeding events and the potentially unethical selection of patient treatment. There is limited practical experience with DOACs, and we lack evidence for safe intervals from drug termination to neuroaxial procedures (144). European guidelines suggest pausing of DOACs in line with their pharmacokinetic properties (145-148). Norwegian guidelines advise waiting at least two days from the last DOAC administration before performing elective surgery, and if possible delaying emergency surgery for at least one half-life of elimination (112). The half-life is approximately 12-14 hours for dabigatran, 12 hours for apixaban, 10-14 hours for edoxaban and 5-9 hours for rivaroxaban (11-13 hours for elderly users) (149). However, guidelines for semi-



---

urgent surgery such as hip fracture surgery are sparsely described. In the recently published Norwegian interdisciplinary guideline for hip fracture treatment (150), hip fracture surgery is advised after one half-life of the DOAC has passed, while neuroaxial anaesthesia can be performed after 24-48 hours. In Norway, 85-90% of hip fracture patients are operated with neuroaxial anaesthesia (63).

## 2 Aims of the study

The aims of this study were:

1. To identify current practice for timing of anticoagulant administration to hip fracture patients. We aimed to evaluate both temporary and long-term use of thromboprophylaxis.
2. To identify perioperative and postoperative outcomes for hip fracture patients by comparing established anticoagulant administration regimens in Norway.
3. To investigate how preoperative factors influence outcomes after the hip fracture by studying time from fracture via admission to surgery and the long-term use of direct oral anticoagulants.

The specific aims of the four papers included in the thesis were:

**Paper I.** To investigate the risk of mortality, reoperations, and intraoperative bleeding complications by comparing preoperative versus postoperative start of low-molecular-weight heparin in femoral neck fracture patients operated with hemiprosthesis.

**Paper II.** To investigate the risk of mortality, reoperations, and intraoperative bleeding complications by comparing preoperative versus postoperative start of low-molecular-weight heparin in hip fracture patients operated with osteosynthesis.

**Paper III.** To investigate whether time from hip fracture to surgery influences one-year mortality and risk of intraoperative medical complications.

**Paper IV.** To compare time to surgery, length of hospital stay, mortality, and bleeding complications for hip fracture patients using direct oral anticoagulants compared to non-users before the hip fracture occurs.

## 3 Materials

### 3.1 The Norwegian Patient Registry

There are 17 mandatory national health registries in Norway. The goal of these regulated registries is to provide reliable information about health and quality of healthcare in Norway (151). Among these registries is the Norwegian Patient Registry (NPR), established in 1997. The NPR is administered by the Norwegian Directorate of Health. The NPR receives information (e.g. ICD-10 codes) from the hospitals regulating activity-based financing, administration, and management for the Norwegian health care services. The information in the NPR has been personally identifiable since 2008 using the 11-digit national identification numbers assigned to each inhabitant of Norway. From then on, we have been able to identify information on the same patient in each hospital and between hospitals. The NPR does not require consent from patients, following an evaluation by the Norwegian government.

In *Paper III*, we extracted time of hospital admission for hip fracture patients from the NPR. Then we extracted time of hip fracture from the Norwegian Hip Fracture Register. The utilization of two registries enabled us to compare total delay (time from fracture to surgery), prehospital delay (time from fracture to admission), and hospital delay (time from admission to surgery) for hip fracture patients.

### 3.2 The Norwegian Hip Fracture Register

In addition to the registries regulated by law, there are more than 200 medical registries in Norway licensed by the Data Inspectorate. One of these is the Norwegian Hip Fracture Register (NHFR). Despite extensive research, there is still no worldwide consensus on optimal hip fracture treatment at the beginning of 2021. With an ageing population increasing the likelihood of fractures, the NHFR was established in 2005 engaged by the Norwegian Orthopaedic Association and is legally managed by the Department of Orthopaedic Surgery at Haukeland University Hospital in Bergen. The NHFR is funded by the Government through the Western Norway Regional Health Authority (Helse Vest RHF) and provides a nationwide service by processing reports from all hospitals treating hip fracture patients in Norway.

The NHFR has permission from the Norwegian Data Inspectorate to gather data on hip fracture patients following written patient consent. Orthopaedic surgeons report by completing a one-page form directly after each surgery (Appendix I). The form contains detailed patient information including the patients' personal identification number. Time of fracture and fracture classification are reported, as is the presence of cognitive impairment. If cognitive impairment is suspected but not known, the form recommends a clock test to determine impairment; here, the patient is asked to draw a clock showing ten minutes past eleven (152) (Appendix I). Comorbidity is reported using the ASA classification (153). Time, duration, and type of surgery are reported. The surgeon also reports chemical thromboprophylaxis given during treatment (whether or not it was used, which medication, dosage, and whether the first dose was given preoperatively or postoperatively). Annual reports from the registry demonstrating time trends and outcomes are sent to all orthopaedic departments and to the health authorities. Since 2017, interactive results from the NHFR can be found at: <https://www.kvalitetsregistre.no/registers/525/resultater>. The interactive results enable each hospital to compare results on national quality indicators. One of the national quality indicators, time from fracture to surgery, was assessed in detail in *Paper III*.

---

The National Directorate of Health aims to reduce bias through validation studies of all registers in Norway. Both in validation studies from 2016 and 2017-2018, the NHFR was found to have a high registration completeness of 88% for osteosyntheses and 94-95% for hemiprostheses compared to the NPR (104, 154).

### **3.3 Mortality, reoperations and complications**

To study postoperative mortality in *Papers I-III*, information on death and emigration was provided by the Norwegian Population Register (155). The Norwegian Data Protection Authority approved the purpose and use of these data.

If patients need secondary surgery following the fracture, reoperations are reported on the same form as listed in Appendix I. In *Papers I-III*, a reoperation was defined as any secondary surgery following the primary operation. Secondary surgery therefore also included closed reduction of a dislocated hemiprosthesis and soft tissue debridement without exchange or removal of a prosthesis. Secondary surgery was linked to the primary operation using the patient's identification number even if the procedures were performed in different hospitals. The completeness of registration of revision surgery in the NHFR was found to be 80% for osteosyntheses and 73% for HA in 2017-2018 (104).

When reporting data to the NHFR directly after surgery (Appendix I), the surgeon should also report intraoperative complications. These complications are individually described by the surgeon. For example, intraoperative complications can arise due to excessive bleeding, which is an endpoint studied in *Papers I-II*. Intraoperative complications can also be divided into surgical complications and medical complications, as we did in *Paper III*.

No studies have been conducted to assure the quality and quantity of reporting of complications to the NHFR.

### 3.4 Medical records

In *Paper IV*, the need for detailed day-to-day information on drug administration, hospital treatment, and adverse outcomes made the use of registries inadequate. We therefore used a retrospective study design by extracting data from medical records from a single trauma centre. 360 patients operated from December 2016 to December 2017 were extracted from the hospital database by using the ICD-10 codes S72.0-S72.2. Admission and discharge papers and day-to-day documentation throughout the hospital stay from both orthopaedic surgeons and anaesthesiologists were used. Drug administration logged by nurses and doctors was assessed. To ensure reproducibility, all records were assessed by one researcher, Sunniva Leer-Salvesen. The Regional Ethics Committee classified the study as quality assurance, which negated the need for ethical assessment (case number 1366/REK). The hospital data protection officer approved the study. The variables studied in *Paper IV* are further described in Table 1.

**Table 1.** Source of information and classification of the variables studied in *Paper IV*

Variable	Source of information	Classification
<b>Patient information</b>		
Age	Personal identification number	Recorded in years.
Sex	Medical records	Male or female
Level of care	Medical records	Description of either home care or long-term care in a nursing home both before and after the fracture
Cognitive impairment	Admission papers and medical records from doctors	If a known diagnosis of documented cognitive impairment was mentioned, the patient was recorded as having cognitive impairment. Unknown cognitive function and patients with suspected delirium were not included in the group defined as

		having cognitive impairment.
ASA class	Anaesthesia records	ASA classification I-V
Preoperative use of anticoagulants	Admission papers from doctors	The active pharmaceutical ingredient was recorded. Dosage was recorded in milligrams. Time of administration was recorded in hours before and after surgery.
Preoperative use of antiaggregants	Admission papers from doctors	The active pharmaceutical ingredient was recorded. Dosage was recorded in milligrams. Time of administration was recorded in hours before and after surgery (if known).
<b>Laboratory tests</b>		
Haemoglobin	Laboratory records	Values in g/dl. Recorded preoperatively, the first morning postoperatively and at the last measurement before discharge.
International normalized ratio	Laboratory records	Value at the time of admission
Thrombocytes	Laboratory records	Value at the time of admission
Creatinine	Laboratory records	Values in $\mu\text{mol/L}$ at the time of admission and the first morning postoperatively
<b>Treatment</b>		
Time from admission to surgery	1. Administration reports identified the time of admission. 2. Anaesthesia reports identified the start of surgery.	Recorded in hours
Type of surgery	Medical records from orthopaedic surgeons	Osteosynthesis (recorded as screw osteosynthesis, intramedullary nail or sliding hip screw) or arthroplasty (recorded as HA or THA)
Duration of surgery	Identified from medical records by anaesthesiologists	Recorded in minutes
Type of anaesthesia	Identified from medical records by anaesthesiologists	Documented in written text, recorded as spinal or general anaesthesia (including both total intravenous anaesthesia and inhalational anaesthesia).
Length of hospital stay	Identified from patient medical records	Recorded in days

<b>Complications</b>		
Readmission to hospital	Identified from medical records covering the first six months following the fracture	Recorded as both dichotomous (readmitted or not) and continuous (number of readmissions).
Excessive bleeding	Intraoperative bleeding described in the medical records from orthopaedic surgeons or anaesthesiologists Postoperative bleeding reported in the orthopaedic surgeon's medical records	Dichotomous recording (excessive bleeding or not). Timing of bleeding was noted (intraoperative or postoperative identification)
Intraoperative blood loss	Anaesthesia record	Recorded based on the routine estimation of blood loss in mL by the surgical team
Need for transfusion	Identified from the medical records signed by both doctors and nurses	Blood transfusion rates and transfusion amounts (number of allogenic red blood cells infused in standard units) were noted.
Change in haemoglobin	Laboratory values	The difference was calculated between the level of haemoglobin at admission and the morning after surgery (change in haemoglobin concentration).
Wound complications	Postoperative medical records from orthopaedic surgeons	If the doctors described a postoperative wound ooze, a case was recorded. Further, wound infections and secondary surgery due to infections were recorded.
Thromboembolic complications	<ol style="list-style-type: none"> <li>1. Written description of VTE in the medical records</li> <li>2. Identification of radiological confirmation in the medical records</li> <li>3. Identification of ICD-10 codes I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, I26.0, I26.9</li> </ol>	Dichotomous recording (VTE or no VTE)
Reoperations	Identification of secondary surgery during the primary hospital stay or readmission the first six months after the fracture	Dichotomous recording (reoperation or not). In addition, the cause of reoperation was described in each case.
Mortality	Administrational reports from the medical records, which includes all deaths recorded in the Norwegian Cause of Death Registry	Dichotomous recording of 30-day and 6-month mortality



## 4. Statistics

Analyses were performed in IBM SPSS Statistics Version 22 (*Paper I*) and 24 (*Papers II-IV*) (IBM Corp., Armonk, NY, USA) and the statistical package R ([www.R-project.org](http://www.R-project.org)).

### 4.1 Survival analysis

In *Papers I-III*, survival analyses were performed using Kaplan-Meier and Cox regression methods to calculate hazard risk ratios for mortality and reoperations. Assessments of proportionality in the Cox models were performed using log minus log plots of the adjusted survival curves, and the proportionality assumptions were fulfilled (156). The Cox multiple regression model was used to compare relative risks of postoperative death and reoperations. Patients who died or emigrated during the follow-up period were identified from files provided by Statistics Norway, and the follow-up period for all patients was censored at the date of death or at the end of the study. In all three papers, calculations were adjusted for age, sex and ASA classification. We did not adjust for patients who were operated for hip fractures on both sides as it has earlier been shown that bilateral surgery will not alter conclusions for the covariates entered (157)

### 4.2 Continuous variables

The independent student's t-test was used to compare mean values in continuous variables in all four papers. The significance level was set to 0.05. Q-Q plots were used to assess normality. In *Paper IV*, the assumption of variance between groups was assessed using Levene's test. Where the assumption held, the student's t-test was used.

### 4.3 Categorical variables

Several statistical methods were used to express categorical variables.

Odds ratios (ORs) quantify the strength of the association between two events. ORs were calculated and presented with 95% confidence intervals in *Papers III- IV*.

Pearson's chi-squared test evaluates how likely it is that observed differences between categorical data sets have arisen by chance. Pearson's chi-squared test was used in *Paper III*. The measure of numbers needed to harm (NNH) indicates how many individuals on average need to be exposed to a risk factor to cause harm to an individual who would otherwise not be harmed. In *Paper II*, NNH was calculated and defined as the number of patients treated preoperatively with LMWH in order to cause one intraoperative bleeding complication because of preoperative start compared with postoperative start, assuming a direct causal effect. NNH was calculated as the inverse of the absolute risk increase. Thus, the number needed to harm was calculated as an inverse value of the risk difference between preoperative and postoperative start of LMWH.

### 4.4 Power analysis

In *Paper IV*, we performed a power analysis to estimate the number of patients necessary to include in order to achieve statistical significance between groups (DOAC users and non-users). We used the main outcome, delay from fracture to surgery, to assess the inclusion. Based on guidelines from the Norwegian Knowledge Centre for the Health Services, hip fracture patients should preferably be operated within 24 hours and no later than 48 hours after admission (158). We calculated a standard deviation of 15.1 hours by using hip fracture patients with a surgical delay of less than 96 hours reported to the NHFR. Based on alpha of 0.05 and beta of 0.9, 28 patients were needed in each group. Since 9.4% of Norwegian patients > 60 years were using DOACs in 2017(102), the total sample size was calculated to be 300. To account for exclusion criteria and missing information, we increased the sample size by 20%.

---

## 5. Summary of Papers I-IV

### 5.1 Paper I

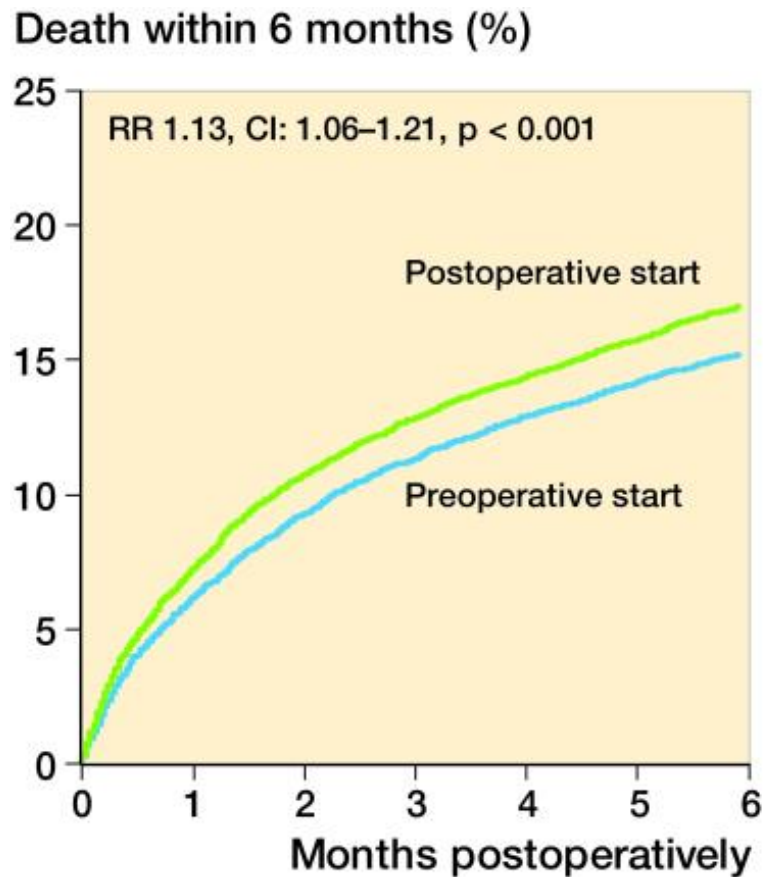
*Leer-Salvesen S, Dybvik E, Dahl OE, Gjertsen JE, Engesæter LB. Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures. Acta Orthop. 2017 Feb;88(1):48-54.*

**Background:** Controversies exist regarding thromboprophylaxis in orthopaedic surgery, especially for the frail hip fracture population. We used data from the nationwide NHFR with postoperative death and reoperation the first six months after surgery as endpoints in the analyses to investigate whether thromboprophylaxis in patients undergoing hemiarthroplasty for femoral neck fracture should start preoperatively or postoperatively.

**Methods:** After each operation for hip fracture in Norway, the surgeon reports information on the patient, the fracture, and the operation to the NHFR. The form also provides information on the chemical thromboprophylaxis given during treatment (whether or not it was used, which drug, dosage, and whether the first dose was given preoperatively or postoperatively). During the period 2005-2014, antithrombotic medication was given to 99% of patients. LMWH predominated with dalteparin in 57% of the operations and enoxaparin in 41%. Only operations with these two drugs and with known information on preoperative or postoperative start of the prophylaxis were included in the analyses (n = 20,241). Cox regression analyses were performed with adjustments for age, ASA classification, gender, type of implant, length of surgery, and year of surgery.

**Results:** Compared to preoperative start of thromboprophylaxis, postoperative start of thromboprophylaxis was associated with a higher risk of death (RR = 1.13, 95% CI: 1.06–1.21; p < 0.001) and a higher risk of reoperation for any reason (RR = 1.19, 95% CI: 1.01–1.40; p = 0.04), whereas we found no effect on reported intraoperative bleeding complications or on the risk of reoperation due to haematoma. The results did not depend on whether the initial dose of prophylaxis was full dosage or half of the standard dosage.

**Conclusion:** Postoperative start of thromboprophylaxis increased the mortality and risk of reoperation compared to preoperative start in femoral neck fracture patients operated with hemiprosthesis. The risks of bleeding and of reoperation due to haematoma were similar in patients who received LMWH preoperatively and in those who received it postoperatively.



**Figure 6.** Postoperative mortality for femoral neck fracture patients treated with hemiprosthesis. The figure is reprinted with permission from the original article in Acta Orthopaedica.

---

## 5.2 Paper II

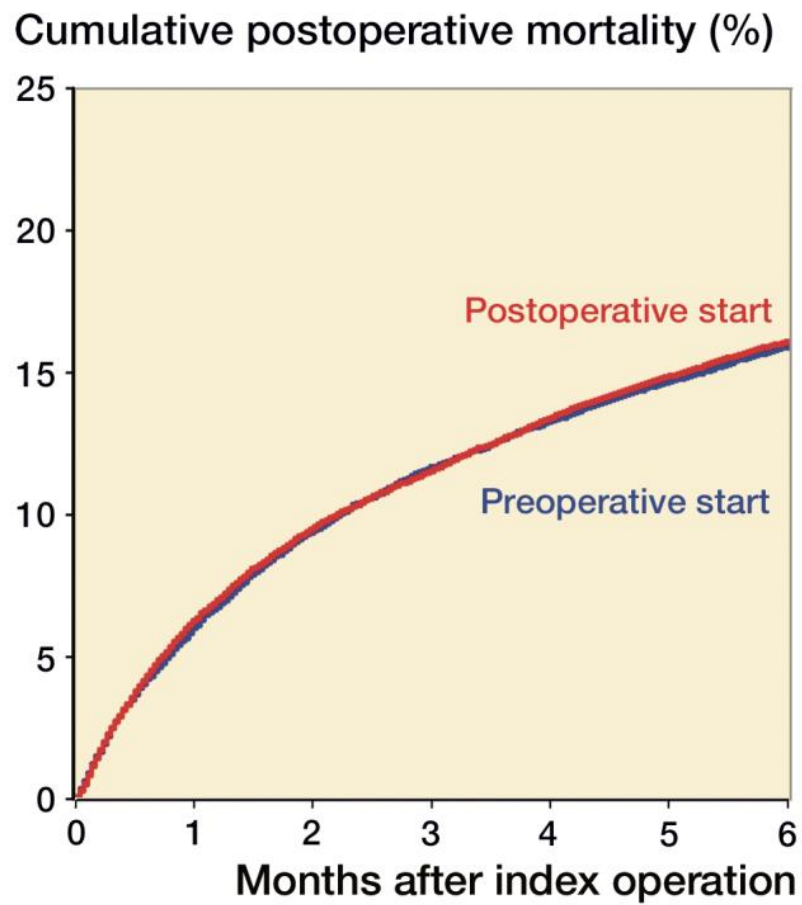
*Leer-Salvesen S, Dybvik E, Engesaeter LB, Dahl OE, Gjertsen JE,. Low-molecular-weight heparin for hip fracture patients treated with osteosynthesis: should thromboprophylaxis start before or after surgery? An observational study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register. Acta Orthop. 2018 Dec;89(6):615-621.*

**Background:** Consensus on thromboprophylaxis administration has not been reached in hip fracture surgery. We studied whether thromboprophylaxis in hip fracture patients treated with osteosynthesis should start before or after surgery. Data were extracted from the NHFR. The risks of postoperative deaths, reoperations, and intraoperative bleeding complications within six months of surgery were studied.

**Methods:** After each hip fracture surgery in Norway, the surgeon reports information on the patient, the fracture, and the operation to the NHFR. Information regarding chemical thromboprophylaxis given during treatment is also reported to the register (whether or not drugs was used, which drug, dosage, and whether the first dose was given preoperatively or postoperatively). From 2005–2016, 96,599 hip fractures were reported to the register. Only osteosyntheses where LMWH was given with a known start of the prophylaxis were included in the analyses ( $n = 45,913$ ). We performed Cox regression analyses with adjustments for age group, ASA classification, sex, duration of surgery, and year of surgery.

**Results:** Dalteparin and enoxaparin were used in 58% and 42% of the operations respectively. Mortality ( $RR = 1.01$ , 95% CI 0.97–1.06) and risk of reoperation ( $RR = 0.99$ , CI 0.90–1.08) were similar when comparing preoperative and postoperative start of LMWH. Postoperative start of LMWH reduced the risk of intraoperative bleeding complications compared with preoperative start ( $RR = 0.67$ , 95% CI 0.51–0.90).

**Conclusion:** The initiation of LMWH did not influence mortality or risk of reoperation in hip fracture patients treated with osteosynthesis. Postoperative start of LMWH could possibly decrease the risk of intraoperative bleeding.



**Figure 7.** Postoperative mortality for hip fracture patients treated with osteosynthesis. The figure is reprinted with permission from the original article in Acta Orthopaedica.

---

### 5.3 Paper III

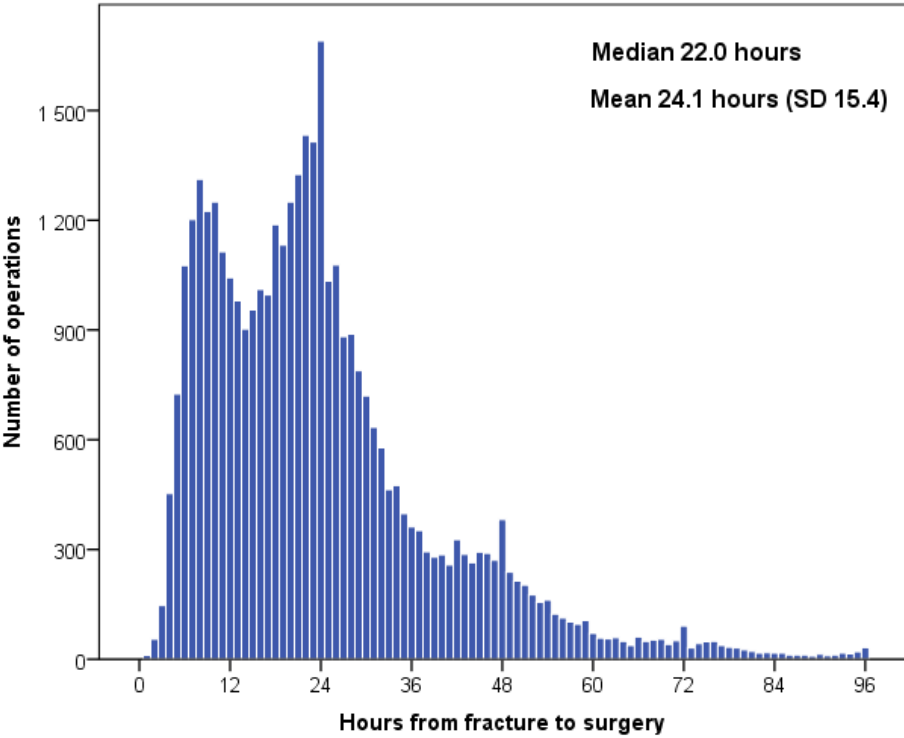
*Leer-Salvesen S, Engesæter LB, Dybvik E, Furnes O, Kristensen TB, Gjertsen JE. Does time from fracture to surgery affect mortality and intraoperative medical complications for hip fracture patients? An observational study of 73,557 patients reported to the Norwegian Hip Fracture Register. Bone Joint J. 2019 Sep;101-B(9):1129-1137*

**Background:** The influence of time from hip fracture to definitive surgery is not clear. Current studies have investigated hospital delay with conflicting results. The aim of this study was to examine mortality and risk of intraoperative medical complications depending on delay from hip fracture to surgery by using data from the NHFR and the NPR.

**Methods:** A total of 83,727 hip fractures were reported to the NHFR between 2008 and 2017. Pathological fractures, unspecified types of fractures or treatment, patients below 50 years of age, unknown delay to surgery, and delays to surgery longer than four days were excluded. We studied total delay (fracture to surgery, n = 38,754) and hospital delay (admission to surgery, n = 73,557). Cox regression analyses were performed to calculate RRs adjusted for sex, age, ASA classification, type of surgery, and type of fracture. ORs were calculated for intraoperative medical complications. We compared delays of 12 hours or less, 13 to 24 hours, 25 to 36 hours, 37 to 48 hours, and more than 48 hours.

**Results:** Mortality remained unchanged when total delay was less than 48 hours. Total delay exceeding 48 hours was associated with increased three-day mortality (RR = 1.69, 95% CI 1.23-2.34; p = 0.001) and one-year mortality (RR = 1.06, 95% CI 1.04-1.22; p = 0.003). More intraoperative medical complications were reported when hospital delay exceeded 24 hours.

**Conclusion:** Hospitals should operate on patients within 48 hours of the fracture to reduce mortality. As our study found more intraoperative medical complications reported in connection with more than 24 hours' hospital delay, we fully support the practice of early surgical intervention in the treatment of patients with hip fractures.



**Figure 8.** Time from fracture to surgery in the study population (n=38,754)



## 5.4 Paper IV

*Leer-Salvesen S, Dybvik E, Ranhoff AH, Husebø BL, Dahl OE, Engesæter LB, Gjertsen JE. Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay, and poorer outcome for hip fracture patients? Eur Geriatr Med. 2020;11(4):563-9*

**Background:** The perioperative consequences for patients taking DOACs before the hip fracture are not sufficiently studied. The primary aim of this study was to determine whether DOAC users have delayed surgery compared to non-users. Secondly, we studied whether length of hospital stay, mortality, reoperations, and bleeding complications were influenced by the use of DOACs.

**Methods:** The medical records of 314 patients operated for a hip fracture between 2016 and 2017 in a single trauma centre were assessed. Patients aged < 60 and patients using other forms of anticoagulation than DOACs were excluded. Patients were followed from admission to six months postoperatively. Surgical delay was defined as time from admission to surgery. Secondary outcomes included length of hospital stay, transfusion rates, perioperative bleeding loss, postoperative wound ooze, mortality, and risk of reoperation. The use of general versus neuroaxial anaesthesia was recorded.

**Results:** 47 hip fracture patients (15%) were taking DOACs. No differences in surgical delay (29 vs. 26 hours,  $p = 0.26$ ) or length of hospital stay (6.6 vs. 6.1 days,  $p = 0.34$ ) were found between DOAC users and non-users. DOAC users operated with neuroaxial anaesthesia had longer surgical delays than those operated with general anaesthesia (35 vs. 22 hours,  $p < 0.001$ ). Perioperative blood loss, transfusion rate, risk of bleeding complications and mortality were similar between groups.

**Conclusion:** Hip fracture patients using DOACs did not have increased surgical delay, length of stay or risk of bleeding complications than patients without anticoagulation prior to surgery. The increased surgical delay found for DOAC users operated under neuroaxial anaesthesia should be interpreted with caution.

Antithrombotic medication				
Hospital stay	Total	No anticoagulants	DOAC	<i>p</i> value
Hours from admission to surgery (SD)	26.5 (18.2)	26.1 (19.0)	28.9 (12.9)	0.26
LOS (SD)	6.2 (2.9)	6.1 (2.9)	6.6 (2.2)	0.34
General anaesthesia (%)	<b>32 (10%)</b>	<b>10 (3.8%)</b>	<b>22 (47%)</b>	<b>0.001</b>
Perioperative complications				<i>p</i> value
Mean blood loss during surgery (SD)	219 mL (208)	218 mL (209)	223 mL (204)	0.9
Mean fall in haemoglobin (SD)	1.90 (1.30)	1.89 (1.25)	1.95 (1.63)	0.8
Mean SAG transfused per patient (SD)	0.81 (1.16)	0.80 (1.17)	0.85 (1.10)	0.8
				OR (95% CI)
Number of patients transfused (%)	134 (43%)	113 (42%)	21 (45%)	1.10 (0.59–2.01)
Reported wound ooze (%)	<b>27 (8.6%)</b>	<b>15 (5.6%)</b>	<b>12 (26%)</b>	<b>5.8 (2.49–13.3)</b>
Mortality				OR (95% CI)
In-hospital mortality	11 (3.5%)	9 (3.4%)	2 (4.3%)	1.27 (0.27–6.09)
30-day mortality	39 (12.4%)	34 (12.7%)	5 (10.6%)	1.23 (0.45–3.31)
6-month mortality	70 (22.3%)	59 (22.1%)	11 (23.4%)	0.93 (0.45–1.94)

Bold values indicate more frequent use of general anaesthesia and higher risk of wound ooze in DOAC-users compared to non-users

**Table 2.** Surgical delay, length of hospital stay, type of anaesthesia, perioperative complications and mortality reported in hip fracture patients with DOAC or no anticoagulation prior to the fracture (n=314). This table is reprinted from the corrected version of the original article (Appendix III).

## 6. Discussion

### 6.1 Observational studies versus randomized controlled trials

Prospective RCTs have the highest level of evidence in science. RCTs are also central to the understanding of treatment of hip fracture patients, where outcomes can diverge significantly when comparing perioperative treatment strategies. The structure of RCTs minimizes the risks of bias and confounding. However, RCTs will not always be feasible due to their use of time and resources, their expense, and subsequently limited patient inclusion and time frames. Due to these limitations, several problems are unsuitable for RCTs. Further, RCTs can only study a limited number of primary outcomes at a time. Metastudies have shown that well-structured observational study designs can provide similar results to RCTs, given that confounding and bias are controlled for (159, 160). It is imperative to understand the strengths and weaknesses of both observational and experimental study designs, which will be discussed in the next section. The strengths and weaknesses of observational study designs are further discussed by Thygesen et al. (161).

