|Clinical Outcomes with Preoperative and Postoperative Start of Thromboprophylaxis in Total Hip Arthroplasty

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"To my surprise"

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LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to by their roman numerals in the text:

Paper I: Borgen PO, Dahl OE, Reikerås O. Preoperative versus postoperative initiation of dalteparin thromboprophylaxis in THA. Hip International 2010; 20 (03): 301- 307.

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LIST OF ABBREVIATIONS

ACCP	American Academy of Chest Physicians
ASA	American Society of Anesthesiologists
CI	Confidence Interval
CNS	Central Nervous System
CT	Computer Tomography
DOAC	Direct Oral Anticoagulants
DIC	Disseminated Intravasal Coagulation
DVT	Deep Venous Thrombosis
F1+2	Prothrombin fragment 1+2
ICD-10	International Classification of Diseases, 10th edition
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
NAR	Norwegian Arthroplasty Register
NOAC	Novel (New) Oral Anticoagulants
NOMESKO	Nordic Medico-Statistical Committee
NPR	Norwegian Patient Register
NSAID	Non-Steroid Anti-Inflammatory Drug
OR	Odds Ratio
PE	Pulmonary Embolism
PTS	Post Thrombotic Syndrome
RCT	Randomized Controlled Trial
SD	Standard Deviation
SEM	Standard Error of Means
THA	Total Hip Arthroplasty
THR	Total Hip Replacement
TG	Thrombin Generation
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

GENERAL INTRODUCTION

TOTAL HIP ARTHROPLASTY

Epidemiology

Implantation of hip prostheses in patients suffering from painful and disabling degenerated hip joints, is a highly successful and cost-effective treatment (Ethgen, Bruyere, Richy et al., 2004; Learmonth, Young, & Rorabeck, 2007). John Charnley introduced the principles of low friction arthroplasty during the 1960s (Charnley, 1961). His work still constitutes the basis for total hip arthroplasty (THA), which has resulted in considerable improvement in the quality of life for millions of patients. THA has been claimed to be the "the operation of the 20th century" (Learmonth, Young, & Rorabeck, 2007). There are more than 1 million THAs performed worldwide each year (Pivec, Johnson, Mears, & Mont, 2012). There is considerable variability in the incidences of THA operations around the world, mainly explained by economic variables and health priorities (De Pina, 2011). The prevalence of THA in Norway and other western countries is high and expected to increase with a more active older population and longer life expectancy. There are similar expectations for the poorer countries and even at a higher rate. Refinement of surgical techniques and hospital care, better implants, growing economic wealth and health budgets together with political priorities, has opened up for broader indications. Not only elderly with disabling hip arthritis but also young people, with high quality-of-life expectations are now candidates for hip replacements. These changes will induce significant burden on health services in general, including hip replacement surgery in the future (Ostendorf, Johnell, Malchau et al., 2002; Kurtz, Ong, Lau et al., 2007). The mean age at operation in Norway is now 68.5 year, and the most common indication for THA is idiopathic osteoarthritis (The Norwegian Arthroplasty Register, 2016). Population projections towards 2040 indicate a 100% increase in the number of people over 75 years in Norway (Eriksen, 2014). These patients have an additional risk for comorbidities and have not the same ability to counteract the pathophysiological process induced by the surgical trauma (Clegg, Young, Iliffe et al., 2013).

Surgical considerations

In a total hip arthroplasty operation, the hip joint is replaced by a stem inserted into the femoral canal and a cup implanted in the acetabulum of the pelvis fixed with or without cement. The articulating surfaces should be low frictional and consist of a metal or ceramic head articulating against a polyethylene (plastic) or ceramic surface. Implant characteristics,

the physical (tribology) and biomechanical (positioning) properties of this artificial joint are essential for good, long lasting results. In the past, patients planned for THA arrived the hospital days before surgery. It was common to use general anesthesia, the operation took hours with extensive incisions leading to large bleeding volumes, use of suction drains contributed to further blood loss, and transfusions were routinely required. After surgery, patients were immobilized for days with several restrictions. The rates of postoperative complications, including infection, anemia, venous thromboembolism (VTE), and mortality were higher than today (Johnson, Green, & Charnley, 1977; Charnley, 1979). Antibiotics, thromboprophylaxis, improvement in surgical and anesthesiological practice gradually led to a reduction of these complications (Khan, Malviya, Muller et al., 2014). High-pressure cementation into trabecular bone was introduced to enhance fixation, but in addition to its chemical procoagulant properties, this cementing technique simultaneously mobilized procoagulant intramedular cell debris and aggregates into the circulation (Dahl, Aspelin, & Lyberg, 1995). To avoid "bone-cement implantation syndrome", circulatory disturbances and systemic thrombus formation, high-pressure irrigation of the bone marrow became routine (Donaldson, Thomson, Harper, & Kenny, 2009). More use of uncemented implants was suggested to reduce complications related to cement, but without substantial evidence of beneficial clinical effect on the before mentioned events (Levine, Hirsh, Gent et al., 1991; Kim, Oh, & Kim, 2003). During the last decade, increased focus on cost-effectiveness has emphasized reorganization of surgery. Fast track surgery includes better preoperative preparation, with optimization of comorbidities and anemia, smaller incisions, use of tranexamic acid, more use of uncemented implants, less use of drugs, faster mobilization and shorter hospital stay (Kehlet, 2013). Reports show that these actions had a positive effect on venous thromboembolism, mortality, and other clinical complications (Lassen & Borris, 1991; Pearse, Caldwell, Lockwood, & Hollard, 2007; Husted, Otte, Kristensen et al., 2010).

Anesthesiological considerations

Preoperative risk assessment is performed to minimize the possibility of complications related to surgery. Most commonly used is the scoring method of the American Society of Anesthesiologists (ASA score), which is an index designed to assess the overall physical status of the patient (Saklad, 1941; Fitz-Henry, 2011). The score was initially proposed as a useful statistical tool, and not to prognosticate the effect of a surgical procedure on the patient's physical status. It has undergone several revisions since then and is now a useful clinical tool to quantify the patient physiological status before surgery.

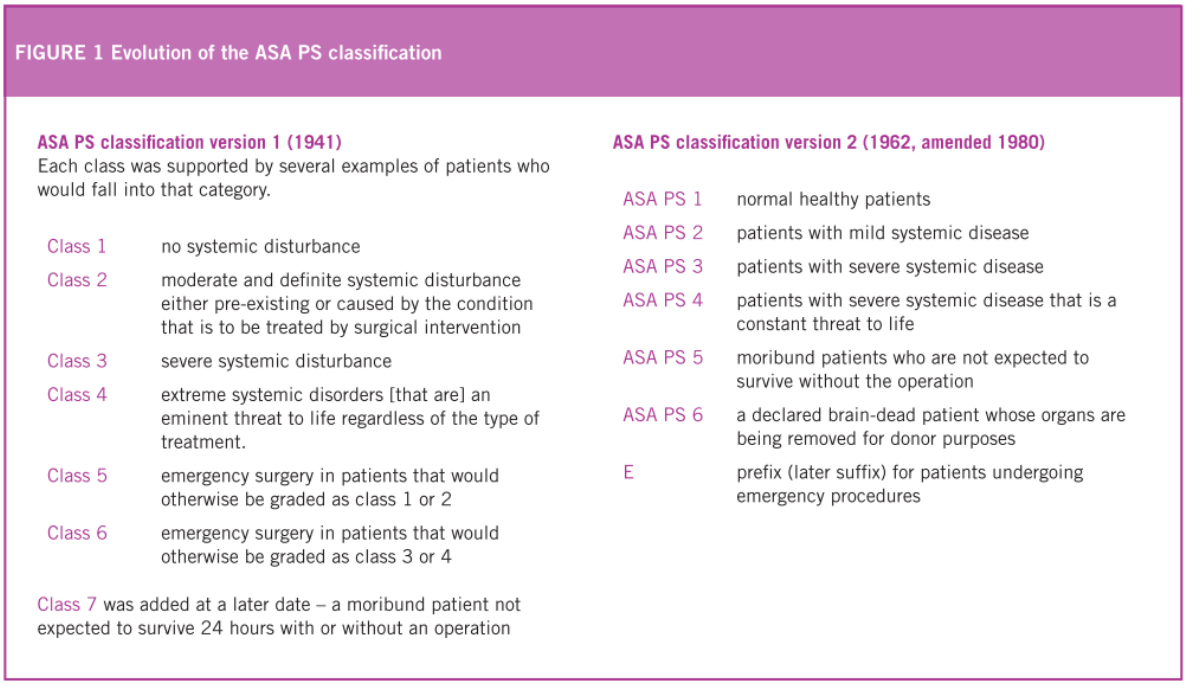

FIGURE 1 Evolution of the ASA PS classification

ASA PS classification version 1 (1941)
Each class was supported by several examples of patients who would fall into that category.

Class 1	no systemic disturbance
Class 2	moderate and definite systemic disturbance either pre-existing or caused by the condition that is to be treated by surgical intervention
Class 3	severe systemic disturbance
Class 4	extreme systemic disorders [that are] an eminent threat to life regardless of the type of treatment.
Class 5	emergency surgery in patients that would otherwise be graded as class 1 or 2
Class 6	emergency surgery in patients that would otherwise be graded as class 3 or 4

Class 7 was added at a later date – a moribund patient not expected to survive 24 hours with or without an operation

ASA PS classification version 2 (1962, amended 1980)

ASA PS 1	normal healthy patients
ASA PS 2	patients with mild systemic disease
ASA PS 3	patients with severe systemic disease
ASA PS 4	patients with severe systemic disease that is a constant threat to life
ASA PS 5	moribund patients who are not expected to survive without the operation
ASA PS 6	a declared brain-dead patient whose organs are being removed for donor purposes
E	prefix (later suffix) for patients undergoing emergency procedures

Figure 1. The American Society of Anesthesiologists (ASA) score.

According to the Norwegian Arthroplasty Register, the ASA class distribution of Norwegian hip arthroplasty patients has shown a slight tendency to more comorbid patients over the years (The Norwegian Arthroplasty Register, 2013)

Table 1. ASA classification - primary THA in Norway

Year	ASA1	ASA2	ASA3	ASA4	ASA5	missing	Total
2012	1 160	5 000	1 542	24	0	60	7 786
2011	1 295	4 548	1 407	25	0	82	7 357
2010	1 430	4 344	1 350	23	0	146	7 293
2009	1 765	3 863	1 322	24	0	135	7 109
2008	1 805	3 580	1 280	27	0	155	6 847
2007	1 797	3 332	1 258	30	0	243	6 660
2006	1 875	3 020	1 160	40	0	224	6 319
2005	2 202	2 833	1 054	24	0	484	6 597

Regional anesthesia for THA surgery relies on neuraxial blockade by injections of local anesthetic drugs into either the subarachnoid space (spinal anesthesia) or into the epidural space (epidural anesthesia). Hypotensive regional anesthesia has been found to induce less thrombotic complications, better muscle relaxation, less blood in the cement-bone interface

and reduced blood loss compared to general anesthesia. It has therefore been preferred in hip replacement surgery (Modig, Borg, Karlstrom et al., 1983; Mauermann, Shilling, & Zuo, 2006). However, there have been concerns about the potential for spinal bleeding when anticoagulants are combined with neuraxial blockade (Horlocker, Wedel, Rowlingson et al., 2010). The incidence of neurologic injuries resulting from hemorrhage is not known. A large Swedish survey investigated serious neurologic complications among 1.2 million spinal and 450000 epidural blocks over a ten-year period, and found 33 spinal hematomas (Moen, Dahlgren, & Irestedt, 2004). Reports from North America showed a higher risk, explained by different modalities of thromboprophylaxis with higher doses administered closer to surgery (Horlocker, Wedel, Rowlingson et al., 2010). The risk of spinal hematoma has consistently been higher with epidural than spinal blockades, and especially after removal of epidural catheters in the postoperative period (Vandermeulen, Van Aken, & Vermylen, 1994). However, a recent Cochrane review comparing neuraxial to general anesthesia for hip fractures did not reveal any differences in neurological injuries (Guay, Parker, Gajendragadkar, & Kopp, 2016). There are several suggested recommendations and guidelines for management of neuraxial anesthesia and analgesia to avoid spinal injury (Breivik, Bang, Jalonen et al., 2010; Horlocker, Wedel, Rowlingson et al., 2010).

Assessment of Results

The outcome of hip arthroplasty is good, and the majority of the patients are satisfied for years after their operation (Brokelman, van Loon, & Rijnberg, 2003). Traditionally, radiographic evaluations and surgeon-based hip scores with an assessment of function, movement, and relief of pain are used to judge the outcome of surgery (Garellick, Herberts, & Malchau, 1999; Nilsdotter & Bremander, 2011). Later patient-based assessments have been developed, and are extensively used to assess clinical outcome after surgery (Arden, Kiran, Judge et al., 2011). However, they are criticized because they are lengthy, disrupt the clinical flow, have incomplete survey responses, low response rate and to be of limited value due to individual expectations (Lyman, Lee, Franklin et al., 2016). Survival analyses, with removal of implants regarded as a failure, was first published by Dobbs in 1980 (Dobbs, 1980), and has been the primary outcome in the national population-based hip arthroplasty registers, first established in Sweden in 1979 (Ahnfelt, Herberts, Malchau, & Andersson, 1990), and in Norway in 1987 (Havelin, Espehaug, Vollset et al., 1993). These registers also include data on patient demographics, surgery, implants, and prophylaxis, and provide valuable information about hip arthroplasty practice. Validations using the Norwegian Patients Register (NPR) as

the reference have demonstrated approximately 98% registration completeness for primary THAs in Norway (Espehaug, Furnes, Havelin et al., 2006). Ten and 20-year survival for primary hip arthroplasty reaches now beyond 95% and 75% respectively (The Norwegian Arthroplasty Register, 2016).

COMPLICATIONS TO THA

Bleeding

During total hip arthroplasty, injuries to the blood vessels in the soft tissue, and vacuoles and vessels of the bone induce bleeding. Hemorrhage may be external and easily detected or enclosed in the tissue leading to hematoma and wound bruising. Although factors directly related to the operation lead to bleeding, it can be influenced by, individual predispositions, type of anesthesia and analgesia, use of drains, and medication. The clinical consequences of hemorrhage depend on the rate of bleeding, location and the physical condition of the patient. Significant blood loss may result in hypovolemic shock and death in rare cases, but even small- volume bleeding may be harmful depending on the location.

Blood loss is routinely measured during and after surgery in sponges and drains. However, since a proportion of blood loss is hidden, calculations to estimate this masked blood loss have been proposed (Sehat, Evans, & Newman, 2004; Liu, Zhang, Chen et al., 2011). Blood loss and transfusion requirements vary widely in THA, Table 2. In recent years, it has consequently been reduced, due to better pre- and postoperative preparation of the patient, refinement of anesthesiological and surgical techniques, cessation of drains, focus on transfusion practice and application of tranexamic acid (Henry, Carless, Moxey et al., 2007; Rajesparan, Biant, Ahmad, & Field, 2009; Khan, Malviya, Muller et al., 2014). In the 1970s, Coventry reported an average blood loss of 1650 ml and transfusions of 1144 ml blood (Coventry, Beckenbaugh, Nolan, & Ilstrup, 1974). At our institution, we recorded a mean blood loss of 1200ml with 50% of patients requiring transfusions in 2002 and this was reduced to 500ml and 10% respectively in 2016. Others, Table 1, report similar figures for hip arthroplasty operations. However, high inter center variability in the reported red blood cell loss and blood transfusions during hospitalization has been emphasized, and make these measures uncertain (Bierbaum, Callaghan, Galante et al., 1999; Trice, Walker, D'Lima et al., 1999; Gombotz, Rehak, Shander, & Hofmann, 2007).

Preoperative hemoglobin level below 12g/dl is associated with increased transfusion requirements and postoperative complications (Aderinto & Brenkel, 2004). It is influenced by

several variables such as gender, height, weight, age, fluid balance and deficiency diseases. Abnormalities should be investigated and treated before the operation (Goodnough, Maniatis, Earnshaw et al., 2011). During and after surgery the volume of blood loss and the ability of the patient to rebalance fluid therapy will impact the hemoglobin concentration. It is common to have some form of protocol to guide transfusion decisions. Typically, they include hemoglobin, hematocrit, and comorbidities. Historically, postoperative hemoglobin concentration below 10g/dl triggered transfusions, but now 8g/dl and even 7g/dl are accepted in a patient without significant comorbidities (Carson, Terrin, Noveck et al., 2011).

Bleeding leading to blood transfusions is associated with an increased risk of adverse outcomes, including infection, myocardial infarction and even death, and may also increase the length of hospital stay and total hospital charges (Parvizi, Ghanem, Joshi et al., 2007; Patel, Walsh, Sehgal et al., 2007; Rao, Eikelboom, Granger et al., 2007; Walsh, Preston, Bong et al., 2007; Kwong, Kistler, Mills et al., 2012; Jorgensen & Kehlet, 2016). Even small bleeding volumes may lead to severe complications depending on location. In addition to the neural injuries previously discussed, there have been reports of a possible correlation between anticoagulation, bleeding and surgical-site infections (Moen, Dahlgren, & Irestedt, 2004; Parvizi, Ghanem, Joshi et al., 2007). Consequently, some surgeons and anesthesiologists question the use of aggressive prophylaxis (Huang, Parvizi, Hozack et al., 2016).