In both RCTs and observational studies, there is a risk of data dredging, where many hypotheses are tested and only the significant ones are reported. Several efforts have been made to reduce the risk of dredging and publication bias, yet there is still a long way to go to achieve a change of attitude in the research community to increase publication of null results. One initiative in observational studies is the use of checklists to ensure adequate reporting from researchers, in order to evaluate methodological strengths, weaknesses and generalizability for each project. STROBE has been created for all epidemiological observational study designs while RECORD was created as an extension to STROBE to identify potential pitfalls when using routinely collected health data for research purposes (162, 163). The STROBE checklist was used in *Papers I-II*.

### 6.1.1 Strengths of register studies

Medical registries facilitates the use of epidemiological data on a larger scale than other study designs. Coupling of different registries further expands the opportunities. Researchers can thus avoid protracted and expensive data collection. In contrast to RCTs, multiple patient groups and treatment algorithms can be compared in the same study. Further, national registries such as the NHFR report results from the average surgeon from all hospitals treating hip fractures in Norway. Thus, register data can have high external validity. Rare complications, intraoperatively and postoperatively, are outcomes suitable for register study designs as the time lines are flexible and the data sets are large. Such outcomes are presented in *Papers I-II*, where we studied the occurrence of intraoperative bleeding and reoperations due to haematomas.

Large cohort studies and RCTs are dependent on voluntary patient participation. Challenges arise as every fourth hip fracture patient is reported to suffer from cognitive impairment (164). In addition, delirium has been reported at significant rates both before (20%) and after hip fracture surgery (36%) (165). These patients are at risk of non-response and loss to follow-up. The unwanted consequence is that results from patients with cognitive impairment are frequently not reported or excluded from RCTs on hip fracture management (166). In contrast, registries are able to obtain "complete data" for the study population, thereby reducing the risk of selection bias and recall bias. Even for the consent-based NHFR, the high level of completeness compared to the mandatory NPR supports limited selection bias also in our register studies (154).

Observational study designs are particularly well suited for understanding broad populations and safety outcomes, especially when such outcomes are rare or unethical to study in interventional designs. A relevant example for this thesis is the consequences of delay to hip fracture surgery encountered in *Paper III*. It is undoubtedly unethical to randomize hip fracture patients into early and deliberately

---

late surgery. Current evidence-based knowledge reports an increased risk of mortality with delay to surgery (46) as well as slower functional recovery and increased morbidity with late ambulation after hip fracture surgery (167-169). Therefore, safety outcomes following delay to surgery need to be studied in observational study designs.

To summarize, observational study designs continue to play an important role in research by supplementing findings from RCTs.

### **6.1.2 Limitations of register studies**

Observational studies can report associations between exposures and outcomes, yet cannot prove causality. Thus, their level of evidence is lower than that of RCTs, as they are less conclusive. The fundamental source of bias in observational study designs has been attributed to unmeasured confounding. The magnitude of confounding can be reduced by several methods. Sensitivity analyses can assess the influence of unmeasured confounding. Matching or restriction of the treatment group (to only include cases with the same value of the potential confounding factor) can also be used. Regression analysis, such as logistic or Cox regression analysis, is often used to increase statistical control. In these analyses, the concurrent effects of various risk factors can be studied. We are then able to adjust for skewed distribution of known background variables. However, unknown variables remain hidden. The challenge arises because observational studies with large data sets are able to detect small effect sizes due to high statistical power. Firstly, the risk of hidden confounding factors combined with the ability to detect small effect sizes due to the high statistical power can generate incorrect conclusions. Secondly, observational studies risk detecting results of statistically significant yet clinically insignificant value.

A register study encompasses pre-collection of data from others than the researchers themselves in terms of variables, exposures and outcomes (161). Registries may have insufficient information of great value for certain research projects. For example, the long-term use of anticoagulants such as warfarin and DOACs before the hip fracture is not reported to the NHFR. The use of such agents may influence delay to surgery, the

use of intraoperative LMWH, and complications during and after surgery, such as bleeding and wound leakage. Further, these uncontrolled outcome measures may be in insufficient detail or unsuitable for the study being conducted as they are generated for a multi-use register. For example, low-grade infections after hip fracture surgery may be treated with antibiotics instead of reoperation in the frailest patients, and are thus not reported to the NHFR as a complication. In addition, postoperative low-grade bleeding or wound ooze may prolong hospital stay and increase risk of infection. However, the NHFR only receives reports on reoperations due to haematoma or infection, not the conservatively treated cases. The limitations in the use of registries necessitated a different study design in *Paper IV*. By studying medical records instead of using a register, the researcher controls the selection of variables, both exposures and outcomes. Further, the risk of inter-observer variation is eliminated by using only one researcher (SLS).

Register studies risk selection bias and information bias, as the data need to be handled by independent reporters. In 2016, the NHFR was found to have high registration completeness of 88% for osteosynthesis and 95% for HA, compared to the NPR (154). In reality, the completeness of the NHFR may be even higher as re-admissions due to hip fracture complications are sometimes recorded as primary hip fractures in the NPR, leading to an overestimation of 14% in the NPR in one study (170). However, another study demonstrated inconsistency with both underreporting and overreporting of hip fracture diagnoses to the NPR over a seven-year period (171). To conclude, we need to be aware of the different sources of inaccuracy in code-related registries (NPR) and quality registries (NHFR), especially when comparing results.

The high completeness of primary hip fractures in the NHFR may be associated with the relatively straightforward coding for these fractures and subsequent surgeries compared to other diseases requiring long-lasting diagnostic evaluations.

Unfortunately, the completeness has been significantly lower for reoperations than primary operations in the NHFR compared to the NPR: 73% for reoperations after HA and 80% for reoperations after osteosynthesis in 2017-2018 (104). In contrast to the Norwegian Arthroplasty Register, the NHFR defines all secondary procedures as

---

reoperations, including closed reduction of dislocated hemiprostheses and soft tissue revisions. Such a definition may lead to underreporting of minor reoperations. The lower completeness may also be caused by imprecise coding and poor education in the complex and varied coding for secondary surgery. However, the underreporting of reoperations is assumed to be a non-differential misclassification: reoperations are missing regardless of surgical approach, anticoagulant therapy and delay to surgery.

Register studies can also be limited in terms of the correctness of data, partly because a gold standard for comparison is hard to define (172). Relevant to our study outcomes in *Papers I-IV*, surgeons continuously evaluate whether or not complications occurred during each hip fracture operation. However, individual considerations and experience will influence the perception of a complication. Validation studies on complications reported to the register in comparison to medical records are time- and resource-consuming, yet are needed for further evaluation of our findings from the register. However, it is unlikely that complications are selectively reported in relation to thromboprophylaxis, medication use or delay to surgery as studied in this thesis. Thus, the associated risks of complications identified in this thesis may supplement future prospective trials.

## 6.2 Discussion of results

### 6.2.1 Preoperative versus postoperative start of thromboprophylaxis

In *Paper I*, preoperative start of LMWH compared to postoperative start was associated with reduced mortality for femoral neck fracture patients operated with HA. In *Paper II*, which studied hip fracture patients operated with osteosynthesis, no such effect was found. However, preoperative LMWH was associated with more bleeding complications in osteosynthesis, yet not in HA. Our results are only valid for dalteparin and enoxaparin. However, the benefit of a preoperative start may also be valid for other parenteral and oral anticoagulant compounds available.

The divergent mortality outcomes in *Papers I-II* indicate that surgery and postoperative recovery following osteosynthesis and HA have different sensitivity to thromboprophylaxis. One potential reason is that the surgical trauma is not equivalent between HA and osteosynthesis. Accordingly, if an osteosynthesis causes less trauma and thrombin-driven vascular complications, the consequences of LMWH initiation may be less clinically important for patients treated with osteosynthesis compared to HA. A larger trauma, such as HA, can cause intravascular coagulation, which may lead to micro-embolization. Secondary cardiopulmonary effects are more likely to be clinically relevant among the frailest hip fracture patients with limited physical reserves.

Increased intramedullary pressure during cementation contributes to the surgical trauma in HA. Therefore, it has been hypothesized that uncemented arthroplasties generate less significant pressures during surgery, which may influence the need for thromboprophylaxis. Several studies have found increased mortality the first day after cemented HA compared to uncemented HA for FNF (99, 173), including a recent large Norwegian register study (101). Even though the same studies demonstrate equal long-term mortality for patients with both cemented and uncemented HA, the fear of cemented arthroplasty in the elderly has risen. BCIS, a syndrome which is not completely understood, has been postulated to cause the divergent mortality outcomes (89). It has been theorized and demonstrated through cardiac ultrasound that cemented



---

prosthesis implantation causes embolization in the systemic circulation (95, 96). Such an embolic load can cause systemic effects ranging from hypotension to cardiac arrest. A recent RCT investigating THAs demonstrated increased pulmonary arterial pressure during cemented THAs while no such effect was seen in uncemented THAs (174). Based on current findings, the need for thromboprophylaxis might diverge depending on whether an uncemented or a cemented prosthesis is used for hip fracture patients. In *Paper I*, we studied the effects of LMWH initiation for patients with both uncemented and cemented HA. Interestingly, our study found reduced mortality when LMWH was initiated preoperatively compared to postoperatively regardless of whether cemented or uncemented implantation was used. Uncemented HAs thus also seem to produce a cardiovascular disturbance in the hip fracture patient, which benefits from early thromboprophylaxis. These findings also support a multifactorial cause of BCIS. BCIS has been associated with renal impairment, ASA class III-IV and age above 75 years (98). Thus, the choice of prosthesis fixation may be individualized based on such risk factors among hip fracture patients. It is worth noting that several studies have shown increased risk of reoperations, mainly caused by periprosthetic fractures, with the use of uncemented HA (101, 173, 175).

Whether thromboprophylaxis should be started before or after surgery is controversial (176, 177). Therefore, recent guidelines support both preoperative and postoperative anticoagulant initiation for hip fracture surgery (138). Further, trials targeting timing of thromboprophylaxis focus on detecting thrombotic outcomes by using radiology tools including venography or ultrasound. Bleeding-related outcomes have been feared as secondary underestimated outcomes even though bleeding can complicate both surgical and anaesthesia-related interventions (178, 179). Development of haematomas has been associated with periprosthetic infections (180). Shifting away from the operation site, bleeding complications after neuroaxial anaesthesia have been estimated to occur in 1 of 150,000-220,000 patients (144), yet the estimates are uncertain and based on retrospective studies where certain patient groups may have a notably higher risk of such outcomes (181-184).

In theory, it is easier to prevent the formation of a thrombus than to arrest the growth of a thrombus. Therefore, preoperative start of thromboprophylaxis has been suggested in major orthopaedic surgery involving THA. In fact, most studies have evaluated anticoagulation for elective THA. In these procedures, thrombi are expected to form preoperatively or postoperatively as there is no preoperative fracture trauma or immobilization (185). Therefore, intraoperative initiation of thromboprophylaxis has been supported to minimize the risk of perioperative blood loss, need of transfusion and complications related to neuroaxial anaesthesia (177, 186-188). In the same studies, the efficacy of prophylaxis has been regarded as sufficient for preventing VTE when initiated postoperatively. However, we still lack qualitative experimental studies comparing the same compounds in different regimens. Two studies did not find altered risk of bleeding complications if dalteparin was initiated preoperatively compared to postoperatively for THA (189) and total knee arthroplasty (TKA) (190). However, hip fracture patients constitute a different patient group from elective hip replacement patients. Firstly, they suffer a fracture before undergoing surgery, thereby undergoing tissue trauma, stress immobilization, and pressurization before being exposed to the trauma of surgery. Secondly, hip fracture patients are frailer with a mean age of 80 years with comorbidities present in more than 95% of cases (104, 191). Therefore, studies investigating thromboprophylaxis in elective THA patients cannot be directly generalized to hip fracture patients.

To our knowledge, *Papers I-II* are the first of their kind to explore both preoperative and postoperative start of the same thromboprophylactic medication for hip fracture patients. The study is strengthened by a large data set providing unique information from all hospitals treating hip fractures in Norway, which increases the generalizability of our results. A weakness in our study was that the NHFR does not provide sufficient information on the exact time from LMWH administration to surgery (hours) or time from surgery to cessation of LMWH therapy (days). The first is difficult to establish in unpredictable trauma wards. The second would require coordinated information from secondary nursing institutions and home care services to record the exact treatment duration. The NHFR records data from primary and secondary procedures for hip fractures. Since all information is reported by the

---

surgeons immediately after each surgery, data on length of thromboprophylaxis is anticipated and may therefore be inaccurate.

Dr Yang Huilin and Dr Sun Ye published a response to *Paper I* requesting documentation of VTE diagnosis at hospital admission in our study (192) (Appendix II). VTE in hip fracture patients has been little studied. The incidence of DVT seems to rise with increasing delay from hip fracture to surgery with observational rates of 12-62% when screening is used (193-196). The incidence of symptomatic postoperative DVT has been found to be approximately 1.3% in hip fracture patients using thromboprophylaxis (136, 197). However, asymptomatic DVT is markedly more common and requires screening with radiological interventions. One study found a co-occurrence of pulmonary embolism in up to 40% of DVT patients, but it was also mainly asymptomatic (198). Huilin and Ye stated that the association in *Paper I* between timing of thromboprophylaxis and mortality outcomes was hard to interpret in clinical practice as we failed to investigate the rate of VTE occurrences. I agree that additional knowledge of VTE rates both preoperatively and postoperatively could strengthen the beneficial results found after preoperative LMWH initiation.

Unfortunately, several limitations exist when studying the incidence of VTE. Firstly, radiological VTE screening involving venography or ultrasound is primarily aimed at detecting subclinical thrombosis. The methods are technically limited, as age-related reduced kidney function complicates venography and heterogeneous ultrasound protocols pose a risk of inter-observer diagnostic variation (199, 200). Secondly, these time- and resource-consuming radiologic evaluations are not routine in hip fracture treatment and are beyond the scope of a national hip fracture quality register. As discussed earlier, register studies may be limited by the lack of researcher control concerning available outcomes. Whether extraordinary examinations such as VTE screenings are ethically feasible following a trauma the size of a hip fracture is also arguable. Thirdly, surrogate outcomes such as radiologically screened DVTs require a consistent relationship between asymptomatic DVT and symptomatic VTE events (201). If not, a valid comparison between bleeding and thrombotic events cannot be

made. Frail elderly people operated for hip fractures may experience a variety of complications triggered by cell destroying molecules and thrombin activity. Such complications can include respiratory distress, organ ischaemia, hepatic and renal dysfunction and local thrombosis at the trauma site (202). Thus, we have reason to believe that controlling thrombin can reduce mortality beyond merely preventing fatal venous thromboembolism (103). To conclude, *Papers I-II* report associations between the initiation of LMWH and outcomes for hip fracture patients, yet causality cannot be proven given the study design, the available data, and the quality of data in a national quality register.

### **6.2.2 Delay to hip fracture surgery**

In *Paper III*, the average delay from hip fracture to hospital admission (prehospital delay) was six hours, while the average delay from fracture to surgery (total delay) was 24 hours. Mortality increased when surgery was performed more than 48 hours after the fracture. Patients with a high ASA score (3-5) and patients operated with HA seem to be at higher risk if surgery is delayed.

Some studies have reported increased in-hospital mortality and 30-day mortality when delay to hip fracture surgery increases by 12 or 24 hours from admission (hospital delay) (47, 203). However, several other studies found no such association between mortality and hospital delay (41, 49-52). A meta-analysis by Shiga et al. found increased 30-day and one-year mortality when hospital delay exceeded 48 hours, thereby supporting the results in *Paper III* (45). Another systematic review found that early hip fracture surgery within 24, 48 or 72 hours was associated with reduced mortality for all three cut-offs in time (204). Other retrospective studies found increased 30-day mortality if delay to surgery exceeded 12 hours (205) or 24 hours (46). Due to conflicting results, controversies now exist regarding acceptable waiting time to surgery for hip fracture patients. Canadian and American guidelines advise hip fracture surgery within 48 hours (206, 207) while NICE guidelines in the UK advise surgery on the day of, or the day after, admission (59). In Norway, a recommendation by the National Health Institute published in 2014 stated that hip fracture patients

---

should be operated within 24 hours and certainly no later than 48 hours (158). In addition, the Directorate of Health has classified time from admission to hip fracture surgery as a quality indicator in Norway, where rates of surgery within 24 and 48 hours are counted for each hospital (208). Interestingly, these two recommendations do not agree on whether delay begins at the time of fracture or time of admission. Recently, a national interdisciplinary guideline for hip fracture treatment was published in Norway (113).

We aimed to benefit the unique information on delay from fracture to admission (prehospital delay) by coupling data from two registries, the NHFR and NPR. As most studies on hip fracture patients so far have investigated hospital delay (46, 52, 205, 209), a pioneering prehospital perspective strengthens the importance of the results in *Paper III*. A recent international multicentre RCT found an average prehospital delay of three hours, i.e. half the time of our finding of six hours (210). Norway's dominating rural conditions may influence these diverging results. From a medical standpoint, the prehospital delay is important as patients have less medical surveillance and treatment to prevent complications. Unfortunately, the use of fracture time estimates increases the risk of recall and selection bias in our data. Comorbidity, cognitive state, and quality of home care may influence the degree to which patients are able to state the exact time of their fracture. In addition, time of fracture was only reported in 53% of the patients. To strengthen our findings, we also investigated delay from *admission to surgery* in addition to delay from *fracture to surgery*. As time of admission is administratively reported by the hospital, the risk of recall and selection bias is minimized.

In *Paper III*, we found higher comorbidity among patients with a total delay to surgery of more than 48 hours. Comorbidity has also been associated with delayed surgery in other studies (46, 211). The key question is whether surgeries were delayed because of patients' increased risk of adverse outcomes or if adverse outcomes occurred due to in-hospital delayed surgery. As time from admission to surgery represents a crucial window to optimize the patient's medical condition (43), efforts have been made to distinguish between acceptable and unacceptable reasons for delaying interventions

(44). In *Paper III*, we actually found the highest relative risk of three-day mortality when total delay exceeded 48 hours for hip fracture patients with low comorbidity (ASA 1-2). However, the mortality results did not reach significance, probably due to few fractures and deaths in this relatively healthy patient group. Further, the risk of reported intraoperative medical complications increased for both ASA 1-2 and ASA 3-5 groups when hospital delay exceeded 37-48 hours. In conclusion, our results do not support preoperative medical stabilization as an argument to delay hip fracture surgery regardless of comorbidity status. Delay to hip fracture surgery varies enormously around the world due to local practice and health resource capacity. For instance, accessible transport and distance to the nearest hospital will influence prehospital delay both within and between countries. Unfortunately, prehospital delay is not included in most studies investigating delay to surgery. Therefore, comparison of different studies on surgical delay and outcomes can be skewed.

In *Paper III*, we used a retrospective study design, as the randomization of hip fracture patients into early and deliberately late surgery would be ethically unacceptable. While retrospective designs can be well suited for rare outcomes such as intraoperative complications, the use of a register also challenges such investigations. Collection of data on reported unwanted outcomes introduces the risk of recall and misclassification bias as each individual surgeon has to decide whether or not a complication occurred and should be reported to the register. The results concerning complications should therefore be interpreted with caution and seen in relation to existing literature. In *Paper III*, we found that delay from admission to hip fracture surgery of more than 24 hours was associated with more intraoperative medical complications. Another study found increased risk of postoperative respiratory complications and prolonged length of stay when hip fracture patients waited more than 24 hours for surgery (212). The frequency of bed sores and infections has been associated with delayed hip fracture surgery in other studies (49, 204, 213-215). Two studies have identified a strong correlation between delay to hip fracture surgery and incidence of DVT (193, 194). A prolonged preoperative interval will influence the total time to ambulation following a fracture. Slower functional recovery and increased morbidity have been found with late ambulation after hip fracture surgery (167-169).

---

### 6.2.3 Direct oral anticoagulants when the hip fracture occurs

Norway has experienced a substantial growth in DOAC prescriptions of more than 150% from 2014 to 2018, surpassing the much studied warfarin and challenging established perioperative treatment regimens (102). In *Paper IV*, the use of DOACs at the time of hip fracture was not found to influence surgical delay or length of stay compared to non-users. No differences in perioperative blood loss, transfusion rates or risk of bleeding complications between DOAC users and non-users were found.

In 2016, a Norwegian study found that DOAC users waited on average more than twice as long for hip fracture surgery as non-users (44 vs. 21 hours) and also longer than warfarin users (25 hours) (216). Prolonged hospital delay for hip fracture patients taking DOACs has also been confirmed in international studies (217-220). The question is whether the use of DOACs before the hip fracture results in an unnecessarily long surgical delay for these frail patients (219-223). In contrast, DOAC users in our study did not wait significantly longer for surgery than non-users (29 vs. 26 hours, respectively). The use of data from a single large trauma centre with increasing focus on prioritizing hip fracture treatment may explain this finding. Local practice and patient capacity may influence delay to surgery in other hospitals regardless of whether DOACs were used or not. Even with early surgical intervention, DOAC users did not seem to have more bleeding complications than non-users in *Paper IV*. Our findings are supported by several other retrospective studies where DOAC users have similar transfusion rates and blood loss following hip fracture surgery to non-users (219, 223). Mullins et al. studied hip fracture patients taking DOACs compared to matched controls with a median of only 19 hours from admission to surgery; they could not find any association between hospital delay and perioperative blood loss and transfusion rates for these DOAC users (221). Mortality remained unchanged for hip fracture patients irrespective of the use of DOACs prior to the fracture in our study. This is in accordance with other studies (218, 220, 221). To summarize, DOAC users should be prioritized for early surgical intervention as undesirable clinical outcomes such as bleeding and mortality seem to be unchanged.

In Norway, 80-90% of all hip fracture patients receive neuroaxial anaesthesia (63). In *Paper IV*, 3.8% of the hip fracture patients not taking DOACs were operated under general anaesthesia while 47% of DOAC users had general anaesthesia. DOAC users who received neuroaxial anaesthesia waited on average 13 hours longer for surgery than when general anaesthesia was used (35 vs. 22 hours). As discussed in *Paper III*, increasing delay to surgery may increase mortality and intraoperative complications. Thus, prolonged delay to surgery for hip fracture patients taking DOACs seems unfortunate. Surgery may be scheduled for delay due to the fear of neuroaxial bleeding. However, it is also likely that surgery for some DOAC users is delayed for other reasons, such as access to theatre and need for preoperative medical stabilization. Neuroaxial anaesthesia can then be administered with a safe time interval between DOAC administration and neuroaxial incision. Hip fracture patients taking DOACs also had a higher rate of comorbidity than non-users, which is strongly related to the approval of DOACs for prevention of recurrent VTE and non-valvular atrial fibrillation (126-128). As discussed in *Paper III*, a higher burden of comorbidity is associated with longer delay to hip fracture surgery. The rate of comorbidity can also influence the choice of anaesthesia and may have confounded our results. Regardless of the cause of prolonged delay for half of the DOAC users (those expected to receive neuroaxial anaesthesia), mortality remained unchanged within six months compared to non-users. However, DOAC users with neuroaxial anaesthesia tended to have longer hospital stays than those with general anaesthesia. The results remained insignificant, probably due to low power. Conversely, general anaesthesia has previously been associated with longer stays than neuroaxial anaesthesia (224), yet a meta-study of 400,000 hip fracture patients revealed a clinically insignificant difference of only 0.3 days (225). Financial incentives will favour treatment strategies that shorten hospital stays. There is a need for future studies of optimal anaesthesia for the growing pool of DOAC users, as hip fracture patients present with polypharmacy, altered medication distribution and reduced kidney function in addition to a need for semi-urgent surgery.



---

The primary aim in *Paper IV* was to determine whether hip fracture patients using DOACs prior to the fracture have delayed surgery compared to non-users. Therefore, we determined the inclusion of patients based on a power analysis related to the main outcome. However, we also assessed several secondary adverse outcomes following hip fracture surgery in our paper, potentially working with insufficient sample sizes and lack of power. The study size also prevented stratified analyses of different drugs in the DOAC group (dabigatran, apixaban, and rivaroxaban were present in our material). Due to these limitations, secondary outcomes in *Paper IV* must be interpreted with caution. To increase quality and reproducibility, the study was performed in a large trauma centre using medical records processed by one experienced researcher. We believe these findings from a university hospital are also representative of other Norwegian hospitals. However, our findings cannot be generalized to all hospitals nationally or internationally as local perioperative treatment strategies will influence outcomes. One example studied in *Papers I-II* is the initiation of perioperative thromboprophylaxis for hip fracture patients with diverging practice both nationally and internationally: bridging regimens from long-term anticoagulants to perioperative thromboprophylaxis can influence surgical and medical outcomes. To my knowledge, no studies have addressed optimal bridging of long-term and perioperative anticoagulants for hip fracture patients.

In conclusion, the findings in *Paper IV* should be controlled in prospective trials. It is essential to know the safety outcomes of DOACs before and after hip fracture surgery as the marked of anticoagulants is rapidly changing.

## 7. Conclusions

### Paper I:

- Postoperative start compared to preoperative start of LMWH was associated with increased mortality and risk of reoperation for femoral neck fracture patients operated with hemiprosthesis. Both short- and long-term mortality increased.
- The risk of intraoperative bleeding complications and reoperation due to haematoma did not change whether thromboprophylaxis was started before or after the hemiarthroplasty.

### Paper II:

- Preoperative start compared to postoperative start of LMWH did not alter mortality or risk of reoperation for hip fracture patients operated with osteosynthesis.
- More bleeding complications were reported with a preoperative start of LMWH for hip fracture patients operated with osteosynthesis, especially for patients treated with a sliding hip screw.

### Paper III:

- Both total delay and hospital delay to surgery exceeding 48 hours increased short- and long-term mortality for hip fracture patients. All hospitals should strive to operate on hip fractures within 48 hours of the fracture, in line with several national guidelines.
- More medical intraoperative complications were reported when hospital delay exceeded 24 hours, supporting early hip fracture surgery within 24 hours.

**Paper IV:**

- Patients taking DOACs at the time of hip fracture did not have longer hospital delay or length of stay compared to non-users.
- The use of DOACs did not influence intraoperative blood loss, transfusion rates, bleeding complications or mortality after hip fracture surgery
- Hip fracture patients taking DOACs were ten times more likely to be operated under general anaesthesia than non-users and these patients had shorter hospital delay than DOAC users receiving neuroaxial anaesthesia.

## 8. Future research

### 8.1 Timing and duration of thromboprophylaxis

While several studies have investigated preoperative versus postoperative initiation of thromboprophylaxis in elective THAs and TKAs (177, 186-188), timing of thromboprophylaxis is sparsely studied in hip fracture patients. In contrast to elective arthroplasties, hip fracture patients need semi-urgent surgery in trauma departments with unpredictable schedules. In *Papers I-II*, we used a national register to compare preoperative versus postoperative *start* of LMWH. However, hip fracture patients are at risk of thromboembolic complications from the time of fracture, through surgery, and into the postoperative period of immobilization. Therefore, further studies are needed to investigate timing of thromboprophylaxis beyond the start of therapy. For example, LMWHs have half-lives of 3-4 hours (dalteparin) and 5-7 hours (enoxaparin) in non-uremic patients. LMWH administered 24 hours before surgery will generate therapeutic windows earlier than LMWH administered ten hours before surgery or six hours after surgery. Reduced kidney function in elderly hip fracture patients may also affect drug excretion. Further, duration of LMWH therapy after surgery can influence long-term outcomes. Norwegian guidelines strongly advise thromboprophylaxis for the first ten days after hip fracture surgery and suggest prolonged duration until 35 days for all patients (143). To my knowledge, no studies have looked into the actual duration and effects of postoperative thromboprophylaxis for hip fracture patients in Norway. The effects of timing and duration of thromboprophylaxis should be explored in a prospective RCT or a prospective cohort study to supplement the observational findings from *Papers I-II*. Duration of LMWH treatment is not possible to surveillance from the surgeon's perspective (reporting to NHFR) as it would require information from secondary nursing institutions and home care. As of today, the NHFR does not provide sufficient information on the exact time from LMWH administration to surgery.

---

## **8.2 Fast track algorithms for hip fracture treatment to reduce mortality and complications**

Several studies and guidelines now recommend hip fracture surgery within 24 or 48 hours of admission to avoid unwanted outcomes, as discussed in *Paper III*. The next step is then to identify the effects of accelerated surgery. Fast track protocols for hip fracture patients have been suggested to reduce unwanted outcomes (204, 226, 227). Such algorithms could also reduce workloads in emergency departments. To date, there are few studies of the practice and effects of fast track hip fracture surgery. Protocols can also be difficult to compare as actions to accelerate treatment will vary. Some studies have found reduced prehospital delay (time from fracture to ward admission) with accelerated care (226, 228). While fast track can reduce delay to surgery (210, 229), others do not find reduced delay (226). Recently, the first large multicentre RCT from 17 countries and 69 hospitals allocated hip fracture patients into an accelerated-surgery group (median delay to surgery 6 hours) and a standard care group (median delay to surgery 24 hours) (210). Accelerated care did not change a composite of major complications. However, accelerated care did reduce the risk of stroke, urinary tract infections, delirium, and postoperative pain. Several fast track algorithms seem to reduce length of hospital stay, while mortality remains unchanged (210, 229). Hopefully, more prospective trials will investigate accelerated care by confirming or disproving current findings. Due to the high mortality and expensive treatment of hip fracture patients, there is much to be gained if such protocols improve patient outcomes and length of stays.

## 9. References

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* 2006;17(12):1726-33.
2. Bacon WE, Maggi S, Looker A, Harris T, Nair CR, Giaconi J, et al. International comparison of hip fracture rates in 1988-89. *Osteoporos Int.* 1996;6(1):69-75.
3. Elffors I, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J, et al. The variable incidence of hip fracture in southern Europe: the MEDOS Study. *Osteoporos Int.* 1994;4(5):253-63.
4. Havelin L, Furnes O, Engesaeter, LB, Fenstad AM, Dybvik E. Annual report. *Norwegian Arthroplasty Register 2014*:130.
5. Frihagen F, Nordsletten L, Madsen JE. Hemiarthroplasty or internal fixation for intracapsular displaced femoral neck fractures: randomised controlled trial. *BMJ.* 2007;335(7632):1251-4.
6. Osnes EK, Lofthus CM, Meyer HE, Falch JA, Nordsletten L, Cappelen I, et al. Consequences of hip fracture on activities of daily life and residential needs. *Osteoporos Int.* 2004;15(7):567-74.
7. Bertram M, Norman R, Kemp L, Vos T. Review of the long-term disability associated with hip fractures. *Inj Prev.* 2011;17(6):365-70.
8. Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, et al. The aftermath of hip fracture: discharge placement, functional status change, and mortality. *Am J Epidemiol.* 2009;170(10):1290-9.
9. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int.* 2004;15(11):897-902.
10. Lonnroos E, Kautiainen H, Karppi P, Huusko T, Hartikainen S, Kiviranta I, et al. Increased incidence of hip fractures. A population based-study in Finland. *Bone.* 2006;39(3):623-7.
11. Falch JA, Ilebekk A, Slungaard U. Epidemiology of hip fractures in Norway. *Acta Orthop Scand.* 1985;56(1):12-6.