In pharmaceutical trials evaluating prophylaxis, bleeding has frequently been a secondary safety outcome. Therefore, this has been difficult to assess due to lack of standard operating procedures and a variety of definitions (Dahl, Quinlan, Bergqvist, & Eikelboom, 2010). Bleeding is reported according to the site, severity, the volume of blood loss, transfusion requirements and the decrease in hemoglobin, and according to complex estimations of hidden blood loss during exposure of an anticoagulant compound (Nadler, Hidalgo, & Bloch, 1962; Sehat, Evans, & Newman, 2004). Further, a variety of terms are used including insignificant, superficial, minimal, minor, moderate, major, serious, severe, excessive, overt, clinically relevant, non-major and fatal (Dahl, Quinlan, Bergqvist, & Eikelboom, 2010). Differences in definitions and terms of the result of these trials must be kept in mind when evaluating the publications (Fihn, Callahan, Martin et al., 1996; Committee for Medicinal Products for Human Use (CHMP), 2007). Lack of criteria and standard bleeding definitions and the multifactorial nature of bleeding make it difficult for surgeons to conclude on the influence of anticoagulants on bleeding complications (Eroglu, Uzunlar, & Erciyes, 2005).

Table 2. Comparison of blood loss and transfusion requirements

Study	Study design	Number of patients	Interaction	Blood loss (mL)	% patients who had transfusions	Followup
(Warwick, Bannister, Glew et al., 1995)	Thromboprophylaxis THA RCT	78 78	Enoxaparin Control	1207 1231	1.65 units 1.47 units (% not available)	Not described (14 days?)
(Francis, Pellegrini, Totterman et al., 1997)	Thromboprophylaxis THA RCT	279 271	Wa rfarin 12 hours preoperative vs Dalteparin 2 hours preoperative	1601 1600	% patients transfused not described	7 ± 2 days
(Colwell, Chelly, Murkin et al., 2007)	Thromboprophylaxis THA RCT	176 177	Aprotinin Control	709 957	17% 32%	Not described ("analyzed if at least one efficacy measurement")
(Hull, Pineo, Francis et al., 2000)	Thromboprophylaxis THA RCT	496 487 489	Dalteparin 2 hours preoperative 12-24 hours postoperative Warfarin postoperative	 1512 1503 1471	Day 0 42% Days 1-8 43% Day 0 41% Days 1-8 38% Day 0 38% Days 1-8 28%	Not described ("central adjudication of safety events in our trial included all events from the commencement of surgery up to postoperative day 8")
(Walsh, Preston, Bong et al., 2007)	Risk for transfusion Retrospective THA	1034	LMWH and Coumadin® vs aspirin and foot pump	502 (perioperative, no drain?)	50% (RR 2.8 and 1.54)	Reviewed retrospectively
(Johansson, Pettersson, & Lisander, 2005)	Tranexamic acid THA RCT	47 53	Tranexamic acid Control	969 1324	(8/47) 17% (23/53) 43%	6-8 weeks
(Borgen, Dahl, & Reikeras, 2010)	Timing of prophylaxis THA Retrospective	298 301	Fragmin 12 hours preoperative 6 hours postoperative	1230 1084	53% 35%	6 months
(Borgen, Dahl, & Reikeras, 2012)	Timing of prophylaxis. THA RCT	40 40	Fragmin 12 hours preoperative vs 6 hours after surgery	1081 1023	30% 12.5%	6 months

Thromboembolism

"The possibility of fatal pulmonary embolism after total hip replacement is a hip surgeon's constant worry . . . no matter how rare this might be" (Charnley, 1979).

The hemostatic process is usually well balanced, and blood with all its constituents is maintained in a fluid, clot-free state. Thrombosis is the formation of a blood clot inside the vessel. Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality in the general population. In a systematic review, Fowkes et al. estimated the annual incidence of the first DVT of approximately five person pr. 10000, and increasing with age (Fowkes, Price, &

Fowkes, 2003). White estimated that about 6% and 12% of patients diagnosed with DVT and PE respectively, died within a month (White, 2003). Hospitalization attributed to more than half the cases of VTE, and the increased risk was associated with high age, race (Caucasians), a history of venous thromboembolism, concomitant diseases like cancer and cardiovascular disease, trauma and surgery.

Total hip arthroplasty leads to venous stasis, vessel injury and hypercoagulability (Stamatakis, Kakkar, Sagar et al., 1977; Sharrock, Go, Harpel et al., 1995). According to Virchow (Virchow, 1856), these factors are the cornerstones of clot formation and favor thromboembolism (Bagot & Arya, 2008). The blood flow in the veins is slow, and their soft vessel-walls make them prone to stasis. Immobilization during and after surgery with reduced muscle action, kinking of the femoral veins during insertion of the femoral component and additional postoperative hematoma and tissue-edema, contributes to reduced blood flow and stasis (Stamatakis, Kakkar, Sagar et al., 1977; Planes, Vochelle, & Fagola, 1990; Sharrock, Go, Harpel et al., 1995; Warwick, Harrison, Glew et al., 1998). Stasis provokes thrombosis formation (Wessler, 1962) by the accumulation of clotting factors, tissue hypoxia, endothelial injury and distension of valves exposing sub endothelial matrix (Furie & Furie, 1992). The vessel injuries produced by surgery also causes endothelial injury that presents the blood to procoagulant constituents and tissue factor leading to activation of coagulation. Damage to the bone marrow and cancellous bone tissue causes a release of fat, cell debris and proteins (tissue factor, interleukins, etc.) (Modig, Busch, Olerud, & Saldeen, 1974; Sharrock, Go, Harpel et al., 1995). All these mechanisms trigger local prothrombotic processes and inflammation at the point of trauma and may trigger cellular entrapment. If these substances are carried through the circulation, they may cause cell toxic damage and failure of distant organs (Dahl, 1997). In cases of patent foramen ovale or other septal defects of the circulation, which has been estimated to affect up to 25% of the population (Hari, Pai, & Varadarajan, 2015), these substances may enter the arterial circulation leading to systemic complications (Dahl, Harenberg, Wexels, & Preissner, 2015).

Deep venous thrombosis is the most common form of venous thromboembolism, but may be difficult to diagnose due to postoperative edema or hematoma. Thromboembolism is a dynamic process, progression and resolution may proceed simultaneously, and therefore the majority of thrombi generated during, and after surgery are asymptomatic and dissolves spontaneously (Kearon, 2003; Kim, Oh, & Kim, 2003; Cordell-Smith, Williams, Harper, & Gregg, 2004). The superficial thrombi are often asymptomatic and rarely produce emboli. They may cause pain, swelling, varicose veins and chronic skin ulcers of the leg, eventually

leading to post-thrombotic syndrome (PTS) (Clagett, Anderson, Geerts et al., 1998). Thrombosis of the proximal deep veins is more often symptomatic, and may eventually release fragments, emboli, with the previously mentioned consequences. Larger thromboembolic masses may result in obstruction of the pulmonary circulation, chronic reduced pulmonary capacity and sometimes death.

Suspect venous thromboembolism is one of the most common causes of readmissions after THA (Seagroatt, Tan, Goldacre et al., 1991). Due to diffuse symptoms, differences in surgical and hospital care, development after discharge, demographic variations and low rates of autopsies there is a high variation in the reported rates of VTE (Bjornara, Gudmundsen, & Dahl, 2006). Charnley reported symptomatic deep venous thrombosis in 30 to 70%, clinical diagnosed pulmonary embolism in about 10%, and mortality in the range of 1-3% after hip arthroplasties without thromboprophylaxis (Charnley, 1979). Chemical prophylaxis reduced these figures (Coventry, Beckenbaugh, Nolan, & Ilstrup, 1974; Johnson, Green, & Charnley, 1977). Kakkar confirmed the rate of deep venous thrombosis by using the objective composite endpoint venographically detected DVT, and demonstrated a significant reduction in DVT with the application of unfractionated heparin and later low-molecular-weight-heparin (LMWH) prophylaxis (Kakkar, Corrigan, Spindler et al., 1972; Kakkar, 1975). Tilleul et al. estimated an in-hospital VTE rate of 1,4% in THA patients evaluating a national disease-related group database (Tilleul, LaFuma, Colin, & Ozier, 2006). A Norwegian study reported a cumulative incidence of venous thromboembolism within six months of 2.7%, of which 1.5% had DVT, 1.1% had PE, and 0.6% had both, and that the majority occurred after discharge (Bjornara, Gudmundsen, & Dahl, 2006).

Evaluations indicate that there has been progress in reducing thromboembolism and its complications after surgery over the years (Collins, Scrimgeour, Yusuf, & Peto, 1988; Geerts, Bergqvist, Pineo et al., 2008). This progress is due to the praxis of prophylaxis, but also influenced by better risk assessments, refinement in surgical technique and earlier mobilization (Husted, Otte, Kristensen et al., 2010; Jorgensen & Kehlet, 2016). The American Academy of Chest Physicians (ACCP) panelist estimated symptomatic PE rate of approximately 0.55% the first 35 postoperative days with LMWHs (Geerts, Pineo, Heit et al., 2004). In 2012, Januel et al. performed a meta-analysis and found that approximately 1 out of 200 THA patients developed thromboembolic symptoms with adequate prophylaxis (Januel, Chen, Ruffieux et al., 2012).

Awareness of the risk of postoperative venous thromboembolism is cornerstones in the diagnosis. However, the majority of DVTs are non-symptomatic, and only a small percentage

of patients dying of PE have previous symptoms of DVT (Sandler & Martin, 1989). Unfortunately, simple and reliable methods to detect thrombin generation and separate benign and harmful thrombosis activity after THA are lacking. Ultrasonography is usually performed to diagnose deep venous thrombosis in clinically suspected patients, but due to low specificity supplementary venography is often needed (Borris, Christiansen, Lassen et al., 1989). Computer tomography (CT) angiography and ventilation/perfusion scintigraphy CT is the most available methods to detect pulmonary embolism, but there are concerns about the high doses of radiation (Hess, Frary, Gerke, & Madsen, 2016). Blood assays are useful in monitoring drugs, but insufficient to identify individual thrombosis activity in a clinical setting (Panteleev & Hemker, 2015). Plasma D-dimers increases by any condition in which fibrin is formed and degraded by plasmin. It is used to rule out clinically suspected VTE due to high sensitivity, but the specificity is too low for a positive diagnosis. Other laboratory tests do not have acceptable sensitivity or specificity, and can even remain normal in patients at risk of thrombosis and bleeding. Therefore, there is need for new and better methods to diagnose thrombosis risk. The development of new global assays combining laboratory methods for detection of thrombosis generation may be one way to go (Panteleev & Hemker, 2015). Another method utilize prothrombin fragment (F1+2), a split product produced from the conversion of prothrombin to thrombin that can be measured by Enzyme-Linked Immunosorbent Assay (ELISA) (Bezeaud, Aronson, Menache, & Guillin, 1978). These small molecules, with a half-life in plasma of 90 minutes, are excreted in urine, and both blood and urine levels of F1+2 increases during THA, and remains elevated for several days reflecting thrombotic activity (Cofrancesco, Cortellaro, Corradi et al., 1998; Arnesen, Dahl, Aspelin et al., 2003; Borris, Breindahl, Ryge et al., 2007). Plasmin-α2-antiplasmin complex (PAP) is an index of recent fibrinolytic activity, which increases with thrombosis generation, and therefore might be higher in patients with elevated risk of thrombosis (elderly, coronary artery disease, atrial fibrillation, previous VTE) (Feinberg, Macy, Cornell et al., 1999).

Other clinical complications

Complications directly related to the operation are few. Profuse bleeding, fractures around the prosthesis, and clinical signs of nerve injuries are serious but infrequent with an incidence below 1% (Winther, Foss, Wik et al., 2015). The rate of prosthesis dislocation varies widely up to 10% (Alberton, High, & Morrey, 2002; Werner & Brown, 2012). Surgical site infections tend to increase, and affect approximately 1-2 % of THA patients (Dale, Hallan, Hallan et al., 2009). As with venous thromboembolism, it will impose a heavy burden on the health

services (Kurtz, Ong, Schmier et al., 2007). A link between anticoagulation therapy, surgical site bleeding, hematoma formation and infection have been suggested, but like thromboembolic and bleeding complications, it is usually difficult to assess single risk factors (Saleh, Olson, Resig et al., 2002; Parvizi, Ghanem, Joshi et al., 2007). As described earlier the production and dissemination of procoagulant factors may give rise to many conditions on the venous and arterial side, e.g. stroke, myocardial ischemia, acute respiratory distress syndrome (ARDS), fat embolus and disseminated intravasal coagulation (DIC). There is a need for standard criteria in reporting of complications after THA (Clavien, Barkun, de Oliveira et al., 2009; Healy, Iorio, Clair et al., 2016). This will enhance comparisons between studies and make them more reliable.

Readmissions

Readmissions after surgery have gained more attention and have been a key quality measure as the rates of operations continuously increase (Weinberg, Kraay, Fitzgerald et al., 2017). Among surgeons, procedure-relevant outcome assessments using scoring systems and register data have been popular, but systematic approaches to assess complications leading to readmissions have not gained the same attention. Mednick et al. analyzed the American College of Surgeons–National Surgical Quality Improvement Program data for 2011 and found 3.7% readmissions 30 days following a primary total hip arthroplasty (Mednick, Alvi, Krishnan et al., 2014). The most common surgical and medical complications leading to readmissions were wound infections, venous thromboembolism, blood transfusion and urinary tract infection. Preoperative comorbidities significantly increased the rate of readmissions, and increased overall comorbidities and ASA class were associated with increased readmission risk. Weinberg et al. reported a 5% 30-days and a 6% 90-days readmission rate, and the early readmissions were more likely to be surgery related, while medical conditions dominated later on (Weinberg, Kraay, Fitzgerald et al., 2017).

Death

Deaths in patients undergoing total hip arthroplasty are infrequent. These patients have undergone thorough preoperative assessments and are prepared for surgery under standardized conditions. In the 1970s, Charnley et al. reported that 1-3% of the patient died after replacement of the hip joint (Charnley, 1979). The leading cause of deaths in these patients not receiving thromboprophylaxis was a pulmonary embolism. More recent publications indicate that, deaths due to ischemic heart disease and cerebrovascular events

have been more common, which is also the main cause of death in the general population (Lie, Engesaeter, Havelin et al., 2002; Blom, Pattison, Whitehouse et al., 2006). Some even claim that the routine use of potent anticoagulation has neither reduced the overall mortality, the symptomatic PE rate or the proportion of deaths due to pulmonary embolism (Murray, Britton, & Bulstrode, 1996; Poultsides, Gonzalez, Memtsoudis et al., 2012; Lieberman, Cheng, & Cote, 2017). However, there are uncertainties about the reporting of causes of deaths due to the low rate of autopsies (Alfsen & Maehlen, 2012). Seagroatt et al. analyzed data from the Oxford Record linkage study and found an excess mortality of 1.1% within 90 days of a THA, and most deaths were related to cardiovascular events (Seagroatt, Tan, Goldacre et al., 1991). Similar figures were reported from the Norwegian arthroplasty register reporting a 90-day mortality of 0.9% (Lie, Engesaeter, Havelin et al., 2000). They found an excess mortality during the first three postoperative months, followed by reduced mortality compared to the general population. The main cause of death was ischemic heart disease (Lie, Pratt, Ryan et al., 2010). A recent review of patients undergoing THA by Berstock et al. published an incidence of all-cause mortality after 90 days of 0,7% (Berstock, Beswick, Lenguerrand et al., 2014). In an extensive register study from the National Joint Registry of England and Wales, Hunt et al. a decrease in mortality within 90 days after THA, from in 0.6% in 2003 to 0.3% in 2011, was reported (Hunt, Ben-Shlomo, Clark et al., 2013). Together, these reports indicate a trend towards reduced mortality after THA in recent years although more patients with more comorbidity are operated.

THROMBOPROPHYLAXIS

The balance of thrombosis and bleeding.

The risk of venous thromboembolism relates not only to the procedure (the type of surgery), but also to genetic traits (deficiencies and mutations), and acquired factors (age, obesity, malignancy, trauma, hormones) (Caprini, 2010). A system that could account for all these factors and calculate the individual risk would likely be valuable as a guideline for VTE prevention. At present, there are mainly two approaches to make decisions on thrombosis prevention measures.