- 
12. Falch JA, Kaastad TS, Bohler G, Espeland J, Sundsvold OJ. Secular increase and geographical differences in hip fracture incidence in Norway. *Bone*. 1993;14(4):643-5.
  13. Finsen V, Benum P. Changing incidence of hip fractures in rural and urban areas of central Norway. *Clin Orthop Relat Res*. 1987(218):104-10.
  14. Lofthus CM, Osnes EK, Falch JA, Kaastad TS, Kristiansen IS, Nordsletten L, et al. Epidemiology of hip fractures in Oslo, Norway. *Bone*. 2001;29(5):413-8.
  15. Rogmark C, Sernbo I, Johnell O, Nilsson JA. Incidence of hip fractures in Malmo, Sweden, 1992-1995. A trend-break. *Acta Orthop Scand*. 1999;70(1):19-22.
  16. Huusko TM, Karppi P, Avikainen V, Kautiainen H, Sulkava R. The changing picture of hip fractures: dramatic change in age distribution and no change in age-adjusted incidence within 10 years in Central Finland. *Bone*. 1999;24(3):257-9.
  17. Chevalley T, Guilley E, Herrmann FR, Hoffmeyer P, Rapin CH, Rizzoli R. Incidence of hip fracture over a 10-year period (1991-2000): reversal of a secular trend. *Bone*. 2007;40(5):1284-9.
  18. Sambrook P, Cooper C. Osteoporosis. *Lancet*. 2006;367(9527):2010-8.
  19. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet*. 1993;341(8837):72-5.
  20. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int*. 2005;16 Suppl 2:S3-7.
  21. Meyer HE, Tverdal A, Falch JA, Pedersen JI. Factors associated with mortality after hip fracture. *Osteoporos Int*. 2000;11(3):228-32.
  22. Bhandari M, Koo H, Saunders L, Shaughnessy SG, Dunlop RB, Schemitsch EH. Predictors of in-hospital mortality following operative management of hip fractures. *Int J Surg Investig*. 1999;1(4):319-26.
  23. Lie SA, Engesaeter LB, Havelin LI, Gjessing HK, Vollset SE. Mortality after total hip replacement: 0-10-year follow-up of 39,543 patients in the Norwegian Arthroplasty Register. *Acta Orthop Scand*. 2000;71(1):19-27.
  24. Hallan G, Dybvik E, Furnes O, Havelin LI. Metal-backed acetabular components with conventional polyethylene: a review of 9113 primary components with a follow-up of 20 years. *J Bone Joint Surg Br*. 2010;92(2):196-201.

25. Badawy M, Fenstad AM, Indrekvam K, Havelin LI, Furnes O. The risk of revision in total knee arthroplasty is not affected by previous high tibial osteotomy. *Acta Orthop*. 2015;86(6):734-9.
26. Omsland TK, Emaus N, Tell GS, Magnus JH, Ahmed LA, Holvik K, et al. Mortality following the first hip fracture in Norwegian women and men (1999-2008). A NOREPOS study. *Bone*. 2014;63:81-6.
27. Hektoen LF, Saltvedt I, Sletvold O, Helbostad JL, Luras H, Halsteinli V. One-year health and care costs after hip fracture for home-dwelling elderly patients in Norway: Results from the Trondheim Hip Fracture Trial. *Scand J Public Health*. 2016;44(8):791-8.
28. Kazley JM, Banerjee S, Abousayed MM, Rosenbaum AJ. Classifications in Brief: Garden Classification of Femoral Neck Fractures. *Clin Orthop Relat Res*. 2018;476(2):441-5.
29. Meinberg EG, Agel J, Roberts CS, Karam MD, Kellam JF. Fracture and Dislocation Classification Compendium-2018. *J Orthop Trauma*. 2018;32 Suppl 1:S1-S170.
30. Strickland D, Stranges AN. X-rays: laying the foundation of modern radiology, 1896-1930. *Med Secoli*. 1991;3(2-3):207-22.
31. Rang M. Adult Hip. *The Story of Orthopaedics*. 2000:35-63.
32. CH M. Has a solution to the unsolved fracture been found? Problems and complications of fractures of femoral neck. *J Am Med Assoc*. 1953;153(6):536-40.
33. Tay E. Hip fractures in the elderly: operative versus nonoperative management. *Singapore Med J*. 2016;57(4):178-81.
34. Jain R, Basinski A, Kreder HJ. Nonoperative treatment of hip fractures. *Int Orthop*. 2003;27(1):11-7.
35. Shuqiang M, Kunzheng W, Zhichao T, Mingyu Z, Wei W. Outcome of non-operative management in Garden I femoral neck fractures. *Injury*. 2006;37(10):974-8.
36. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth*. 2000;85(1):109-17.
37. Butler SA, Salipas A, van der Rijt A. Comparative study of outcomes for elderly hip fractures presenting directly to a referral hospital versus those transferred from peripheral centres. *ANZ J Surg*. 2019;89(10):1314-8.



- 
38. Lawless AM, Narula S, D'Alessandro P, Jones CW, Seymour H, Yates PJ. Time to surgery and transfer-associated mortality for hip fractures in Western Australia. *ANZ J Surg.* 2020;90(9):1750-3.
  39. Cannon J, Silvestri S, Munro M. Imaging choices in occult hip fracture. *J Emerg Med.* 2009;37(2):144-52.
  40. Dominguez S, Liu P, Roberts C, Mandell M, Richman PB. Prevalence of traumatic hip and pelvic fractures in patients with suspected hip fracture and negative initial standard radiographs--a study of emergency department patients. *Acad Emerg Med.* 2005;12(4):366-9.
  41. Parker MJ, Pryor GA. The timing of surgery for proximal femoral fractures. *J Bone Joint Surg Br.* 1992;74(2):203-5.
  42. Lubovsky O, Liebergall M, Mattan Y, Weil Y, Mosheiff R. Early diagnosis of occult hip fractures MRI versus CT scan. *Injury.* 2005;36(6):788-92.
  43. Orosz GM, Magaziner J, Hannan EL, Morrison RS, Koval K, Gilbert M, et al. Association of timing of surgery for hip fracture and patient outcomes. *JAMA.* 2004;291(14):1738-43.
  44. Association of Anaesthetists of Great B, Ireland, Griffiths R, Alper J, Beckingsale A, Goldhill D, et al. Management of proximal femoral fractures 2011: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia.* 2012;67(1):85-98.
  45. Shiga T, Wajima Z, Ohe Y. Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. *Can J Anaesth.* 2008;55(3):146-54.
  46. Pincus D, Ravi B, Wasserstein D, Huang A, Paterson JM, Nathens AB, et al. Association Between Wait Time and 30-Day Mortality in Adults Undergoing Hip Fracture Surgery. *JAMA.* 2017;318(20):1994-2003.
  47. Nyholm AM, Gromov K, Palm H, Brix M, Kallemose T, Troelsen A, et al. Time to Surgery Is Associated with Thirty-Day and Ninety-Day Mortality After Proximal Femoral Fracture: A Retrospective Observational Study on Prospectively Collected Data from the Danish Fracture Database Collaborators. *J Bone Joint Surg Am.* 2015;97(16):1333-9.
  48. Uzoigwe CE, Burnand HG, Cheesman CL, Aghedo DO, Faizi M, Middleton RG. Early and ultra-early surgery in hip fracture patients improves survival. *Injury.* 2013;44(6):726-9.

49. Grimes JP, Gregory PM, Noveck H, Butler MS, Carson JL. The effects of time-to-surgery on mortality and morbidity in patients following hip fracture. *Am J Med.* 2002;112(9):702-9.
50. Moran CG, Wenn RT, Sikand M, Taylor AM. Early mortality after hip fracture: is delay before surgery important? *J Bone Joint Surg Am.* 2005;87(3):483-9.
51. Holt G, Smith R, Duncan K, McKeown DW. Does delay to theatre for medical reasons affect the peri-operative mortality in patients with a fracture of the hip? *J Bone Joint Surg Br.* 2010;92(6):835-41.
52. Rae HC, Harris IA, McEvoy L, Todorova T. Delay to surgery and mortality after hip fracture. *ANZ J Surg.* 2007;77(10):889-91.
53. Chao EY, Inoue N, Koo TK, Kim YH. Biomechanical considerations of fracture treatment and bone quality maintenance in elderly patients and patients with osteoporosis. *Clin Orthop Relat Res.* 2004(425):12-25.
54. Tidermark J. Quality of life and femoral neck fractures. *Acta Orthop Scand Suppl.* 2003;74(309):1-42.
55. Blomfeldt R, Tornkvist H, Ponzer S, Soderqvist A, Tidermark J. Internal fixation versus hemiarthroplasty for displaced fractures of the femoral neck in elderly patients with severe cognitive impairment. *J Bone Joint Surg Br.* 2005;87(4):523-9.
56. Blomfeldt R, Tornkvist H, Eriksson K, Soderqvist A, Ponzer S, Tidermark J. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. *J Bone Joint Surg Br.* 2007;89(2):160-5.
57. Gjertsen JE, Dybvik E, Furnes O, Fevang JM, Havelin LI, Matre K, et al. Improved outcome after hip fracture surgery in Norway. *Acta Orthop.* 2017;88(5):505-11.
58. Roberts KC, Brox WT, Jevsevar DS, Sevarino K. Management of hip fractures in the elderly. *J Am Acad Orthop Surg.* 2015;23(2):131-7.
59. National Institute for Health and Care Excellence (NICE). Hip fracture: management. 2011 [internet]. Accessed 03.03.21. Available from: <https://www.nice.org.uk/guidance/cg124>.

- 
60. Grose AW, Gardner MJ, Sussmann PS, Helfet DL, Lorich DG. The surgical anatomy of the blood supply to the femoral head: description of the anastomosis between the medial femoral circumflex and inferior gluteal arteries at the hip. *J Bone Joint Surg Br.* 2008;90(10):1298-303.
61. Tseng FJ, Chia WT, Pan RY, Lin LC, Shen HC, Wang CH, et al. Comparison of arthroplasty vs. osteosynthesis for displaced femoral neck fractures: a meta-analysis. *J Orthop Surg Res.* 2017;12(1):131.
62. Parker MJ, Khan RJ, Crawford J, Pryor GA. Hemiarthroplasty versus internal fixation for displaced intracapsular hip fractures in the elderly. A randomised trial of 455 patients. *J Bone Joint Surg Br.* 2002;84(8):1150-5.
63. Furnes O, Engesaeter L, Gjertsen JE, Fenstad AM, Bartz- Johannessen C, Dybvik E, Fjeldsgaard K, Gundersen T, Hallan G Annual report. Norwegian Arthroplasty Register. 2019; 211.
64. Shehata MSA, Aboelnas MM, Abdulkarim AN, Abdallah AR, Ahmed H, Holton J, et al. Sliding hip screws versus cancellous screws for femoral neck fractures: a systematic review and meta-analysis. *Eur J Orthop Surg Traumatol.* 2019;29(7):1383-93.
65. Bjorgul K, Reikeras O. Hemiarthroplasty in worst cases is better than internal fixation in best cases of displaced femoral neck fractures: a prospective study of 683 patients treated with hemiarthroplasty or internal fixation. *Acta Orthop.* 2006;77(3):368-74.
66. Anglen JO, Weinstein JN, American Board of Orthopaedic Surgery Research C. Nail or plate fixation of intertrochanteric hip fractures: changing pattern of practice. A review of the American Board of Orthopaedic Surgery Database. *J Bone Joint Surg Am.* 2008;90(4):700-7.
67. Rogmark C, Spetz CL, Garellick G. More intramedullary nails and arthroplasties for treatment of hip fractures in Sweden. *Acta Orthop.* 2010;81(5):588-92.
68. Parker MJ, Handoll HH. Gamma and other cephalocondylic intramedullary nails versus extramedullary implants for extracapsular hip fractures in adults. *Cochrane Database Syst Rev.* 2010(9):CD000093.
69. Matre K, Vinje T, Havelin LI, Gjertsen JE, Furnes O, Espehaug B, et al. TRIGEN INTERTAN intramedullary nail versus sliding hip screw: a prospective, randomized multicenter study on pain, function, and complications in 684 patients with an intertrochanteric or subtrochanteric fracture and one year of follow-up. *J Bone Joint Surg Am.* 2013;95(3):200-8.

70. Palm H, Lysen C, Krashennikoff M, Holck K, Jacobsen S, Gebuhr P. Intramedullary nailing appears to be superior in pertrochanteric hip fractures with a detached greater trochanter: 311 consecutive patients followed for 1 year. *Acta Orthop.* 2011;82(2):166-70.
71. Bretherton CP, Parker MJ. Femoral Medialization, Fixation Failures, and Functional Outcome in Trochanteric Hip Fractures Treated With Either a Sliding Hip Screw or an Intramedullary Nail From Within a Randomized Trial. *J Orthop Trauma.* 2016;30(12):642-6.
72. Matre K, Havelin LI, Gjertsen JE, Espehaug B, Fevang JM. Intramedullary nails result in more reoperations than sliding hip screws in two-part intertrochanteric fractures. *Clin Orthop Relat Res.* 2013;471(4):1379-86.
73. Swart E, Makhni EC, Macaulay W, Rosenwasser MP, Bozic KJ. Cost-effectiveness analysis of fixation options for intertrochanteric hip fractures. *J Bone Joint Surg Am.* 2014;96(19):1612-20.
74. Rogmark C, Carlsson A, Johnell O, Sernbo I. Primary hemiarthroplasty in old patients with displaced femoral neck fracture: a 1-year follow-up of 103 patients aged 80 years or more. *Acta Orthop Scand.* 2002;73(6):605-10.
75. Gjertsen JE, Vinje T, Engesaeter LB, Lie SA, Havelin LI, Furnes O, et al. Internal screw fixation compared with bipolar hemiarthroplasty for treatment of displaced femoral neck fractures in elderly patients. *J Bone Joint Surg Am.* 2010;92(3):619-28.
76. Chaplin VK, Matharu GS, Knebel RW. Complications following hemiarthroplasty for displaced intracapsular femoral neck fractures in the absence of routine follow-up. *Ann R Coll Surg Engl.* 2013;95(4):271-4.
77. Investigators H, Bhandari M, Einhorn TA, Guyatt G, Schemitsch EH, Zura RD, et al. Total Hip Arthroplasty or Hemiarthroplasty for Hip Fracture. *N Engl J Med.* 2019;381(23):2199-208.
78. Rogmark C, Johnell O. Orthopaedic treatment of displaced femoral neck fractures in elderly patients. *Disabil Rehabil.* 2005;27(18-19):1143-9.
79. Svenoy S, Westberg M, Figved W, Valland H, Brun OC, Wangen H, et al. Posterior versus lateral approach for hemiarthroplasty after femoral neck fracture: Early complications in a prospective cohort of 583 patients. *Injury.* 2017;48(7):1565-9.
80. Baker RP, Squires B, Gargan MF, Bannister GC. Total hip arthroplasty and hemiarthroplasty in mobile, independent patients with a displaced intracapsular

---

fracture of the femoral neck. A randomized, controlled trial. *J Bone Joint Surg Am.* 2006;88(12):2583-9.

81. Noailles T, Brulefert K, Chalopin A, Longis PM, Gouin F. What are the risk factors for post-operative infection after hip hemiarthroplasty? Systematic review of literature. *Int Orthop.* 2016;40(9):1843-8.

82. Duckworth AD, Phillips SA, Stone O, Moran M, Breusch SJ, Biant LC. Deep infection after hip fracture surgery: predictors of early mortality. *Injury.* 2012;43(7):1182-6.

83. Guren E, Figved W, Frihagen F, Watne LO, Westberg M. Prosthetic joint infection-a devastating complication of hemiarthroplasty for hip fracture. *Acta Orthop.* 2017;88(4):383-9.

84. Orsini EC, Byrick RJ, Mullen JB, Kay JC, Waddell JP. Cardiopulmonary function and pulmonary microemboli during arthroplasty using cemented or non-cemented components. The role of intramedullary pressure. *J Bone Joint Surg Am.* 1987;69(6):822-32.

85. Parvizi J, Holiday AD, Ereth MH, Lewallen DG. The Frank Stinchfield Award. Sudden death during primary hip arthroplasty. *Clin Orthop Relat Res.* 1999(369):39-48.

86. Engesaeter LB, Strand T, Raugstad TS, Husebo S, Langeland N. Effects of a distal venting hole in the femur during total hip replacement. *Arch Orthop Trauma Surg.* 1984;103(5):328-31.

87. Gresham GA, Kuczynski A, Rosborough D. Fatal fat embolism following replacement arthroplasty for transcervical fractures of femur. *Br Med J.* 1971;2(5762):617-9.

88. Duncan JA. Intra-operative collapse or death related to the use of acrylic cement in hip surgery. *Anaesthesia.* 1989;44(2):149-53.

89. Donaldson AJ, Thomson HE, Harper NJ, Kenny NW. Bone cement implantation syndrome. *Br J Anaesth.* 2009;102(1):12-22.

90. de Froidmont S, Bonetti LR, Villaverde RV, del Mar Lesta M, Palmiere C. Postmortem findings in bone cement implantation syndrome-related deaths. *Am J Forensic Med Pathol.* 2014;35(3):206-11.

91. Hayakawa M, Fujioka Y, Morimoto Y, Okamura A, Kemmotsu O. Pathological evaluation of venous emboli during total hip arthroplasty. *Anaesthesia*. 2001;56(6):571-5.
92. Bengtson A, Larsson M, Gammer W, Heideman M. Anaphylatoxin release in association with methylmethacrylate fixation of hip prostheses. *J Bone Joint Surg Am*. 1987;69(1):46-9.
93. Lamade WR, Friedl W, Schmid B, Meeder PJ. Bone cement implantation syndrome. A prospective randomised trial for use of antihistamine blockade. *Arch Orthop Trauma Surg*. 1995;114(6):335-9.
94. Tryba M, Linde I, Voshage G, Zenz M. [Histamine release and cardiovascular reactions to implantation of bone cement during total hip replacement]. *Anaesthesist*. 1991;40(1):25-32.
95. Ereth MH, Weber JG, Abel MD, Lennon RL, Lewallen DG, Ilstrup DM, et al. Cemented versus noncemented total hip arthroplasty--embolism, hemodynamics, and intrapulmonary shunting. *Mayo Clin Proc*. 1992;67(11):1066-74.
96. Lafont ND, Kalonji MK, Barre J, Guillaume C, Boogaerts JG. Clinical features and echocardiography of embolism during cemented hip arthroplasty. *Can J Anaesth*. 1997;44(2):112-7.
97. Kotyra M, Houltz E, Ricksten SE. Pulmonary haemodynamics and right ventricular function during cemented hemiarthroplasty for femoral neck fracture. *Acta Anaesthesiol Scand*. 2010;54(10):1210-6.
98. Rassir R, Schuiling M, Sierevelt IN, van der Hoeven CWP, Nolte PA. What Are the Frequency, Related Mortality, and Factors Associated with Bone Cement Implantation Syndrome in Arthroplasty Surgery? *Clin Orthop Relat Res*. 2020.
99. Talsnes O, Vinje T, Gjertsen JE, Dahl OE, Engesaeter LB, Baste V, et al. Perioperative mortality in hip fracture patients treated with cemented and uncemented hemiprostheses: a register study of 11,210 patients. *Int Orthop*. 2013;37(6):1135-40.
100. Ekman E, Laaksonen I, Isotalo K, Liukas A, Vahlberg T, Makela K. Cementing does not increase the immediate postoperative risk of death after total hip arthroplasty or hemiarthroplasty: a hospital-based study of 10,677 patients. *Acta Orthop*. 2019;90(3):270-4.

- 
101. Kristensen TB, Dybvik E, Kristoffersen M, Dale H, Engesaeter LB, Furnes O, et al. Cemented or Uncemented Hemiarthroplasty for Femoral Neck Fracture? Data from the Norwegian Hip Fracture Register. *Clin Orthop Relat Res.* 2020;478(1):90-100.
  102. Search for prescribed anticoagulant drugs in all ages in 2019 and between 2014 and 2018 [Internet]. Norwegian Prescription Database. 2020 [cited 17.09.20]. Available from: <https://reseptregisteret.no/Prevalens.aspx>.
  103. Dahl OE, Caprini JA, Colwell CW, Jr., Frostick SP, Haas S, Hull RD, et al. Fatal vascular outcomes following major orthopedic surgery. *Thromb Haemost.* 2005;93(5):860-6.
  104. Furnes O, Gjertesen JE, Hallan G, Visnes H, Gundersen T, Kvinnesland I, Fenstad AM, Dybvik E, Kroken G. . Annual Report. Norwegian Arthroplasty Register. 2020:242, 56.
  105. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318(18):1162-73.
  106. Vera-Llonch M, Hagiwara M, Oster G. Clinical and economic consequences of bleeding following major orthopedic surgery. *Thromb Res.* 2006;117(5):569-77.
  107. Eikelboom JW, Quinlan DJ, O'Donnell M. Major bleeding, mortality, and efficacy of fondaparinux in venous thromboembolism prevention trials. *Circulation.* 2009;120(20):2006-11.
  108. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. *Perspect Clin Res.* 2015;6(4):184-9.
  109. Julia S, James U. Direct Oral Anticoagulants: A Quick Guide. *Eur Cardiol.* 2017;12(1):40-5.
  110. ltd BI. Praxbind™ Product Monograph. Canada, April 29, 2016.
  111. Pharmaceuticals P. AnedexXa™ package insert. San Francisco, CA: Portola Pharmaceuticals 2018.

112. Norwegian Directorate of Health. Information concerning warfarin and direct oral anticoagulants dabigatran, rivaroxaban and apixaban. National specialist group in anticoagulation. [internet]. 2015;8,15. Accessed 03.03.21. Available from: <https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/433/Informasjon-om-warfarin-og-de-perorale-antikoagulasjonsmidlene-dabigatran-rivaroxaban-og-apixaban-IS-2050-Fullversjon.pdf>
113. Ranhoff AH, Saltvedt I, Frihagen F, Raeder J, Maini S, Sletvold O. Interdisciplinary care of hip fractures.: Orthogeriatric models, alternative models, interdisciplinary teamwork. *Best Pract Res Clin Rheumatol.* 2019;33(2):205-26.
114. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. *J Thromb Haemost.* 2013;11(3):402-11.
115. Wright IS. Thrombophlebitis. *Bull N Y Acad Med.* 1941;17(5):348-72.
116. Homans J. Thrombophlebitis of the Lower Extremities. *Ann Surg.* 1928;87(5):641-51.
117. Bauer G. Thrombosis; early diagnosis and abortive treatment with heparin. *Lancet.* 1946;1(6396):447-54.
118. Mannucci PM. Venous thrombosis: the history of knowledge. *Pathophysiol Haemost Thromb.* 2002;32(5-6):209-12.
119. Kumar DR, Hanlin E, Glurich I, Mazza JJ, Yale SH. Virchow's contribution to the understanding of thrombosis and cellular biology. *Clin Med Res.* 2010;8(3-4):168-72.
120. Mueller RL, Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. *Circulation.* 1994;89(1):432-49.
121. Charles AF, Scott DA. Studies on heparin: Observations on the chemistry of heparin. *Biochem J.* 1936;30(10):1927-33.
122. Barrowcliffe TW. History of heparin. *Handb Exp Pharmacol.* 2012(207):3-22.
123. Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. *Br J Haematol.* 2008;141(6):757-63.
124. Bauer G. Nine years' experience with heparin in acute venous thrombosis. *Angiology.* 1950;1(2):161-9.



- 
125. Crafoord C. Preliminary report on post-operative treatment with heparin as a preventive of thrombosis. *Acta Chir Scandinavia*. 1937(79):407– 26.
126. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-51.
127. Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol*. 2014;63(11):1082-7.
128. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-91.
129. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-92.
130. Sevitt S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. *Lancet*. 1959;2(7110):981-9.
131. Myhre HO, Holen A. [Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study]. *Nord Med*. 1969;82(49):1534-8.
132. Medin E, Goude F, Melberg HO, Tediosi F, Belicza E, Peltola M, et al. European Regional Differences in All-Cause Mortality and Length of Stay for Patients with Hip Fracture. *Health Econ*. 2015;24 Suppl 2:53-64.
133. Galasko CS, Edwards DH, Fearn CB, Barber HM. The value of low dosage heparin for the prophylaxis of thromboembolism in patients with transcervical and intertrochanteric femoral fractures. *Acta Orthop Scand*. 1976;47(3):276-82.
134. Borgstroem S, Greitz T, Van Der Linden W, Molin J, Rudics I. Anticoagulant Prophylaxis of Venous Thrombosis in Patients with Fractured Neck of the Femur; a Controlled Clinical Trial Using Venous Phlebography. *Acta Chir Scand*. 1965;129:500-8.

135. Eskeland G, Solheim K, Skjorten F. Anticoagulant prophylaxis, thromboembolism and mortality in elderly patients with hip fractures. A controlled clinical trial. *Acta Chir Scand.* 1966;131(1):16-29.
136. Rosencher N, Vielpeau C, Emmerich J, Fagnani F, Samama CM, group E. Venous thromboembolism and mortality after hip fracture surgery: the ESCORTE study. *J Thromb Haemost.* 2005;3(9):2006-14.
137. Bjornara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *J Bone Joint Surg Br.* 2006;88(3):386-91.
138. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e278S-e325S.
139. Fared J, Bick R, International Academy of C, Applied Thrombosis H, Vascular M. Differentiation of low-molecular-weight heparins: practical implications. *Clin Appl Thromb Hemost.* 2004;10(4):299-300.
140. National Institute for Health and Care Excellence (NICE). National Institute for Health and Care Excellence (NICE) guidelines: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2018.
141. Ettema HB, Mulder MC, Nurmohamed MT, Buller HR, Verheyen CC. Dutch orthopedic thromboprophylaxis: a 5-year follow-up survey. *Acta Orthop.* 2009;80(1):109-12.
142. Pedersen AB, Johnsen SP, Sorensen HT. Increased one-year risk of symptomatic venous thromboembolism following total hip replacement: a nationwide cohort study. *J Bone Joint Surg Br.* 2012;94(12):1598-603.
143. Vandvik PO. Retningslinjer for antitrombotisk behandling og profylakse Norsk Selskap for Trombose og Hemostase. 2016.
144. Li J, Halaszynski T. Neuraxial and peripheral nerve blocks in patients taking anticoagulant or thromboprophylactic drugs: challenges and solutions. *Local Reg Anesth.* 2015;8:21-32.

- 
145. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med.* 2010;35(1):64-101.
146. Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM, et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol.* 2010;27(12):999-1015.
147. Wysokinski WE, McBane RD, 2nd. Periprocedural bridging management of anticoagulation. *Circulation.* 2012;126(4):486-90.
148. Narouze S, Benzon HT, Provenzano DA, Buvanendran A, De Andres J, Deer TR, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med.* 2015;40(3):182-212.
149. David A. Garcia TGD. Anticoagulation in the Perioperative Period. In: Craig S. Kitchens CMK, Barbara A. Konkle, Michael B. Streiff, David A. Garcia, editor. *Consultative Hemostasis and Thrombosis (Fourth Edition)*2019. p. 721-33.
150. Legeforening DN. Norske retningslinjer for tverrfaglig behandling av hoftebrudd. 2018:16.
151. Norwegian Institute of Public Health. Overview of the national health registries 2019 [internet]. Accessed 03.03.21. Available from: <https://www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/2019>
152. Shulman KI. Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry.* 2000;15(6):548-61.
153. Dripps RD. New classification of physical status. *Anaesthesiology* 1963;111.
154. Furnes O, Gjertsen JE, Hallan G, Visnes H, Gundersen T, Fenstad AM, Dybvik E, Bartz-Johannessen C. Annual Report. Norwegian Arthroplasty Register. 2018:234.
155. Administration TNT. Registering a death 2020 [Available from: <https://www.skatteetaten.no/en/person/national-registry/registering-a-death/>].

156. Ranstam J, Karrholm J, Pulkkinen P, Makela K, Espehaug B, Pedersen AB, et al. Statistical analysis of arthroplasty data. II. Guidelines. *Acta Orthop*. 2011;82(3):258-67.
157. Lie SA, Engesaeter LB, Havelin LI, Gjessing HK, Vollset SE. Dependency issues in survival analyses of 55,782 primary hip replacements from 47,355 patients. *Stat Med*. 2004;23(20):3227-40.
158. Lindahl AK TO, Figved W, Ranhoff AH, Vesterhus EB, Roald OK. Tiltak for økt overlevelse etter hoftebrudd. Nasjonalt kunnskapssenter for helsetjenesten: Notat fra Kunnskapssenteret. [Actions to increase survival after hip fractures]. 2014. Norwegian.
159. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342(25):1887-92.
160. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med*. 2000;342(25):1878-86.
161. Thygesen LC, Ersboll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol*. 2014;29(8):551-8.
162. von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-7.
163. Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885.
164. Furnes O, Engesaeter LB, Gjertsen JE, Fenstad AM, Bartz-Johannessen C, Dybvik E, Fjeldsgaard K, Gundersen T, Hallan G. Annual report. Norwegian Arthroplasty Register. 2017:179.
165. Juliebo V, Bjoro K, Krogseth M, Skovlund E, Ranhoff AH, Wyller TB. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *J Am Geriatr Soc*. 2009;57(8):1354-61.
166. Mundi S, Chaudhry H, Bhandari M. Systematic review on the inclusion of patients with cognitive impairment in hip fracture trials: a missed opportunity? *Can J Surg*. 2014;57(4):E141-5.

- 
167. Kamel HK, Iqbal MA, Mogallapu R, Maas D, Hoffmann RG. Time to ambulation after hip fracture surgery: relation to hospitalization outcomes. *J Gerontol A Biol Sci Med Sci*. 2003;58(11):1042-5.
168. Oldmeadow LB, Edwards ER, Kimmel LA, Kipen E, Robertson VJ, Bailey MJ. No rest for the wounded: early ambulation after hip surgery accelerates recovery. *ANZ J Surg*. 2006;76(7):607-11.
169. Morri M, Forni C, Marchioni M, Bonetti E, Marseglia F, Cotti A. Which factors are independent predictors of early recovery of mobility in the older adults' population after hip fracture? A cohort prognostic study. *Arch Orthop Trauma Surg*. 2018;138(1):35-41.
170. Lofthus CM, Cappelen I, Osnes EK, Falch JA, Kristiansen IS, Medhus AW, et al. Local and national electronic databases in Norway demonstrate a varying degree of validity. *J Clin Epidemiol*. 2005;58(3):280-5.
171. Emaus N, Heiberg I, Ahmed LA, Balteskard L, Jacobsen BK, Magnus T, et al. Methodological challenges in hip fracture registration: the Harstad Injury Registry. *Int J Inj Contr Saf Promot*. 2011;18(2):135-42.
172. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. *Int J Epidemiol*. 1996;25(2):435-42.
173. Yli-Kyyny T, Ojanpera J, Venesmaa P, Kettunen J, Miettinen H, Salo J, et al. Perioperative complications after cemented or uncemented hemiarthroplasty in hip fracture patients. *Scand J Surg*. 2013;102(2):124-8.
174. Segerstad MHA, Olsen F, Patel A, Houltz E, Nellgard B, Ricksten SE. Pulmonary haemodynamics and right ventricular function in cemented vs uncemented total hip arthroplasty-A randomized trial. *Acta Anaesthesiol Scand*. 2019;63(3):298-305.
175. Rogmark C, Fenstad AM, Leonardsson O, Engesaeter LB, Karrholm J, Furnes O, et al. Posterior approach and uncemented stems increases the risk of reoperation after hemiarthroplasties in elderly hip fracture patients. *Acta Orthop*. 2014;85(1):18-25.
176. Borgen PO, Dahl OE, Reikeras O. Biomarkers of Coagulation and Fibrinolysis during Cemented Total Hip Arthroplasty with Pre- versus Postoperative Start of Thromboprophylaxis. *Thrombosis*. 2013;2013:563217.

177. Raskob GE, Hirsh J. Controversies in timing of the first dose of anticoagulant prophylaxis against venous thromboembolism after major orthopedic surgery. *Chest*. 2003;124(6 Suppl):379S-85S.
178. Dahl OE, Quinlan DJ, Bergqvist D, Eikelboom JW. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *J Thromb Haemost*. 2010;8(9):1966-75.
179. Lachiewicz PF. Comparison of ACCP and AAOS guidelines for VTE prophylaxis after total hip and total knee arthroplasty. *Orthopedics*. 2009;32(12 Suppl):74-8.
180. Parvizi J, Ghanem E, Joshi A, Sharkey PF, Hozack WJ, Rothman RH. Does "excessive" anticoagulation predispose to periprosthetic infection? *J Arthroplasty*. 2007;22(6 Suppl 2):24-8.
181. Tryba M. [Epidural regional anesthesia and low molecular heparin: Pro]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 1993;28(3):179-81. German.
182. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. *Anesthesiology*. 2004;101(4):950-9.
183. Bateman BT, Mhyre JM, Ehrenfeld J, Kheterpal S, Abbey KR, Argalious M, et al. The risk and outcomes of epidural hematomas after perioperative and obstetric epidural catheterization: a report from the Multicenter Perioperative Outcomes Group Research Consortium. *Anesth Analg*. 2013;116(6):1380-5.
184. Leffert LR, Dubois HM, Butwick AJ, Carvalho B, Houle TT, Landau R. Neuraxial Anesthesia in Obstetric Patients Receiving Thromboprophylaxis With Unfractionated or Low-Molecular-Weight Heparin: A Systematic Review of Spinal Epidural Hematoma. *Anesth Analg*. 2017;125(1):223-31.
185. Dahl OE, Gudmundsen TE, Haukeland L. Late occurring clinical deep vein thrombosis in joint-operated patients. *Acta Orthop Scand*. 2000;71(1):47-50.
186. Strebel N, Prins M, Agnelli G, Buller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med*. 2002;162(13):1451-6.
187. Kearon C, Hirsh J. Starting prophylaxis for venous thromboembolism postoperatively. *Arch Intern Med*. 1995;155(4):366-72.

- 
188. Borgen PO, Dahl OE, Reikeras O. Preoperative versus postoperative initiation of dalteparin thromboprophylaxis in THA. *Hip Int.* 2010;20(3):301-7.
189. Borgen PO, Dahl OE, Reikeras O. Blood loss in cemented THA is not reduced with postoperative versus preoperative start of thromboprophylaxis. *Clin Orthop Relat Res.* 2012;470(9):2591-8.
190. Llau JV, Gil-Garay E, Castellet E, investigadores del estudio E. [Thromboprophylaxis with enoxaparin for total knee replacement: an observational, retrospective and multicentre study comparing starting the treatment before and after the operation]. *Rev Esp Anesthesiol Reanim.* 2012;59(6):306-14. Spanish.
191. Nikkel LE, Fox EJ, Black KP, Davis C, Andersen L, Hollenbeak CS. Impact of comorbidities on hospitalization costs following hip fracture. *J Bone Joint Surg Am.* 2012;94(1):9-17.
192. Huilin Y, Ye S. Thromboprophylaxis for venous thromboembolism prevention in hip fracture patients. *Acta Orthop.* 2017;88(2):236-7.
193. Zahn HR, Skinner JA, Porteous MJ. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. *Injury.* 1999;30(9):605-7.
194. Smith EB, Parvizi J, Purtill JJ. Delayed surgery for patients with femur and hip fractures-risk of deep venous thrombosis. *J Trauma.* 2011;70(6):E113-6.
195. Song K, Yao Y, Rong Z, Shen Y, Zheng M, Jiang Q. The preoperative incidence of deep vein thrombosis (DVT) and its correlation with postoperative DVT in patients undergoing elective surgery for femoral neck fractures. *Arch Orthop Trauma Surg.* 2016;136(10):1459-64.
196. Bengoa F, Vicencio G, Schweitzer D, Lira MJ, Zamora T, Klaber I. High prevalence of deep vein thrombosis in elderly hip fracture patients with delayed hospital admission. *Eur J Trauma Emerg Surg.* 2020;46(4):913-7.
197. McNamara I, Sharma A, Prevost T, Parker M. Symptomatic venous thromboembolism following a hip fracture. *Acta Orthop.* 2009;80(6):687-92.
198. Meignan M, Rosso J, Gauthier H, Brunengo F, Claudel S, Sagnard L, et al. Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. *Arch Intern Med.* 2000;160(2):159-64.

199. Needleman L, Cronan JJ, Lilly MP, Merli GJ, Adhikari S, Hertzberg BS, et al. Ultrasound for Lower Extremity Deep Venous Thrombosis: Multidisciplinary Recommendations From the Society of Radiologists in Ultrasound Consensus Conference. *Circulation*. 2018;137(14):1505-15.
200. Hirsh J, Ginsberg JS, Chan N, Guyatt G, Eikelboom JW. Mandatory contrast-enhanced venography to detect deep-vein thrombosis (DVT) in studies of DVT prophylaxis: upsides and downsides. *Thromb Haemost*. 2014;111(1):10-3.
201. Chan NC, Stehouwer AC, Hirsh J, Ginsberg JS, Alazzoni A, Coppens M, et al. Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials. *Thromb Haemost*. 2015;114(5):1049-57.
202. Dahl OE, Harenberg J, Wexels F, Preissner KT. Arterial and venous thrombosis following trauma and major orthopedic surgery: molecular mechanisms and strategies for intervention. *Semin Thromb Hemost*. 2015;41(2):141-5.
203. Daugaard CL, Jorgensen HL, Riis T, Lauritzen JB, Duus BR, van der Mark S. Is mortality after hip fracture associated with surgical delay or admission during weekends and public holidays? A retrospective study of 38,020 patients. *Acta Orthop*. 2012;83(6):609-13.
204. Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, Debeer J, et al. Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. *CMAJ*. 2010;182(15):1609-16.
205. Bretherton CP, Parker MJ. Early surgery for patients with a fracture of the hip decreases 30-day mortality. *Bone Joint J*. 2015;97-B(1):104-8.
206. Canadian Institute for Health Information (CIHI). Benchmarks for treatment and wait time in Canada. 2017. [internet]. Accessed 03.03.21. Available from: <http://waittimes.cihi.ca/All/fracture>: Canadian Institute for Health Information;2017
207. Committee on Trauma, Trauma Quality Improvement Program (TQIP), American College of Surgeons (ACS), Orthopaedic Trauma Association. ACS TQIP best practices in the management of orthopaedic trauma, 2015. [internet]. Accessed 27.10.20. Available from: [https://www.facs.org/-/media/files/quality-programs/trauma/tqip/ortho\\_guidelines.ashx](https://www.facs.org/-/media/files/quality-programs/trauma/tqip/ortho_guidelines.ashx)
208. Norwegian Directorate of Health. Preoperative wait time for hip fracture patients, National Quality Indicator System: Quality indicator description. 2015. [internet]. Accessed 27.10.20. Available from: <https://www.helsedirektoratet.no/statistikk/kvalitetsindikatorer/behandling-av-sykdom-og-overlevelse/hoftebrudd-operert-innen-henholdsvis-24-timer-og-48-timer>



- 
209. Bredahl C, Nyholm B, Hindsholm KB, Mortensen JS, Olesen AS. Mortality after hip fracture: results of operation within 12 h of admission. *Injury*. 1992;23(2):83-6.
210. Investigators HA. Accelerated surgery versus standard care in hip fracture (HIP ATTACK): an international, randomised, controlled trial. *Lancet*. 2020;395(10225):698-708.
211. Bottle A, Aylin P. Mortality associated with delay in operation after hip fracture: observational study. *BMJ*. 2006;332(7547):947-51.
212. Fu MC, Boddapati V, Gausden EB, Samuel AM, Russell LA, Lane JM. Surgery for a fracture of the hip within 24 hours of admission is independently associated with reduced short-term post-operative complications. *Bone Joint J*. 2017;99-B(9):1216-22.
213. Haleem S, Heinert G, Parker MJ. Pressure sores and hip fractures. *Injury*. 2008;39(2):219-23.
214. Verbeek DO, Ponsen KJ, Goslings JC, Heetveld MJ. Effect of surgical delay on outcome in hip fracture patients: a retrospective multivariate analysis of 192 patients. *Int Orthop*. 2008;32(1):13-8.
215. Cordero J, Maldonado A, Iborra S. Surgical delay as a risk factor for wound infection after a hip fracture. *Injury*. 2016;47 Suppl 3:S56-S60.
216. Linnerud I VK, Ranhoff A, Molden E. The use of direct oral anticoagulants and other antithrombotic agents among elderly hip fracture patients; prevalence and clinical aspects: University of Oslo; 2016.
217. Franklin NA, Ali AH, Hurley RK, Mir HR, Beltran MJ. Outcomes of Early Surgical Intervention in Geriatric Proximal Femur Fractures Among Patients Receiving Direct Oral Anticoagulation. *J Orthop Trauma*. 2018;32(6):269-73.
218. Frenkel Rutenberg T, Velkes S, Vitenberg M, Leader A, Halavy Y, Raanani P, et al. Morbidity and mortality after fragility hip fracture surgery in patients receiving vitamin K antagonists and direct oral anticoagulants. *Thromb Res*. 2018;166:106-12.
219. Schermann H, Gurel R, Gold A, Maman E, Dolkart O, Steinberg EL, et al. Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications. *Injury*. 2019;50(2):398-402.
220. Hourston GJ, Barrett MP, Khan WS, Vindlacheruvu M, McDonnell SM. New drug, new problem: do hip fracture patients taking NOACs experience delayed surgery, longer hospital stay, or poorer outcomes? *Hip Int*. 2019:1120700019841351.

221. Mullins B, Akehurst H, Slattery D, Chesser T. Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre. *BMJ Open*. 2018;8(4):e020625.
222. Hoerlyck C, Ong T, Gregersen M, Damsgaard EM, Borris L, Chia JK, et al. Do anticoagulants affect outcomes of hip fracture surgery? A cross-sectional analysis. *Arch Orthop Trauma Surg*. 2019.
223. Lott A, Haglin J, Belayneh R, Konda SR, Leucht P, Egol KA. Surgical Delay Is Not Warranted for Patients With Hip Fractures Receiving Non-Warfarin Anticoagulants. *Orthopedics*. 2019;42(3):e331-e5.
224. Neuman MD, Rosenbaum PR, Ludwig JM, Zubizarreta JR, Silber JH. Anesthesia technique, mortality, and length of stay after hip fracture surgery. *JAMA*. 2014;311(24):2508-17.
225. Van Waesberghe J, Stevanovic A, Rossaint R, Coburn M. General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. *BMC Anesthesiol*. 2017;17(1):87.
226. Larsson G, Holgers KM. Fast-track care for patients with suspected hip fracture. *Injury*. 2011;42(11):1257-61.
227. Jensen TG, Vinstrup LO, Dalskov S, Aasbrenn M, Palm H, Rugolo SA, et al. Introducing the "hip call" to facilitate early surgical treatment of hip fractures: A feasibility study. *Acta Anaesthesiol Scand*. 2020;64(8):1202-9.
228. Ryan J, Ghani M, Staniforth P, Bryant G, Edwards S. "Fast tracking" patients with a proximal femoral fracture. *J Accid Emerg Med*. 1996;13(2):108-10.
229. Pollmann CT, Rotterud JH, Gjertsen JE, Dahl FA, Lenvik O, Aroen A. Fast track hip fracture care and mortality - an observational study of 2230 patients. *BMC Musculoskelet Disord*. 2019;20(1):248.

## **10. Appendices**

**Appendix I:** Operation form from the Norwegian Hip Fracture Register  
(in Norwegian)

**Appendix II:** Correspondence in Acta Orthopaedica: Letter from Dr. Ye and Dr. Huilin regarding Paper I

**Appendix III:** Correction to Paper IV: Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay, and poorer outcome for hip fracture patients?

**Papers I-IV**





**NASJONALT HOFTEBRUDDREGISTER**

Nasjonalt Register for Leddproteser  
Helse Bergen HF, Ortopedisk klinikk  
Haukeland universitetssjukehus  
Møllendalsbakken 7  
5021 BERGEN  
Tlf: 55976452

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

Navn:.....

(Skriv tydelig ev. pasientklirelapp – spesifiser sykehus.)

Sykehus:.....

**HOFTEBRUDD**

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

**AKTUELLE OPERASJON**

1 Primæroperasjon  2 Reoperasjon



**SIDE (ett kryss)** (Bilateral opr.= 2 skjema)

1 Høyre  2 Venstre

**OPR TIDSPUNKT**

(dd.mm.åå) | | | | | | | | kl | | | |

**BRUDD TIDSPUNKT**

(dd.mm.åå) | | | | | | | | kl | | | |

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

**TID FRA BRUDD TIL OPERASJON I TIMER**

1 0-6  2 >6-12  3 >12-24  4 >24-48  5 >48

**KOGNITIV SVIKT**

0 Nei  1 Ja (Se test på baksiden)  2 Usikker

**ASA-KLASSE** (se bakside av skjema for definisjon)

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



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

Se baksiden for klassifikasjon

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

**TYPE PRIMÆROPERASJON** (Kun ett kryss)

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

(Fest produktklirelapp på baksiden eller spesifiser nøyaktig produkt)

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



Navn / størrelse og katalognummer.....

**ÅRSÅK TIL REOPERASJON** (Flere enn ett kryss kan brukes)

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

**TYPE REOPERASJON** (Flere enn ett kryss kan brukes)

(Fest produktklirelapp på baksiden eller spesifiser nøyaktig produkt)

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



Navn / størrelse og katalognummer.....

**FIKSASJON AV HEMIPROTESE**

(For totalprotese sendes eget skjema til hofteproteseregisteret)

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

**PATOLOGISK BRUDD (Annen patologi enn osteoporose)**

0 Nei  1 Ja, type.....

**TILGANG TIL HOFTELEDDET VED HEMIPROTESE** (Kun ett kryss)

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

**ANESTESITYPE**

1 Narkose  2 Spinal  3 Annet, spesifiser.....

**PEROPERATIVE KOMPLIKASJONER**

0 Nei  1 Ja, hvilke(n).....

**OPERASJONSTID** (hud til hud).....minutter.

**ANTIBIOTIKAPROFYLAKSE**

0 Nei  1 Ja



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

**TROMBOSEPROFYLAKSE**

0 Nei  1 Ja: Første dose  1 Preoperativt  2 Postoperativt

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

**FAST TROMBOSEPROFYLAKSE**

0 Nei  1 Ja, type: .....

**FIBRINOLYSEHEMMER**

0 Nei  1 Ja, medikament : ..... Dosering .....

**OPERATØRERFARING**

Har en av operatørene mer enn 3 års erfaring i hoftebruddkirurgi?  0 Nei  1 Ja

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

## RETTLEDNING

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

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

### Kommentarer til enkelte punkt:

#### OPERASJONS- OG BRUDDTIDSPUNKT

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

Ved reoperasjon er ikke klokkeslett nødvendig.

#### KOGNITIV SVIKT

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

#### ASA-KLASSE (ASA=American Society of Anesthesiologists)

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

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

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

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

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

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

ASA-klasse 5: Moribund/døende pasient

#### GARDENS KLASSIFISERING AV LÅRHALSBRUDD

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

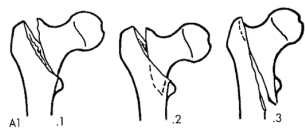
Garden 2: Komplet lårhalsbrudd uten dislokasjon

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

Caputfragmentet ligger uanatomisk i acetabulum.

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

#### AO KLASSIFIKASJON AV TROKANTÆRE BRUDD



A1: Pertrokantært tofragment brudd

A2: Pertrokantært flerfragment brudd

A3: Intertrokantært brudd

Subtrokantært brudd\*

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

#### REOPERASJONSÅRSÅK

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

#### IMPLANTAT

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

#### PEROPERATIVE KOMPLIKASJONER

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

#### ANTIBIOTIKAPROFYLAKSE

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

#### TROMBOSEPROFYLAKSE

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

#### FIBRINOLYSEHEMMER

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

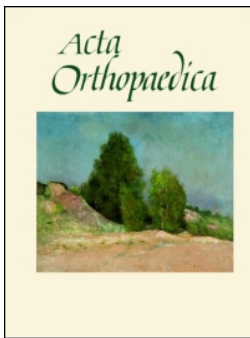
#### Kontaktpersoner vedrørende registreringskjema er:

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

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

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

## PRODUKTKLISTRELAPPER:



# Thromboprophylaxis for venous thromboembolism prevention in hip fracture patients

To cite this article: (2017) Thromboprophylaxis for venous thromboembolism prevention in hip fracture patients, Acta Orthopaedica, 88:2, 236-237, DOI: [10.1080/17453674.2016.1274591](https://doi.org/10.1080/17453674.2016.1274591)

To link to this article: <https://doi.org/10.1080/17453674.2016.1274591>



© 2017 The Author(s). Published by Taylor & Francis on behalf of the Nordic Orthopedic Federation.



Published online: 09 Jan 2017.



Submit your article to this journal [↗](#)



Article views: 771



View related articles [↗](#)



View Crossmark data [↗](#)

## Correspondence

# Thromboprophylaxis for venous thromboembolism prevention in hip fracture patients

*Sir*,—I read with interest the study by Leer-Salvesen et al. (2016) and I would like to compliment the authors for a thorough study. It shows that preoperative start of thromboprophylaxis with low-molecular-weight heparin (LMWH) decreases 6-month mortality in femoral neck fracture patients receiving hemiarthroplasty. In a clinical setting, LMWH is a common chemoprophylaxis for venous thromboembolism (VTE) prevention. From the article, yet no VTE occurrence is stated. VTE is a major problem after hip fracture. Development of VTE is anticipated in the interval between the time of fracture and surgery since hip fracture patients cannot move the injured extremity during this period, while patients undergoing elective total joint arthroplasty are mobile. Preoperative VTE is known to occur in 3–62% of hip fracture patients (Salzman and Harris 1976, Zahn et al. 1999, Song et al. 2016). Yet no preoperative VTE is documented at the time of admission in the study. VTE is also a significant risk factor for mortality. The mortality risks for patients with VTE were markedly higher during the first year, especially within the first 30 days after VTE diagnosis (Søgaard et al. 2014). Still, no association analysis was made between VTE and mortality in the study. Failure to bring VTE into the equation makes the association between thromboprophylaxis strategy and mortality hard to interpret in clinical practice. I would appreciate the authors' thoughts on this.

**Yang Huilin and Sun Ye \***

*Department of Orthopedics, The First Affiliated Hospital of Soochow University, 188, shi zi Road, and Orthopedic Institute, Soochow University, 708, ren min Road, Suzhou, 215006, China.*

*Email: \* sunye881005@163.com*

*Sir*,—We thank dr Yang Huilin and dr Sun Ye for the comments on our recently published article.

The aim of our study was to investigate the effect of preoperative and postoperative low-molecular-weight heparin on hard clinical outcomes in emergency hip fracture patients undergoing surgical treatment with prosthetic implants.

The rationale was based on the following: A tissue trauma and in particular bone trauma (including impaction of cement) causes release of potentially toxic molecules that trigger systemic activation of coagulation. This may cause clot formation at sites of local minor resistance both on the venous and arterial side and organ damage. Frail elderly operated for hip fractures may experience a multitude of complications triggered by cell destroying molecules and thrombin activity like respiratory distress, heart and brain ischaemia, hepatic and renal dysfunction and local limb thrombosis at the site of trauma as reviewed by an international expert group (Dahl et al. 2015). Thus, by controlling thrombin we have reason to believe that mortality can be reduced beyond solely preventing non-fatal and fatal venous thromboembolism (Dahl et al. 2005).

Based on this awareness we conducted the reported clinical study that showed that LMWH administered before surgery was superior to postoperative initiation in frail elderly undergoing hip fracture treatment with prostheses (Leer-Salvesen et al. 2016). Mortality and reoperations were significantly reduced with preoperative LMWH administration already on day 7 and continued to be consistent 1 and 6 months after surgery.

Concerning your statement on venous thrombosis we have the following remarks. Radiological VTE screening has mainly been conducted with venography and even recently ultrasonography. The methods have technical limitations (sensitivity, specificity, interobserver variations, drop outs etc.) and aim to diagnose subclinical thromboses. These challenges and definite diagnostic criteria do explain the huge differences found in the referred articles suggesting a preoperative VTE rate of 3–62% (Salzman and Harris 1976, Zahn et al. 1999, Song et al. 2016).

We expected patients with a long preoperative waiting time to be at a higher risk of severe outcomes. Interestingly, this huge cohort did not reveal any independent effect of preoperative delay on the risk of postoperative death or reoperation. Accordingly, the length of time between fracture and operation did not impact the advantageous effect of a preoperative start of the prophylaxis.



The latest American College of Chest Physicians (ACCP) guideline committee requested studies with clinical outcomes and not surrogate endpoints (Falck-Ytter et al. 2012). Our study responded on this demand.

**Sunniva Leer-Salvesen**<sup>2</sup>

**Eva Dybvik**<sup>1</sup>

**Ola E Dahl**<sup>3,4</sup>

**Jan-Erik Gjertsen**<sup>1,2</sup>

**Lars B Engesæter**<sup>1,2</sup>

<sup>1</sup> *Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway*

<sup>2</sup> *Department of Clinical Medicine, University of Bergen, Bergen, Norway*

<sup>3</sup> *Innlandet Hospital Trust, Elverum, Norway*

<sup>4</sup> *Thrombosis Research Institute, London, United Kingdom*  
Email: lars.birger.engeseter@helse-bergen.no

Dahl O E, Caprini J A, Colwell C W, Frostick S P, Haas S, Hull R D, Laporte S, Stein P. Fatal vascular outcomes following major orthopaedic surgery. *Thromb Haemost* 2005; 93: 860-6.

Dahl O E, Harenberg J, Wexels F, Preissner KT. Arterial and venous thrombosis following trauma and major orthopaedic surgery: Molecular mechanisms and strategies for intervention. *Sem Thromb Hemost* 2015; 41: 14-5.

Falck-Ytter Y, Francis C W, Johanson N M, Curley C, Dahl O E, Schulman S, Ortel T L, Pauker S G, Colwell C W. Prevention of VTE in orthopaedic surgery patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians. Evidence-based clinical practice guidelines. *CHEST* 2012; 14 (2) (Suppl): e278s-e325S.

Leer-Salvesen S, Dybvik E, Dahl O E, Gjertsen J-E, Lars B Engesæter L B. Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures. *Acta Orthop* 2016; [Ahead of print] DOI:10.1080/17453674.2016.1235427

Salzman E W, Harris W H. Prevention of venous thromboembolism in orthopaedic patients. *J Bone Joint Surg Am* 1976; 58(7): 903-13.

Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014; 130(10): 829-36.

Song K, Yao Y, Rong Z, Shen Y, Zheng M, Jiang Q. The preoperative incidence of deep vein thrombosis (DVT) and its correlation with postoperative DVT in patients undergoing elective surgery for femoral neck fractures. *Arch Orthop Trauma Surg* 2016; 136(10): 1459-64.

Zahn H R, Skinner J A, Porteous M J. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. *Injury* 1999; 30(9): 605-7.



# Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay, and poorer outcome for hip fracture patients?

Sunniva Leer-Salvesen<sup>1</sup> · Eva Dybvik<sup>2</sup> · Anette H. Ranhoff<sup>3,4,5</sup> · Bjørn Liljestrand Husebø<sup>6</sup> · Ola E. Dahl<sup>7,8</sup> · Lars B. Engesæter<sup>2</sup> · Jan-Erik Gjertsen<sup>1,2</sup>

Received: 31 January 2020 / Accepted: 31 March 2020  
© The Author(s) 2020, corrected publication 2020

## Key summary points

**Aim** The aim of this study was to determine whether DOAC-users with a hip fracture have delayed surgery, longer length of hospital stay or altered risk of bleeding complications compared to non-users.

**Findings** DOAC-users with a hip fracture did not have increased surgical delay, length of stay or risk of reported bleeding complications compared to patients without anticoagulation prior to surgery.

**Message** Our study does not support delayed surgery for DOAC-users suffering a hip fracture.

## Abstract

**Purpose** The perioperative consequences of direct oral anticoagulants (DOACs) in hip fracture patients are not sufficiently investigated. The primary aim of this study was to determine whether DOAC-users have delayed surgery compared to non-users. Secondly, we studied whether length of hospital stay, mortality, reoperations and bleeding complications were influenced by the use of DOAC.

**Methods** The medical records of 314 patients operated for a hip fracture between 2016 and 2017 in a single trauma center were assessed. Patients aged < 60 and patients using other forms of anticoagulation than DOACs were excluded. Patients were followed from admission to 6 months postoperatively. Surgical delay was defined as time from admission to surgery. Secondary outcomes included length of hospital stay, transfusion rates, perioperative bleeding loss, postoperative wound ooze, mortality and risk of reoperation. The use of general versus neuraxial anaesthesia was registered. Continuous outcomes were analysed using Students *t* test, while categorical outcomes were expressed by Odds ratios.

**Results** 47 hip fracture patients (15%) were using DOACs. No difference in surgical delay (29 vs 26 h,  $p=0.26$ ) or length of hospital stay (6.6 vs 6.1 days,  $p=0.34$ ) were found between DOAC-users and non-users. DOAC-users operated with neuraxial anaesthesia had longer surgical delay compared to DOAC-users operated with general anaesthesia (35 h vs 22 h,  $p<0.001$ ). Perioperative blood loss, transfusion rate, risk of bleeding complications and mortality were similar between groups.

**Conclusion** Hip fracture patients using DOAC did not have increased surgical delay, length of stay or risk of reported bleeding complications than patients without anticoagulation prior to surgery. The increased surgical delay found for DOAC-users operated with neuraxial anaesthesia should be interpreted with caution.

**Keywords** Hip fracture · Orthogeriatrics · Surgical delay · Anaesthesia · Direct oral anticoagulants (DOAC) · New oral anticoagulants (NOAC)

✉ Sunniva Leer-Salvesen  
sunniva.leer-salvesen@helse-bergen.no

<sup>1</sup> Department of Clinical Medicine, University of Bergen, Bergen, Norway

<sup>2</sup> The Norwegian Hip Fracture Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

<sup>3</sup> Department of Clinical Science, University of Bergen, Bergen, Norway

<sup>4</sup> Department of Chronic Diseases and Aging, Norwegian Institute of Public Health, Oslo, Norway

<sup>5</sup> Diakonhjemmet Hospital, Oslo, Norway

<sup>6</sup> Department of Anaesthesia, Haukeland University Hospital, Bergen, Norway

<sup>7</sup> Innlandet Hospital Trust, Elverum, Norway

<sup>8</sup> Thrombosis Research Institute, London, UK

## Introduction

The use of direct oral anticoagulants (DOACs) have emerged based on randomized clinical trials, active marketing and less demands concerning monitoring compared to warfarin. From 2014 to 2018, the prevalence of DOAC-users increased with 150% in Norway and the drugs as a group have surpassed warfarin [1]. Increasing use of DOACs has also been observed in Germany, Belgium and The Netherlands [2]. Suffering a hip fracture results in an evident excess mortality [3], and knowledge on how to reduce complications is, therefore, important. Reduced kidney function, co-medication, drug interaction and altered distribution may affect the clinical outcome in hip fracture patients using such anticoagulant compounds [4].

Systemic thromboembolic events are important causes of mortality [5, 6]. On the other hand, DOACs may accentuate bleeding triggered by trauma and surgery. Whether DOACs should be temporarily paused to avoid surgical and anaesthesiological complications and, if so, when it should be paused remains to be established. Anticoagulation has in several studies been identified as a risk factor for delayed hip fracture surgery [7–10]. Most guidelines advocate that hip fracture surgery should be performed within 48 h after admission, preferably within 24 h, to reduce the rate of medical complications and mortality [11–13]. Earlier studies have indicated that patients exposed for DOAC before the hip fracture wait longer for surgery than recommended in treatment guidelines [14–16]. The consequences of DOAC on semi-urgent surgery such as for hip fracture patients has not been thoroughly investigated.

Currently, there is need for guidelines on how to handle DOACs in the treatment of hip fracture patients. The primary aim of this study was to determine whether hip fracture patients using DOACs prior to the fracture have delayed surgery or longer length of hospital stay compared to non-DOAC-users. Secondly, we wanted to investigate whether mortality and perioperative complications occur more frequently among hip fracture patients using DOAC.

## Methods

### Study design

This is a retrospective descriptive study of hip fracture patients operated at one Norwegian single trauma center December 2016–December 2017. We extracted 360 patients electronically from the hospital database using ICD-10 diagnosis codes S72.0–S72.2. Demographic data and surgical outcomes for the included patients were retrieved directly

from patient records by one experienced researcher (SLS). Patient records at the hospital consisted of day-to-day documentation by the anaesthetists and orthopaedic surgeons and medical records logged by physicians and nurses. The Regional Ethics Committee (REK) classified the study as quality assurance, thus we did not need ethical assessment (case number 1366/REK). The hospital data protection officer approved the study.

### Patients

Patients with acute intracapsular or extracapsular hip fractures undergoing any type of surgery were included in the study. We aimed to compare hip fracture patients using DOAC at time of fracture with patients without anticoagulation at time of fracture. Patients under the age of 60 ( $n=23$ ) and patients using other forms of anticoagulation than DOACs ( $n=23$ ) were excluded, resulting in a study population of 314 patients.

### Outcomes

We stratified the patients according to the American Society of Anesthesiologists (ASA) classes 1–2 and 3–5 to compare comorbidity between the studied groups. When comparing the rate of cognitive impairment reported between the study groups, patients with unknown preoperative cognitive status were excluded ( $n=20$ ). Time from admission to surgery (surgical delay) was reported in hours and length of stay (LOS) in days. In-hospital mortality and both mortality and readmissions within 30 days and within 6 months of operation were registered. Blood transfusion rates and transfusion amounts (allogenic red blood cells infused in standardized units) were collected from the medical records signed by the responsible physicians. In-hospital guidelines recommended blood transfusion therapy to be administered for patients with a haemoglobin below 9 g/dL monitored at the wards. The concentration of haemoglobin was listed at admission and the morning after surgery and the difference was calculated (change in haemoglobin concentration). Intraoperative blood loss estimated by the surgical team was registered from the anaesthesia journal in milliliters (mL). Postoperative bleeding and wound complications were recorded if the intraoperative or postoperative journals by the physicians reported so. Wound ooze was defined as clinically identified ooze with or without bleeding described by the doctors postoperatively. The type of anaesthesia was registered as general anaesthesia (total intravenous anaesthesia (TIVA) or inhalational anaesthesia) or neuraxial anaesthesia (spinal anaesthesia). We compared surgical delay and LOS within the groups receiving neuraxial versus general anaesthesia.