The risk assessment models put the patients into groups (low, moderate, high and very high risk) according to more precise individual scores like, age, weight, comorbidities, medication, type of surgery and presence of additional risk factors, and recommends prophylactic regimens for each patient (Caprini, 2010). These models have been validated and is in clinical

use by several surgeons to help determine a strategy for the type and length of prophylaxis (Bahl, Hu, Henke et al., 2010). Others judge them too complicated to administer and therefore impractical and believe there is a risk for suboptimal compliance to such a prophylaxis protocol (Kulshrestha & Kumar, 2013). A positive effect of an individualized risk assessments strategy, could be higher awareness of symptoms of thromboembolism (Nam, Nunley, Johnson et al., 2016).

Another approach is to target thromboprophylaxis in the majority of the THA patients, which is supported by national and international consensus groups and guidelines (Mont & Jacobs, 2011; Falck-Ytter, Francis, Johanson et al., 2012; Vandvig, 2015). These guidelines include a systematically grading of evidence. Based on this thromboprophylaxis is recommended for all patients undergoing total joint arthroplasty (Guyatt, Eikelboom, Akl et al., 2013). Data from randomized controlled trials are usually the basis for grade 1A recommendations. Thus, there is a risk that these patients are carefully selected, and not representative for the wide spectrum of patients undergoing THA. There is also disagreement between guidelines about how efficacy and safety should be defined, and to what extent the outcome depends on the antithrombotic agents or exogenous factors ranging from the timing and duration to patient characteristics and surgical technique (Cushner & Nett, 2009; Lachiewicz, 2009). Therefore, a large number of publications have reported conflicting information, and no single agent or method has been considered superior and gained general acceptance (Lowe, 1981).

Use of anticoagulants alone is most common, but it is important to have in mind that drugs primarily act on the coagulation system of the blood, which according to Virchoff, is only part of the process of thrombosis formation (Virchow, 1855; Bagot & Arya, 2008). The use of anticoagulants have reduced thromboembolic complications markedly, but also increased the potential for bleeding and other complications (Parvizi, Ghanem, Joshi et al., 2007; Patel, Walsh, Sehgal et al., 2007; Kwong, Kistler, Mills et al., 2012). These factors contribute to the gaps in the provision of prophylaxis.

The ideal drug for thromboprophylaxis should be easy to administer, effective in reducing VTE, have low rate of complications, predictable pharmacokinetics, no need for monitoring, and have no interactions (Bounameaux, 2009). Since thrombin is a critical enzyme in the pro- and anticoagulant process and the extend of generation is individual (high responders and low responders), control of thrombin has been considered crucial. In 1959, Sevitt & Gallagher demonstrated a reduced risk of thromboembolism in hip fracture patients that received phenindione, a drug that have similar action on the coagulation system as warfarin (Sevitt & Gallagher, 1959). Later, the most used anticoagulants have been vitamin K antagonists

(Warfarin) (Amstutz, Friscia, Dorey, & Carney, 1989), unfractionated heparin (UFH) (Sharrock, Go, Harpel et al., 1995) and LMWH (Bergqvist, Benoni, Bjorgell et al., 1996; Kakkar, 1997). They have different limitations related to predictability and administration, which may affect the efficacy-safety balance leading to adverse events, and also the feasibility of the hospital stay. Due to these challenges, there is ongoing research to develop better drugs for clinical use. Recently, new drugs for oral administration has been approved, i.e., Rivaroxaban (Eriksson, Borris, Friedman et al., 2008), Apixaban (Lassen, Gallus, Raskob et al., 2010), and Dabigatran (Eriksson, Dahl, Rosencher et al., 2007). They are still in limited use in orthopedic surgery probably due to fear of bleeding complications (The Norwegian Arthroplasty Register, 2016; Venker, Ganti, Lin et al., 2017).

Table 2. Drugs used for thromboprophylaxis in primary and revision THA in Norway (The Norwegian Arthroplasty Register, 2016)

Drugs	2005-06	2007	2008	2009	2010	2011	2012	2013	2014	2015
Acetylsalicylsyre (Albyl-E, Globoid, Acetyratio, Magnyl E)		0,1 %	0,1 %	0,1 %				0,1 %	0,4 %	0,6 %
Apixiban (Eliquis)							0,1 %	1,2 %	1,5 %	1,5 %
Dabigatranetixalat (Re-Novate, Pradaxa)	1,4 %		0,2 %	0,2 %					0,1 %	0,1 %
Dalteparin (Fragmin)	47,0 %	54,9 %	61,0 %	50,7 %	63,2 %	65,1 %	63,1 %	56,1 %	51,6 %	58,4 %
Dekstran (Macrodex, Dextran)		0,1 %	0,1 %		0,1 %	0,3 %	0,1 %	0,1 %	0,1 %	
Enoksaparin (Klexane)	43,1 %	41,2 %	35,1 %	44,0 %	31,5 %	25,5 %	24,6 %	27,9 %	31,4 %	24,1 %
Rivaroksaban (Xarelto)					0,3 %	2,9 %	2,0 %	2,3 %	2,2 %	1,5 %
Warfarin (Marevan)	0,1 %	0,1 %	0,1 %	0,1 %	0,1 %		0,1 %			0,1 %
Ximelagatran (Exanta, Malagatran)	1,1 %		0,1 %	0,1 %	0,1 %					
Other			0,1 %	0,1 %					0,1 %	
Combination of 2 drugs	1,2 %	1,0 %	1,2 %	3,3 %	3,9 %	5,2 %	8,4 %	10,8 %	10,6 %	11,5 %
Clinical study	1,1 %	0,3 %	1,1 %	0,7 %	0,1 %					
Unknown							0,1 %		0,1 %	
No drugs		0,1 %	0,1 %	0,1 %						
Missing	5,0 %	2,2 %	0,9 %	0,7 %	0,7 %	0,9 %	1,5 %	1,4 %	2,0 %	2,2 %
Total	**14981**	**7711**	**7971**	**8325**	**8591**	**8660**	**9177**	**9448**	**9442**	**9809**

Acetylsalicylic acid, which inhibits blood plates adherence to the vessel wall, have been shown to be effective for thrombosis prevention especially in combination with mechanical devices (Lotke, 2007). Acetylsalicylic acid is used by a large proportion of patients undergoing THA to prevent ischemic heart disease and stroke, and have gained increased attention in recent years (Wilson, Poole, Chauhan, & Rogers, 2016; Azboy, Barrack, Thomas et al., 2017). Acetylsalicylic acid was included as an alternative for thromboprophylaxis in the 9th ACCP edition (Falck-Ytter, Francis, Johanson et al., 2012), and recently in the Norwegian Directorate of Health recommendations (Vandvig, 2015).

LMWHs (dalteparin and enoxaparin) have been the most commonly used anticoagulant for prophylaxis in Norway for decades (The Norwegian Arthroplasty Register, 2016). LMWHs are pentasaccharides with a molecular weight below 8000 Dalton derived from unfractionated heparin (UFH). They replaced UFH in clinical use in the 1980/90s mainly due to reports of excessive bleeding (Patterson, Marchand, & Ranawat, 1989). They convert circulating anti-thrombin (antithrombin III) from a slow to a rapid inhibitor of factor Xa and factor IIa (thrombin) and induce their action through the release of tissue factor pathway inhibitor (TFPI). Although the different LMWHs to some extent have different pharmacokinetic properties and anticoagulant profiles, and therefore are not entirely interchangeable, their clinical efficacies in the prevention of thrombosis after surgery are similar (White, 2003). LMWHs are injected subcutaneously, usually in fixed doses for prophylactic use, have a bioavailability of about 90%, and a half-life in plasma of 3-6 hours. Elimination is mainly by the kidneys. There is no antidote, but protamine sulfate can inhibit some of the anti-Xa activity. LMWHs have several favorable properties compared to unfractionated heparin. It has a weaker inhibition of thrombin, more predictable dose-response relationship (reduced binding to other plasma proteins), longer plasma half-life (decreased binding to macrophages and endothelial cells), and lower incidence of heparin-induced thrombocytopenia (less binding to blood plates). Weaker inhibition of thrombin and decreased platelet interaction are believed to reduce bleeding complication rates compared to unfractionated heparin (Vinazzer & Woler, 1986). However, there are reported an inter-individual variation on the response to LMWHs, and as they are administered routinely in fixed doses without control of their effect on coagulation, they might not always be optimal (Al Dieri, Alban, Beguin, & Hemker, 2006). Initiation of LMWH prophylaxis before surgery has been most common, but has in recent years been replaced by postoperative administration (The Norwegian Arthroplasty Register, 2016).

Intuitively, surgeons avoid drugs that interfere with hemostasis and tend to prefer mechanical devices as graduated compression stockings (GCS), intermittent pneumatic compression devices (IPC) and foot pumps for thrombosis prevention. By this they increase flow in leg veins and reduce stasis, which to some extent are believed to induce fibrinolysis. The ease of use, compliance, and costs also influence their application. A meta-analysis performed by National Health Service (NHS) showed a 60-72% odds reduction of VTE with the use of these devices (Roderick, Ferris, Wilson et al., 2005; Urbankova, Quiroz, Kucher, & Goldhaber, 2005). Evidence-based clinical guidelines recommend against mechanical devices

alone, except for patients with high bleeding risk (Geerts, Bergqvist, Pineo et al., 2008). Therefore, their use is mainly in combination with anticoagulants.

There are few well-designed studies explicitly targeting the effect of early mobilization on thromboembolic complications, and up today the scientific evidence is considered to be weak (Lassen & Borris, 1991; Pearse, Caldwell, Lockwood, & Hollard, 2007; Husted, Otte, Kristensen et al., 2010). Fast-track surgery which includes early mobilization is increasingly adapted and shown to enhance recovery post-surgery and supported by consensus-based guidelines (Mont & Jacobs, 2011). This approach may open up for and influence new strategies for thromboprophylaxis practice.

A prevalence of 15-30% of venographically detected deep venous thrombosis has been demonstrated at the time of hospital discharge in patients undergoing THA (Sharrock, Go, Harpel et al., 1995). There seems to be a continuous activation of coagulation for days to weeks after the initial trauma that can trigger late VTE (White, Romano, Zhou et al., 1998; Colwell, Collis, Paulson et al., 1999; Dahl, Gudmundsen, & Haukeland, 2000; Arnesen, Dahl, Aspelin et al., 2003). Further, a 3-6% recurrence rate of VTE during the first 3 months after an acute thromboembolism episode has been reported (Leizorovicz, 1998). Thus, extended prophylaxis has been recommended (Geerts, Bergqvist, Pineo et al., 2008), but recent Cochrane review concluded that the rate of severe clinical thromboembolism or deaths from pulmonary embolism was not changed when prophylaxis was extended for more than 14 days (Forster & Stewart, 2016).

BACKGROUND OF THE STUDY

The application of chemical thromboprophylaxis is an ongoing debate among surgeons due to the downsides of anticoagulation and the conflicting recommendations (Lachiewicz, 2009). Low molecular weight heparins are anticoagulants with proven effect against venous thromboembolism. In 2016, it was still the most common anticoagulant used for orthopedic thrombosis prevention in Norway, with a market share above 80% (The Norwegian Arthroplasty Register, 2016). Recommendations of the timing of the first dose of LMWH in relation to surgery have varied widely (Strebel, Prins, Agnelli, & Buller, 2002). Initially, LMWH was injected close to surgery, but this approach revealed excessive bleeding. (Bergqvist, Burmark, Frisell et al., 1986). Starting LMWH prophylaxis more than 12 hours before surgery was proven to be effective and safe (Bergqvist, Matzsch, Burmark et al., 1988). Consequently, to impose protective effects before the surgical trauma and subsequent

thrombin activation, the preoperative start of anticoagulation became the recommended method in the European countries (Hirsh & Levine, 1992; Bergqvist, Burmark, Flordal et al., 1995). In North America, Turpie et al. reported LMWH to be effective when initiated 12-24 hours after surgery, and the postoperative start was preferred, mainly to avoid blood loss and bleeding complications (Turpie, Levine, Hirsh et al., 1986; Kearon & Hirsh, 1995; Horlocker, Wedel, Benzon et al., 2003). Hull et al. performed a systematic review and a randomized controlled trial to investigate preoperative versus postoperative initiation of LMWH (dalteparin) prophylaxis in THA. In the systematic review (1999) they found less frequent DVT and bleeding with the preoperative approach (Hull, Brant, Pineo et al., 1999). The randomized controlled study compared pre- versus postoperative prophylaxis and "the just in time" principle (Hull, Pineo, Francis et al., 2000). The study included 3 treatment arms; 2500IU dalteparin injected 2 hours before surgery, 2500IU injected 4-6 hours postoperatively, and warfarin administered the evening of surgery. They concluded that both dalteparin regimens showed reduced risk for DVT compared with warfarin, and that the postoperative approach provided superior efficacy without increased major bleeding compared to warfarin. Strebel et al. performed a systematic review to assess efficacy and safety with three approaches of starting LMWH prophylaxis (Strebel, Prins, Agnelli, & Buller, 2002). They found similar efficacy and safety for the pre- and postoperative regimen. The third alternative, using perioperative start was more effective but associated with an increased risk of major bleeding. Based on these studies, together with other post-marketing trials comparing different drugs, subgroups analyses of controlled trials with single anticoagulants and indirect comparisons across systematic reviews, the ACCP guideline from 2003 recommended postoperative initiation of prophylaxis (Raskob & Hirsh, 2003). However, other evidence-based guidelines continued to provide conflicting recommendations (Lachiewicz, 2009). There has been a shift towards postoperative initiation of thromboprophylaxis in Europe for several reasons (Table 3). There is a potential for less bleeding complications when surgery and neuraxial blockade is not influenced by anticoagulants. The increased attention to fast-track surgery, with same day admission and shorter hospital stay, makes postoperative initiation beneficial. The new oral anticoagulants (NOAC) developed for postoperative commencement have been introduced to the marked, and were expected to replace three decades of LMWH use (Weitz, Hirsh, Samama, & American College of Chest, 2008; Ferrandis, Castillo, de Andres et al., 2013). Although, these drugs have not yet gained success among orthopedic surgeons in Norway, the idea of starting prophylaxis after surgery has been increasingly adapted (The Norwegian Arthroplasty Register, 2016).

Table 3. Initiation of pharmacological thromboprophylaxis in primary THA. 1-Preoperative, 2-postoperative, 3-missing information on medication start, 4-no prophylaxis

Year	1	2	3	4	Missing	Total
2015	1058 (13%)	6244 (74%)	954 (11%)	56 (1%)	90 (1%)	**8402**
2014	1113 (14%)	5946 (73%)	962 (12%)	31 (0%)	76 (1%)	**8128**
2013	1340 (17%)	5632 (70%)	1047 (13%)	10 (0%)	63 (1%)	**8092**
2012	1579 (20%)	4851 (62%)	1322 (17%)	9 (0%)	82 (1%)	**7843**
2011	2219 (30%)	4304 (58%)	795 (11%)	3 (0%)	38 (1%)	**7359**
2010	2365 (32%)	4308 (59%)	610 (8%)	4 (0%)	43 (1%)	**7330**
2009	2606 (37%)	3861 (54%)	578 (8%)	3 (0%)	67 (1%)	**7115**
2008	3133 (46%)	3059 (45%)	574 (8%)	8 (0%)	75 (1%)	**6849**
2007	3546 (53%)	2432 (37%)	530 (8%)	10 (0%)	142 (2%)	**6660**
2006	3927 (62%)	1544 (24%)	678 (11%)	15 (0%)	155 (2%)	**6319**
2005	4393 (67%)	679 (10%)	1093 (17%)	6 (0%)	426 (6%)	**6597**

Total hip arthroplasties are performed on stable patients under standardized conditions with low acceptance for complications. LMWH provides thrombosis prevention, but there is a delicate balance between efficacy and safety. Venographically detected DVT (a surrogate endpoint) has been the main endpoint in pharmaceutical trials, and there might have been an underestimation of the downsides of chemical thromboprophylaxis, such as bleeding, transfusion, infections and other postoperative complications (Parvizi, Ghanem, Joshi et al., 2007; Rao, Eikelboom, Granger et al., 2007; Sharrock, Gonzalez, Go et al., 2008). Although bleeding complications are few, they might be serious leading to disability. There are few studies primarily targeting how different timing of the same LMWH influences blood loss, bleeding events and other clinical complications after THA. With the increased frequency of THA procedures, evaluations of efficacy and safety of any regimens used to avoid thrombosis during surgery are important, and also the downsides of these generalized regimens.

AIMS OF THE STUDY

The general purpose of this project was to analyze and clarify clinical consequences of a shift from preoperative to the postoperative start of low-molecular-weight-heparin (dalteparin) prophylaxis in patients undergoing total hip arthroplasty. We used dalteparin for this project, because it was and still is, by far the most common drug used for thromboprophylaxis in orthopedic surgery in Norway. We performed the project stepwise including four studies applying different research designs but keeping the outcomes similar.

Due to a vast number of publications using venous thromboembolism as a primary endpoint, we decided to focus on bleeding events. The primary goal was to evaluate if there were clinically important differences in surgical blood loss and total blood loss when we initiated LMWH prophylaxis before or after surgery. Second, we sought to evaluate differences in bleeding events, clinical thromboembolic episodes, and other prophylaxis related complications, readmission, and deaths.

Paper 1:

Retrospective cohort study: to evaluate blood loss, transfusion requirements, and other potentially prophylaxis related complications in two cohorts undergoing primary THA before and after a change from preoperative to the postoperative start of LMWH thromboprophylaxis.

Paper 2:

Prospective randomized clinical trial: to evaluate the effect on the same endpoints as in the retrospective study.

Paper 3:

Prospective randomized laboratory study: to study laboratory markers of coagulation and fibrinolysis (F1+2, PAP, D-dimer) comparing dalteparin injection the evening before or 6 hours after THR.

Paper 4:

Register study: to evaluate bleeding complications, thromboembolic events and other clinical complications and death, starting LMWH prophylaxis before or after total hip arthroplasty, using a population-based study design combining two national registers.

SUMMARY OF THE PAPERS

Paper I

Preoperative versus postoperative initiation of dalteparin thromboprophylaxis in THA.

Pål O. Borgen, Ola E. Dahl, Olav Reikerås

Background Chemical thromboprophylaxis in total hip arthroplasty may increase surgical site bleeding. The drug dose and timing of such therapy is important. **Methods** We studied two cohorts of 298 and 301 patients undergoing elective cemented THA at Martina Hansens Hospital before and after a routine shift from pre- to postoperative start of thromboprophylaxis. The first group received their first dose of dalteparin (Fragmin) 5000IU the evening before surgery and the second group half dose six hours postoperatively followed by 5000IU daily, according to the hospitals policy. Patient characteristics were similar concerning gender, age, BMI and ASA classification. Seventy percent were females. **Results** Blood loss was reduced by 146 ml from 1230 ml to 1084ml ($p<0.001$) with postoperative prophylaxis alone. The number of patients receiving blood was reduced from 53%to 35% ($p<0.001$), and the use of transfused packed red blood cells was reduced from 1.25 to 0.83 units per patient ($p=0.001$). The overall rates of non-vascular complications 6 months after surgery were 12% and 11%, bleeding related events 6.0% and 4.0%, and thromboembolic related events were 2.0% and 2.3% in the preoperative and the postoperative cohorts. Two patients died in the preoperative group and one in the postoperative group due to venous and arterial thromboembolism. **Interpretation** This study showed that 2500IU Fragmin started six hours postoperatively significantly reduced blood loss and transfusions compared to 5000IU injected the evening before surgery without differences in thromboembolic events.

Paper II

Blood Loss in Cemented THA is not Reduced with Postoperative Versus Preoperative Start of Thromboprophylaxis.

Pål O. Borgen, Ola E. Dahl, Olav Reikerås

Background Preoperative start of pharmacological thromboprophylaxis has been preferred on the assumption that thrombin formation commences during surgery. However, because of the potential for increased surgical bleeding, some surgeons advocate postoperative initiation. Trials on the timing of thromboprophylaxis have been designed primarily to detect thromboembolic events, and it has been difficult to interpret the magnitude of blood loss and bleeding events owing to lack of information for bleeding volume and underpowered bleeding

end-points. We asked therefore whether there are differences in blood loss, transfusion requirements, and other postoperative complications with the two regimens. **Methods** In a double-blind, randomized controlled trial, 80 patients undergoing primary cemented THA were allocated to dalteparin injections starting the evening before or 6 hours after surgery. Blood loss was measured by weighing sponges and drapes, volume in suction drains during surgery, and wound drains until removal 24 hours postoperatively. Hemoglobin and hematocrit were recorded at predefined times during and after surgery. **Results** We found no differences in blood loss, bleeding-related events or number of patients who had transfusions with preoperative and postoperative thromboprophylaxis, respectively. Other complications were few in both groups. **Interpretation** Our data suggest that blood loss is similar with preoperative and postoperative initiation of dalteparin thromboprophylaxis, without significant differences in other postoperative complications.

Paper III

Biomarkers of Coagulation and Fibrinolysis during Cemented Total Hip Arthroplasty with Pre- versus Postoperative. Start of Thromboprophylaxis.

Pål O. Borgen, Ola E. Dahl, O Reikerås

Background Thromboprophylaxis is recommended in THA surgery. Clinical trials suggest that the drug dose and timing of initiating prophylaxis influence antithrombotic effectiveness and safety. **Methods** We studied the time course and gradients of plasma coagulation and fibrinolysis during cemented THA in twenty patients that were randomly assigned to have the first dose of 5000IU dalteparin injected the evening before or 6 hours after surgery. Specific biomarkers detecting coagulation (prothrombin fragment 1+2 (F1+2)) and fibrinolytic activity (plasmin-α2- antiplasmin complex (PAP) and D-dimer) were collected at six events during hospitalization and analyzed. **Results** There were no significant group differences in the biomarkers at any time point. The highest concentrations were measured 6 hours after surgery and before the first postoperative injection. A marked decrease followed at the first postoperative day, and then a second increase in plasma concentrations was observed six days after surgery. **Interpretation** This study showed that activation of coagulation and fibrinolysis by the operative trauma was the same when the first dose of dalteparin was injected the evening before or 6 hours after THA surgery

Paper IV

Similar Clinical Outcome with Preoperative and Postoperative Start of Thromboprophylaxis in THA: A Register-based Study.

Pål O. Borgen, Are H. Pripp, Eva Dybvik, Lilian Leistad, Ola E. Dahl, Olav Reikerås

Background Total hip arthroplasty has been associated with a variety of thrombin-generated complications affecting both venous and arterial vascular system with symptoms manifesting from a number of organs. Although these events may be less common now than they were in the past, they can be serious, and most patients undergoing the procedure still receive thromboprophylaxis. However, chemical thromboprophylaxis may also be responsible for prophylaxis related complications. With reduced mortality and morbidity, and an expected increase in THA procedures, evaluations of the safety of any regimens preventing thrombosis are increasingly important. The timing of anticoagulants related to surgery is still controversial. We, therefore, asked whether there is a difference in bleeding events, thromboembolic episodes, and other clinical prophylaxis related complications, readmissions, and deaths with the pre- versus postoperative start of thromboprophylaxis. **Methods** We used a population-based follow-up design with predefined data based on international health codification to assess clinical effects of LMWH prophylaxis initiated before or after THA. We took data limited to primary THA performed in Norway between January 1, 2008, and December 31, 2011, from the Norwegian Arthroplasty Register and the National Patient Register. The two registers were merged, after identifying patients with their 11- digit personal identification number (Social Security number). We obtained data regarding demographics, administrative and surgical details, and episode histories for prophylaxis related events within 180 days of surgery. A total of 25163 patients were included for analysis, and 9977(40%) versus 15186(60%) received pre- and postoperative LMWH, respectively. Clinical effect of LMWH thromboprophylaxis initiated before or after surgery was assessed. **Results** After adjustment for age, sex, operation time, operation year and ASA class, we could not demonstrate major differences in bleeding events; (odds ratio [OR], 1.04; 95% CI, 0.88–1.22; p = 0.660), thromboembolic episodes; (OR, 1.03; 95% CI, 0.84–1.27; p = 0.786), or other postoperative clinical complications; (OR, 0.86; 95% CI, 0.76–0.99; p = 0.034), with the two regimens. Six months' mortality were similar; (OR, 0.76; 95% CI, 0.56–1.05; p = 0.093), and the readmission rate higher in the preoperative group; (OR, 0.92; 95% CI, 0.85–0.97; p = 0.016). **Interpretation** Our data suggest that the risk of postoperative complications is comparable whether LMWH prophylaxis is initiated before or after THA, but the risk of readmission was higher with preoperative administration.

GENERAL DISCUSSION

PATIENTS AND METHODS

Paper I, II, and III of this thesis are based on data from patients undergoing primary cemented total hip arthroplasty at Martina Hansens Hospital. Paper IV is prepared in collaboration with the Norwegian Arthroplasty Register and the National Patient Register.

The four papers have different designs. In paper I we used a retrospective approach, to be able to formulate a hypothesis, to perform a power analysis and obtain information regarding the feasibility of a prospective study. Planning the prospective study, we also included a randomized study on hemostatic markers. Finally, we combined data from two national registers in order to compare results from the randomized trials with similar outcomes in patients routinely operated with THA.

In the first study (paper I) we evaluated the consequences of a shift from pre- to postoperative initiation of dalteparin in two consecutive cohorts. Surgical and total blood losses were the primary endpoints. Transfusion requirements and other prophylaxis related outcomes were also assessed. The retrospective design was feasible for several reasons. We had easy access to the patient files and the data used in the analyses. It was cheap, because we needed relatively few resources. It provided quick estimates of possible effects of the shift from pre- to postoperative administration on blood loss. Measures of associations, were used in planning future studies and interventions. Retrospective studies are difficult to control for confounding factors which may affect our results. Selection bias is another weakness that applies both to studies with prospective and retrospective design. To minimize the risk of selection bias we included the majority of patients admitted for hip replacements at our institution during the study period, 298 out of 338 (88%) patients in the first cohort and 301 out of 389 (77%) in the postoperative cohort. The project was conducted in a specialized hospital, with the highest number of elective hip replacements among hospitals in Norway, and recruiting patients from all part of the country. The surgery was highly standardized, with only minor changes in hospital staff, clinical pathway, anesthesia, surgical technique, implants and postoperative rehabilitation between the two study periods. The basic characteristics of the two cohorts were similar and representative for patients operated with THA in Norway at that time (The Norwegian Arthroplasty Register, 2013), which strengthened the external validity of the study. There is a risk of recall bias when the data of interest are obtained retrospectively. Simple data such as hemoglobin, hematocrit, measurements of blood loss in drains and sponges, and units of blood transfusions were collected from the patient's files

during the hospital stay according to well-established routines, and are therefore most likely reliable (Johansson, Lisander, & Ivarsson, 1999). Nevertheless, we cannot exclude that the staff's attention towards blood loss and transfusions changed due to the routine shift. We may also have missed data in patients referred to other centers after discharge. Lastly, confounding variables may exist such as individual surgeon technique within the groups, and patient characteristics such as differences in comorbidity.

In the second study (paper II), we recruited patients to a double-blind, prospective randomized controlled trial to test the hypotheses generated in the retrospective study. A randomized controlled trial is considered to be the gold standard for causal inference and to provide the highest level of evidence. The random inclusion of patients allowed us to control for possible confounding factors with a known or unknown influence on the outcomes, and thereby reduce the risk of confounding. The participants were recruited from our regular pool of patients as was the case for the retrospective study, inclusion and exclusion criteria and surgery were similar, and we used the same outcome variables. After this study was approved by the regional ethics committee, we prospectively randomized 80 patients 50 years or older who underwent cemented THA for primary osteoarthritis between March and June 2008. During that same time-frame, we treated a total of 104 patients with primary cemented THAs for osteoarthritis. After obtaining a written informed consent from the eligible participant, a nurse that was otherwise not involved in the study performed randomization of the patients and prepared the syringes with dalteparin or placebo injected the evening before surgery. Concealment is vital to avoid observer bias, and the randomization was performed in blocks to ensure an equal balance between the two treatment arms. We kept the randomization numbers in closed envelopes throughout the study to prevent manipulation of treatment. The contents of the injections were blinded to the investigator, hospital staff, and the patient throughout the study to prevent biased assessments. Patients included in the study followed the normal clinical pathway for patients undergoing THA at the institution, which made the study acceptable for both patients and the staff. We assume this resulted in good compliance; indeed all patients completed the survey. We did not use predefined classifications of bleeding events because variability in definition and reporting has made it difficult to compare between trials. We therefore merely measured the volume of blood loss by weighing sponges and drapes, volume in suction drains during surgery and wound drains until removal 24 hours postoperatively according to the routine. We assessed patients on a daily basis, and if they showed any clinical sign of thromboembolic events, we performed objective tests, including ECG, blood gases, plain chest radiography, venography, and spiral CT after a clinical

examination. We also recorded and stored information of all other complications in the clinical research file (CRF) on a daily basis, and this reduced the risk of recall bias. The CRF contained complete registration of all the outcome variables for all the study participants at the end of the survey, indicating proper organization and conduction during all phases. The research file was stored safely throughout, and the blinding was not broken until all patients had completed the study. We performed the survey following the CONSORT (Consolidated Standards of Reporting Trials) statement, which constitutes guidelines for reporting parallel group randomized trials, and is a checklist used to compare the conduct of trials and the validity of results (Schulz, Altman, Moher, & Group, 2010). By following these instructions, we reduced the risk of biased results due to methodological errors. We also registered the study in ClinicalTrials.gov, where readers could follow the trial during all phases from planning to publication, which contributes to transparency (Anand, Cahan, & Ghosh, 2017). In the third study (paper III) we analyzed markers of coagulation and fibrinolysis in patients who received either dalteparin or placebo before surgery. After informed written consent twenty patients, representing one of the randomization blocks in the prospective trial were included. We obtained venous blood samples at six different time points; the day before surgery (T1), after anesthesia but before surgery (T2), at the end of wound closure (T3), at 6 hours after surgery (T4), at the first day after surgery (T5), and at 6 days after surgery (T6). These time-points represent surgical and anesthesiological interventions that induce activation of coagulation and fibrinolysis and increase the chance of obtaining relevant data on the effect of dalteparin. The investigator, to ensure proper handling of the materials, collected all blood samples. Blood was obtained from peripheral veins in citrate vacutainers, using a 21–gauge needle with minimal stasis, and stored on ice. Within one hour, the samples were prepared by double centrifugation, and then frozen and stored at -80 degrees C, until analyzed. An experienced bioengineer performed the analyses at the coagulation laboratory of Oslo University Hospital, Rikshospitalet. The collection of venous blood may not have been optimal, as earlier studies have demonstrated a more moderate expression of the levels of biomarkers in peripheral venous blood compared to arterial blood (Dahl, Molnar, Vinje et al., 1988). We measured prothrombin fragment 1+2 (F1+2) and plasmin/α2-antiplasmin complex (PAP) by the enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Enzygnost F1+2 and PAP, Dade Behring, Marburg, Germany) following manufacturer's instructions. D-dimer was determined using STA-Liatest, D-Dimer assay, which is an automated and rapid micro latex D-dimer assay. An additional assessment of clinical

endpoints was possible because we had already included these patients in the prospective clinical study.

Acknowledging the limitations of the three previous studies regarding selection bias, statistical power and external validity, we performed a fourth observational survey (paper IV) combining two national registers. The strength of such a study design is the high number of unselected subjects included and with data prospectively registered independent of the study. The likelihood of more robust evidence increases due to the statistical power provided by these large observational studies.

The Norwegian Arthroplasty Register (NAR) receives clinical data in a standardized form identified by the Social Security number, and the surgeons fill it in at the time of the operation. The form holds information on patient characteristics, diagnosis, surgical details, and included data about thromboprophylaxis in 2005. Until 2017 they only received additional information when the implant was revised, limited to information about the cause of revision. The NAR is linked to Statistics Norway who provides information on deaths. The Norwegian Patient Register (NPR) is a national health register and contains administrative, medical and demographic data for all patients having received treatment in the specialist services. The NPR gets information about diagnosis using the International Classification of Diseases (ICD-10), and treatment using the Nordic Medico-Statistical Committee (NOMESKO) Classification of Surgical and Medical Procedures. Using these internationally accepted and applied classification systems makes comparisons between studies more accessible and potentially more reliable. From 2008 onward, data was linked to the Social Security number making tracking of particular individuals possible for research purposes. The regulations allow linkage of the Norwegian Arthroplasty Register and the Norwegian Patient Register, with a potential to obtain data about clinical events after discharge. Observational studies are more suitable to detect rare effects of treatment and are more likely to provide information on what is achieved under normal clinical circumstances. With this approach, the investigator can assess a vast number of variables with less workload. Due to the large numbers of patients in the national registers, one might find significant results earlier than in randomized studies. The difference between statistical and clinical significance in studies with a large sample-size has to be considered. The results of register studies also possess an excellent potential for generalization, being more representative for all the patients undergoing a procedure.

We assumed that the change from pre- to postoperative start of prophylaxis occurred gradually from 2008 and onwards and therefore included all primary THA patients operated

in Norway between 01.01.2008 and 31.12.2011. However, the two cohorts were dissimilar in sample-size and in several basic characteristics, which influenced the statistical analyses. As with the two previous studies, we followed the patients for six months, which might be a too long observation period, due to effects of concomitant diseases and other conditions influencing the outcomes and making the interpretations difficult ("dilution of outcomes over time").