## Statistical analysis

Our main outcome, surgical delay, was used to calculate the number of patients needed to achieve statistical significance between the groups. Based on guidelines from the Norwegian Knowledge Center hip fracture patients should preferably be operated within 24 h and no later than 48 h after admission [12]. Standard deviation was calculated from hip fracture patients with a surgical delay of less than 96 h reported to the Norwegian Hip Fracture Register and found to be 15.1 h. Based on alpha of 0.05 and beta of 0.9, 28 patients were needed in each group. Since 9.4% of Norwegian patients > 60 years were using DOAC in 2017 (Norwegian Institute of Public Health 2019), the total sample size was calculated to be 300. To account for exclusion criteria's and missing information, we increased the sample size with 20%.

We performed univariate exploration of study variables; for continuous data, the assumption of homogeneity of variance between groups was assessed using the Levene's test. Where the assumption holds a Student's *t* test was used, otherwise the Welch's *t* test was applied. Odds ratios (ORs) were used to express categorical outcomes and patients without DOAC were used as a reference group. IBM SPSS Statistics (version 24.0; IBM Corp. Armonk, New York) for Windows was used for the statistical analyses.

## Results

Of the 314 included patients, 47 patients (15%) were DOAC-users before the hip fracture and 267 patients (85%) were not using anticoagulation before the fracture (Table 1). Hip

fracture patients using DOAC were more likely to have a high ASA class (ASA 3–5) compared to non-users.

## Time to surgery and hospital stay

DOAC-users and non-anticoagulated patients had similar time interval from admission to surgery (29 vs 26 h,  $p=0.26$ , respectively) and similar length of hospital stay (LOS) (6.6 vs 6.1 days,  $p=0.34$ , respectively) (Table 2).

## Complications

The mean blood loss during surgery for all patients ( $n=314$ ) was 219 mL. Mean blood loss, fall in haemoglobin and transfusion rates were comparable in both groups (Table 2).

Bleeding complications were reported in three patients (0.9% of all patients); two patients had an excessive bleeding during surgery, while a third patient developed a postoperative haematoma restricted to the operation site. No bleeding complications were reported among the DOAC-users.

Wound oozing with or without bleeding were described in 27 patients (8.6%) and more frequently among DOAC-users than patients without anticoagulation (26% vs 5.6%, respectively) (Table 2). Among all patients ( $n=314$ ), postoperative wound leakage was associated with a longer hospital stay than for patients without wound exudation (LOS 9 vs 6 days, respectively,  $p<0.001$ ).

The 30-day mortality for all patients ( $n=314$ ) was 12%. DOAC-users had corresponding mortality in the hospital, within 30 days and within 6 months compared to non-users (Table 2). Furthermore, 30-day and 6-month risk of readmission were similar between DOAC-users and non-users [30 days: 26% vs 17%, respectively, OR 1.65 (0.80–3.41)] [6 months: 36% vs 26%, OR 1.63 (0.85–3.13)].

**Table 1** Baseline data for the included hip fracture patients in our study ( $n=337$ )

	Antithrombotic medication			<i>p</i> value
	Total	No anticoagulants	DOAC	
Total <i>n</i> (%)	314 (100)	267 (85)	47 (15)	
Mean age (SD)	82.1 (9.2)	81.8 (9.5)	84.2 (7.4)	0.05
Women (%)	221 (70)	190 (71)	31 (66)	0.47
Cognitive impairment (%)	108 (34)	93 (34.8)	15 (31.9)	0.61
ASA class (%)				0.003 <sup>a</sup>
ASA 1	8 (2.5)	8 (3.0)	0 (0.0)	
ASA 2	120 (39)	110 (42)	10 (21)	
ASA 3	158 (51)	128 (48)	30 (64)	
ASA 4	27 (8.0)	20 (7.5)	7 (15)	
ASA 5	1 (0.3)	1 (0.4)	0 (0.0)	

<sup>a</sup>Pearson Chi Square test has been used to compare patients in each anticoagulant group with either ASA classes 1–2 or class 3–5. When comparing the rate of cognitive impairment reported between the study groups, patients with unknown preoperative cognitive status were excluded ( $n=20$ )

**Table 2** Surgical delay, length of hospital stay, type of anaesthesia, perioperative complications and mortality reported among hip fracture with DOAC or no anticoagulation prior to the fracture ( $n=314$ )

Antithrombotic medication				
Hospital stay	Total	No anticoagulants	DOAC	<i>p</i> value
Hours from admission to surgery (SD)	26.5 (18.2)	26.1 (19.0)	28.9 (12.9)	0.26
LOS (SD)	6.2 (2.9)	6.1 (2.9)	6.6 (2.2)	0.34
General anaesthesia (%)	<b>32 (10%)</b>	<b>10 (3.8%)</b>	<b>22 (47%)</b>	<b>0.001</b>
Perioperative complications				<i>p</i> value
Mean blood loss during surgery (SD)	219 mL (208)	218 mL (209)	223 mL (204)	0.9
Mean fall in haemoglobin (SD)	1.90 (1.30)	1.89 (1.25)	1.95 (1.63)	0.8
Mean SAG transfused per patient (SD)	0.81 (1.16)	0.80 (1.17)	0.85 (1.10)	0.8
				OR (95% CI)
Number of patients transfused (%)	134 (43%)	113 (42%)	21 (45%)	1.10 (0.59–2.01)
Reported wound ooze (%)	<b>27 (8.6%)</b>	<b>15 (5.6%)</b>	<b>12 (26%)</b>	<b>5.8 (2.49–13.3)</b>
Mortality				OR (95% CI)
In-hospital mortality	11 (3.5%)	9 (3.4%)	2 (4.3%)	1.27 (0.27–6.09)
30-day mortality	39 (12.4%)	34 (12.7%)	5 (10.6%)	1.23 (0.45–3.31)
6-month mortality	70 (22.3%)	59 (22.1%)	11 (23.4%)	0.93 (0.45–1.94)

Bold values indicate more frequent use of general anaesthesia and higher risk of wound ooze in DOAC-users compared to non-users

## Antiaggregants

Among the DOAC-users, two hip fracture patients were also using clopidogrel (4.3%) while the remaining 45 patients where not using antiaggregant therapy (95.7%).

In the non-anticoagulated group, 92 patients (34.5%) were using 1 antiplatelet drug while ten patients (3.7%) were using two antiplatelet drugs. Time to surgery, perioperative blood loss, transfusion rate, risk of bleeding complications and mortality were similar between non-anticoagulated patients and DOAC-patients both when including and excluding patients with clopidogrel in addition to DOAC.

## Anaesthesia

General anaesthesia was administered to 32 (10%) of all patients. When comparing general to neuraxial anaesthesia, no differences in time from admission to surgery (surgical delay) or LOS was found. A significantly higher percentage of DOAC-users received general anaesthesia than non-users [22 patients (47%) vs 10 (3.8%),  $p < 0.001$ ]. The DOAC-users that received neuraxial anaesthesia ( $n=25$ ) had significantly longer surgical delay compared to those who received general anaesthesia (35 h vs 22 h,  $p < 0.001$ ). DOAC-users treated with neuraxial anaesthesia trended toward a longer LOS, yet the results were not significant (7.1 vs 6.1 days,  $p=0.1$ ).

## Discussion

In this single-centre retrospective descriptive study investigating hip fracture patients, the use of DOACs at the time of fracture was not found to influence surgical delay or length of stay compared to non-users. Furthermore, no differences in perioperative blood loss, transfusion rates or risk of bleeding complications between DOAC-users and non-users were disclosed. Hip fracture surgery was more frequently performed in general anaesthesia in DOAC-users, and the use of neuraxial anaesthesia for DOAC-users was associated with a longer surgical delay. This should be seen in relation to primary findings of no difference in surgical delay and length of stay between the compared groups. The high rate of cognitive impairment reported in this study was in line with a previous Norwegian study where 38% of home-dwelling hip fracture patients had cognitive impairment [17].

Studies investigating hip fracture treatment and the use of anticoagulants have so far reported conflicting results. While increased risk of complications was detected in one study [18], other studies discovered no such effect [19, 20]. These diverse findings could be explained by different perioperative administration of anticoagulant drugs. Due to a lack of international established guidelines, patients tend to be treated according to local routines in each hospital.

DOACs are approved for prevention of thromboembolism from non-valvular atrial fibrillation and to treat or prevent recurring deep vein thrombosis and pulmonary embolism [21–23]. These indications may explain why a higher burden of comorbidity was found among hip fracture patients using a DOAC compared to non-users in our study. Despite this increased comorbidity, we were not able to find increased risk of perioperative blood loss, transfusion rates, bleeding complications or mortality for the DOAC-users compared to the less comorbid non-users. Our findings are in contrast to another study reporting a higher one-year mortality among hip fracture patients using DOAC compared to non-users [24]. However, the excess mortality may be explained by higher age, more comorbidity and longer surgical delay than in our patients.

Earlier hip fracture surgery has been associated with reduced LOS and reduced frequency of immobilization-related complications [25–28], and large resources have been applied to promote earlier surgical interventions [29]. Several studies have found increased surgical delay for DOAC-users [16, 18, 24], and the authors question whether the use of DOAC before the hip fracture results in unnecessary long surgical delay [14, 24, 30–32]. In contrast, our DOAC-using patients did not wait significantly longer for surgery than the non-users. Another study investigated hip fracture patients using DOACs compared to matched controls with a median of only 19 h from admission to surgery [30]; no association between surgical delay and perioperative fall in haemoglobin, transfusion rate or reoperation for DOAC-users was found. As our study did not find increased bleeding—and transfusion—complications among patients using DOAC, early surgical interventions appear safe.

The prevalence and risk factors for surgical site infections is sparsely studied in the geriatric hip fracture population even though high age has been identified as a potential risk factor for such infections [33]. Our study revealed wound oozing five times more frequently among DOAC-users than patients without anticoagulation. Still, none of these patients underwent a reoperation due to wound ooze. We need to acknowledge that reoperation due to wound ooze is a late solution to persisting oozing. One earlier study has investigated DOAC-users' risk of reoperation due to wound ooze and found no relation to surgical delay [30]. On the other hand, when studying hip fracture patients not accounting for chronic anticoagulation, surgical delay has been found to be a risk factor for wound infections [28, 33]. The association between wound ooze and longer LOS found in our study might have implications for health costs and patient treatment following a hip fracture.

In Norway, 80–90% of hip fracture patients are given neuraxial anaesthesia [34], correlating well to the prevalence found in our hospital (90%). There is no international

consensus on neuraxial versus general anaesthesia for hip fracture patients [35]. General anaesthesia has earlier been associated with a longer LOS compared to neuraxial anaesthesia [36], yet a meta-study of 400,000 hip fracture patients revealed a clinically insignificant difference of only 0.3 days [37]. The increasing use of DOACs challenge current clinical practice because the potential ramifications of neuraxial anaesthesia in the anticoagulated patient [38]. European guidelines recommend that DOACs should be discontinued before surgery in line with their pharmacokinetic properties [39–42]. Potential neuraxial bleeding can be avoided by giving the hip fracture patients general anaesthesia, possibly explaining why general anaesthesia was used ten times more frequently in patients using DOAC at the time of fracture compared to non-users in our study. One explanation to this finding could be that some DOAC-users were scheduled for delayed surgery to be operated with neuraxial anaesthesia. Another likely explanation is that for these DOAC-users, the chosen modality ended up being neuraxial anaesthesia, because their surgery already had been delayed for other reasons, in example access to theatre and preoperative medical stabilization.

## Strengths and limitations

We studied patients treated at a large trauma hospital using patient records processed by one researcher, thereby increasing the quality and reproducibility of our work. We cannot generalize our findings to other hospitals or countries with other treatment algorithms. However, we believe that our university hospital is representable also for hip fracture treatment in other Norwegian hospitals. Similar surgical delay between DOAC-users and non-users further support comparable preoperative management of all the studied patients.

The sample size was calculated based on our main outcome surgical delay using data from the Norwegian Hip Fracture Register [13]. However, we assessed several other outcomes as well in our study, thereby potentially working with insufficient sample sizes and lack of power. Unfortunately, the size of our study prevented stratified analyses of the different types of DOAC. The retrospective study design allowed us to report associations between DOAC and perioperative outcomes, yet causality cannot be proven. For example, we cannot exclude the risk of confounding by comorbidity when it comes to the choice of anaesthesia and surgical delay. Due to the abovementioned weaknesses of our study, we request future prospective clinical trials targeting hip fracture patients exposed for DOACs and the consequences of fast track surgery versus surgery timed after drug excretion. Further, we acknowledge a need for further studies structurally targeting wound assessment and wound ooze for DOAC-users suffering a hip fracture.

## Conclusion

In our cohort of 314 hip fracture patients DOAC-users did not have increased surgical delay, LOS or risk of reported bleeding complications compared to patients without anti-coagulation prior to surgery. Our study does not support delayed surgery for DOAC-users. The increased surgical delay found for DOAC-users operated with neuraxial anaesthesia compared to general anaesthesia should be interpreted with caution.

**Acknowledgements** Open Access funding provided by University of Bergen.

**Author contributions** SLS conducted the study of patient records. All authors participated in the study protocol, the application for ethical assessment and the manuscript.

**Funding** No funding was received.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** The Regional Ethics Committee (REK) classified the study as quality assurance, thus we did not need ethical assessment (case number 1366/REK). The hospital data protection officer approved the study.

**Consent to participate** Our study involves hip fracture patients with a 1 year mortality of 25% and an even larger prevalence of cognitive impairment. We have performed a descriptive study using patient records without consent due to the patient demographics (age, mortality and cognitive impairment) by conducting a risk assessment taking into account the potential gain in quality of future patient treatment. The Regional Ethics Committee (REK) classified the study as quality assurance, thus we did not need ethical assessment (case number 1366/REK). The hospital data protection officer approved the study.

**Consent for publication** The hospital data protection officer approved the study. We refer to the classification from the Regional Ethics Committee.

**Availability of data and material** Our data have been deidentified and stored in a secure server area only available for Eva Dybvik and Sunniva Leer-Salvesen. The data will be deleted 5 years after the study.

**Code availability** IBM SPSS Statistics (version 24.0; IBM Corp. Armonk, New York) for Windows was used for the statistical analyses.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will

need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

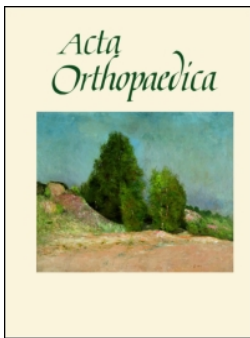
## References

1. No authors listed (2019) Norwegian Institute of Public Health, The prescription registry. Individual site for retrieving data accessed 05.12.19. <https://reseptregisteret.no/Prevalens.aspx>
2. de Jong LA, Knoop M, Gout-Zwart JJ, Beinema MJ, Hemels MEW, Postma MJ, Boruwers JRB (2018) Trends in direct oral anticoagulant (DOAC) use: health benefits and patient preference. *Neth J Med* 76(10):426–430
3. Solbakken SM, Meyer HE, Stigum H, Sjøgaard AJ, Holvik K, Magnus JH, Omsland TK (2017) Excess mortality following hip fracture: impact of self-perceived health, smoking, and body mass index. A NOREPOS study. *Osteoporos Int* 28(3):881–887
4. Verma A, Ha ACT, Rutka JT, Verma S (2018) What surgeons should know about non-vitamin K oral anticoagulants: a review. *JAMA Surg* 153(6):577–585
5. Vera-Llonch M, Hagivara M, Oster G (2006) Clinical and economic consequences of bleeding following major orthopedic surgery. *Thromb Res* 117(5):569–577
6. Dahl OE, Caprini JA, Colwell CW Jr et al (2005) Fatal vascular outcomes following major orthopedic surgery. *Thromb Haemost* 93(5):860–866
7. Fantini MP, Fabbri G, Laus M et al (2011) Determinants of surgical delay for hip fracture. *Surgeon* 9(3):130–134
8. Eardley WG, Macleod KE, Freeman H, Tate A (2014) “Tiers of delay”: warfarin, hip fractures, and target-driven care. *Geriatr Orthop Surg Rehabil* 5(3):103–108
9. Tran T, Delluc A, de Wit C, Petrich W, Le Gal G, Carrier M (2015) The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. *Thromb Res* 136(5):962–965
10. Ranhoff AH, Martinsen MI, Holvik K, Solheim LF (2011) Use of warfarin is associated with delay in surgery for hip fracture in older patients. *Hosp Pract* 39(1):37–40
11. No authors listed (2015) Norwegian Directorate of Health (Helsedirektoratet). Preoperative wait time for hip fracture patients, National Quality Indicator System: Quality indicator description. <https://www.helsedirektoratet.no/statistikk/statistikk/kvalitetsindikatorer/behandling-av-sykdom-og-overlevelse/hoftebrudd-operert->
12. Lindahl AK, Talsnes O, Figved W et al (2014) Measures for increased survival after hip fractures. Publication from The National Knowledge Center for the Health Service. <https://www.fhi.no/globalassets/dokumenterfiler/notater/2014/tiltak-for-okt-overlevelse-etter-hoftebrudd2> (date last accessed 16 July 2019)
13. Leer-Salvesen S, Engesaeter LB, Dybvik E, Furnes O, Kristensen TB, Gjertsen JE (2019) Does time from fracture to surgery affect mortality and intraoperative medical complications for hip fracture patients? An observational study of 73 557 patients reported to the Norwegian Hip Fracture Register. *Bone Jt J* 101-B(9):1129–1137
14. Hourston GJ, Barrett MP, Khan WS, Vindlacheruvu M, McDonnell SM (2019) New drug, new problem: do hip fracture patients taking NOACs experience delayed surgery, longer hospital stay, or poorer outcomes? *Hip Int.* <https://doi.org/10.1177/1120700019841351>
15. Linnerud I, Viktil K, Ranhoff A, Molden E (2016) Bruk av direktevirkende orale antikoagulantia og andre antitrombotika blant eldre hoftebruddspasienter; prevalens og kliniske aspekter. [The use of direct oral anticoagulants and other antithrombotic agents

- among elderly hip fracture patients; prevalence and clinical aspects] Master thesis in clinical pharmacology at the University of Oslo in 2016. <https://www.duo.uio.no/bitstream/handle/10852/51405/Ina-Linnerud-masteroppg-2016-DOAK-og-hoftebrudd.pdf?sequence=8>. Accessed 05 Dec 2019
16. Franklin NA, Ali AH, Hurlley RK, Mir HR, Beltran MJ (2018) Outcomes of early surgical intervention in geriatric proximal femur fractures among patients receiving direct oral anticoagulation. *J Orthop Trauma* 32(6):269–273
  17. Ranhoff AH, Holvik K, Martinsen MI, Domaas K, Solheim LF (2010) Older hip fracture patients: three groups with different needs. *BMC Geriatr* 10:65
  18. Frenkel Rutenberg T, Velkes S, Vitenberg M, Leader A, Halavy Y, Raanani P et al (2018) Morbidity and mortality after fragility hip fracture surgery in patients receiving vitamin K antagonists and direct oral anticoagulants. *Thromb Res* 166:106–112
  19. Gleason LJ, Mendelson DA, Kates SL, Friedman SM (2014) Anticoagulation management in individuals with hip fracture. *J Am Geriatr Soc* 62(1):159–164
  20. Cohn MR, Levack AE, Trivedi NN, Villa JC, Wellman DS, Lyden JP et al (2017) The hip fracture patient on warfarin: evaluating blood loss and time to surgery. *J Orthop Trauma* 31(8):407–413
  21. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361(12):1139–1151
  22. Flaker G, Lopes RD, Hylek E, Wojdyla DM, Thomas L, Al-Khatib SM, Sullivan RM, Hohnloser SH, Garcia D, Hanna M, Amerena J, Harjola VP, Dorian P, Avezum A, Keltai M, Wallentin L, Granger CB, ARISTOTLE Committees and Investigators (2014) Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. *J Am Coll Cardiol* 64(15):1541–1550. <https://doi.org/10.1016/j.jacc.2014.07.967>
  23. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365(10):883–891
  24. Schermann H, Gurel R, Gold A, Maman E, Dolkart O, Steinberg EL et al (2019) Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications. *Injury* 50(2):398–402
  25. Grimes JP, Gregory PM, Noveck H, Butler MS, Carson JL (2002) The effects of time-to-surgery on mortality and morbidity in patients following hip fracture. *Am J Med* 112(9):702–709
  26. Verbeek DO, Ponsen KJ, Goslings JC, Heetveld MJ (2008) Effect of surgical delay on outcome in hip fracture patients: a retrospective multivariate analysis of 192 patients. *Int Orthop* 32(1):13–18
  27. Haleem S, Heinert G, Parker MJ (2008) Pressure sores and hip fractures. *Injury* 39(2):219–223
  28. Cordero J, Maldonado A, Iborra S (2016) Surgical delay as a risk factor for wound infection after a hip fracture. *Injury* 47(Suppl 3):S56–S60
  29. Larsson G, Holgers KM (2011) Fast-track care for patients with suspected hip fracture. *Injury* 42(11):1257–1261
  30. Mullins B, Akehurst H, Slattery D, Chesser T (2018) Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre. *BMJ Open* 8(4):e020625
  31. Lott A, Haglin J, Belayneh R, Konda SR, Leucht P, Egol KA (2019) Surgical delay is not warranted for patients with hip fractures receiving non-warfarin anticoagulants. *Orthopedics* 42(3):e331–e335
  32. Hoerlyck C, Ong T, Gregersen M, Damsgaard EM, Borris L, Chia JK et al (2020) Do anticoagulants affect outcomes of hip fracture surgery? A cross-sectional analysis. *Arch Orthop Trauma Surg* 140(2):171–176
  33. Liu X, Dong Z, Li J, Feng Y, Cao G, Song X et al (2019) Factors affecting the incidence of surgical site infection after geriatric hip fracture surgery: a retrospective multicenter study. *J Orthop Surg Res* 14(1):382
  34. Furnes O, Engesaeter, LB, Gjertsen JE, Fenstad AM, Bartz-Johannessen C, Dybvik E, Fjeldsgaard K, Gundersen T, Hallan G (2019) Annual report, Norwegian Arthroplasty Register 2019. [https://nrlweb.ihelse.net/eng/Rapporter/Report2019\\_english.pdf](https://nrlweb.ihelse.net/eng/Rapporter/Report2019_english.pdf)
  35. Johansen A, Golding D, Brent L, Close J, Gjertsen JE, Holt G, Hommel A, Pedersen AB, Rock ND, Thorngren KG (2017) Using national hip fracture registries and audit databases to develop an international perspective. *Inj Int J Care Inj* 48(10):2174–2179
  36. Neuman MD, Rosenbaum PR, Ludwiq JM, Zubizarreta JR, Silber JH (2014) Anesthesia technique, mortality, and length of stay after hip fracture surgery. *JAMA* 311(25):2508–2517
  37. Van Waesberghe J, Stevanovic A, Rossaint R, Coburn M (2017) General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. *BMC Anesthesiol* 17:8
  38. Jinlei L, Halaszynski T (2015) Neuraxial and peripheral nerve blocks in patients taking anticoagulant or thromboprophylactic drugs: challenges and solutions. *Local Reg Anesth* 8:21–32
  39. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT et al (2010) Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (third edition). *Reg Anesth Pain Med* 35(1):64–101
  40. Gogarten W, Vandermuelen E, Van Aken H et al (2010) Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 27:999
  41. Wysokinski WE, McBane RD (2012) Periprocedural bridging management of anticoagulation. *Circulation* 126:486
  42. Narouze S, Benxon HT, Provenzano DA, Buvanendran A, De Andres J, Deer TR, Rauck R, Huntoon M (2015) Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med* 40(3):182–212

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.





## Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures

Sunniva Leer-Salvesen, Eva Dybvik, Ola E Dahl, Jan-Erik Gjertsen & Lars B EngesæTer

To cite this article: Sunniva Leer-Salvesen, Eva Dybvik, Ola E Dahl, Jan-Erik Gjertsen & Lars B EngesæTer (2016): Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures, *Acta Orthopaedica*, DOI: [10.1080/17453674.2016.1235427](https://doi.org/10.1080/17453674.2016.1235427)

To link to this article: <http://dx.doi.org/10.1080/17453674.2016.1235427>



© 2016 The Author(s). Published by Taylor & Francis on behalf of the Nordic Orthopedic Federation.



Published online: 23 Sep 2016.



Submit your article to this journal [↗](#)



View related articles [↗](#)



View Crossmark data [↗](#)

# Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures

## An observational study of 20,241 hemiprostheses reported to the Norwegian Hip Fracture Register

Sunniva LEER-SALVESEN<sup>2</sup>, Eva DYBVIK<sup>1</sup>, Ola E DAHL<sup>3,4</sup>, Jan-Erik GJERTSEN<sup>1,2</sup>, Lars B ENGESÆTER<sup>1,2</sup>

<sup>1</sup> The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen; <sup>2</sup> Department of Clinical Medicine, University of Bergen, Bergen; <sup>3</sup> Innlandet Hospital Trust, Elverum, Norway; <sup>4</sup> Thrombosis Research Institute, London, United Kingdom.  
Correspondence: lars.birger.engeseter@helse-bergen.no  
Submitted 2016-02-22. Accepted 2016-08-02.

**Background and purpose** — Controversies exist regarding thromboprophylaxis in orthopedic surgery. Using data in the nationwide Norwegian Hip Fracture Register (NHFR) with postoperative death and reoperation in the first 6 months after surgery as endpoints in the analyses, we determined whether the thromboprophylaxis in patients who undergo hemiarthroplasty for femoral neck fracture should start preoperatively or postoperatively.

**Patients and methods** — After each operation for hip fracture in Norway, the surgeon reports information on the patient, the fracture, and the operation to the NHFR. Cox regression analyses were performed with adjustments for age, ASA score, gender, type of implant, length of surgery, and year of surgery.

**Results** — During the period 2005–2014, 25,019 hemiarthroplasties as treatment for femoral neck fractures were reported to the registry. Antithrombotic medication was given to 99% of the patients. Low-molecular-weight heparin predominated with dalteparin in 57% of the operations and enoxaparin in 41%. Only operations with these 2 drugs and with known information on preoperative or postoperative start of the prophylaxis were included in the analyses (n = 20,241). Compared to preoperative start of thromboprophylaxis, postoperative start of thromboprophylaxis gave a higher risk of death (risk ratio (RR) = 1.13, 95% CI: 1.06–1.21; p < 0.001) and a higher risk of reoperation for any reason (RR = 1.19, 95% CI: 1.01–1.40; p = 0.04), whereas we found no effect on reported intraoperative bleeding complication or on the risk of postoperative reoperation due to hematoma. The results did not depend on whether the initial dose of prophylaxis was the full dosage or half of the standard dosage.

**Interpretation** — Postoperative start of thromboprophylaxis increased the mortality and risk of reoperation compared to pre-

operative start in femoral neck fracture patients operated with hemiprostheses. The risks of bleeding and of reoperation due to hematoma were similar in patients who received low-molecular-weight heparin preoperatively and in those who received it postoperatively. ■

Elderly patients with hip fractures are a frail group with a high risk of perioperative complications. Vascular events caused by thrombosis are common, and the use of chemical thromboprophylaxis is therefore a well-established routine in the treatment of these fractures. However, the risk of perioperative bleeding is also a major concern for the surgeon. Perioperative bleeding increases both the time of surgery and the postoperative risk of reoperation (Vera-Llonch et al. 2006). We must therefore balance the competing risks of thrombotic and hemorrhagic complications to avoid unwanted outcomes.

Whether the prophylaxis should start preoperatively or postoperatively is still controversial (Borgen et al. 2013). In Europe, the use of low-molecular-weight heparin (LMWH) in orthopedics has traditionally started before surgery (Ettema et al. 2009), while in North America a higher dose initiated several hours after surgery has been common (Gomez-Outes et al. 2012, Lassen et al. 2012). A possible way to answer this central issue is by using data from an established registry. By using data in the nationwide Norwegian Hip Fracture Register (NHFR) (Gjertsen et al. 2008), we compared the relative effects of preoperative start and postoperative start of thromboprophylaxis, concentrating on mortality and risk of reoperation.

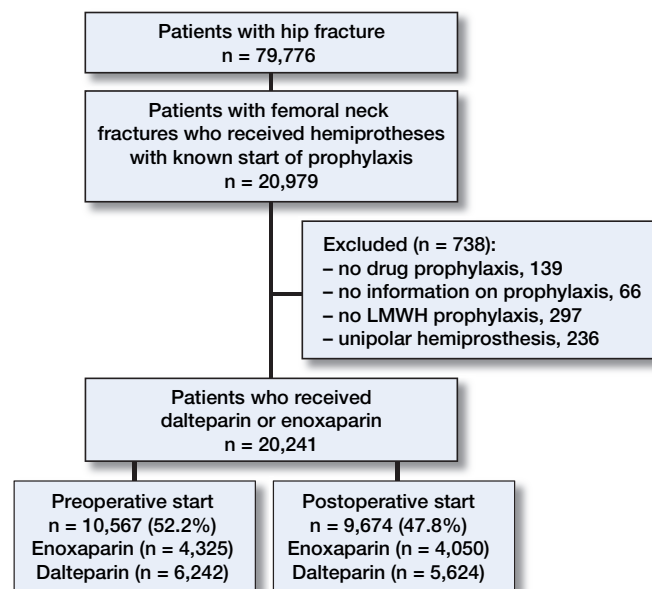


Figure 1. Flow chart for patients included in the study.

## Patients and methods

The NHFR started registration of primary operations and reoperations for all hip fractures in Norway in 2005. Immediately after each operation, the surgeon fills in a 1-page paper form. The form includes information on age, sex, cognitive function, type of fracture (with femoral neck fractures being classified as Garden 1–2 or 3–4), and ASA class (Garden 1961). The form also provides information on the chemical thromboprophylaxis given during treatment (whether or not it was used, which drug, dosage, and whether the first dose was given preoperatively or postoperatively). The choice of implants and the surgical technique were left to the discretion of the surgeons at the reporting orthopedic units. Information regarding deceased patients was obtained from Statistics Norway. Compared to the Norwegian Patient Registry, the completeness of primary operations in the NHFR has been found to be 94% for hemiarthroplasties (Havelin et al. 2014).