By encrypting and replace the social security numbers by a study allocation number before the two register files were merged, we ensured data protection of the individual patient. We excluded patient operated for fractures and those who had bilateral one-stage procedures because they probably represent another pathophysiological challenge (0.2%). We also excluded patients with no information about LMWH treatment (1%). The distribution of pre- and postoperative start of prophylaxis was unbalanced, with 40% and 60% of the patients respectively. Based on ICD-10 and NOMESKO codification, we selected 21 clinical diagnoses and treatments that we assumed were associated with anticoagulation and thromboembolism. To compare with the previous three studies, we categorized these events into the same three groups, - bleeding events, - thromboembolic episodes, - and other clinical complications associated with anticoagulation. We also assessed readmissions and mortality of all causes during the first 180 days after surgery for the whole population and the two cohorts separately. The register-based data was also available for subgroup-analyses. The NPR database does not link date of readmissions to the primary diagnoses and the readmission diagnosis, which make it difficult to determine causality between complications and readmissions, without performing a manual assessment. Information about the date of readmissions and deaths were more accessible to track from the study file. Otherwise, the NPR file was somewhat unorganized and needed revision ahead of analyzing the data.

The records of NOMESKO codes NFB 20, 30, 40, 99 in the Norwegian Arthroplasty register are regularly validated, and the completeness has been good (The Norwegian Arthroplasty Register, 2016). The latter is probably due to well-defined end-points and adherence among the surgeons to the registration process (Arthursson, Furnes, Espehaug et al., 2005). The Norwegian Patient Register is defined as a gold standard, and validation of data quality are based on that assumption. The patient registers in Sweden and Denmark have been validated and show overall high to moderate data quality (Pedersen, Johnsen, Overgaard et al., 2004; Ludvigsson, Andersson, Ekbom et al., 2011). However, the quality of data regarding other outcomes of interest such as modalities of thromboprophylaxis and postoperative complications other than dose directly related to the implant are more difficult to evaluate.

Further, there might be a complication cascade where the most serious complication is registered, whereas the following less serious events are omitted. Registrations of serious and definite events are probably more valid than the less severe and diffuse complications (Gunnarsson, Seligsohn, Jestin, & Pahlman, 2003). There is also a risk of bias in the reports to a register made for administrative purposes and linked to the reimbursement system. The NPR holds data on all diagnoses and treatments and is the reference register when the other patients registered are evaluated. However, if the input of ICD-10 and NOMESKO records to the Norwegian Patient Register varies considerably from the centers, this makes the term "gold standard" somehow uncertain. We have asked NPR for validation studies for other disease entities, but received only a few, analyzing orthopedic and neurological conditions. Data on other diagnosis and treatment codes are probably more insecure. We believe that there is a potential for better input to the registers to make them more valuable for research and not only administrative purposes. There are some general limitations for all large register surveys. These include missing data, unreported cases and duplications, delays in reporting, misclassification of diagnoses and treatment, which means that the results must be interpreted cautiously. However, since we compared two large cohorts, there is a reason to believe that the lack of such data was similarly distributed in the two cohorts of the present study. The study was completed and published according to the STROBE (Strengthening the reporting of observational studies in epidemiology) checklist for Level III observational studies (von Elm, Altman, Egger et al., 2007). At the time, we were not aware of the RECORD Reporting of studies Conducted using Observational Routinely-collected health data statement (Nicholls, Quach, von Elm et al., 2015) developed in recent years.

Statistics

We applied IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA) for statistical analyses in all four papers. We also used Stata SE 14.1 for Windows (Stata Corp LLC, College Station, TX, USA) for estimation of statistical power in the fourth study. For all statistical evaluations, a probability value (p-value) of < 0.05 was considered significant.
In the first study (paper I), the main outcome variable was surgical blood loss (ml) and total blood loss (ml). The sample sizes were considered large enough to apply the central limit theorem regarding normally distributed samples means. Thus, the continuous data were compared using independent samples t-test to assess our hypothesis, i.e. different volumes of blood loss with the two regimens. For count data, such as the number of blood transfusions,

assumed not to be normally distributed, we used the Mann-Whitney U-test. For categorical data, such as frequencies of patients transfused, we used Pearson chi-square test.

In the second study (paper II), we performed a power analysis based on two earlier studies of blood loss in patients undergoing THA, and with transfusion requirements considered to be clinical relevant. In a prospective controlled study in patients undergoing THA, Johansson et al. found that a 27% reduction in total blood loss (355 mL) significantly reduced ($p = 0.009$) the number of patients who received transfusions by 30% (Johansson, Pettersson, & Lisander, 2005). In a retrospective study (Borgen, Dahl, & Reikeras, 2010), we found that a similar reduction in total blood loss (30%) (370 ml) significantly reduced ($p = 0.006$) the number of patients who received transfusions by 28%. With 80% power (alpha = 0.05), at least 37 patients were required in each group. We randomized 80 patients to compensate for patients who might withdraw consent. The continuous data were compared between the two groups using independent samples t-test. Mann-Whitney U test was used to compare count data as the number of transfusions. Pearson chi-square and Fisher's exact tests were performed to compare categorical data with low number of events.

In the third study (paper III), the sample size was calculated based on previously published data on F1+2 during THA (Reikeras & Clementsen, 2009). We found that ten patients in each treatment group would be adequate based on the sample sizes used in comparable studies and with expected large differences between time points. Independent samples t-test was used to compare descriptive variables. Two-ways analysis of variance (ANOVA) was performed to evaluate time-dependent changes between the two groups and individuals inside the groups. If significant differences were indicated, we used a Last Significance Difference (LSD) post hoc test to evaluate the effect of all combinations of the individuals or the interactions by comparing them stepwise. Pearson correlation coefficient was used to evaluate correlations between the biomarkers. The sample size was small, not normally distributed, and we considered using non-parametric tests. However, we did not detect differences between groups applying variance analysis, and it is unlikely that nonparametric tests (Spearman) could afford additional information.

In the fourth study (paper IV), differences in baseline characteristics between pre- and the postoperative group were assessed with independent samples t-test or Pearson's chi-squared test for continuous or categorical variables, respectively. Binary outcome variables were further evaluated with logistic regression (unadjusted and adjusted) and presented as odds ratio (OR) with 95% confidence interval. To control for possible confounders comparison was made after statistical adjustment for differences in baseline characteristics using multivariate

logistic regression. We adjusted for observed confounders considered to be important, such as sex, age, year of operation, ASA classification, and operation time. Adjustment of differences in baseline characteristics using multivariable regression models is a common statistical method in cohort studies. To account for time at risk, data was also assessed using alternative statistical methods, including multivariable Cox regression and Poisson regression. The study had 80% statistical power to detect 0,5%, 1,0%, and 1,5% differences between post-and preoperative groups of defined events with rates of 2,0%, 10% and 20%.
This approach estimated an odds ratio of the defined event for pre- and postoperative groups adjusted for sex, age, and year of operation, ASA classification, and operation time. Although we performed multivariate analyses, unmeasured and residual confounding remains a threat to all observational studies, and therefore, we should not overestimate small differences among treatments, and change clinical practice based on marginal differences.

Ethics

All the studies of this project followed the declaration of Helsinki, which is an official policy document of the World Medical Association first adopted in 1964 (World Medical Association, 2013). For study I and IV, no interventions were representing ethical challenges. The relevant authorities including the hospitals Data Protection Official for Research, the Biobank register, and the Regional Ethics committee approved all four studies. In the first study, we assessed data retrospectively from the patient's hospital files. In study IV, we evaluated data after merging the files from the two national registers. The social security number of the patients identified in the two databases were first encrypted and then replaced by a study allocation number. The research file contained no information that could identify the patient at any time. The NAR has permission from the Norwegian Data Inspectorate to collect patient data, based on obtained written consent from the patient. Permission was last issued Sept. 15, 2014; reference number 03/00058-20/CGN, and with the intention to compare data between different registers. A written agreement between the three parties, NAR, NPR and Martina Hansens Hospital about the process, was signed before the fourth study. We do not believe that the two different prophylaxis regimens received by the patients in study II and III impose any ethical challenges as both regimens were internationally recommended and in regular use. It is unethical to include too many patients in trials with deviations from the routine. We, therefore, used sample size calculations to provide enough patients to detect relevant clinical differences. We obtained a few extra ml of blood from participants in the laboratory study, but without any likely risk for the patients. In the randomized controlled

trials, all patients received oral and written information, and a signed written informed consent before inclusion. The follow-up period of six months was according to the institutions routine for patients undergoing primary THA. The randomized trials were registered in ClinicalTrials.gov and performed according to the STROBE guidelines to ensure transparency of all phases of the study (von Elm, Altman, Egger et al., 2007). The publication of the fourth survey followed the CONSORT statement for observational studies (Schulz, Altman, Moher, & Group, 2010).

RESULTS

Bleeding and transfusion

There were no essential differences in baseline characteristics, ASA class, operation time or pre and postoperative hemoglobin between the two groups in the clinical studies (paper I and II). Characteristics corresponded to the typical patient reported by the Norwegian Arthroplasty Register (The Norwegian Arthroplasty Register, 2013). In the two clinical studies we recorded a total volume of blood loss measured in sponges and drains of 1230/1084 in the retrospective study and 1081/1023 in the randomized trial. These volumes correspond to blood loss reported in other THA studies before cessation of suction drains and the application of tranexamic acid (Trice, Walker, D'Lima et al., 1999; Hull, Pineo, Francis et al., 2000; Sehat, Evans, & Newman, 2004). Performing the randomized trial, using the full dose of LMWH, we could not reaffirm the minor difference in blood loss recorded in the retrospective study. The similar blood loss observed in the randomized trial, indicate that full dose of LMWHs given postoperatively is safe. This could be an alternative also in patients with elevated risk of VTE but the trial was not designed to compare pre- and postoperative administration particularly in these patients. We have measured merely the intraoperative and postoperative drainage. There is an additional proportion of blood loss due to extravasation of blood in the tissues, residual blood in the joint and loss due to hemolysis. These volumes of blood loss are challenging to estimate clinically, although several methods and indices for calculation of hidden blood loss have been proposed (Nadler, Hidalgo, & Bloch, 1962; Sehat, Evans, & Newman, 2004; Liu, Zhang, Chen et al., 2011). We assumed that this masked blood loss was equally distributed, due to the large sample sizes and similar baseline characteristics in the retrospective study, and due to randomization in the prospective study. The operation time and pre- and postoperative hemoglobin and hematocrit were the same in the preoperative

and postoperative groups of the clinical studies, which indicate standardized surgery and similar standardized indications for blood transfusions.

Publications report wide variation in definitions of bleeding events, and together with lack of statistical power, this may have resulted in a misleading interpretation of the bleeding assessments (Dahl, Quinlan, Bergqvist, & Eikelboom, 2010). We only found one randomized controlled study, investigating preoperative versus postoperative start of anticoagulation in THA using the same drug (Hull, Pineo, Francis et al., 2000). In The North American Fragmin Trial, 2500 IU dalteparin was injected either 2 hours before or 4-6 hours after surgery and both regimens were compared to warfarin initiated 12 to 24 hours postoperatively. Different surgical procedures were included, i.e., primary THA and revisions. There was less radiographically detected deep venous thrombosis for both dalteparin regimens compared to warfarin. Predefined bleeding events were similar in all groups, but the proportion of patients receiving transfusions was higher for the dalteparin groups, and particularly for those with preoperative dalteparin injections. Consequently, they recommended a 6-hour postoperative dalteparin regimen despite the trial was underpowered to detect the trial-specified bleeding difference.

Systematic reviews and meta-analyses are frequently used to evaluate differences between treatments. Hull et al. identified studies comparing the different timing of LMWH to warfarin, and demonstrated higher major bleeding rate for the 4-6 hours postoperative dalteparin regimen (Hull, Pineo, Stein et al., 2001). Strebel et al. identified studies with LMWH initiated 12 hours preoperatively, 2 hours preoperatively, 4 hours postoperatively and 12-48 hours postoperatively (Strebel, Prins, Agnelli, & Buller, 2002). They could not find a reduced risk of VTE with the preoperative approach, but demonstrated higher pooled bleeding rates in the perioperative regimens, which consequently were abandoned. A weakness of such pooled studies is that the underlying outcome variables might not be exactly the same. Variability in reporting of these bleeding events is confusing and makes it difficult to compare results from different trials. Therefore, we reported blood loss according to clinical terms reflecting daily practice.

Many patients undergoing major orthopedic surgery receive blood transfusions (Table2). A publication evaluating new oral anticoagulants reported transfusion frequencies of about 30% to 40% (Kakkar, Brenner, Dahl et al., 2008). Another recent review found an even more considerable variation in transfusions ranging from 16% to 50% in patients who had hip replacement operations (Barr, Donnelly, Cardwell et al., 2011). We found also similar variations in the transfusion frequencies. The parameters known to affect transfusion

requirements such as preoperative and postoperative hemoglobin level, ASA classification, weight, and age, were similar in both groups in the clinical studies and are unlikely to influence the results. In the retrospective study, we found a reduction in patients receiving blood transfusions (p=0.001), and the number of transfused packed red blood cells units decreased (p=0.001) after the postoperative start of dalteparin. In the randomized trial, we found the same trend towards more patients receiving transfusions in the preoperative group, 30% vs. 12,5%, although not formally statistically significant (p=0.071). However, these studies were not powered to conclude on differences in transfusions. The tendency towards fewer transfusions in the postoperative group may be important important as blood transfusions increases the risk of an adverse outcome due to volume overload, transfusion reactions, exposure to infectious agents and antigens, leading to increased hospital stay and costs (Lemaire, 2008). Blood transfusion itself may carry a risk for an ischemic outcome that is independent of bleeding (Mercuriali & Inghilleri, 1999; Rao, Eikelboom, Granger et al., 2007). Transfusion practice varies widely, the clinical assessment of bleeding requiring treatment may be difficult, and although we have recommendations and guidelines for transfusion, the decision for transfusion may be subjective. There is a reported association between preoperative and postoperative hemoglobin levels under 13g/dl and transfusion requirements (Bierbaum, Callaghan, Galante et al., 1999; Salido, Marin, Gomez et al., 2002). In the retrospective study, there were more patients in the preoperative group with hemoglobin below this level, and this may contribute to the difference in transfusions. In the randomized study, there were five patients (5/40) in each group with preoperative hemoglobin below 13g/dl. Our overall incidence of bleeding complications was higher than reported by others (Lachiewicz, 2009), which could reflect the method of collecting and classifying data. It is common to include a decrease in hemoglobin greater than 2 g/dl in the definition of major bleeding in pharmacological trials (Francis, Pellegrini, Totterman et al., 1997; Graafsma, Prins, Lensing et al., 1997; Hull, Pineo, Francis et al., 2000; Johansson, Pettersson, & Lisander, 2005; Novicoff, Brown, Cui et al., 2008). In the randomized study, we found such a decrease in hemoglobin for the majority of patients until the first postoperative injection (83% versus 90%) and the day after surgery (93% versus 90%). These figures suggest that a decrease in hemoglobin > 2 g/dl is common in THA. There is a need for a consensus or new research in order to define defining major bleeding in patients undergoing THA.

In study I, II and IV, we also included clinical bleeding events other than blood loss and transfusions in the analyses. We recorded 2.8 % clinical bleeding events in both groups in the register survey, similar to what was reported by a US-based study from 2006 using the ICD-9

codification (Vera-Llonch, Hagiwara, & Oster, 2006). In a case-control study, Parvizi et al. demonstrated an influence of anticoagulation on postoperative hematoma, transfusion requirements and infection comparing warfarin and controls (Parvizi, Ghanem, Joshi et al., 2007). Episodes of excessive bleeding, wound hematoma, wound secretion, hematemesis/melena, anemia, shock, and reoperations due to bleeding and infection were recorded in all four studies included in this thesis, but we were not able to demonstrate differences between the two regimens.

Spinal hematoma is a feared complication of epidural and spinal analgesia and associated with prophylactic use of anticoagulants (Moen, Dahlgren, & Irestedt, 2004; Horlocker, Wedel, Rowlingson et al., 2010). THA patients have been identified to be prone to this complication due to high age and incidence of lumbar stenosis among the patients. Spinal hematoma was not a predefined outcome in the registry study, but by performing in-depth analyses of the study file, we could not record any patients with neural injuries.

Although we could not demonstrate differences in bleeding between the two approaches of LMWH prophylaxis, there were differences in the rate of bleeding events across the studies, with approximately 10% in the randomized study, 5% in the retrospective study and 3% in the register study. These bleeding rates corresponds to the rates found by others applying similar study designs; 9.7% in a randomized study (Hull, Pineo, Francis et al., 2000), 4,2% in a retrospective clinical study of patients undergoing THA (Kistler, Kramers-de Quervain, Munzinger, & Kucher, 2008), and 2,8% in a register study where bleeding events were identified by the ICD-10 codes in a register database (Vera-Llonch, Hagiwara, & Oster, 2006). The differences between these studies might be explained by the different study designs and variations in bleeding definitions. We could not detect important clinical differences in bleeding and its complications starting thromboprophylaxis before or after surgery.

Thromboembolic episodes

The primary aim of this project was to evaluate the effect on blood loss and bleeding with a shift from pre- to postoperative start of thromboprophylaxis. We also included clinical thromboembolic events in the analyses although not powered to detect for these events. The prevalence of such events was consistent across the studies, with 2,0% in the RCT, 2,0% in the retrospective study and 1,7% in the register study. An explanation of this consistency of thromboembolic events across the studies might be that DVT and PE are more dramatic and often diagnosed by objective methods, while the perception and recordings of bleeding events

are more subjective and more prone to observation error. Episodes of DVT and PE were infrequent, which might be explained by good compliance to the antithrombotic regimens. The frequencies of these events are similar to other register studies reporting incidences of VTE (symptomatic and non-symptomatic) within 3 months of THA ranging from 1.4% to 6.0%, symptomatic deep venous thrombosis ranging from 0.2% to 4.4%, and fatal and nonfatal pulmonary embolism ranging from 0.1% to 0.3%, in patients receiving prophylaxis (Pedersen, Sorensen, Mehnert et al., 2010). In the register study, we found only 0.1% of patients reported to have post-thrombotic syndrome, which is similar to another report (0.2%) (Fitzgerald, McAndrew, Kraay, & Goldberg, 2011). We assume that the national registers only receive reports of a post-thrombotic syndrome with the most noticeable symptoms. Again, there were no differences between the groups, and the similarities between the cohorts indicate the same protective benefit against symptomatic thromboembolism with starting LMWH before or after surgery.

Other clinical complications, readmissions, and death

The number of patients with other complications was low in the clinical studies and too small for meaningful analyses. In the register study, the proportion of patients with predefined other complications were slightly higher in the preoperative group ($p<0.034$). Heart diseases and complications directly related to the procedure were most frequent. When we looked at cardiac-related events separately, this difference was even more significant ($p<0.017$). Myocardial ischemia is a major cause of deaths in the general population and patients undergoing THA (Pedersen, Baron, Overgaard, & Johnsen, 2011; Lu, Misra, Neogi et al., 2015). The odds ratio of death within 180 days' follow-up did not reveal differences between the cohorts. However, we demonstrated a higher 30 days mortality ($p<0.030$) in the preoperative group even after adjustment for gender, age, operation year, operation time and ASA classes. We have not been able to find other studies exclusively reporting 180 days postoperative death rate after THA. Compared to the general population, there is an excess mortality for patients undergoing hip replacement in the early postoperative period, followed by reduced mortality the following months (Lie, Pratt, Ryan et al., 2010). This may indicate that a six-month follow up is too long to assess meaningful data on mortality related to operative details. Hunt et al. reported a steady decrease in the 90-day death rate for patients having hip replacement in the UK from 0.56% in 2003 to 0.29% in 2011 (Hunt, Ben-Shlomo, Clark et al., 2013). Similar trends have been reported by others, and have been explained by better pre-, per- and postoperative treatment (Lie, Engesaeter, Havelin et al., 2002). The

mortality for the total study population was higher than reported by Hunt et al. However, Pedersen et al. performed a review of death certificates in Denmark for patients who underwent THA between 1995 and 2006 and found an overall death rate after 90 days of 1.0%, which was higher than in our study populations (Pedersen, Sorensen, Mehnert et al., 2010). Due to the general decrease in mortality among THA patients over time years, the imbalance observed in our register study, with more patients starting prophylaxis postoperatively late in the study period, may be an explanation why we observed a tendency for fewer deaths in the postoperative group. We have not analyzed data regarding reasons for death because numerous patients died outside the institutions reporting to the NPR, and these data are in general of low quality due to low rates of autopsies (Alfsen & Maehlen, 2012). Also, we had no information of preoperative comorbidities.

The overall readmission rate at 30, 60 and 180 days were higher than reported by others (Mednick, Alvi, Krishnan et al., 2014; Weinberg, Kraay, Fitzgerald et al., 2017; Williams, Kester, Bosco et al., 2017). The explanation may be that we have included all readmissions in all hospitals for all reasons during these periods. Another reason might be the long follow-up of 180 days in our register study. The readmission rate may also be influenced by separate unrelated incidents occurring over time from the index procedure (Epstein, Bogen, Dreyer, & Thorpe, 1991). The NPR database does not link date of readmissions to the primary diagnoses and the readmission diagnosis. Therefore, it is difficult to evaluate the association between complications and readmissions, without performing a manual assessment of readmission dates and codes for diagnoses and treatments, which we did not. We are aware of the differences in baseline characteristics between the two cohorts of our register study, but they are similar to typical THA populations. With the high number of patients in the register study, it should be easier to demonstrate statistically significant differences in the outcome parameters, which we did not. The large sample size, broad geographic representation, and varied hospital types within the data set make our observations relevant for the Norwegian hospitals performing total hip arthroplasty. The advantage of study IV is the original design using national registers with real-life data providing new insight into the controversial issue of timing of prophylaxis.

In the third study (paper III), we measured the activation pattern of biomarkers of coagulation and fibrinolysis with the two LMWH regimens. At baseline, during anesthesia and until the operation started, the plasma concentration of the biomarkers was similar between the two groups, and unaffected by the preoperative procedures. The operation caused a marked increase in all biomarkers synchronously in both groups, reached the maximum 6 hours

postoperatively, and declined the next 12 hours. All the biomarkers were significantly higher at the end of the first postoperative week. Preoperative and postoperative administration of dalteparin did not change this hemostatic pattern. This variation in pro- and anticoagulant activities over time is in accordance with other studies (Kluft, Verheijen, Jie et al., 1985; Dahl, Pedersen, Kierulf et al., 1993). It also confirmed the primary endpoint, that is, the bleeding parameters in our clinical trial that showed the same bleeding whether 5000IU dalteparin was injected 12 hours before or 6 hours after surgery (Borgen, Dahl, & Reikeras, 2012). At all time-points, there were marginal differences in F1+2 between the two groups, and we are aware that with an increased number of patients these differences might have been statistically significant. However, to reach statistically significant differences between these treatment groups, the number of patients had to be over 400 in each group, which indicate that this difference is of no clinical relevance. From an ethical point of view, an expansion of the study population would have been questionable. The levels of biomarkers were similar at baseline and before surgery. This could be expected, as hemostasis was not yet activated. However, lack of group differences during and after surgery was not anticipated since preoperative administered dalteparin was thought to neutralize thrombin activity. An explanation might be that the substantial thrombin generation caused by the operation masked the remaining effect of dalteparin injected 12 hours before surgery, due to its bioavailability with a half-life of 3-4 hours (Hirsh & Levine, 1992; Fareed, Ma, Florian et al., 2004). Increased plasma concentrations of F1+2 and D-dimer are found to correlate with thrombosis, but with relatively low specificity and predictability (Boneu, Bes, Pelzer et al., 1991; Cofrancesco, Cortellaro, Corradi et al., 1998). We have reported a similar amount of bleeding with pre- and postoperative dalteparin throughout the studies of this project, and the present laboratory study is in harmony with these observations.

There are some additional limitations to those discussed in each paper. These studies have only highlighted the effect of different timing of anticoagulation relative to the operation. Our clinical outcomes have included several diagnoses and procedures that can occur due to other factors than the timing of prophylaxis or the operation. One reason for the ongoing discussion and controversy about thromboprophylaxis is the wide variety of clinical praxis. In the clinical studies, we have only evaluated a shift from pre to the postoperative start of one compound applied on patients undergoing elective cemented hip arthroplasty, while in the register study we included patients with different implants and varying drug- doses and duration of treatment. The results might not be valid for other drugs, doses, duration of

treatment and differences in surgery. We are also aware that our findings might be otherwise in countries were genetic and demographic properties are different.

The term prophylaxis refers to preventing consequences of actions. If anticoagulation primarily inhibits thrombin activation during surgery, the postoperative approach should probably more correctly be called treatment. However, anticoagulants also prevent thrombus propagation and attachment to vessel walls after surgery.

Treatment decisions should be based on the highest available evidence. The four papers of this study have different study designs highlighting different timing of chemical thromboprophylaxis in THA surgery. We have included a hypothesis generating retrospective study, a randomized controlled trial to provide robust evidence and a large observational study to detect rare effects of treatment and to provide information about what is achieved under normal clinical circumstances. There are strengths and limitations associated with all study designs, but by applying such an approach to a single research question, we believe the evidence for our conclusions turn out to be stronger.

Our studies support the current trend of starting LMWH prophylaxis after the surgical trauma for the majority of patients undergoing THA.

GENERAL CONCLUSIONS

There were no significant differences in surgical and total blood loss when dalteparin thromboprophylaxis was initiated the evening before THA surgery compared to 6 hours after surgery (Paper I and II).

We could not detect important clinical differences in bleeding events, thromboembolic episodes, other prophylaxis related complications, readmissions, and death between pre- and postoperative start of low-molecular-weight-heparin prophylaxis in patients undergoing primary total hip arthroplasty (Paper I, II and IV).

Total hip arthroplasty induced the same biochemical pattern with preoperative and postoperative start with dalteparin (Paper III).

PERSPECTIVES

At present, administration of drugs to the majority of patients has been most beneficial. However, the downsides of anticoagulation call for more individualized solutions. Extensive development of computerized algorithms, will probably result in electronic applications for individual risk assessment and decision making for prevention of thromboembolism and other complications (Agoritsas, Heen, Brandt et al., 2015). Laboratory tests to detect increased thrombotic activity and identify those individuals with elevated thrombosis risk during treatment will be accessible. So far, simple blood tests have shown too low sensitivity or specificity to be reliable, and instead, global tests including more than one hemostatic marker are proposed (Panteleev & Hemker, 2015). Another fascinating idea is a simple, applicable urine test detecting elevated levels of split products from coagulation (Borris, Breindahl, Ryge et al., 2007). Strategies for refining and validating risk assessment models related to postoperative complications including thromboembolism are required. There is a need for consensus on how to define, classify and grade postoperative complications, and the recent initiative by the Hip Society is most welcomed (Healy, Iorio, Clair et al., 2016). Proper organization and precise determined relevant outcome data will allow valid comparisons between therapies and centers. Computerized documentation of comorbidities, medication and procedures obtained by the national registers provide a potential for future research, especially for infrequent outcomes. Improvement in the reporting of data to the registers and more coordinated organization of these data between the registers will make them more easy to combine and valuable for future research.

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Paper I

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ORIGINAL ARTICLE

Preoperative versus postoperative initiation of dalteparin thromboprophylaxis in THA

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Abstract. *Chemical thromboprophylaxis in total hip arthroplasty (THA) may increase surgical site bleeding. The drug dose and timing of such therapy is therefore important. We studied two cohorts of 298 and 301 patients undergoing THA. The first group received their first dose of dalteparin sodium 5000 IU subcutaneously the evening before surgery and the second group a half dose six hours post-operatively, followed by 5000 units daily in both groups. Blood loss was reduced by 146ml from 1230 ml to 1084 ml (p<0.001) with postoperative prophylaxis alone. The number of patients receiving blood transfusion decreased from 53% to 35% (p=0.001), and the use of transfused packed red blood cells was reduced from 1.25 to 0.83 units per patient (p=0.001). The overall rates of non-vascular complications 6 months after surgery were 12% and 11%, bleeding related events 6.0% and 4.0%, and thromboembolic related events were 2.0% and 2.3% in the preoperative and the postoperative cohorts. Two patients died in the preoperative group and one in the postoperative group due to venous and arterial thromboembolism. This study show that 2500 IU dose of dalteparin started 6 hours after surgery significantly reduced blood loss and transfusions compared to 5000 IU dalteparin injected 12 hours before surgery. Few thromboembolic events occurred, and these were equally distributed.*

Key Words: *Bleeding, Thromboprophylaxis, Total hip replacement, Transfusion*

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INTRODUCTION

In patients undergoing THA without thromboprophylaxis up to 60% deep vein thrombosis (DVT) has been reported in surveillance studies (1, 2). Haemostatic processes triggered by trauma provide the basis for thrombosis and for potential thrombotic expansion. Control of thrombin activity is therefore crucial to prevent clinical thrombotic events. However, practise regarding initiation of thromboprophylaxis differs (3, 4). In Europe there is contemporary emphasis on thrombosis prevention, and preoperative initiation of prophylaxis is common. In North America, because of concern about surgical site bleeding complications, prophylaxis is usually postponed until 12-24 hours after surgery (5-7). Recent trials with different drugs, doses and designs have reported comparison of preoperative standard dose low-molecular-weight-heparin (LMWH) with postoperative oral antithrombotics and have favoured postoperative drug administration (8-10). In our practice, a drive for efficiency has resulted in patients arriving shortly before surgery, shortened hospital stay and efforts to reduce costs, and therefore postoperative initiation of thromboprophylaxis has become attractive. We analysed two THA cohorts receiving either 5000 IU dalteparin subcutaneously 12 hours before surgery or a half dose 6 hours afterwards, to determine whether the new regimen had any impact on bleeding, transfusion rate, thromboembolic events and other complications.

PATIENTS AND METHODS

Two series of 298 and 301 consecutive THA patients were studied, reflecting our change from preoperative to postoperative initiation in 2005. Patients were excluded from analysis if they had bleeding disorders, had any condition contraindicating the use of dalteparin or required dalteparin dose adjustment, including severe renal impairment. Other ineligibility criteria included significant liver disease, active treatment for malignancy, pregnancy or breastfeeding, concomitant use of HIV protease inhibitors, use of fibrinolytic therapy or the requirement for an anticoagulant that could not be discontinued. Patients with a history of deep vein thrombosis (DVT) or pulmonary emboli (PE) and patients who had had major operations, stroke or cardiac infarction the 3 months prior to surgery were also excluded. Data for each patient were recorded in the patient file before hospital discharge, and at 6 months follow up. THA patients were requested to fill in a questionnaire relating to pain, function, symptoms and signs of DVT, infection, dislocation, and other complications. All data were obtained by retrospective review of the medical records by the lead investigator (POB). In all patients the operative procedure was standardized with a posterolateral approach and the use of an Exeter hip prosthesis (Stryker, Herouville Sant-Clair Cedex, France), inserted with Simplex cement with tobramycin (Howmedica Limerick, Ireland). The patients were mobilized on the first postoperative day. All patients received lumbar spinal anaesthesia with bupivacaine 5 mg/ml (Marcain®, AstraZeneca, Södertälje, Sweden). Cephalotin (Keflin®, EuroCept Pharmaceuticals BV, Kortenhoef, Netherland) 2g x 4 was given intravenously as prophylaxis against infection. Patients were requested to stop all medication with antihaemostatic properties one week before the operation. Low dose aspirin i.e. <160mg was allowed. Paracetamol + codeine sulphate (Paralgin forte®, Weifa AS, Oslo, Norway) and ketobemidon (Ketorax®, Jenahexal Pharma, Jena, Germany) generally provided postoperative analgesia, and the use of anti-inflammatory drugs was avoided. In the first series thromboprophylaxis was given as a subcutaneous injection of 5000 IU dalteparin (Fragmin®, Pharmacia and Upjohn, Stockholm, Sweden) 12 hours before surgery (preoperative group) and in the evening after the operation. In the second series 2500 IU dalteparin was injected 6 hours after the operation (postoperative group). The day after surgery and the consecutive 33 days 5000 IU dalteparin was injected once daily in all patients in both groups. No mechanical prophylaxis was used. The primary outcome variable studied was blood loss. Blood loss was measured as millilitres (ml) suction during the operation. Sponges and drapes were also weighed, and the blood loss estimated (1mg=1ml) according to established methods (11). Postoperatively the volume of blood loss was measured in the drains until they were removed 24 hours postoperatively. Secondary variables included the amount of blood transfused, and differences in haemoglobin concentration post-operatively in the two groups, with the objective of keeping haemoglobin between 9-10 g/L. All transfusions were performed with units of SAGMAN blood i.e. homologous packed red cells. The decision to transfuse a patient was made by the duty physician after the clinical assessment of anaemia. Other outcomes included clinically relevant bleeding events defined as serious, moderate and mild as described in the recent literature (12). Emphasis was on clinically significant thromboembolic events such as DVT, PE, stroke and cardiac infarction, all confirmed by objective tests, together with prolonged discharge, and any other complications up to 6 months. The study was approved by the regional ethics committee.

Statistical analysis

Results and data are presented as mean and one standard deviation (SD) or 95% Confidence interval (CI) (SPSS Inc., Chicago, Ill, USA). Continuous data are compared using Students t-test. For discontinuous data, such as number of blood transfusions, the Mann-Whitney U-test was used to compare data. Chi square test was used to compare frequencies. The level of significance was set to $p<0.05$.

RESULTS

There were no differences in baseline characteristics between the two groups, except for significantly higher body weight in the postoperative group of patients ($p=0.043$) (Tab. I). Operation time did not differ between the two groups, and there were no significant differences in haemoglobin concentration; either preoperatively, postoperatively at day 1 or at day 6 after surgery (Tab. II). Bleeding during operation was significantly ($p=0.002$) reduced by 79 ml (CI 30-129), and total bleeding volume was reduced by 146 ml (CI 80-212) ($p<0.001$) in the postoperative as compared to the preoperative group. Transfusion with packed red cells was

154 units versus 107 units in the two groups. In the postoperative group, blood transfusion was reduced by 0.4 (CI 0.2-0.6) units of packed red cells compared to the preoperative group (p<0.001) (Tab. II). In addition, the frequencies of transfusion was reduced (p=0.001). In the preoperative group 38 patients needed transfusions with 3 units SAGMAN blood or more as opposed to 26 patients in the postoperative group (Fig. 1). In the preoperative group there were 18 cases of bleeding related events (Tab. III). One patient required reoperation the same day for excessive ongoing wound bleeding, and 3 needed evacuation of wound haematomas. Fourteen patients had wound discharge which caused prolonged hospitalization or readmission, but no reoperation, and six patients had thromboembolic events.