The inclusion and exclusion of patients are summarized in Figure 1. In the period 2005–2014, 79,776 primary operations for hip fractures were reported to the registry. Femoral neck fractures treated with hemiprosthesis with known start of thromboprophylaxis constituted 20,979 (26.3%) of these operations. In 139 of the operations (0.5%) no thromboprophylaxis was used, and in 66 operations (0.3%) no information on prophylaxis was reported. 12 different types of drugs for prophylaxis were given. Low-molecular-weight heparin (LMWH) predominated entirely, with dalteparin (Fragmin; Pfizer) being used in 57% (14,538 operations) and enoxaparin (Klexane; Sanofi-Aventis) being used in 41% (10,498 operations). In order to obtain an adequately homogenous material

for further analysis, only operations with these 2 drugs were included. Furthermore, operations with no information on whether the first dose of the prophylaxis was given preoperatively or postoperatively were excluded ( $n = 4,284$ ).

Bipolar hemiprotheses constituted 98.8% of the hemiarthroplasties. Operations with unipolar hemiprotheses (236 operations, 1.2%) were therefore excluded to generate a study material that was a fair representation of the modern treatment of hip fractures in Norwegian orthopedic departments.

As a result, 20,241 operations remained for further analysis, with dalteparin being used in 59% (11,866 operations) and enoxaparin in 41% (8,375 operations). Prophylaxis was given preoperatively in 52% (10,567 operations) and postoperatively in 48% (9,674 operations) (Figure 1).

A reoperation was defined as any secondary surgery following the primary hemiarthroplasty, including closed reduction of a dislocated prosthesis and soft tissue debridement without exchange or removal of prosthesis components.

Standard doses of LMWH, as recommended by the British National Formulary, were defined as 5,000 IU dalteparin or 40 mg enoxaparin. Consequently, half-standard doses were defined as 2,500 IU dalteparin and 20 mg enoxaparin (Heidari et al. 2012). To compare the influence of the amount of LMWH given as the initial dose, stratified analyses were performed to compare full dosage and half of standard dosage at preoperative start of the prophylaxis.

As a preoperative start of the thromboprophylaxis could be considered to be more important for those with a rather long preoperative waiting time, separate stratified analyses were performed regarding preoperative waiting time, either with the preoperative waiting time dichotomized ( $< 24$  hours and  $\geq 24$  hours) or divided into 5 intervals ( $\leq 6$  hours,  $> 6$  and  $\leq 12$  hours,  $> 12$  and  $\leq 24$  hours,  $> 24$  and  $\leq 48$  hours, and  $> 48$  hours).

## Statistics

Survival analyses were performed using the Kaplan-Meier and Cox regression methods. Patients who died or emigrated during follow-up were identified from files provided by Statistics Norway, and the follow-up time for prostheses in these patients was censored at the date of death or emigration. Only the first 6 postoperative months were included in the analyses, as this period was considered most relevant in the present investigation.

The Cox multiple regression model was used to compare the relative risk of postoperative death and revision (failure-rate ratios) in patients where the thromboprophylaxis started preoperatively compared to postoperatively, with adjustments for possible influences of sex, age of the patient at surgery, ASA classification, type of fixation (uncemented, cemented with antibiotic-loaded cement, or cemented without antibiotic-loaded cement), and year of surgery. We did not adjust for patients who were operated on both sides, since it has previously been shown that this will not alter the

Table 1. Baseline characteristics of the patients/operations

	Preoperative start of prophylaxis	Postoperative start of prophylaxis
Hemiarthroplasties, n (%)	10,567 (52)	9,674 (48)
Mean age at fracture (SD)	82.3 (7.9)	82.6 (8.1)
Women, n (%)	7,648 (72)	6,941 (72)
ASA-groups, n (%)		
ASA 1	311 (2.9)	249 (2.6)
ASA 2	3,490 (33)	3,238 (33)
ASA 3	5,862 (55)	5,550 (57)
ASA 4	748 (7.1)	531 (5.5)
ASA 5	9 (0.1)	4 (0.0)
Missing	147 (1.4)	102 (1.1)
Type of surgery, n (%)		
Cemented with AB	8,513 (81)	5,959 (62)
Uncemented	1,787 (17)	3,439 (36)
Cemented without AB	51 (0.5)	36 (0.4)
Missing	216 (2.0)	240 (2.3)

conclusion for the covariates entered (Lie et al. 2004). We performed stratified analyses for ASA classes (1–2 or 3–5), type of femoral stem fixation (cemented or uncemented), and preoperative dosage of LMWH (full dosage or half-standard dosage).

Assessments of proportionality in the Cox models were performed using log-minus-log plots of the adjusted survival curves, and the proportionality assumptions were fulfilled. For the statistical analyses, we used IBM SPSS Statistics version 22.0 and the statistical package R version 3.0.2 (<http://www.R-project.org>). Any p-values less than 0.05 were considered statistically significant.

## Results

Baseline information regarding the patients is given in Table 1. During the study period (2005–2014), postoperative start of thromboprophylaxis became more common (Figure 2).

### Risk of death and reoperation (Figure 3)

Patients with femoral neck fractures treated with bipolar hemiprostheses (n = 20,241) had a higher risk of death (RR = 1.13, 95% CI: 1.06–1.21; p < 0.001) with a postoperative start of prophylaxis than with a preoperative start. A postoperative start also resulted in an increased risk of reoperation for any reason (RR = 1.19, 95% CI: 1.01–1.40; p = 0.04) compared to a preoperative start (Table 2).

When we analyzed the risk of reoperation due to infection, no statistically significant effect of the timing of the start of prophylaxis could be detected (RR = 1.25, 95% CI: 0.99–1.57; p = 0.06).

Similar analyses on mortality and risk of reoperation within 7 days postoperatively, within 30 days postoperatively, and within 180 days (6 months) postoperatively were performed (Table 2). The increased risk of death proved to be consistent for all 3 intervals in the postoperative period.

Separate analyses on the risk of reoperation due to hematoma did not reveal any statistically significant effect of the timing of the start of prophylaxis (RR = 0.7, 95% CI: 0.4–1.2; p = 0.2) (Table 2).

Furthermore, intraoperative complications were reported to the registry. 42 of the complications reported were intraoperative bleeding (4.7% of all reported complications). However,

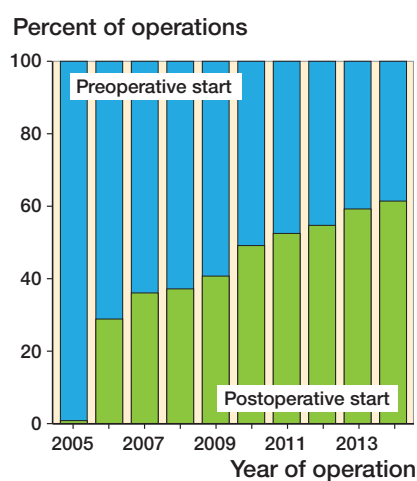


Figure 2. The timeline demonstrates the development in start of thromboprophylaxis from 2005–2014 for the patients observed in the study. Femoral neck fractures treated with bipolar hemiarthroplasty with known start of thromboprophylaxis (dalteparin or enoxaparin).

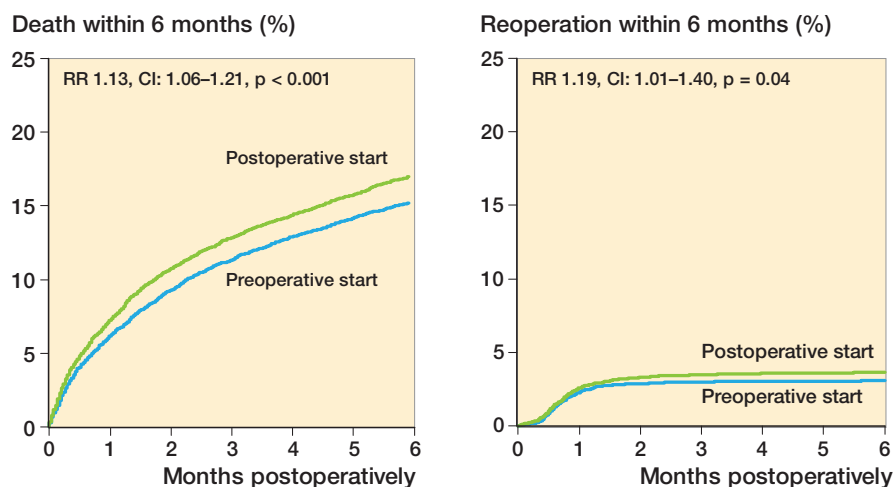


Figure 3. Postoperative mortality and risk of reoperation for patients with femoral neck fractures treated with hemiprostheses.

Table 2. Mortality and risk of reoperation 7 days, 30 days and 180 days postoperatively after bipolar hemiarthroplasty due to femoral neck fractures. Cox relative risk ratio (RR) (with preoperative start of prophylaxis as reference) is given with adjustments for possible influences of sex, ASA-class, age of the patient at surgery, type of surgery, duration of surgery and year of surgery

	Total n (%)	Preoperative start n (%)	Postoperative start n (%)	RR (95% CI)	p-value
7 days postoperative					
Mortality	610 (3.0%)	290 (2.8%)	320 (3.4%)	1.36 (1.15–1.61)	< 0.001
Reoperations	39 (0.2%)	15 (0.1%)	24 (0.3%)	1.50 (0.75–2.99)	0.3
Reoperation due to infection	5 (0.0%)	2 (0.0%)	3 (0.0%)		
Reoperation due to hematoma	5 (0.0%)	4 (0.0%)	1 (0.0%)		
30 days postoperative					
Mortality	1,580 (7.8%)	780 (7.7%)	800 (8.5%)	1.20 (1.08–1.33)	0.001
Reoperations	457 (2.3%)	215 (2.1%)	242 (2.6%)	1.07 (0.88–1.30)	0.5
Reoperation due to infection	261 (1.3%)	124 (1.2%)	137 (1.4%)	1.10 (0.85–1.42)	0.5
Reoperation due to hematoma	49 (0.2%)	31 (0.3%)	18 (0.2%)	0.55 (0.30–1.01)	0.05
180 days postoperative					
Mortality	3,661 (18%)	1,869 (18%)	1,792 (19%)	1.13 (1.06–1.21)	< 0.001
Reoperations	642 (3.2%)	292 (2.9%)	350 (3.7%)	1.19 (1.01–1.40)	0.04
Reoperation due to infection	331 (1.6%)	151 (1.5%)	180 (1.9%)	1.25 (0.99–1.57)	0.06
Reoperation due to hematoma	52 (0.3%)	31 (0.3%)	21 (0.2%)	0.65 (0.36–1.18)	0.2

Table 3. Mortality and risk of reoperation 180 days postoperatively in patients receiving an uncemented and cemented hemiarthroplasty (HA). Cox relative risk ratio (RR) (with preoperative start of prophylaxis as reference) is given with adjustments for possible influences of sex, ASA-class, age of the patient at surgery, duration of surgery and year of surgery

	Total n (%)	Preoperative start n (%)	Postoperative start n (%)	RR (95% CI)	p-value
Uncemented HA					
Mortality	5,226				
Mortality	907 (17%)	294 (17%)	613 (18%)	1.22 (1.05–1.42)	0.008
Reoperations	240 (4.6%)	72 (4.0%)	168 (4.9%)	1.21 (0.91–1.61)	0.2
Reoperation due to infection	104 (2.2%)	28 (1.6%)	76 (2.2%)	1.36 (0.87–2.14)	0.2
Reoperation due to hematoma	21 (0.4%)	12 (0.7%)	9 (0.3%)	0.50 (0.20–1.25)	0.1
Cemented HA					
Mortality	14,472				
Mortality	2,674 (18%)	1,540 (19%)	1,134 (20%)	1.11 (1.03–1.20)	0.01
Reoperations	381 (2.6%)	211 (2.6%)	170 (2.9%)	1.16 (0.94–1.43)	0.2
Reoperation due to infection	215 (2.0%)	118 (1.4%)	97 (1.6%)	1.19 (0.91–1.57)	0.2
Reoperation due to hematoma	31 (0.2%)	19 (0.2%)	12 (0.2%)	0.84 (0.40–1.76)	0.6

there was no difference in the risk of bleeding complications between the patients who had a preoperative start of LMWH (22 bleeding complications) and those who had a postoperative start of LMWH (19 bleeding complications) (RR = 0.9, 95% CI: 0.5–1.7; p = 0.7).

### Cemented and uncemented hemiarthroplasties

In order to investigate the risk of death and reoperation further, we stratified for the type of femoral stem fixation. Hemiprostheses with antibiotic-loaded cement (n = 14,472) and uncemented hemiprostheses (n = 5,226) gave a higher risk of death with a postoperative start of prophylaxis (Table 3). The increased risk of death proved to be consistent at all 3 intervals in the postoperative period (7 days, 30 days, and 180 days).

### ASA classification

When we assessed the healthiest patient group operated for femoral neck fracture with hemiarthroplasty (ASA 1–2), the benefit of a preoperative start of the prophylaxis was less evident (Table 4). For these patients, a postoperative start of LMWH had no effect on the risk of death, reoperation for any reason, or reoperation due to infection or hematoma.

For the most morbid patients (ASA 3–5), increased mortality with a postoperative start of thromboprophylaxis was found (Table 4). Again, the increased risk of death proved to be consistent for all 3 intervals of the postoperative period. The timing of the start of LMWH did not have a statistically significant effect on the risk of reoperation for any reason or of reoperation due to infection or hematoma.

### Dosage of low-molecular-weight heparin

For patients with a preoperative start of thromboprophylaxis, the standard dosage (5,000 IU dalteparin or 40 mg enoxaparin)

**Table 4.** Effect of postoperative start of thromboprophylaxis versus preoperative start 180 days postoperatively in healthy patients (ASA 1-2) and in morbid patients (ASA 3-5) with femoral neck fracture operated with bipolar hemiprosthesis. Cox relative risk ratio (RR) (with preoperative start of prophylaxis as reference) is given with adjustments for possible influences of sex, age of the patient at surgery, type of surgery, duration of surgery and year of surgery

	Total n (%)	Preoperative start n (%)	Postoperative start n (%)	RR (95% CI)	p-value
ASA 1-2	7,288				
Mortality	636 (8.7%)	329 (8.9%)	307 (9.1%)	1.12 (0.95-1.31)	0.1
Reoperations	217 (3.0%)	98 (2.7%)	119 (3.5%)	1.20 (0.91-1.60)	0.2
Reoperation due to infection	109 (1.5%)	54 (1.5%)	55 (1.6%)	1.16 (0.78-1.72)	0.5
Reoperation due to hematoma	18 (0.2%)	10 (0.3%)	8 (0.2%)	0.70 (0.26-1.90)	0.5
ASA 3-5	12,704				
Mortality	2,990 (24%)	1,520 (24%)	1,470 (25%)	1.13 (1.05-1.22)	0.002
Reoperations	420 (3.3%)	190 (3.0%)	230 (3.9%)	1.18 (0.96-1.45)	0.1
Reoperation due to infection	219 (1.7%)	95 (1.5%)	124 (2.1%)	1.29 (0.97-1.71)	0.07
Reoperation due to hematoma	33 (0.3%)	20 (0.3%)	13 (0.2%)	0.65 (0.31-1.36)	0.3

**Table 5.** Mortality and risk of reoperation 180 days postoperatively in patients operated with hemiprosthesis with a preoperative start of thromboprophylaxis (n= 9,370) where the primary dose was of full standard (5 000 IU dalteparin or 40 mg enoxaparin) or half standard (2 500 IU dalteparin or 20 mg enoxaparin) dosage. Cox relative risk ratio (RR) (with full dose at start of prophylaxis as reference) is given with adjustments for possible influences of sex, ASA-class, age of the patient at surgery, type of surgery, duration of surgery and year of surgery

Preoperative start dose	Total n	Events	RR (95% CI)	p-value
Mortality	9,370	1,653 (18%)		
Full	5,253	738 (14%)	1	
Half	4,117	915 (22%)	0.98 (0.88-1.08)	0.6
Reoperations	9,370	264 (2.8%)		
Full	5,253	108 (2.6%)	1	
Half	4,117	156 (3.0%)	1.02 (0.79-1.32)	0.8
Reoperation due to infection	9,370	139 (1.5%)		
Full	5,253	62 (1.5%)	1	
Half	4,117	77 (1.5%)	1.10 (0.75-1.56)	0.6
Reoperation due to hematoma	9,370	27 (0.3%)		
Full	5,253	18 (0.3%)	1	
Half	4,117	9 (0.2%)	0.83 (0.36-1.92)	0.7

was given in 51% and half of the standard dosage (2 500 IU dalteparin or 20 mg enoxaparin) was given in 49%. We found no differences in mortality, in the risk of reoperation for any reason, or in the risk of reoperation due to infection or hematoma when the analyses were performed on half-standard dosage and full standard dosage (Table 5). All the patients who had a postoperative start of thromboprophylaxis received a full standard dosage.

#### Time interval between fracture and operation

The median amount of time elapsed between fracture and start of surgery for hip fracture patients was 21 hours. No

independent effect of the preoperative waiting time on the risk of death or reoperation could be detected. Accordingly, the length of time between fracture and operation had no influence on the advantageous effect of a preoperative start of the prophylaxis.

## Discussion

The data in our nationwide hip fracture registry showed that a postoperative start of thromboprophylaxis with low-molecular-weight heparin in patients operated with hemiprostheses for femoral neck fracture resulted in higher mortality and higher overall risk of reoperation than with a preoperative start.

In Norway, 99% of the antithrombotic drugs used as prophylaxis for hip fracture patients are low-molecular-weight heparin (LMWH): 56% are dalteparin and 43% are enoxaparin. A similar predominance of LMWH has also been reported from the Netherlands (79%) and Denmark (97%) for patients who undergo total hip replacement (Ettema et al. 2009, Pedersen et al. 2012). Our results are only valid for dalteparin and enoxaparin. However, the benefit of a preoperative start may also be valid for other parenteral and oral antithrombotic compounds that are available.

The trauma of hip fracture activates the coagulation system. The subsequent operation constitutes a second trauma. The process of implanting a hemiprosthesis appears to give more severe trauma than osteosynthesis. Animal studies showed that deaths due to respiratory distress were eliminated when a thrombin inhibitor was administered before induction of the same standard trauma that triggered blood cell aggregation in the lung vessels (Giercksky et al. 1976). When the femoral stem is inserted in the femoral canal during hemiarthroplasty, high pressure seems to squeeze procoagulant cell fragments, microparticles, and small molecules such as RNA and histones into the venous system (Dahl et al. 2015). The subse-

quent activation of the coagulation system could be fatal (Pitto et al. 1999, Dahl et al. 2005, Ettema et al. 2008, Talsnes et al. 2013). A pressure release hole (diameter 4.5 mm) drilled into the medullary canal at the distal end of the femur appears to reduce the release of tissue factor into the venous system (Engesæter et al. 1984). For patients with fracture of the hip and also patients undergoing total hip replacement, chemical thromboprophylaxis has been found to reduce postoperative mortality (Lie et al. 2010, Heidari et al. 2012, Hunt et al. 2013).

Our registry-based cohort was stratified in 2 roughly equal arms of preoperative and postoperative administration of standard doses of LMWH in hip fracture patients. The results showed that a preoperative start reduced fatalities within 6 months of surgery. This favorable effect of preoperative LMWH administration was most pronounced in close relation to surgery. Nevertheless, the preoperative effect was also robust over time and no catch-up effect was noticed during 6 months of observation. Furthermore, a preoperative start of thromboprophylaxis provided a lower risk of reoperation compared to postoperative start. In previous discussions, the risk of reoperation in particular has been brought forward as an argument for starting thromboprophylaxis postoperatively (Lassen et al. 2012). This argument was partly based on the fear of perioperative bleeding complicating the surgical intervention. This might also be the explanation for the gradual shift from preoperative to postoperative initiation of LMWH that has been observed during the last decade (Figure 2). In the present study, no higher risk of intraoperative bleeding nor increased risk of reoperation due to postoperative hematoma could be detected when the prophylaxis was initiated preoperatively.

Patients with symptomatic comorbidity (ASA  $\geq$  3) had a higher risk of fatal outcome following a femoral neck fracture than healthier patients (ASA 1 or 2). This result is in accordance with other studies on hip fracture patients, with increased mortality from 1 in 120 to 1 in 30 when the ASA score was 4 rather than 1 (Talsnes et al. 2011, Kan et al. 2013, Pripp et al. 2014). Accordingly, patients with comorbidities appear to benefit more from preoperative LMWH protection than those who are healthy.

The median length of time between fracture and the start of surgery in the present study was only 21 hours. In comparison, 40% of hip fractures in England were operated more than one day after the admission (Bottle et al. 2006). Our rather short preoperative interval (from fracture to operation) could be a possible explanation for why we were not able to reveal any independent effect of preoperative delay on the risk of postoperative death or reoperation. Furthermore, the positive effect of a preoperative start shown here, irrespective of the time elapsed between fracture and operation, indicates that preoperative inhibition of the coagulation system is fundamental.

Bone cement to anchor prostheses has been shown to increase mortality close to surgery (Talsnes et al. 2013, Pripp et al. 2014, Yli-Kyyny et al. 2014). In the present study, patients

operated with uncemented hemiprostheses also had a higher mortality when the thromboprophylaxis was initiated postoperatively rather than preoperatively. This indicates that insertion of the femoral stem, irrespective of whether cemented or uncemented fixation is used, appears to produce a potent cardiovascular trauma intraoperatively. This would explain why patients operated with either uncemented or cemented hemiprostheses appeared to profit from a preoperative start of the prophylaxis.

A recent paper from England concerning hip fracture patients advocated administration of LMWH in half the dose recommended by the British National Formulary (Heidari et al. 2012). This is in keeping with our findings showing no differences in mortality or risk of reoperation whether the initial LMWH dose given preoperatively was half of the standard dose (i.e. 2,500 IU dalteparin or 20 mg enoxaparin) or the full standard dose (i.e. 5,000 IU dalteparin or 40 mg enoxaparin). To conclude, a half-standard dose of LMWH appeared to be a sufficient amount to initiate prophylaxis.

The present study was not a randomized, controlled trial and it may therefore be described as being a hypothesis-generating study. The data in the study were observational, so causality cannot be proven. Nevertheless, to our knowledge this is the first study of its kind to be conducted in this area. Previously published trials have used 2 compounds, mainly the exploratory compound in the postoperative arm and the reference drug (mostly enoxaparin) in the preoperative arm. No trials have compared preoperative and postoperative benefit of the same compound. All the trials reported have been designed to show potentially favorable effects of new regimens compared to well-established regimens. The strength of our study was the inclusion of data from all the surgical units that treat hip fractures in an entire country. Accordingly, the external validity of the results is high. The data regarding the start of LMWH were filled in by the responsible surgeon immediately after surgery. Even though the study had some weaknesses, the results are based on a large number of patients and also consistent reporting of timing of LMWH treatment to the register. Thus, our data strongly indicate that preoperative administration of LMWH to elderly patients undergoing hip fracture surgery with hemiarthroplasty gives fewer fatalities than postoperative administration.

In summary, this study has shown that a postoperative start of LMWH prophylaxis in patients with femoral neck fractures operated with hemiprostheses leads to a higher risk of postoperative death and reoperation than a preoperative start of prophylaxis. There was no significant difference in the risk of bleeding complications or in the risk of reoperation due to hematoma between the patients who had a preoperative start of treatment with LMWH and those who had a postoperative start.

SLS, LBE, and ED performed the statistical analyses. SLS and LBE were mainly responsible for writing the manuscript. All the authors participated in

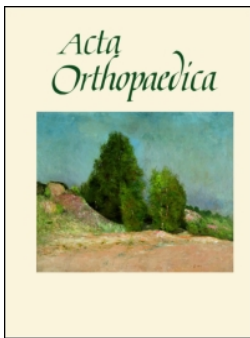
the design of the study, in interpretation of the results, and in development of the manuscript.

No competing interests declared.

We thank all the Norwegian orthopedic surgeons who have loyally reported to the Norwegian Hip Fracture Register.

- Bottle A, Aylin P. Mortality associated with delay in operation after hip fracture: observational study. *BMJ* 2006; 332 (7547): 947-51.
- Dahl O E, Caprini J A, Colwell C W Jr, et al. Fatal vascular outcomes following major orthopedic surgery. *Thrombosis and haemostasis* 2005; 93(5): 860-6.
- Dahl O E, Harenberg J, Wexels F, Preissner K T. Arterial and venous thrombosis following trauma and major orthopedic surgery: Molecular mechanisms and strategies for intervention. *Semin Thromb Hemost* 2015; 41: 141-5.
- Engesaeter L B, Strand T, Raugstad T S, Husebo S, Langeland N. Effects of a distal venting hole in the femur during total hip replacement. *Arch Orthop Trauma Surg* 1984; 103(5): 328-31.
- Ettema H B, Kollen B J, Verheyen C C, Buller H R. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *J Thromb Haemost* 2008; 6(7): 1093-8.
- Ettema H B, Mulder M C, Nurmohamed M T, Buller H R, Verheyen C C. Dutch orthopedic thromboprophylaxis: a 5-year follow-up survey. *Acta Orthop* 2009; 80(1): 109-12.
- Giercksky KE, Bjorklid E, Prydz H. The effect of intravenous injection of purified human tissue thromboplastin in rats. *Scand J Haematol* 1976; 16(4): 300-10.
- Gjertsen J E, Engesaeter LB, Furnes O, et al. The Norwegian Hip Fracture Register: experiences after the first 2 years and 15,576 reported operations. *Acta Orthop* 2008; 79(5): 583-93.
- Gomez-Outes A, Terleira-Fernandez A I, Suarez-Gea M L, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 2012; 344: e3675.
- Havelin L, Furnes O, Engesaeter, LB, Fenstad AM, Dybvik E. Annual report. Norwegian Arthroplasty Register 2014 [www.http://nrlweb.ihelse.net/Rapporter/Rapport2014.pdf](http://nrlweb.ihelse.net/Rapporter/Rapport2014.pdf)
- Heidari N, Jehan S, Alazzawi S, Bynoth S, Bottle A, Loeffler M. Mortality and morbidity following hip fractures related to hospital thromboprophylaxis policy. *Hip Int* 2012; 22(1): 13-21.
- Hunt L P, Ben-Shlomo Y, Clark E M, et al. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *Lancet* 2013; 382(9898): 1097-104.
- Kan J W, Kim K J, Lee S K, Kim J, Jeug S W, Choi H G. Predictors of mortality in patients with hip fractures for persons aging more than 65 years old. *International Journal of Bio-science and Bio-technology* 2013; 5(2): 27-33.
- Lassen M R, Gent M, Kakkar A K, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. *J Bone Joint Surg Br* 2012; 94(11): 1573-8.
- Lie S A, Engesaeter LB, Havelin L I, Gjessing H K, Vollset S E. Dependency issues in survival analyses of 55,782 primary hip replacements from 47,355 patients. *Stat Med* 2004; 23(20): 3227-40.
- Lie S A, Pratt N, Ryan P, et al. Duration of the increase in early postoperative mortality after elective hip and knee replacement. *J Bone Joint Surg Am* 2010; 92(1): 58-63.
- Pedersen A B, Johnsen S P, Sorensen H T. Increased one-year risk of symptomatic venous thromboembolism following total hip replacement: a nationwide cohort study. *J Bone Joint Surg Br* 2012; 94(12): 1598-603.
- Pitto RP, Koessler M, Kuehle J W. Comparison of fixation of the femoral component without cement and fixation with use of a bone-vacuum cementing technique for the prevention of fat embolism during total hip arthroplasty. A prospective, randomized clinical trial. *J Bone Joint Surg Am* 1999; 81(6): 831-43.
- Pripp A H, Talsnes O, Reikeras O, Engesaeter L B, Dahl O E. The proportion of perioperative mortalities attributed to cemented implantation in hip fracture patients treated by hemiarthroplasty. *Hip Int* 2014; 24(4): 363-8.
- Talsnes O, Hjelmstedt F, Dahl OE, Pripp AH, Reikeras O. Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly. *Int Orthop* 2011; 35(6): 903-7.
- Talsnes O, Vinje T, Gjertsen J E, et al. Perioperative mortality in hip fracture patients treated with cemented and uncemented hemiprostheses: a register study of 11,210 patients. *Int Orthop* 2013; 37(6): 1135-40.
- Vera-Llonch M, Hagivara M, Oster G. Clinical and economic consequences of bleeding following major orthopedic surgery. *Thromb Res* 2006; 117(5): 569-77
- Yli-Kyyny T, Sund R, Heinanen M, Venesmaa P, Kroger H. Cemented or uncemented hemiarthroplasty for the treatment of femoral neck fractures? *Acta Orthop* 2014; 85(1): 49-53.
- Garden R S. Low-angle fixation in fractures of the femoral neck. *J Bone Joint Surg Br* 1961; 43-B: 647-63.





# Low-molecular-weight heparin for hip fracture patients treated with osteosynthesis: should thromboprophylaxis start before or after surgery? An observational study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register

Sunniva Leer-Salvesen, Eva Dybvik, Lars B Engesaeter, Ola E Dahl & Jan-Erik Gjertsen

To cite this article: Sunniva Leer-Salvesen, Eva Dybvik, Lars B Engesaeter, Ola E Dahl & Jan-Erik Gjertsen (2018): Low-molecular-weight heparin for hip fracture patients treated with osteosynthesis: should thromboprophylaxis start before or after surgery? An observational study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register, Acta Orthopaedica, DOI: [10.1080/17453674.2018.1519101](https://doi.org/10.1080/17453674.2018.1519101)

To link to this article: <https://doi.org/10.1080/17453674.2018.1519101>



© 2018 The Author(s). Published by Taylor & Francis on behalf of the Nordic Orthopedic Federation.



Published online: 17 Oct 2018.



Submit your article to this journal [↗](#)



View Crossmark data [↗](#)

# Low-molecular-weight heparin for hip fracture patients treated with osteosynthesis: should thromboprophylaxis start before or after surgery? An observational study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register

Sunniva LEER-SALVESEN<sup>1</sup>, Eva DYBVIK<sup>2</sup>, Lars B ENGESÆTER<sup>1,2</sup>, Ola E DAHL<sup>3,4</sup>, and Jan-Erik GJERTSEN<sup>1,2</sup>

<sup>1</sup> Department of Clinical Medicine, University of Bergen, Bergen, Norway; <sup>2</sup> Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway; <sup>3</sup> Innlandet Hospital Trust, Elverum, Norway; <sup>4</sup> Thrombosis Research Institute, London, UK  
Correspondence: sunniva.leer-salvesen@helse-bergen.no  
Submitted 2018-04-09. Accepted 2018-07-12.

**Background and purpose** — Controversies exist regarding thromboprophylaxis in orthopedic surgery. We studied whether the thromboprophylaxis in hip fracture patients treated with osteosynthesis should start preoperatively or postoperatively. Data were extracted from the nationwide Norwegian Hip Fracture Register (NHFR). The risks of postoperative deaths, reoperations, and intraoperative bleeding were studied within 6 months after surgery.

**Patients and methods** — After each operation for hip fracture in Norway the surgeon reports information on the patient, the fracture, and the operation to the NHFR. Cox regression analyses were performed with adjustments for age group, ASA score, sex, duration of surgery, and year of surgery. During the period 2005–2016, 96,599 hip fractures were reported to the register. Only osteosyntheses where low-molecular-weight heparin (LMWH) were given and with known information on preoperative start of the prophylaxis were included in the analyses. Dalteparin and enoxaparin were used in 58% and 42% of the operations respectively (n = 45,913).