Two patients in the preoperative group died during the study (one during surgery due to a possible cement reaction with findings of fat embolism and "sludge" / cement debris in the pulmonary artery at autopsy), and one died suddenly 4 weeks postoperatively from assumed pulmonary embolism, but no autopsy was performed. One patient had a myocardial infarction the day after operation, and another had chest pain with spontaneous remission. Two patients had clinical signs of DVT with positive venography.

In the postoperative group one patient had a haematemesis the day after the operation with successful conservative treatment. Four patients developed hematomas, but only one was evacuated surgically. Prolonged wound discharge was noted in 7 patients. Thromboembolic events were diagnosed in 7 patients; one of these developed clinical signs of acquired respiratory distress syndrome five days after surgery, and died after 2 months of intensive care treatment. In three patients DVT was confirmed by venography. Two patients were examined by the cardiologists for chest pain, but none had a diagnosis of myocardial infarction.

TABLE I - PATIENT CHARACTERISTICS

	Preoperative group	**Postoperative group**
Study population	298	301
Gender (% males)	29.2	30.5
Age (years)	71.2 ± 8.3 (51-89)	69.8 ± 9.9 (33-89)
Height (cm)	168.2 ± 9.0 (140-191)	168.9 ± 9.3 (149-198)
Weight (kg)	74.3 ± 14.6 (45-126	76.8 ± 16.3 (36-139)
BMI (kg/m^2)	26.2 ± 4.3 (16.3-45.2)	26.8 ± 4.7 (14.6-43.8)
ASA classification	2 (1-4)	2 (1-4)

Mean ± SD and range.

TABLE II - OPERATION TIME, BLOOD LOSS, BLOOD TRANSFUSION, AND HAEMOGLOBIN IN PREOPERATIVE AND POSTOPERATIVE GROUPS

	Preoperative group n=298	**Postoperative group n=301**	**p-value**
Operation time (min)	88.7 ± 17.7 (50-180)	87.4 ± 22.3 (37-205)	427
Peroperative blood loss (ml)	681 ± 343 (70-2700)	602 ± 270 (100-2100)	0.002
Total blood loss (m	1230 ± 429 (300-3200)	1084 ± 395 (275-2900)	<0.001
SAGMAN blood (units)	1.25 ± 1.53 (0-10)	0.83 ± 1.38 (0-7)	0.001
Hgb pre op (g/dl)	13.7 ± 1.2 (10.6-16.9)	13.8 ± 1.3 (9.4-17.4	0.073
Hgb post op (g/dl)	10.9 ± 1.1 (8.0-14.7)	11.1 ± 1.3 (8.2-14.7)	0.068
Hgb day 1 (g/dl)	10.7 ± 1.0 (7.2-15.1)	11.1 ± 1.1 (7.0-15.2)	0.101
Hgb departure (g/dl)	10.8 ± 1.0 (8.4-14.0)	10.8 ± 1.1 (7.9-14.5)	0.642

Mean ± SD and range.

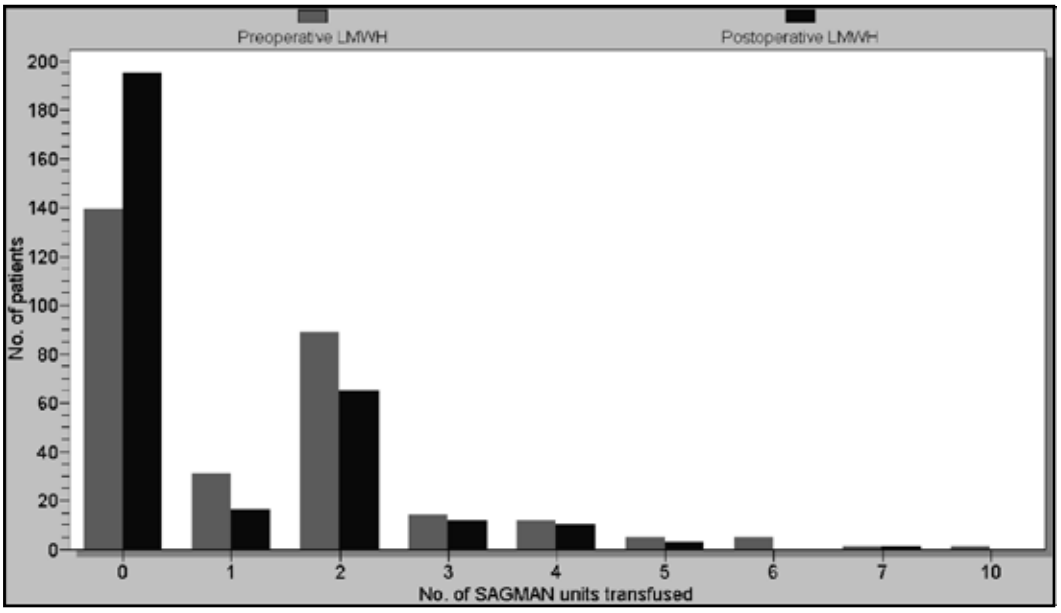

Fig. 1 - *Number of patients given packed red cell (SAGMAN) transfusion in preoperative group (grey) and postoperative group (black). The patient transfused with 10 units of packed red cell had a reoperation same evening because of excessive ongoing bleeding. The total number of units of transfusions in the two groups was 371 versus 252.*

TABLE III - COMPLICATIONS RECORDED DURING OPERATION AND UNTIL 6 MONTHS FOLLOW-UP

	Preoperative group n=298	Postoperative group n=301
Bleeding related events		
Ongoing bleeding	1	0
Hematemesis	0	1
Wound hematoma	3	4
Wound discharge	14	7
Total	18	12
Thrombotic events		
DVT	2	3
PE	0	1
Death	2	1
Myocardial infarction	1	0
Chest pain	1	2
Total	6	7
Other complications		
Deep infection	4	2
Dislocations	2	5
Nerve injuries	3	4
Postoperative confusion	2	2
Periprosthetic fractures	2	2
Total	13	15

DISCUSSION

The primary aim of this study was to estimate blood loss in two THA cohorts starting thromboprophylaxis with low molecular weight heparin preoperatively or postoperatively. Patients who started with 2500 IU dalteparin 6 hours after surgery had significantly less blood loss and fewer blood transfusions compared to those receiving 5000 IU dalteparin 12 hours before surgery. The number of patients with prolonged wound discharge was higher in the preoperative group. However, in both series of patients clinical bleeding events were infrequent and similar, and overall rates of complications were the same. We are not aware of other studies with the primary aim of measuring blood loss in relation to timing of thromboprophylaxis. The strength of our study is the high numbers of patients, all with the same inclusion criteria for surgery, with a diagnosis of hip osteoarthritis, undergoing total hip arthroplasty in the same hospital and with the same surgical technique and prosthesis. The weakness is that we studied two non-randomized subsequent patient series in which patients prone to bleeding may not be equally distributed. In addition, the clinical assessment of bleeding requiring treatment may be difficult, and although we have recommendations and guidelines for transfusion, the decision for transfusion may be subjective. Nonetheless, these limitations are mitigated by very similar patient characteristics in the two groups (Tab. I). The need for transfusion in orthopaedic surgery is a concern. Studies on surgical bleeding and transfusion have reported increased risk of adverse outcome associated with transfusions. Orthopaedic patients are often old, and minimizing bleeding and the need for transfusion is not only cost-saving, but also associated with decreased patient risk for complications including volume overload, transfusion reactions and exposure to infectious agents and antigens (13, 14). LMWH is an effective antithrombotic, both when administered preoperatively and postoperatively (2, 15). One pooled analysis has indicated that preoperative may be superior to postoperative initiation, but others have supported postoperative initiation (8, 16, 17). It is well accepted that various venous and arterial thrombi may commence perioperatively, epidemiological studies showing the highest death rate and occurrence of myocardial infarction the day of surgery (18, 19). Hence, in our region preoperative initiation of chemical thromboprophylaxis has traditionally been preferred. The disadvantage, however, may be increased bleeding and need for transfusion. Various factors influence blood loss in joint replacement surgery, and haemoglobin concentration is influenced by a number of variables such as preoperative fluid balance, haemodilution during and after surgery and the ability of the patient to rebalance fluid. Blood loss during and after THA has been recorded from about 800 to 2600 ml, with a weighted overall mean of about 1500 ml (20). In the literature approximately 50% of patients require transfusion with an average transfusion requirement of 2 units SAGMAN blood (21). The blood loss in our patients was similar to these reports, but our transfusion rates were lower. This is clinically important in an era of reduced access to blood products and the risk of disease transmission and induction of antibody formation. Our results are in agreement with Hull et al (22) who found increased surgical site bleeding in patients receiving 2500IU dalteparin one to two hours before surgery compared with those receiving the same amount 6-8 hours after surgery. This finding of increased bleeding with preoperative prophylaxis has been confirmed in two meta analysis (4, 16). In contrast Warwick et al. reported that enoxaparin 40 mg given 12 hours preoperatively and 12 hours and 36 hours postoperatively did not increase bleeding and haemorrhagic side effects as compared to placebo, while they reported increased bruising in the enoxaparin group (2). In our study, the bleeding difference between the two groups was less than 150 ml. Although statistically significant, the clinical importance of this finding can be questioned. We also found a higher rate of wound discharge in the patients receiving preoperative thromboprophylaxis. Several studies report an association between a preoperative haemoglobin level equal to or lower than 13.0 g/dl and transfusion requirement (21, 23). In our study, there was a significant association between lower preoperative as well as postoperative haemoglobin and transfusion ($p<0.001$). More patients had a preoperative haemoglobin equal to or lower than 13 g/dl in the preoperative versus the postoperative dalteparin group (31% versus 21%) ($p=0.07$) (Tab. II). In the preoperative group these patients were given 55% (203/371) of the total units transfused, while in the postoperative group these patients consumed 49% (123/252) out of total transfused units. A decision to transfuse is influenced by factors in addition to the haemoglobin level. In analysing different subgroups i.e. Hgb <8 g/dl, <9 g/dl and <10 g/dl, only 5 patients in the preoperative group had postoperative haemoglobin less than 9 g/dl versus 11 in the postoperative group. These numbers are too small for meaningful statistical analyses.

Our practise was to keep postoperative haemoglobin between 9 and 10 g/dl. Postoperative haemoglobin under 10 g/dl was recorded in 110 patients in the preoperative and in 90 patients in the postoperative group. Of these, 55 versus 59 had transfusion. The pattern of transfusion in these patients was the same as in the overall series, which indicate the same clinical practice in both cohorts. The rather marginal differences of blood loss and transfusion requirements with pre versus postoperative start of thromboprophylaxis have to be weighed against the risk of severe thrombotic manifestations in some patients. To sort out this delicate problem, a randomized trial sufficiently powered for relevant bleeding and thrombosis is needed.

Each author certifies that all investigations were conducted in conformity with ethical principles of research.

Each author certifies that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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Paper II

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CLINICAL RESEARCH

Blood Loss in Cemented THA is not Reduced with Postoperative Versus Preoperative Start of Thromboprophylaxis

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Abstract

Background Thrombin formation commences perioperatively in orthopaedic surgery and therefore some surgeons prefer preoperative initiation of pharmacologic thromboprophylaxis. However, because of the potential for increased surgical bleeding, the postoperative initiation of thromboprophylaxis has been advocated to reduce blood loss, need for transfusion, and bleeding complications. Trials on timing of thromboprophylaxis have been designed primarily to detect thrombotic events, and it has been difficult to interpret the magnitude of blood loss and bleeding events owing to lack of information for bleeding volume and underpowered bleeding end points.

Questions/purposes We therefore asked whether there are differences in blood loss, transfusion requirements, and other postoperative clinical complications with preoperative versus postoperative start of thromboprophylaxis with dalteparin.

Methods In a double-blind, randomized controlled trial, 80 patients undergoing primary cemented THA were allocated to dalteparin injections starting 12 hours before or 6 hours after surgery. Blood loss was measured by weighing sponges and drapes, volume in suction drains during surgery, and wound drains until removal 24 hours postoperatively. Hemoglobin and hematocrit were recorded at predefined times during and after surgery.

Results We found no differences in blood loss (1081 mL ± 424 mL versus 1023 mL ± 238 mL), bleeding-related events (10% versus 17%), or number of patients who had transfusions (12 versus five) with preoperative and postoperative thromboprophylaxis, respectively. Other complications were few in both groups.

Conclusions Our data suggest blood loss is similar with preoperative and postoperative initiation of dalteparin thromboprophylaxis, but indicate a trend toward fewer transfusion requirements which might favor postoperative start of thromboprophylaxis.

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Each author certifies that his institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
This study was performed at Martina Hansens Hospital, Baerum Postterminal, Norway.

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Level of Evidence Level I, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Blood loss in patients undergoing THA can be substantial and induce postoperative complications [20]. Surgical site bleeding and hematomas may cause nerve compression, prolonged wound drainage, infection, extended hospital stay, and extended rehabilitation [21, 22]. Anemia may aggravate vascular diseases [4], and homologous blood transfusions carry a small risk of infection, immunologic reactions, and fluid overload and may increase costs [19]. Surgical bleeding depends on the magnitude of surgery, the procedure, and patient-specific factors.

In THA, deep vein thrombosis (DVT) and other thrombin-driven events may originate during surgery and in a few patients nonfatal or fatal pulmonary embolisms (PE) develop. General chemical prophylaxis therefore has been recommended [10, 27]. Type of antithrombotic drug, dosage, and timing of the first dose may influence bleeding and development of thrombosis. Low-molecular-weight heparins (LMWHs) are widely used antithrombotics because of their favorable efficacy-to-safety profiles [9, 23], but the best timing of the first dose remains controversial [24, 28]. Preoperative initiation 12 hours before surgery has been based on the premise that DVT starts during surgery and that preoperative initiation is necessary to optimize antithrombotic effectiveness [17, 27]. In contrast, the premise for prophylaxis started after surgery has been to avoid the potential for increased bleeding complications. In clinical trials on antithrombotic regimens, venographically detected DVT has been a primary end point and bleeding a secondary underpowered outcome. Owing to various bleeding definitions, these trials have been criticized for underestimating the risk of bleeding and related complications [6, 7, 14].

We therefore asked if (1) there is a clinically important difference in total blood loss in THA between preoperative or postoperative start of thromboprophylaxis, and (2) there is a difference between the two regimens in transfusion requirements, incidence of bleeding events, and other complications detected up to 6 months after surgery.

Patients and Methods

After this study was approved by the regional ethics committee, we prospectively randomized 80 patients 50 years or older who underwent cemented THA for primary osteoarthritis between March and June 2008. During that same time, we treated a total of 104 patients with primary cemented THAs for osteoarthritis. Exclusion criteria were allergy to LMWH, bleeding disorders, renal failure, hepatic disease, active treatment for malignancy, ongoing antithrombotic treatment, history of DVT or PE, and patients experiencing major operations, traumas, stroke, or cardiac infarction the last 3 months before surgery. All patients were routinely hospitalized the day before surgery. We excluded 10 patients from enrollment owing to antithrombotic treatment, five patients with a history of DVT or PE, and two patients with liver disease. Seven patients refused to participate in the study. This left 80 patients for study. None of the 80 patients was lost to followup 6 months after surgery, and data collection was completed for all participants.

We performed a power analysis based on two earlier studies in which a significant reduction in the number of patients who had transfusions showed a 30% reduction in total blood loss [3, 15]. We considered this reduction clinically relevant. The effect size was based on blood loss and transfusion requirements in two earlier studies [3, 15]. In a prospective controlled study on patients who had THAs, Johansson et al. [15], found a 27% reduction in total blood loss (355 mL) reduced ($p = 0.009$) the number of patients who had transfusions. In a retrospective study [3], we found a 30% reduction in total blood loss (370 mL) reduced ($p = 0.006$) the number of patients who received transfusions by 28%. We believe a reduced risk for being exposed to blood transfusions is clinically relevant. With 80% power (alpha = 0.05), at least 37 patients were required in each group. We randomized a total of 80 patients to compensate for patients who might withdraw consent.

There were no differences between patients who received preoperative or postoperative start of thromboprophylaxis in terms of demographics (Table 1). We found no difference in operative times and length of hospitalization (Table 2), and preoperative laboratory values also were similar (Table 3).

In the hospital's written patient information, patients are advised to stop antiplatelet medication (ie, NSAIDs and high-dose aspirin) 1 week before surgery. A complete record of the patients' medications during the study period was recorded.