**Results** — Mortality (RR = 1.01, 95% CI 0.97–1.06) and risk of reoperation (RR = 0.99, CI 0.90–1.08) were similar comparing preoperative and postoperative start of LMWH. Postoperative start reduced the risk of intraoperative bleeding complications compared with preoperative start (RR = 0.67, CI 0.51–0.90).

**Interpretation** — The initiation of LMWH did not influence the mortality or the risk of reoperation in hip fracture patients treated with osteosynthesis. Postoperative start of LMWH could possibly decrease the risk of intraoperative bleeding.

Among elderly hip fracture patients, vascular events caused by thrombosis are common and the use of chemical thromboprophylaxis is a well-established routine in the management of these patients. On the other hand, the risk of intraoperative bleeding also represents a major concern that may increase both the duration of surgery and risk of reoperation, anemia and transfusions (Vera-Llonch et al. 2006). The potential complications following both bleeding and thromboembolic events can in turn prolong the need for hospitalization and rehabilitation.

The Norwegian Hip Fracture Register (NHFR) has collected nationwide information on hip fractures since 2005 (Gjertsen et al. 2008). In a previous article based on data from the NHFR we found that postoperative start of LMWH increased both mortality and risk of reoperation compared with preoperative start after femoral neck fractures treated with hemiarthroplasty (Leer-Salvesen et al. 2017). On the other hand, preoperative start of the thromboprophylaxis did not increase the risk of intraoperative bleeding complications or reoperation due to hematoma.

Knowledge concerning the administration of thromboprophylaxis in hip fracture patients treated with osteosynthesis is, on the contrary, still sparse. By using data in the nationwide NHFR we wanted to compare the effect of preoperative start versus postoperative start of thromboprophylaxis in hip fracture patients treated with osteosynthesis. Primary endpoints were mortality and reoperations in the first 6 months after surgery and intraoperative bleeding complications. Secondary endpoints were reoperations due to infection or hematoma.

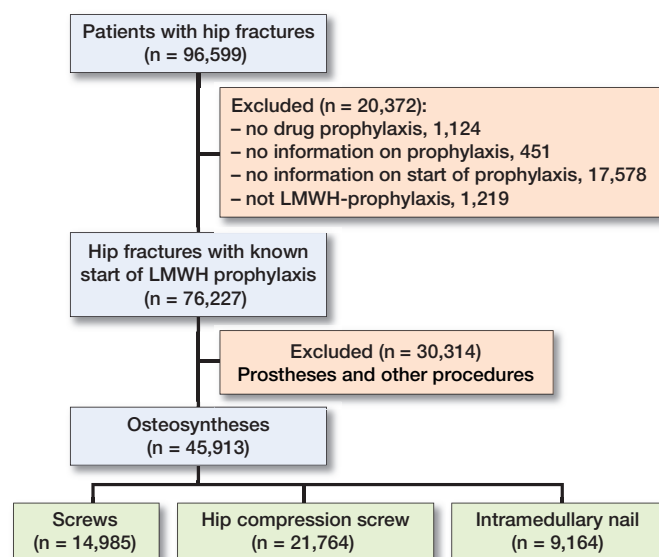


Figure 1. Flow chart for patients included in the study.

## Patients and methods

The NHFR started registration of primary operations and reoperations for all hip fractures in Norway in 2005 (Gjertsen et al. 2008). Compared with the Norwegian Patient Registry, the completeness of primary operations in the NHFR is 88% for osteosyntheses (Furnes et al. 2018). After each operation the surgeon fills in a one-page paper form. The form includes information on age, sex, cognitive function, type of fracture (intracapsular femoral neck fractures classified as Garden 1–2 or 3–4; trochanteric fractures classified as 2-fragmented [AO/OTA A1], multi-fragmented [AO/OTA A2], or intertrochanteric [AO/OTA A3]; and subtrochanteric fractures), ASA class, and duration of surgery. The form further provides information on the chemical thromboprophylaxis given (if used or not, which drug, dosage, and whether the first dose was given preoperatively or postoperatively). The surgeon should also report intraoperative complications, including major bleeding complications, to the register. A reoperation was defined as any secondary surgery following the primary operation. The cause of reoperation is reported by the surgeon on a similar paper form to that used for the primary operation.

In the period 2005–2016, 96,599 primary operations for hip fractures were reported to the NHFR (Figure 1). 15 different types of drugs for prophylaxis had been used. However, low-molecular-weight heparin (LMWH) dominated entirely. To obtain a more homogeneous study group, operations with drugs other than LMWH were excluded. 45,913 patients operated with osteosynthesis were included. Dalteparin (Fragmin, Pfizer) was used in 58% (26,469 operations) and enoxaparin (Klexane, Sanofi-Aventis) was used in 42% (19,444 operations).

## Statistics

Survival analyses were performed using the Kaplan–Meier and Cox regression methods. Patients who died or emigrated during follow-up were identified from files provided by Statistics Norway, and the follow-up time for these patients was censored at the date of death or emigration. Only the first 6 postoperative months were included in the analyses as this period was considered most relevant in the present investigation.

The Cox multiple regression model was used to compare the relative risks of postoperative death and revision (failure-rate ratios) among patients where the thromboprophylaxis started preoperatively compared with postoperatively, with adjustments for possible influences of sex, duration of surgery, age of the patient at surgery (grouped in decades), ASA classification and year of surgery. Analyses on mortality and risk of reoperations within 7 days postoperatively, within 30 days postoperatively, and within 6 months postoperatively were performed. In addition to reoperations for any reason, we also investigated reoperations due to infection or hematoma and reported intraoperative bleeding complications. When investigating reoperations due to hematomas, patients with concurrent other causes for reoperation were excluded from the analyses.

95% confidence intervals (CIs) were calculated for relative risks. Number needed to harm (NNH) was calculated and defined as the number of patients treated with preoperative start of LMWH in order to cause 1 intraoperative bleeding complication because of preoperative start compared with postoperative start assuming a direct causal effect. The number needed to harm was calculated as an inverse value of the risk difference between the preoperative and postoperative start of LMWH.

## Sub-analyses

The osteosyntheses were divided into 3 sub-groups to investigate the most frequently used surgical procedures: screw osteosynthesis (14,985 operations, 33%), hip compression screw (21,764 operations, 47%), and intramedullary nail (9,164 operations, 20%).

Further, sub-analyses were performed for ASA classes 1–2 and 3–5. Lastly, duration of surgery was investigated: Group 1 with a short duration of surgery (less than 16 minutes for screws, less than 40 minutes for nails or compression screws, 25% of the study populations), group 2 with a median duration of surgery (16–30 minutes for screws, 40–75 minutes for compression screws and 40–84 minutes for nails, 25–75% of the study populations), and group 3 with a long duration of surgery (more than 30 minutes for screws, more than 75 minutes for compression screws and more than 84 minutes for nails, 25% of the study populations).

Assessments of proportionality in the Cox models were performed using log minus log plots of the adjusted survival curves, and the proportionality assumptions were fulfilled. We used the statistical software packages IBM SPSS® Statistics,

Table 1. Patients included in the study

Factor	Start of prophylaxis	
	Preoperative	Postoperative
Hip fractures with osteosynthesis, n (%)	20,563 (45)	25,350 (55)
Mean duration of surgery <sup>a</sup>	51 (33)	51 (34)
Mean age at fracture (years) (SD)	80 (12)	80 (13)
Women (%)	69	69
ASA groups, n (%)		
ASA 1	1,363 (6.6)	1,857 (7.3)
ASA 2	7,015 (34)	8,793 (35)
ASA 3	10,362 (50)	12,860 (51)
ASA 4	1,475 (7)	1,520 (6)
ASA 5	34 (0.2)	27 (0.1)
Missing	314 (1.5)	293 (1.2)
Type of surgery <sup>b</sup>		
Screws, n (%)	6,781 (45)	8,204 (55)
Mean duration of surgery <sup>a</sup>	26 (14)	26 (14)
Hip compression screw, n (%)	9,939 (46)	11,825 (54)
Mean duration of surgery <sup>a</sup>	62 (31)	61 (30)
Intramedullary nail, n (%)	3,843 (42)	5,321 (58)
Mean duration of surgery <sup>a</sup>	66 (38)	66 (41)

<sup>a</sup> Values are minutes (SD)

<sup>b</sup> Screws include operations with Olmed screws. Hip compression screws include operations with a dynamic hip screw (DHS) with or without a support plate. Intramedullary nails include long and short nails with or without the use of an interlocking screw.

version 24.0 for Windows (IBM Corp, Armonk, NY, USA) and the statistical package R, version 3.4.0, (<http://www.R-project.org>), for the statistical analyses. P-values < 0.05 were considered statistically significant.

### Ethics, funding, and potential conflicts of interest

The NHFR has permission from the Norwegian Data Inspectorate to collect patient data based on written consent from the patients. (Permission issued January 3, 2005; reference Number 2004/1658-2 SVE/-). Informed consent from patients entered in the medical records at each hospital. The Norwegian Hip Fracture Register is financed by the Western Norway. The authors declare no competing interests.

## Results

Table 1 presents baseline information on the patients included. Thromboprophylaxis was given preoperatively in 45% (20,563 operations) and postoperatively in 55% (25,350 operations). When comparing patients with a preoperative versus postoperative start of LMWH, no statistically significant differences in age, sex, comorbidity, or duration of surgery were found. There was an increase in postoperative initiation of LMWH during the studied period (Figure 2).

### Mortality

Overall mortality after 6 months was 19% (8,751 of 45,913 patients). No statistically significant difference in mortality

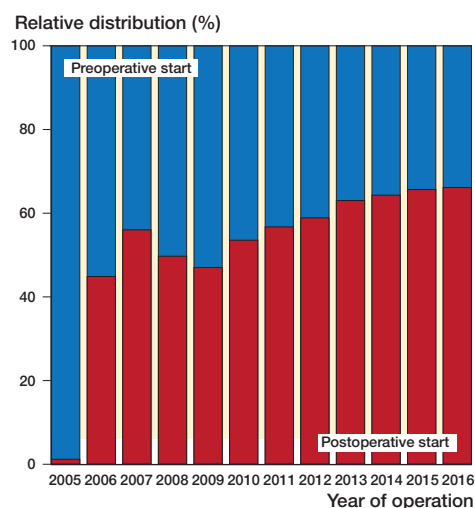


Figure 2. Timeline demonstrates the development in start of thromboprophylaxis from 2005 to 2016 for the patients observed in the study (n = 45,913). Hip fracture patients operated with osteosynthesis with known start of LMWH thromboprophylaxis (dalteparin or enoxaparin).

between preoperative and postoperative start of LMWH could be found. The results were consistent after 7, 30, and 180 days (Table 2, Figure 3).

### Reoperations

After 6 months 4.5% (2,067 of 45,913 operations) had been reoperated. There were 115 reoperations (0.3%) due to infection. Only 19 reoperations due to hematoma were reported to the register. No statistically significant differences in reoperations for any cause, reoperations due to infection, or reoperation due to hematoma could be found when comparing a preoperative versus postoperative start of thromboprophylaxis (Table 2, Figure 4).

### Intraoperative bleeding complications

1,294 (3.0%) intraoperative complications were reported after osteosyntheses. 208 (16% of all reported complications) were intraoperative bleedings. Postoperative start of LMWH decreased the risk of intraoperative bleeding complications compared with preoperative start (RR = 0.67 (CI 0.51–0.90), NNH = 434) (Table 3).

### Type of osteosynthesis

The hip fractures were reviewed in subgroups based on the type of osteosynthesis performed (Table 4). There was an increased 30-day mortality risk after operation with hip compression screw when LMWH was initiated postoperatively compared with preoperatively (RR = 1.10; CI 1.00–1.21). For other types of osteosyntheses, the startup time of LMWH prophylaxis had no statistically significant influence on mortality 7, 30, or 180 days after surgery. After operation with intramedullary nail there was an increased 180-day risk of reoperation due to infection after postoperative start of throm-

Table 2. Mortality and risk of reoperation 180 days postoperatively after osteosynthesis for hip fracture

	Total, n (%)	Start of prophylaxis, n (%)		RR <sup>a</sup>	95% CI	p-value
		Preoperative	Postoperative			
7 days postoperatively (n = 45,913)						
Mortality	1,050 (2.3)	481 (2.3)	569 (2.2)	1.02	0.90–1.16	0.7
Reoperations	190 (0.4)	76 (0.4)	114 (0.4)	1.18	0.88–1.58	0.3
Reoperation due to infection	5 (0.0)	1 (0.0)	4 (0.0)	3.50	0.38–32.0	0.3
Reoperation due to hematoma	9 (0.0)	3 (0.0)	6 (0.0)	1.86	0.46–7.49	0.4
30 days postoperatively (n = 45,913)						
Mortality	3,534 (7.7)	1,606 (7.8)	1,928 (7.6)	1.05	0.98–1.12	0.2
Reoperations	627 (1.4)	275 (1.3)	352 (1.4)	1.12	0.95–1.32	0.2
Reoperation due to infection	66 (0.1)	30 (0.1)	36 (0.1)	0.88	0.54–1.44	0.6
Reoperation due to hematoma	18 (0.0)	6 (0.0)	12 (0.0)	2.04	0.71–5.82	0.2
180 days postoperatively (n = 45,913)						
Mortality	8,751 (19)	4,049 (20)	4,702 (19)	1.01	0.97–1.06	0.6
Reoperations	2,067 (4.5)	966 (4.7)	1,101 (4.3)	0.99	0.90–1.08	1.0
Reoperation due to infection	115 (0.3)	49 (0.2)	66 (0.3)	1.02	0.70–1.49	0.9
Reoperation due to hematoma	19 (0.0)	6 (0.0)	13 (0.1)	2.18	0.78–6.18	0.1

<sup>a</sup> Cox relative revision risk (RR) (with preoperative start of prophylaxis as reference) is given with adjustments for possible influences of sex, ASA class, age group of the patient at surgery, duration of surgery, and year of surgery.

Table 3. Risk of intraoperative bleeding complications after osteosynthesis (n = 45,913) in hip fractures receiving screws (n = 14,985), hip compression screws (n = 21,764), or medullary nails (n = 9,164)

Treatment	Intraoperative bleeding, n (%)			p-value	Risk Preop.– Postop.	Risk difference	NNH <sup>b</sup>
	Preop. start	Postop. start	RR <sup>a</sup> (95% CI)				
Osteosynthesis	118 (0.6)	90 (0.4)	0.67 (0.51–0.90)	0.007	0.0060 – 0.0037	0.0023	434
Screws	3 (0.0)	2 (0.0)	0.43 (0.07–2.68)	0.4	0.0004 – 0.0002	0.0002	4,940
HCS	102 (1.0)	71 (0.6)	0.64 (0.47–0.87)	0.004	0.0108 – 0.0063	0.0045	222
Intramedullary nail	13 (0.3)	17 (0.3)	1.06 (0.50–2.26)	0.9	0.0036 – 0.0034	0.0002	4,684

<sup>a</sup> See Table 2.

<sup>b</sup> NNH: Number of patients treated with preoperative start of LMWH in order to cause one intraoperative bleeding complication because of preoperative LMWH start compared with postoperative LMWH start if there is a direct causal effect. The NNH was calculated as an inverse value of the risk difference (RD) between the methods [ $1/(\text{risk preoperative start} - \text{risk postoperative start})$ ].

Table 4. Mortality and risk of reoperation 180 days postoperatively after osteosynthesis in hip fractures receiving screws, hip compression screw, or medullary nails

	Total, n (%)	Start of prophylaxis, n (%)		RR <sup>a</sup>	95% CI	p-value
		Preoperative	Postoperative			
Screws (n = 14,985)						
Mortality	2,776 (19)	1,353 (21)	1,423 (18)	1.01	0.92–1.08	1.0
Reoperations	1,226 (8.2)	593 (9.1)	633 (8.0)	0.97	0.86–1.09	0.6
Reoperation due to infection	20 (0.1)	11 (0.2)	9 (0.1)	0.76	0.30–1.9	0.6
Reoperation due to hematoma	4 (0.0)	0 (0.0)	4 (0.1)	–	–	–
Hip compression screw (n = 21,764)						
Mortality	4,264 (20)	1,942 (20)	2,322 (20)	1.01	0.98–1.1	0.2
Reoperations	580 (2.7)	266 (2.7)	314 (2.7)	0.97	0.82–1.2	0.7
Reoperation due to infection	77 (0.4)	35 (0.4)	42 (0.4)	0.92	0.58–1.4	0.7
Reoperation due to hematoma	11 (0.1)	4 (0.0)	7 (0.1)	1.9	0.49–7.6	0.3
Intramedullary nail (n = 9,164)						
Mortality	1,711 (19)	754 (20)	957 (18)	0.96	0.87–1.1	0.4
Reoperations	261 (2.8)	107 (2.8)	154 (2.9)	1.2	0.91–1.5	0.2
Reoperation due to infection	18 (0.2)	3 (0.1)	15 (0.3)	3.7	1.04–13	0.04
Reoperation due to hematoma	4 (0.1)	2 (0.1)	2 (0.0)	1.2	0.14–9.8	0.9

<sup>a</sup> See Table 2.

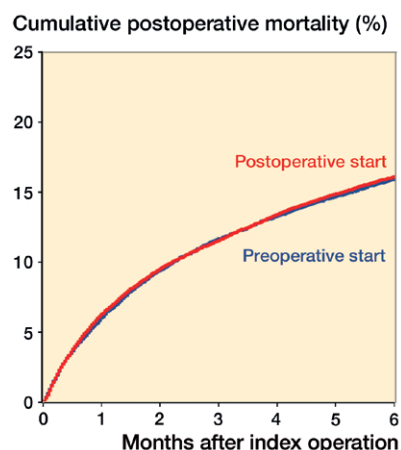


Figure 3. Postoperative mortality for hip fracture patients treated with osteosynthesis.

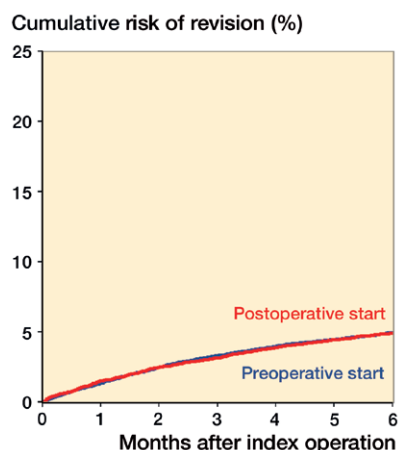


Figure 4. Risk of reoperation for hip fracture patients treated with osteosynthesis.

boprophylaxis compared with preoperative start (RR = 3.7; CI 1.04–13.2). No other statistically significant differences in risk for reoperation due to any cause, reoperation due to infection, or reoperation due to hematoma could be found (Table 4). After operation with hip compression screw there was a decreased risk of intraoperative bleeding complications after postoperative start of LMWH compared with preoperative start (RR = 0.64; CI 0.47–0.87) (see Table 3).

### ASA classification

Patients were stratified into ASA classes 1–2 and ASA classes 3–5. For both subgroups, no statistically significant differences in mortality or risk of reoperation could be found within 180 days of follow-up between preoperative and postoperative start of LMWH (data not shown).

### Duration of surgery

Patients treated with intramedullary nail with long duration of surgery (> 84 minutes, upper quartile) had the most marked increased risk of reoperation due to infection after postoperative start of LMWH compared with preoperative start (RR = 8.2; CI 1.03–65). The startup time of LMWH did not statistically significantly influence the risk of reoperation due to infection in patients treated with intramedullary nails with shorter operation time or for other osteosyntheses (data not shown).

For patients treated with hip compression screw the risk of intraoperative bleeding complication decreased after postoperative start of LMWH with long duration of surgery (> 75 minutes, upper quartile) (RR = 0.68; CI 0.47–0.99). The startup time of LMWH did not influence the risk of intraoperative bleeding complication in patients treated with hip compression screw with shorter operation time (data not shown).

## Discussion

When comparing preoperative versus postoperative start of LMWH for hip fracture patients treated with osteosynthesis, no differences in mortality or risk of reoperation were found. Preoperative start of LMWH was found to give more intraoperative bleeding complications for patients treated with hip compression screws, but not for patients receiving intramedullary nails or screws.

Whether chemical prophylaxis should start preoperatively or postoperatively is controversial (Ettema et al. 2009, Borgen et al. 2013). In Europe the LMWH prophylaxis has traditionally started before hip fracture surgery (Ettema et al. 2009), while in North

America a postoperative initiation has been common (Kearon and Hirsh 1995, Gomez-Outes et al. 2012, Lassen et al. 2012). This divergent practice between the continents may be continued based on traditional consequences. The fear of bleeding-related complications has been most critical for surgeons in North America due to medico-legal issues. In Europe, on the other hand, such complications have been the common responsibility of the department and the main focus has been to prevent local and systemic thromboembolic events. Due to the tremendous costs of antithrombotic drug development, several companies have recently developed a common regimen for both continents. Nevertheless, timing in relation to surgery has been considered important for the efficacy-to-safety balance in any pharmaceutical anticoagulant program. Trials funded by the industry have primarily focused on detecting thromboses with mandatory radiology following the surgical intervention. Unfortunately, some studies have been criticized for underestimating the challenges bleeding and wound complications can present following surgery (Parvizi et al. 2007, Lachiewicz 2009, Dahl et al. 2010). Second, the reported trials have been designed to show potential favorable effects of new experimental regimes versus established regimes (Yoshida et al. 2013). In contrast, our register study compares the same compounds when investigating preoperative versus postoperative start of thromboprophylaxis. To our knowledge, there no study of this size has been conducted investigating the startup time of thromboprophylaxis in hip fracture surgery.

When studying femoral neck fractures treated with hemiarthroplasty, preoperative start of thromboprophylaxis reduced mortality within 6 months of surgery (Leer-Salvesen et al. 2017). This favorable effect of preoperative LMWH administration was most pronounced in the first postoperative weeks. Nevertheless, the preoperative effect was also robust over time and no catch-up effect was noticed during 6 months of observation. In the present study investigating hip fractures treated with osteosynthesis, no such protective effect of preoperative

start of LMWH could be detected, either for the whole group or for subgroups of patients receiving screw osteosynthesis, hip compression screw, or intramedullary nail. In the frail elderly undergoing hip fracture, the primary trauma and subsequent surgery have been shown to significantly impact the immediate and long-term mortality (Talsnes et al. 2011, 2013). As shown in our previous study, preoperative administration of LMWH may contribute to reducing mortality following hemiarthroplasty (Leer-Salvesen et al. 2017). Importantly, osteosynthesis for hip fractures seem to induce less trauma and thrombin-driven vascular complications as compared with surgery with hemiprosthesis. Thus, the start of prophylaxis in relation to surgery might be less important when conducting osteosynthesis procedures.

Preoperative start of thromboprophylaxis did not increase the risk of reoperation after osteosyntheses compared with postoperative start. In previous discussions, the risk of reoperation has in particular been brought forward as an argument to start thromboprophylaxis postoperatively (Lassen et al. 2012). This argument has partly been based on the fear of intraoperative bleeding complicating the surgical intervention. The fear of bleeding might also explain the gradual shift from preoperative to postoperative initiation of LMWH observed during the last decade. Relevantly, our study did demonstrate a decreased risk of intraoperative bleeding when the LMWH was initiated postoperatively compared with preoperatively for patients receiving osteosynthesis. In contrast, we did not find a decreased risk of intraoperative bleeding when the LMWH was initiated postoperatively in femoral neck fractures treated with hemiarthroplasty (Leer-Salvesen et al. 2017).

Postoperative start of LMWH decreased the risk of intraoperative bleeding in connection with hip compression screws. However, in patients operated with screw osteosynthesis or intramedullary nail a postoperative start of LMWH did not influence the risk of intraoperative bleeding. Screw osteosynthesis and intramedullary nail for hip fractures are most often performed as mini-invasive surgery, which may explain why risk of intraoperative bleeding complications is not affected by LMWH. Since displaced femoral neck fractures in the elderly are most often treated with an arthroplasty (Gjertsen et al. 2017), patients treated with screw osteosynthesis are younger than patients treated with osteosynthesis for extracapsular hip fractures. Less preoperative bleeding and younger age might explain why the start of LMWH administration does not significantly affect the risk of mortality, reoperation, or bleeding when using screw fixation.

Extracapsular hip fractures may be treated with hip compression screw or intramedullary nail. The complexity of the fracture will affect the risks of infection, bleeding, and reoperation. Intramedullary nails are increasingly used for complex trochanteric and subtrochanteric fractures. Postoperative start of LMWH compared with preoperative start increased the risk of reoperations due to infection after intramedullary nails. Hip fractures with time-consuming intramedullary nail-

ing (more than 84 minutes, upper quartile) had a more than 8 times increased risk of reoperation due to infection after postoperative start of LMWH compared with preoperative start. A possible explanation could be that preoperative start of thromboprophylaxis induces bleeding earlier, which allows hemostasis or hematoma evacuation during surgery. Contrariwise, postoperative start of thromboprophylaxis LMWH may postpone traumatic bleeding and produce a late hematoma, which predispose to infection. A longer duration of surgery is often related to complex fractures, other concurrent intraoperative complications, or less experienced surgeons. These factors may also influence the risk of infection and potentiate the protective effect of a preoperative LMWH. However, due to limited number of patients in the sub-studies the results may be interpreted with caution.

### **Strength and limitations**

Our study is not a randomized controlled study (RCT) and may consequently be categorized as a hypothesis-creating study. However, when examining rare adverse events and large patient numbers, observational register studies remain an achievable method compared with RCTs. Nevertheless, this is, to our knowledge, the first study of its kind comparing preoperative versus postoperative benefit of the same compounds. The strength in our study is the inclusion of data from all surgical units treating hip fractures in one country. Accordingly, the external validity of the results is high. The inclusion of multiple hospitals may influence our results. However, as we believe each hospital has routines in thromboprophylaxis administration, the inclusion of all hospitals has not been used as a confounder in our analyses. The register is dependent on volunteer reporting from individual surgeons. According to earlier coverage analyses, reoperations are more frequently left unreported to the register than primary operations, and such a tendency may affect our endpoints (Wiik et al 2014). It is, however, unlikely that differences in the reporting of reoperations after preoperative versus postoperative initiation of LMWH exist. Data concerning the start of LMWH are entered immediately after surgery by the responsible surgeon. Unfortunately, the NHFR only receives limited information concerning the usage of thromboprophylaxis in treatment of hip fractures. The surgeons do not report the exact moment in time of LMWH administration before and after surgery. Therefore, consequences of preoperative versus postoperative LMWH startup regimes are still partly unknown. The exact duration of LMWH treatment may not always be possible to predict immediately after surgery as later events or complications may alter the originally planned duration of treatment. Furthermore, after each operation the surgeon has to interpret whether the intraoperative bleeding was so extensive that it should be reported as a complication. Therefore, the findings regarding intraoperative bleeding must be interpreted with caution. Even though the study has weaknesses, the results are based on a large number of patients as well as consistent reporting of LMWH initiation to the register.

## Conclusion

Our data strongly indicate that preoperative compared with postoperative administration of LMWH does not influence mortality or risk of reoperation in hip fracture patients treated with osteosynthesis. However, postoperative start of LMWH does decrease the risk of reported intraoperative bleeding complications for operations with hip compression screw, but not with intramedullary nail or screw osteosynthesis.

The loyal reporting from all orthopedic surgeons made our studies possible.

The manuscript was produced by close teamwork between all authors. SLS and ED performed the statistical analyses. All authors contributed to the study design and interpretation of results.

Acta thanks Gerold Labek and other anonymous reviewers for help with peer review of this study.

- Borgen P O, Dahl O E, Reikeras O. Biomarkers of coagulation and fibrinolysis during cemented total hip arthroplasty with pre- versus postoperative start of thromboprophylaxis. *Thrombosis* 2013; 2013: 563217.
- Dahl O E, Quinlan D J, Bergqvist D J, Eikelboom J W. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *J Thromb Haemost* 2010; 8: 1966-75.
- Ettema H B, Mulder M C, Nurmohamed M T, Buller H R, Verheyen C C. Dutch orthopedic thromboprophylaxis: a 5-year follow-up survey. *Acta Orthop* 2009; 80(1): 109-12.
- Furnes O, Gjertsen J E, Hallan G, Visnes H, Gundersen T, Fenstad A M, Dybvik E, Bartz-Johannessen C. Annual report. Norwegian Arthroplasty Register 2018; <http://nrlweb.ihelse.net/Rapporter/Rapport2018.pdf>. p. 234
- Gjertsen J E, Engesaeter L B, Furnes O, et al. The Norwegian Hip Fracture Register: experiences after the first 2 years and 15,576 reported operations. *Acta Orthop* 2008; 79(5): 583-93.
- Gjertsen J E, Dybvik E, Furnes O, Fevang J M, Havelin L I, Matre K, Engesaeter L B. Improved outcome after hip fracture surgery in Norway. *Acta Orthop* 2017; 88(5): 505-11.
- Gomez-Outes A, Terleira-Fernandez A I, Suarez-Gea M L, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 2012; 344:e 3675.
- Kearon C, Hirsh J. Starting prophylaxis for venous thromboembolism postoperatively. *Arch Intern Med* 1995; 155:3 66-72.
- Lachiewicz P F. Comparison of ACCP and AAOS guidelines for VTE prophylaxis after total hip and total knee arthroplasty. *Orthopedics* 2009; 32: 74-8.
- Lassen M R, Gent M, Kakkar A K, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. *J Bone Joint Surg Br* 2012; 94(11): 1573-8.
- Leer-Salvesen S, Dybvik E, Dahl O E, Gjertsen J-E, Engesaeter L B. Postoperative start compared to preoperative start of low-molecular-weight heparin increases mortality in patients with femoral neck fractures. *Acta Orthop* 2017; 88(1): 48-54
- Parvizi J, Ghanem E, Joshi A, Sharkey P F, Hozack W J, Rothman R H. Does "excessive" anticoagulation predispose to periprosthetic infection? *J Arthroplasty* 2007; 22: 24-8.
- Talsnes O, Hjelmstedt F, Dahl O E, Pripp A H, Reikeras O. Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly. *Int Orthop* 2011; 35(6): 903-7.
- Talsnes O, Vinje T, Gjertsen J E, et al. Perioperative mortality in hip fracture patients treated with cemented and uncemented hemiprostheses: a register study of 11,210 patients. *Int Orthop* 2013; 37(6): 1135-40.
- Vera-Llonch M, Hagiwara M, Oster G. Clinical and economic consequences of bleeding following major orthopedic surgery. *Thromb Res* 2006; 117(5): 569-77.
- Wiik R, Baste V, Gjertsen J E, Engesaeter L B. Dekningsgradsanalyse for Nasjonalt Hoftebruddregister 2008-2012. Helsedirektoratet 13/11218. <https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/675/Dekningsgradsanalyse-for-nasjonalt-hoftebruddregister-2008-2012-IS-2210.pdf>
- Yoshida Rde A, Yoshida W B, Maffei F H, El Dib R, Nunes R, Rollo H A. Systematic review of randomized controlled trials of new anticoagulants for venous thromboembolism prophylaxis in major orthopedic surgeries, compared with enoxaparin. *Ann Vas Surg* 2013; 27(3): 355-69.





# Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay, and poorer outcome for hip fracture patients?

Sunniva Leer-Salvesen<sup>1</sup> · Eva Dybvik<sup>2</sup> · Anette H. Ranhoff<sup>3,4,5</sup> · Bjørn Liljestrand Husebø<sup>6</sup> · Ola E. Dahl<sup>7,8</sup> · Lars B. Engesæter<sup>2</sup> · Jan-Erik Gjertsen<sup>1,2</sup>

Received: 31 January 2020 / Accepted: 31 March 2020 / Published online: 23 July 2020  
© The Author(s) 2020, corrected publication 2020

## Key summary points

**Aim** The aim of this study was to determine whether DOAC-users with a hip fracture have delayed surgery, longer length of hospital stay or altered risk of bleeding complications compared to non-users.

**Findings** DOAC-users with a hip fracture did not have increased surgical delay, length of stay or risk of reported bleeding complications compared to patients without anticoagulation prior to surgery.

**Message** Our study does not support delayed surgery for DOAC-users suffering a hip fracture.

## Abstract

**Purpose** The perioperative consequences of direct oral anticoagulants (DOACs) in hip fracture patients are not sufficiently investigated. The primary aim of this study was to determine whether DOAC-users have delayed surgery compared to non-users. Secondly, we studied whether length of hospital stay, mortality, reoperations and bleeding complications were influenced by the use of DOAC.

**Methods** The medical records of 314 patients operated for a hip fracture between 2016 and 2017 in a single trauma center were assessed. Patients aged < 60 and patients using other forms of anticoagulation than DOACs were excluded. Patients were followed from admission to 6 months postoperatively. Surgical delay was defined as time from admission to surgery. Secondary outcomes included length of hospital stay, transfusion rates, perioperative bleeding loss, postoperative wound ooze, mortality and risk of reoperation. The use of general versus neuraxial anaesthesia was registered. Continuous outcomes were analysed using Students *t* test, while categorical outcomes were expressed by Odds ratios.

**Results** 47 hip fracture patients (15%) were using DOACs. No difference in surgical delay (29 vs 26 h,  $p=0.26$ ) or length of hospital stay (6.6 vs 6.1 days,  $p=0.34$ ) were found between DOAC-users and non-users. DOAC-users operated with neuraxial anaesthesia had longer surgical delay compared to DOAC-users operated with general anaesthesia (35 h vs 22 h,  $p<0.001$ ). Perioperative blood loss, transfusion rate, risk of bleeding complications and mortality were similar between groups.

**Conclusion** Hip fracture patients using DOAC did not have increased surgical delay, length of stay or risk of reported bleeding complications than patients without anticoagulation prior to surgery. The increased surgical delay found for DOAC-users operated with neuraxial anaesthesia should be interpreted with caution.

**Keywords** Hip fracture · Orthogeriatrics · Surgical delay · Anaesthesia · Direct oral anticoagulants (DOAC) · New oral anticoagulants (NOAC)

✉ Sunniva Leer-Salvesen  
sunniva.leer-salvesen@helse-bergen.no

<sup>1</sup> Department of Clinical Medicine, University of Bergen, Bergen, Norway

<sup>2</sup> The Norwegian Hip Fracture Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

<sup>3</sup> Department of Clinical Science, University of Bergen, Bergen, Norway

<sup>4</sup> Department of Chronic Diseases and Aging, Norwegian Institute of Public Health, Oslo, Norway

<sup>5</sup> Diakonhjemmet Hospital, Oslo, Norway

<sup>6</sup> Department of Anaesthesia, Haukeland University Hospital, Bergen, Norway

<sup>7</sup> Innlandet Hospital Trust, Elverum, Norway

<sup>8</sup> Thrombosis Research Institute, London, UK

## Introduction

The use of direct oral anticoagulants (DOACs) have emerged based on randomized clinical trials, active marketing and less demands concerning monitoring compared to warfarin. From 2014 to 2018, the prevalence of DOAC-users increased with 150% in Norway and the drugs as a group have surpassed warfarin [1]. Increasing use of DOACs has also been observed in Germany, Belgium and The Netherlands [2]. Suffering a hip fracture results in an evident excess mortality [3], and knowledge on how to reduce complications is, therefore, important. Reduced kidney function, co-medication, drug interaction and altered distribution may affect the clinical outcome in hip fracture patients using such anticoagulant compounds [4].

Systemic thromboembolic events are important causes of mortality [5, 6]. On the other hand, DOACs may accentuate bleeding triggered by trauma and surgery. Whether DOACs should be temporarily paused to avoid surgical and anaesthesiological complications and, if so, when it should be paused remains to be established. Anticoagulation has in several studies been identified as a risk factor for delayed hip fracture surgery [7–10]. Most guidelines advocate that hip fracture surgery should be performed within 48 h after admission, preferably within 24 h, to reduce the rate of medical complications and mortality [11–13]. Earlier studies have indicated that patients exposed for DOAC before the hip fracture wait longer for surgery than recommended in treatment guidelines [14–16]. The consequences of DOAC on semi-urgent surgery such as for hip fracture patients has not been thoroughly investigated.

Currently, there is need for guidelines on how to handle DOACs in the treatment of hip fracture patients. The primary aim of this study was to determine whether hip fracture patients using DOACs prior to the fracture have delayed surgery or longer length of hospital stay compared to non-DOAC-users. Secondly, we wanted to investigate whether mortality and perioperative complications occur more frequently among hip fracture patients using DOAC.

## Methods

### Study design

This is a retrospective descriptive study of hip fracture patients operated at one Norwegian single trauma center December 2016–December 2017. We extracted 360 patients electronically from the hospital database using ICD-10 diagnosis codes S72.0–S72.2. Demographic data and surgical outcomes for the included patients were retrieved directly

from patient records by one experienced researcher (SLS). Patient records at the hospital consisted of day-to-day documentation by the anaesthetists and orthopaedic surgeons and medical records logged by physicians and nurses. The Regional Ethics Committee (REK) classified the study as quality assurance, thus we did not need ethical assessment (case number 1366/REK). The hospital data protection officer approved the study.

### Patients

Patients with acute intracapsular or extracapsular hip fractures undergoing any type of surgery were included in the study. We aimed to compare hip fracture patients using DOAC at time of fracture with patients without anticoagulation at time of fracture. Patients under the age of 60 ( $n=23$ ) and patients using other forms of anticoagulation than DOACs ( $n=23$ ) were excluded, resulting in a study population of 314 patients.

### Outcomes

We stratified the patients according to the American Society of Anesthesiologists (ASA) classes 1–2 and 3–5 to compare comorbidity between the studied groups. When comparing the rate of cognitive impairment reported between the study groups, patients with unknown preoperative cognitive status were excluded ( $n=20$ ). Time from admission to surgery (surgical delay) was reported in hours and length of stay (LOS) in days. In-hospital mortality and both mortality and readmissions within 30 days and within 6 months of operation were registered. Blood transfusion rates and transfusion amounts (allogenic red blood cells infused in standardized units) were collected from the medical records signed by the responsible physicians. In-hospital guidelines recommended blood transfusion therapy to be administered for patients with a haemoglobin below 9 g/dL monitored at the wards. The concentration of haemoglobin was listed at admission and the morning after surgery and the difference was calculated (change in haemoglobin concentration). Intraoperative blood loss estimated by the surgical team was registered from the anaesthesia journal in milliliters (mL). Postoperative bleeding and wound complications were recorded if the intraoperative or postoperative journals by the physicians reported so. Wound ooze was defined as clinically identified ooze with or without bleeding described by the doctors postoperatively. The type of anaesthesia was registered as general anaesthesia (total intravenous anaesthesia (TIVA) or inhalational anaesthesia) or neuraxial anaesthesia (spinal anaesthesia). We compared surgical delay and LOS within the groups receiving neuraxial versus general anaesthesia.

## Statistical analysis

Our main outcome, surgical delay, was used to calculate the number of patients needed to achieve statistical significance between the groups. Based on guidelines from the Norwegian Knowledge Center hip fracture patients should preferably be operated within 24 h and no later than 48 h after admission [12]. Standard deviation was calculated from hip fracture patients with a surgical delay of less than 96 h reported to the Norwegian Hip Fracture Register and found to be 15.1 h. Based on alpha of 0.05 and beta of 0.9, 28 patients were needed in each group. Since 9.4% of Norwegian patients > 60 years were using DOAC in 2017 (Norwegian Institute of Public Health 2019), the total sample size was calculated to be 300. To account for exclusion criteria's and missing information, we increased the sample size with 20%.

We performed univariate exploration of study variables; for continuous data, the assumption of homogeneity of variance between groups was assessed using the Levene's test. Where the assumption holds a Student's *t* test was used, otherwise the Welch's *t* test was applied. Odds ratios (ORs) were used to express categorical outcomes and patients without DOAC were used as a reference group. IBM SPSS Statistics (version 24.0; IBM Corp. Armonk, New York) for Windows was used for the statistical analyses.

## Results

Of the 314 included patients, 47 patients (15%) were DOAC-users before the hip fracture and 267 patients (85%) were not using anticoagulation before the fracture (Table 1). Hip

fracture patients using DOAC were more likely to have a high ASA class (ASA 3–5) compared to non-users.

## Time to surgery and hospital stay

DOAC-users and non-anticoagulated patients had similar time interval from admission to surgery (29 vs 26 h,  $p=0.26$ , respectively) and similar length of hospital stay (LOS) (6.6 vs 6.1 days,  $p=0.34$ , respectively) (Table 2).

## Complications

The mean blood loss during surgery for all patients ( $n=314$ ) was 219 mL. Mean blood loss, fall in haemoglobin and transfusion rates were comparable in both groups (Table 2).

Bleeding complications were reported in three patients (0.9% of all patients); two patients had an excessive bleeding during surgery, while a third patient developed a postoperative haematoma restricted to the operation site. No bleeding complications were reported among the DOAC-users.

Wound oozing with or without bleeding were described in 27 patients (8.6%) and more frequently among DOAC-users than patients without anticoagulation (26% vs 5.6%, respectively) (Table 2). Among all patients ( $n=314$ ), postoperative wound leakage was associated with a longer hospital stay than for patients without wound exudation (LOS 9 vs 6 days, respectively,  $p<0.001$ ).

The 30-day mortality for all patients ( $n=314$ ) was 12%. DOAC-users had corresponding mortality in the hospital, within 30 days and within 6 months compared to non-users (Table 2). Furthermore, 30-day and 6-month risk of readmission were similar between DOAC-users and non-users [30 days: 26% vs 17%, respectively, OR 1.65 (0.80–3.41)] [6 months: 36% vs 26%, OR 1.63 (0.85–3.13)].

**Table 1** Baseline data for the included hip fracture patients in our study ( $n=337$ )

	Antithrombotic medication			<i>p</i> value
	Total	No anticoagulants	DOAC	
Total <i>n</i> (%)	314 (100)	267 (85)	47 (15)	
Mean age (SD)	82.1 (9.2)	81.8 (9.5)	84.2 (7.4)	0.05
Women (%)	221 (70)	190 (71)	31 (66)	0.47
Cognitive impairment (%)	108 (34)	93 (34.8)	15 (31.9)	0.61
ASA class (%)				0.003 <sup>a</sup>
ASA 1	8 (2.5)	8 (3.0)	0 (0.0)	
ASA 2	120 (39)	110 (42)	10 (21)	
ASA 3	158 (51)	128 (48)	30 (64)	
ASA 4	27 (8.0)	20 (7.5)	7 (15)	
ASA 5	1 (0.3)	1 (0.4)	0 (0.0)	

<sup>a</sup>Pearson Chi Square test has been used to compare patients in each anticoagulant group with either ASA classes 1–2 or class 3–5. When comparing the rate of cognitive impairment reported between the study groups, patients with unknown preoperative cognitive status were excluded ( $n=20$ )

**Table 2** Surgical delay, length of hospital stay, type of anaesthesia, perioperative complications and mortality reported among hip fracture with DOAC or no anticoagulation prior to the fracture ( $n=314$ )

Antithrombotic medication				
Hospital stay	Total	No anticoagulants	DOAC	<i>p</i> value
Hours from admission to surgery (SD)	26.5 (18.2)	26.1 (19.0)	28.9 (12.9)	0.26
LOS (SD)	6.2 (2.9)	6.1 (2.9)	6.6 (2.2)	0.34
General anaesthesia (%)	<b>32 (10%)</b>	<b>10 (3.8%)</b>	<b>22 (47%)</b>	<b>0.001</b>
Perioperative complications				<i>p</i> value
Mean blood loss during surgery (SD)	219 mL (208)	218 mL (209)	223 mL (204)	0.9
Mean fall in haemoglobin (SD)	1.90 (1.30)	1.89 (1.25)	1.95 (1.63)	0.8
Mean SAG transfused per patient (SD)	0.81 (1.16)	0.80 (1.17)	0.85 (1.10)	0.8
				OR (95% CI)
Number of patients transfused (%)	134 (43%)	113 (42%)	21 (45%)	1.10 (0.59–2.01)
Reported wound ooze (%)	<b>27 (8.6%)</b>	<b>15 (5.6%)</b>	<b>12 (26%)</b>	<b>5.8 (2.49–13.3)</b>
Mortality				OR (95% CI)
In-hospital mortality	11 (3.5%)	9 (3.4%)	2 (4.3%)	1.27 (0.27–6.09)
30-day mortality	39 (12.4%)	34 (12.7%)	5 (10.6%)	1.23 (0.45–3.31)
6-month mortality	70 (22.3%)	59 (22.1%)	11 (23.4%)	0.93 (0.45–1.94)

Bold values indicate more frequent use of general anaesthesia and higher risk of wound ooze in DOAC-users compared to non-users

## Antiaggregants

Among the DOAC-users, two hip fracture patients were also using clopidogrel (4.3%) while the remaining 45 patients where not using antiaggregant therapy (95.7%).

In the non-anticoagulated group, 92 patients (34.5%) were using 1 antiplatelet drug while ten patients (3.7%) were using two antiplatelet drugs. Time to surgery, perioperative blood loss, transfusion rate, risk of bleeding complications and mortality were similar between non-anticoagulated patients and DOAC-patients both when including and excluding patients with clopidogrel in addition to DOAC.

## Anaesthesia

General anaesthesia was administered to 32 (10%) of all patients. When comparing general to neuraxial anaesthesia, no differences in time from admission to surgery (surgical delay) or LOS was found. A significantly higher percentage of DOAC-users received general anaesthesia than non-users [22 patients (47%) vs 10 (3.8%),  $p < 0.001$ ]. The DOAC-users that received neuraxial anaesthesia ( $n=25$ ) had significantly longer surgical delay compared to those who received general anaesthesia (35 h vs 22 h,  $p < 0.001$ ). DOAC-users treated with neuraxial anaesthesia trended toward a longer LOS, yet the results were not significant (7.1 vs 6.1 days,  $p=0.1$ ).

## Discussion

In this single-centre retrospective descriptive study investigating hip fracture patients, the use of DOACs at the time of fracture was not found to influence surgical delay or length of stay compared to non-users. Furthermore, no differences in perioperative blood loss, transfusion rates or risk of bleeding complications between DOAC-users and non-users were disclosed. Hip fracture surgery was more frequently performed in general anaesthesia in DOAC-users, and the use of neuraxial anaesthesia for DOAC-users was associated with a longer surgical delay. This should be seen in relation to primary findings of no difference in surgical delay and length of stay between the compared groups. The high rate of cognitive impairment reported in this study was in line with a previous Norwegian study where 38% of home-dwelling hip fracture patients had cognitive impairment [17].

Studies investigating hip fracture treatment and the use of anticoagulants have so far reported conflicting results. While increased risk of complications was detected in one study [18], other studies discovered no such effect [19, 20]. These diverse findings could be explained by different perioperative administration of anticoagulant drugs. Due to a lack of international established guidelines, patients tend to be treated according to local routines in each hospital.

DOACs are approved for prevention of thromboembolism from non-valvular atrial fibrillation and to treat or prevent recurring deep vein thrombosis and pulmonary embolism [21–23]. These indications may explain why a higher burden of comorbidity was found among hip fracture patients using a DOAC compared to non-users in our study. Despite this increased comorbidity, we were not able to find increased risk of perioperative blood loss, transfusion rates, bleeding complications or mortality for the DOAC-users compared to the less comorbid non-users. Our findings are in contrast to another study reporting a higher one-year mortality among hip fracture patients using DOAC compared to non-users [24]. However, the excess mortality may be explained by higher age, more comorbidity and longer surgical delay than in our patients.

Earlier hip fracture surgery has been associated with reduced LOS and reduced frequency of immobilization-related complications [25–28], and large resources have been applied to promote earlier surgical interventions [29]. Several studies have found increased surgical delay for DOAC-users [16, 18, 24], and the authors question whether the use of DOAC before the hip fracture results in unnecessary long surgical delay [14, 24, 30–32]. In contrast, our DOAC-using patients did not wait significantly longer for surgery than the non-users. Another study investigated hip fracture patients using DOACs compared to matched controls with a median of only 19 h from admission to surgery [30]; no association between surgical delay and perioperative fall in haemoglobin, transfusion rate or reoperation for DOAC-users was found. As our study did not find increased bleeding—and transfusion—complications among patients using DOAC, early surgical interventions appear safe.

The prevalence and risk factors for surgical site infections is sparsely studied in the geriatric hip fracture population even though high age has been identified as a potential risk factor for such infections [33]. Our study revealed wound oozing five times more frequently among DOAC-users than patients without anticoagulation. Still, none of these patients underwent a reoperation due to wound ooze. We need to acknowledge that reoperation due to wound ooze is a late solution to persisting oozing. One earlier study has investigated DOAC-users' risk of reoperation due to wound ooze and found no relation to surgical delay [30]. On the other hand, when studying hip fracture patients not accounting for chronic anticoagulation, surgical delay has been found to be a risk factor for wound infections [28, 33]. The association between wound ooze and longer LOS found in our study might have implications for health costs and patient treatment following a hip fracture.

In Norway, 80–90% of hip fracture patients are given neuraxial anaesthesia [34], correlating well to the prevalence found in our hospital (90%). There is no international

consensus on neuraxial versus general anaesthesia for hip fracture patients [35]. General anaesthesia has earlier been associated with a longer LOS compared to neuraxial anaesthesia [36], yet a meta-study of 400,000 hip fracture patients revealed a clinically insignificant difference of only 0.3 days [37]. The increasing use of DOACs challenge current clinical practice because the potential ramifications of neuraxial anaesthesia in the anticoagulated patient [38]. European guidelines recommend that DOACs should be discontinued before surgery in line with their pharmacokinetic properties [39–42]. Potential neuraxial bleeding can be avoided by giving the hip fracture patients general anaesthesia, possibly explaining why general anaesthesia was used ten times more frequently in patients using DOAC at the time of fracture compared to non-users in our study. One explanation to this finding could be that some DOAC-users were scheduled for delayed surgery to be operated with neuraxial anaesthesia. Another likely explanation is that for these DOAC-users, the chosen modality ended up being neuraxial anaesthesia, because their surgery already had been delayed for other reasons, in example access to theatre and preoperative medical stabilization.

## Strengths and limitations

We studied patients treated at a large trauma hospital using patient records processed by one researcher, thereby increasing the quality and reproducibility of our work. We cannot generalize our findings to other hospitals or countries with other treatment algorithms. However, we believe that our university hospital is representable also for hip fracture treatment in other Norwegian hospitals. Similar surgical delay between DOAC-users and non-users further support comparable preoperative management of all the studied patients.

The sample size was calculated based on our main outcome surgical delay using data from the Norwegian Hip Fracture Register [13]. However, we assessed several other outcomes as well in our study, thereby potentially working with insufficient sample sizes and lack of power. Unfortunately, the size of our study prevented stratified analyses of the different types of DOAC. The retrospective study design allowed us to report associations between DOAC and perioperative outcomes, yet causality cannot be proven. For example, we cannot exclude the risk of confounding by comorbidity when it comes to the choice of anaesthesia and surgical delay. Due to the abovementioned weaknesses of our study, we request future prospective clinical trials targeting hip fracture patients exposed for DOACs and the consequences of fast track surgery versus surgery timed after drug excretion. Further, we acknowledge a need for further studies structurally targeting wound assessment and wound ooze for DOAC-users suffering a hip fracture.

## Conclusion

In our cohort of 314 hip fracture patients DOAC-users did not have increased surgical delay, LOS or risk of reported bleeding complications compared to patients without anti-coagulation prior to surgery. Our study does not support delayed surgery for DOAC-users. The increased surgical delay found for DOAC-users operated with neuraxial anaesthesia compared to general anaesthesia should be interpreted with caution.

**Acknowledgements** Open Access funding provided by University of Bergen.

**Author contributions** SLS conducted the study of patient records. All authors participated in the study protocol, the application for ethical assessment and the manuscript.

**Funding** No funding was received.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** The Regional Ethics Committee (REK) classified the study as quality assurance, thus we did not need ethical assessment (case number 1366/REK). The hospital data protection officer approved the study.

**Consent to participate** Our study involves hip fracture patients with a 1 year mortality of 25% and an even larger prevalence of cognitive impairment. We have performed a descriptive study using patient records without consent due to the patient demographics (age, mortality and cognitive impairment) by conducting a risk assessment taking into account the potential gain in quality of future patient treatment. The Regional Ethics Committee (REK) classified the study as quality assurance, thus we did not need ethical assessment (case number 1366/REK). The hospital data protection officer approved the study.

**Consent for publication** The hospital data protection officer approved the study. We refer to the classification from the Regional Ethics Committee.

**Availability of data and material** Our data have been deidentified and stored in a secure server area only available for Eva Dybvik and Sunniva Leer-Salvesen. The data will be deleted 5 years after the study.

**Code availability** IBM SPSS Statistics (version 24.0; IBM Corp. Armonk, New York) for Windows was used for the statistical analyses.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will

need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. No authors listed (2019) Norwegian Institute of Public Health, The prescription registry. Individual site for retrieving data accessed 05.12.19. <https://reseptregisteret.no/Prevalens.aspx>
2. de Jong LA, Knoop M, Gout-Zwart JJ, Beinema MJ, Hemels MEW, Postma MJ, Boruwers JRB (2018) Trends in direct oral anticoagulant (DOAC) use: health benefits and patient preference. *Neth J Med* 76(10):426–430
3. Solbakken SM, Meyer HE, Stigum H, Sjøgaard AJ, Holvik K, Magnus JH, Omsland TK (2017) Excess mortality following hip fracture: impact of self-perceived health, smoking, and body mass index. *A NOREPOS study. Osteoporos Int* 28(3):881–887
4. Verma A, Ha ACT, Rutka JT, Verma S (2018) What surgeons should know about non-vitamin K oral anticoagulants: a review. *JAMA Surg* 153(6):577–585
5. Vera-Llonch M, Hagivara M, Oster G (2006) Clinical and economic consequences of bleeding following major orthopedic surgery. *Thromb Res* 117(5):569–577
6. Dahl OE, Caprini JA, Colwell CW Jr et al (2005) Fatal vascular outcomes following major orthopedic surgery. *Thromb Haemost* 93(5):860–866
7. Fantini MP, Fabbri G, Laus M et al (2011) Determinants of surgical delay for hip fracture. *Surgeon* 9(3):130–134
8. Eardley WG, Macleod KE, Freeman H, Tate A (2014) “Tiers of delay”: warfarin, hip fractures, and target-driven care. *Geriatr Orthop Surg Rehabil* 5(3):103–108
9. Tran T, Delluc A, de Wit C, Petrich W, Le Gal G, Carrier M (2015) The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. *Thromb Res* 136(5):962–965
10. Ranhoff AH, Martinsen MI, Holvik K, Solheim LF (2011) Use of warfarin is associated with delay in surgery for hip fracture in older patients. *Hosp Pract* 39(1):37–40
11. No authors listed (2015) Norwegian Directorate of Health (Helsedirektoratet). Preoperative wait time for hip fracture patients, National Quality Indicator System: Quality indicator description. <https://www.helsedirektoratet.no/statistikk/statistikk/kvalitetsindikatorer/behandling-av-sykdom-og-overlevelse/hoftebrudd-operert->
12. Lindahl AK, Talsnes O, Figved W et al (2014) Measures for increased survival after hip fractures. Publication from The National Knowledge Center for the Health Service. <https://www.fhi.no/globalassets/dokumenterfiler/notater/2014/tiltak-for-okt-overlevelse-etter-hoftebrudd2> (date last accessed 16 July 2019)
13. Leer-Salvesen S, Engesaeter LB, Dybvik E, Furnes O, Kristensen TB, Gjertsen JE (2019) Does time from fracture to surgery affect mortality and intraoperative medical complications for hip fracture patients? An observational study of 73 557 patients reported to the Norwegian Hip Fracture Register. *Bone Jt J* 101-B(9):1129–1137
14. Hourston GJ, Barrett MP, Khan WS, Vindlacheruvu M, McDonnell SM (2019) New drug, new problem: do hip fracture patients taking NOACs experience delayed surgery, longer hospital stay, or poorer outcomes? *Hip Int.* <https://doi.org/10.1177/1120700019841351>
15. Linnerud I, Viktil K, Ranhoff A, Molden E (2016) Bruk av direktevirkende orale antikoagulantia og andre antitrombotika blant eldre hoftebruddspasienter; prevalens og kliniske aspekter. [The use of direct oral anticoagulants and other antithrombotic agents

- among elderly hip fracture patients; prevalence and clinical aspects] Master thesis in clinical pharmacology at the University of Oslo in 2016. <https://www.duo.uio.no/bitstream/handle/10852/51405/Ina-Linnerud-masteroppg-2016-DOAK-og-hoftebrudd.pdf?sequence=8>. Accessed 05 Dec 2019
16. Franklin NA, Ali AH, Hurlley RK, Mir HR, Beltran MJ (2018) Outcomes of early surgical intervention in geriatric proximal femur fractures among patients receiving direct oral anticoagulation. *J Orthop Trauma* 32(6):269–273
  17. Ranhoff AH, Holvik K, Martinsen MI, Domaas K, Solheim LF (2010) Older hip fracture patients: three groups with different needs. *BMC Geriatr* 10:65
  18. Frenkel Rutenberg T, Velkes S, Vitenberg M, Leader A, Halavy Y, Raanani P et al (2018) Morbidity and mortality after fragility hip fracture surgery in patients receiving vitamin K antagonists and direct oral anticoagulants. *Thromb Res* 166:106–112
  19. Gleason LJ, Mendelson DA, Kates SL, Friedman SM (2014) Anticoagulation management in individuals with hip fracture. *J Am Geriatr Soc* 62(1):159–164
  20. Cohn MR, Levack AE, Trivedi NN, Villa JC, Wellman DS, Lyden JP et al (2017) The hip fracture patient on warfarin: evaluating blood loss and time to surgery. *J Orthop Trauma* 31(8):407–413
  21. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361(12):1139–1151
  22. Flaker G, Lopes RD, Hylek E, Wojdyla DM, Thomas L, Al-Khatib SM, Sullivan RM, Hohnloser SH, Garcia D, Hanna M, Amerena J, Harjola VP, Dorian P, Avezum A, Keltai M, Wallentin L, Granger CB, ARISTOTLE Committees and Investigators (2014) Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. *J Am Coll Cardiol* 64(15):1541–1550. <https://doi.org/10.1016/j.jacc.2014.07.967>
  23. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365(10):883–891
  24. Schermann H, Gurel R, Gold A, Maman E, Dolkart O, Steinberg EL et al (2019) Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications. *Injury* 50(2):398–402
  25. Grimes JP, Gregory PM, Noveck H, Butler MS, Carson JL (2002) The effects of time-to-surgery on mortality and morbidity in patients following hip fracture. *Am J Med* 112(9):702–709
  26. Verbeek DO, Ponsen KJ, Goslings JC, Heetveld MJ (2008) Effect of surgical delay on outcome in hip fracture patients: a retrospective multivariate analysis of 192 patients. *Int Orthop* 32(1):13–18
  27. Haleem S, Heinert G, Parker MJ (2008) Pressure sores and hip fractures. *Injury* 39(2):219–223
  28. Cordero J, Maldonado A, Iborra S (2016) Surgical delay as a risk factor for wound infection after a hip fracture. *Injury* 47(Suppl 3):S56–S60
  29. Larsson G, Holgers KM (2011) Fast-track care for patients with suspected hip fracture. *Injury* 42(11):1257–1261
  30. Mullins B, Akehurst H, Slattery D, Chesser T (2018) Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre. *BMJ Open* 8(4):e020625
  31. Lott A, Haglin J, Belayneh R, Konda SR, Leucht P, Egol KA (2019) Surgical delay is not warranted for patients with hip fractures receiving non-warfarin anticoagulants. *Orthopedics* 42(3):e331–e335
  32. Hoerlyck C, Ong T, Gregersen M, Damsgaard EM, Borris L, Chia JK et al (2020) Do anticoagulants affect outcomes of hip fracture surgery? A cross-sectional analysis. *Arch Orthop Trauma Surg* 140(2):171–176
  33. Liu X, Dong Z, Li J, Feng Y, Cao G, Song X et al (2019) Factors affecting the incidence of surgical site infection after geriatric hip fracture surgery: a retrospective multicenter study. *J Orthop Surg Res* 14(1):382
  34. Furnes O, Engesaeter, LB, Gjertsen JE, Fenstad AM, Bartz-Johannessen C, Dybvik E, Fjeldsgaard K, Gundersen T, Hallan G (2019) Annual report, Norwegian Arthroplasty Register 2019. [https://nrlweb.ihelse.net/eng/Rapporter/Report2019\\_english.pdf](https://nrlweb.ihelse.net/eng/Rapporter/Report2019_english.pdf)
  35. Johansen A, Golding D, Brent L, Close J, Gjertsen JE, Holt G, Hommel A, Pedersen AB, Rock ND, Thorngren KG (2017) Using national hip fracture registries and audit databases to develop an international perspective. *Inj Int J Care Inj* 48(10):2174–2179
  36. Neuman MD, Rosenbaum PR, Ludwiq JM, Zubizarreta JR, Silber JH (2014) Anesthesia technique, mortality, and length of stay after hip fracture surgery. *JAMA* 25(311):2508–2517
  37. Van Waesberghe J, Stevanovic A, Rossaint R, Coburn M (2017) General vs. neuraxial anaesthesia in hip fracture patients: a systematic review and meta-analysis. *BMC Anesthesiol* 17:8
  38. Jinlei L, Halaszynski T (2015) Neuraxial and peripheral nerve blocks in patients taking anticoagulant or thromboprophylactic drugs: challenges and solutions. *Local Reg Anesth* 8:21–32
  39. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT et al (2010) Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (third edition). *Reg Anesth Pain Med* 35(1):64–101
  40. Gogarten W, Vandermuelen E, Van Aken H et al (2010) Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 27:999
  41. Wysokinski WE, McBane RD (2012) Periprocedural bridging management of anticoagulation. *Circulation* 126:486
  42. Narouze S, Benxon HT, Provenzano DA, Buvaendran A, De Andres J, Deer TR, Rauck R, Huntoon M (2015) Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med* 40(3):182–212

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.