We assigned patients to either 5000 IU dalteparin (Fragmin®; Pharmacia and Upjohn, Stockholm, Sweden) subcutaneously or placebo (saline) injected 12 hours before surgery. All patients had 5000 IU dalteparin subcutaneously 6 hours after surgery and each day until the 35th postoperative day. Randomization was prepared in blocks of 20. Treatment group assignment was concealed by the hospital staff. The syringes with 5000 IU dalteparin and placebo with the same volume in each syringe were

Table 1. Patient characteristics

Characteristic	Preoperative group	Postoperative group	p value
Number of patients	40	40	
Sex (% males)	30	40	
Age (years)*	67.0 ± 9.2 (51–84)	69.3 ± 8.0 (58–85)	0.234
Height (cm)*	169.7 ± 8.8 (153–189)	170.9 ± 8.5 (155–192)	0.552
Weight (kg)*	75.9 ± 17.1 (52–119)	79.9 ± 12.9 (61–112)	0.245
BMI (kg/m^2)*	25.8 ± 4.5 (18–40)	27.0 ± 4.2 (21–39)	0.222
ASA classification*	1.9 ± 0.6	2.0 ± 0.6	

* Values are expressed as mean ± SD, with range in parentheses; ASA = American Society of Anesthesiologists.

Table 2. Surgery time, blood loss, and days of hospitalization in preoperative and postoperative groups

Variable	Preoperative group (n = 40)	Postoperative group (n = 40)	p value
Surgery time (minutes)	70.6 ± 14.2 (47–112)	66.0 ± 15.9 (44–119)	0.170
Perioperative blood loss (mL)	519 ± 299 (200–1650)	435 ± 125 (200–800)	0.107
Blood loss during injection (mL)	310 ± 13 (100–625)	323 ± 141 (100–700)	0.668
Blood loss during injection drain removal (mL)	249 ± 194 (0–1240)	278 ± 171 (0–900)	0.471
Total blood loss (mL)	1081 ± 423 (500–3000)	1023 ± 238 (600–1550)	0.460
Days of hospitalization	8.5 ± 2.6 (6–20)	8.2 ± 1.9 (5–16)	0.592

Values are expressed as mean ± SD, with range in parentheses.

Table 3. Preoperative and postoperative hemoglobin and hematocrit values

Variable	Preoperative group (n = 40)	Postoperative group (n = 40)	p value
Hemoglobin (g/dL)			
Preoperative	13.6 ± 1.4 (9.7–16.6)	13.6 ± 1.1 (10.8–15.7)	0.928
6 hours postoperative	10.4 ± 1.5 (7.2–13.0)	10.5 ± 1.2 (8.6–13.4)	0.617
Day 1	9.9 ± 1.3 (7.8–13.6)	10.3 ± 1.1 (8.2–13.0)	0.155
Day 3	9.7 ± 1.4 (7.8–13.7)	10.0 ± 1.3 (7.7–12.9)	0.275
Day 6	10.0 ± 1.5 (7.4–14.0)	10.1 ± 1.0 (8.7–11.3)	0.600
Hematocrit (%)			
Preoperative	40.9 ± 4.2 (28–49)	40.8 ± 3.3 (32–46)	0.882
6 hours postoperative	30.8 ± 4.4 (20–41)	32.2 ± 3.5 (32–46)	0.114
Day 1	30.4 ± 3.9 (22–40)	31.6 ± 3.3 (24–39)	0.145
Day 3	29.6 ± 3.7 (23–40)	30.6 ± 3.8 (22–38)	0.242
Day 6	30.6 ± 4.3 (22–41)	31.1 ± 3.2 (25–40)	0.530

Values are expressed as mean ± SD, with range in parentheses.

prepared by a study nurse who otherwise was not engaged in the study, according to randomized strata. The injection was blinded to the investigator, hospital staff, and the patient. The study blinding was broken after all patients had completed 6 months of followup.

All patients received spinal anesthesia without hypotensive effect with 5 mg/mL bupivacaine (Marcain®; AstraZeneca, Södertälje, Sweden) injected at the lumbar level. Cephalothin (Keflin®; EuroCept Pharmaceuticals BV, Kortenhoef, The Netherlands) 2 g was administered within 30 minutes of the arthroplasty. An equivalent dose subsequently was given 3 hours, 9 hours, and 15 hours after surgery as prophylaxis against infection. Voluven® and Ringer's acetate (Fresenius KABI, Bad Homburg, Germany) were used as plasma substitutes.

The operation was performed with the patient in the lateral position, using a standardized posterior approach where only the piriformis muscle was detached and with capsular repair at the end of the procedure. All procedures were performed by two surgeons with at least one being

experienced in performing THAs. All patients received stem and cups (Exeter®; Stryker Orthopaedics, Mahwah, NJ, USA) embedded in Simplex® tobramycin bone cement (Stryker Howmedica, Limerick, UK).

Postoperative analgesia was administered according to a standard protocol consisting of paracetamol + codeine sulfate (Paralgin forte®; Weifa AS, Oslo, Norway) and ketobemidone (Ketorax®; Jenahexal Pharma, Jena, Germany). Closed postoperative drainage was used for 24 hours. All patients were mobilized on the first postoperative day, and a program for simple self-administrated exercises was provided by the physiotherapists during hospitalization. Walking with the use of crutches was advised 6 to 8 weeks after surgery. Regular outpatient physiotherapy was not recommended until 2 months after surgery. We did not allow concomitant mechanical prophylaxis against DVT.

Hemoglobin and hematocrit were measured during surgery, before the first postoperative injection of dalteparin, and on postoperative Days 1, 3, and 6. We recorded the number of blood transfusions and plasma substitutes. The primary outcome was the volume of blood loss measured by weighing sponges and drapes (1 mg = 1 mL), volume in suction drains during surgery, and wound drains until removal 24 hours postoperatively [20]. We also recorded the number of patients who received transfusions, consumption of units of allogeneic leukodepleted erythrocyte concentrate, and decrease in hemoglobin concentration postoperatively in the two groups. We used a standard protocol with transfusion thresholds where a hemoglobin level less than 8 g/dL triggered transfusion and patients with a level greater than 10 g/dL did not receive a transfusion. Hemoglobin level on its own may be a poor indicator of tissue hypoxia, and the decision to transfuse patients with hemoglobin between 8 and 10 g/dL will, to some extent, be influenced by other parameters such as concomitant disease, weight, age, and others [1]. RBCs were given in 300-mL units, and autologous blood was not used. We evaluated all patients on a daily basis during hospitalization for possible bleeding events, such as hematoma, ongoing excessive bleeding, prolonged wound drainage (greater than 7 days), infections, and other complications. Overall surgical complications were classified according to Dindo et al. [8].

If patients showed any clinical sign of thromboembolic events, such as respiratory distress, chest pain, unstable hemodynamics, and a swollen, red, painful leg, we performed objective tests, including ECG, blood gases, plain chest radiography, venography, and spiral CT, after a clinical examination. Routine ultrasound screening, venography, or CT was not performed. A clinical research file (CRF) (Appendix 1; supplemental materials are available with the online version of CORR) was completed on a daily basis during hospitalization and at 6 months' followup.

The data are presented as mean, range, and 1 SD or 95% CI. Patient characteristics, blood loss, hemoglobin, hematocrit, fluid volume, and operation time were compared between the two groups using Student's t-test. We used the Mann-Whitney U test to compare the number of blood transfusions. Chi-square and Fisher's exact tests were used to compare frequencies. We used SPSS Statistics Version 17 (IBM Inc, Chicago, IL, USA) for all analyses.

Results

The total volumes of blood loss during surgery and until drain removal were similar ($p = 0.460$) in the preoperative and postoperative prophylaxis groups: 1081 mL ± 424 mL versus 1023 mL ± 238 mL, respectively (Table 2). Blood loss until the first postoperative injection of dalteparin ($p = 0.202$) or after the first postoperative injection and until removal of drains ($p = 0.471$) also was similar. We observed the same decrease in hemoglobin in the two groups (Table 3). Decreases in hemoglobin greater than 2.0 g/dL were measured for 82.5% versus 90% of patients during surgery and until the first postoperative injection and 92% versus 90% of patients during surgery and the day after surgery. There were no differences in hematocrit between the two groups at any time. Neither hemoglobin nor hematocrit had recovered to preoperative levels on Postoperative Day 6.

We found no difference in the total amount of transfusion requirements among the groups. More ($p = 0.099$) patients in the preoperative group received blood transfusions during hospitalization (12 of 40 versus five of 40). Both groups received a similar ($p = 1.000$) number of RBC units until the first postoperative injection of dalteparin (two with two units of packed red cells and two with one unit in both groups) (Table 4). Altogether, 27 units of RBCs were transfused in the preoperative versus 11 units in the postoperative group ($p = 0.071$). The volumes of colloids and fluids were the same.

In the preoperative group, four patients had bleeding-related events (Table 5). Three patients had wound hematomas, of which one was evacuated 5 days after surgery. One patient had wound drainage leading to prolonged hospitalization, but there were no positive bacteriologic cultures indicating infection. In the postoperative group, one patient had excessive bleeding after surgery, which was treated by surgical hemostasis. Four patients experienced hematomas and two had wound drainage without a positive culture that resulted in prolonged hospitalization. In the preoperative group, two patients had clinically suspected venous thrombosis not venographically confirmed. One patient with chest pain was examined by the cardiologist without obtaining any specific diagnosis. None had suspected PE during 6 months of followup. In the

Table 4. Transfusion, units of RBCs, and other fluids

Variable	Preoperative group (n = 40)	Postoperative group (n = 40)	p value
RBC (units)			
First injection	0.15 ± 0.48 (0–2)	0.15 ± 0.48 (0–2)	1.000
Total	0.67 ± 1.16 (0–4)	0.28 ± 0.75 (0–3)	0.071
Voluven® (mL)			
Perioperative	550 ± 189 (500–1500)	510 ± 108 (100–1000)	0.250
6 hours postoperative	440 ± 138 (0–500)	426 ± 149 (0–500)	0.658
Total	1200 ± 316 (1000–2500)	1100 ± 232 (500–1500)	0.111
Fluids (mL)			
Perioperative	2051 ± 417 (1000–3000)	1871 ± 459 (1000–3000)	0.070
6 hours postoperative	1013 ± 454 (0–2400)	1154 ± 555 (200–2500)	0.217
Total	4411 ± 591 (3500–6000)	4215 ± 462 (3000–5000)	0.102

Values are expressed as mean ± SD, with range in parentheses; RBC = allogeneic red blood cells.

Table 5. Complications recorded during surgery and until 6-month followup

Complication	Preoperative group (n = 40)	Postoperative group (n = 40)
Bleeding-related events		
Excessive bleeding	0	1
Wound hematoma	3 (1 reoperation)	4
Wound secretion	1	2
Other bleeding events	0	0
Total	4 (10%)	7 (17.5%)
Thrombotic events		
Deep vein thrombosis	0	0
Pulmonary embolus	0	1
Other thromboembolic events	1 (chest pain)	0
Total	1 (2.5%)	1 (2.5%)
Other complications		
Deep infection	1	0
Dislocations	1	0
Subileus	0	1
Total	2 (5%)	1 (2.5%)
Death	0	0

postoperative group, one patient had clinical and radiographically (spiral CT) confirmed PE 6 days after surgery and was treated according to protocol. The number of patients with other complications was low. In the preoperative group, one patient experienced a deep infection 3 months after surgery, and one patient dislocated the hip 2 months after surgery. In the postoperative group, one patient was admitted to another hospital with ileus, which spontaneously resolved. According to the classification of Dindo et al. [8] of surgical complications, three versus seven complications were Grade 1, 13 versus seven were Grade 2, and three versus zero were Grade 3 in the preoperative group versus the postoperative group.

Discussion

Pharmacologic thromboprophylaxis is recommended in major orthopaedic surgery but potentially may increase bleeding and transfusion requirements, which makes its use controversial [18]. LMWH has been associated with increased operative blood loss and transfusions [29], and to reduce bleeding and its side effects, the first injection has been postponed until after surgery. However, the scientific basis for such a change in practice is uncertain and needs further attention. In this double-blind, randomized study of patients undergoing THA, we compared preoperative with postoperative start of 5000 IU dalteparin. We asked if (1) there is a clinically important difference in total blood loss in THA between these two approaches of thromboprophylaxis, and (2) there is a difference between the two regimens in transfusion requirements, incidence of bleeding events, and other complications detected up to 6 months after surgery.

There are some limitations to this study. First, our sample size was small, but it was powered to detect a difference in total blood loss as the primary outcome of the study and with clinical relevance related to transfusion [3, 15]. Second, a proportion of blood loss after surgery is hidden. The volume of hematomas is difficult to estimate clinically or by ultrasonography, although several methods and indices for calculation of hidden blood loss have been proposed [20, 26]. However, any underestimation of such masked blood loss should be equally distributed randomly in groups. We recorded hemoglobin, hematocrit, and volume of fluids transfused at fixed times during and after surgery and found these recordings consistent across the two groups and followed the same pattern. Third, our transfusion guidelines leave a gray zone between upper and lower transfusion thresholds where transfusion decisions are based on numerous factors, including preoperative and

Table 6. Comparison of blood loss and transfusion requirements

Study	Study design	Number of patients	Interaction	Blood loss (mL)	% patients who had transfusions		Followup
Warwick et al. [30]	Thromboprophylaxis						Not described (14 days?)
	THA	78	Enoxaparin	1207	1.65 units		
	RCT	78	Control	1231	1.47 units (% not available)		
Francis. et al. [9]	Thromboprophylaxis						
	THA	279	Warfarin 12 hours preoperative versus	1601	% patients who received transfusions not described		7 ± 2 days
	RCT	271	dalteparin 2 hours preoperative	1600			
Colwell et al. [5]	Thromboprophylaxis						
	THA	176	Aprotinin	709	17%		Not described ("analysed if at least one efficacy measurement")
	RCT	177	Control	957	32%		
Hull et al. [13]	Thromboprophylaxis	496	Dalteparin	1512	Day 0	42%	Not described ("central adjudication of safety events in our trial included all events from the commencement of surgery up to postoperative day 8")
			2 hours preoperative		Days 1–8	43%	
	THA	487	12–24 hours postoperative	1503	Day 0	41%	
					Days 1–8	38%	
	RCT	489	Warfarin postoperative	1471	Day 0	38%	
					Days 1–8	28%	
Walsh et al. [29]	Risk for transfusion Retrospective THA	1034	LMWH and Coumadin® versus aspirin and foot pump	502 (perioperative, no drain?)	50% (RR 2.8 and 1.54)		Reviewed retrospectively
Johansson et al. [15]	Tranexamic acid						
	THA	47	Tranexamic acid	969	(8/47)	17%	6–8 weeks
	RCT	53	Control	1324	(23/53)	43%	
Borgen et al. [3]	Timing of thromboprophylaxis		Fragmin				
	THA	298	12 hours preoperative	1230	53%		6 months
	Retrospective	301	6 hours postoperative	1084	35%		
Current study	Timing of thromboprophylaxis		Fragmin				
	THA	40	12 hours preoperative versus	1081	30%		6 months
	RCT	40	6 hours after start	1023	12.5%		

postoperative hemoglobin levels, age, BMI, additional comorbidities, physicians preferences, and others [1, 2, 25]. However, as there were no differences in any parameters between the two groups, we consider the decision to transfuse to be equal in the two groups. Fourth, we did not use predefined classifications of bleeding events. Variability in reporting of these events makes it difficult to compare between trials. Therefore, we rather described them in clinical terms, and there were no major differences between our two groups.

Trials of thromboprophylactic agents have shown wide variation in bleeding definitions and recording of bleeding events, and together with lack of statistical power, this may have resulted in misleading interpretation of the findings for bleeding [7, 12, 14]. This inconsistency also makes it difficult to draw conclusions from meta-analyses and make recommendations. In The North American Fragmin Trial, 2500 IU dalteparin was given either 1 hour before or 6 hours after surgery and compared with warfarin initiated 12 to 24 hours postoperatively [13]. Different surgical procedures were included, ie, primary THA and revisions. Fewer radiographic DVTs were recorded for both dalteparin regimens compared with warfarin. Predefined bleeding events were similar in all groups, but the proportion of patients receiving transfusions was greater for the dalteparin groups, particularly for those receiving dalteparin preoperatively. Consequently, a 6-hour postoperative dalteparin regimen was recommended even if the study was underpowered to assess the trial-specified bleeding. In a retrospective study, we found a reduction in total blood loss during THA when the first dose of dalteparin was postponed from 12 hours before to 6 hours after surgery [3], but the clinical importance of this reduction was questioned. In the current study in which the same drug and dose were compared, we could not find differences in total blood loss during and after surgery or in decrease in hemoglobin or hematocrit at any time until discharge after approximately 1 week. Other parameters that could influence blood loss, such as operative time, type of surgery, age, and BMI, were similar in the two study groups and strengthen our observations.

Our overall incidence of bleeding complications was greater than reported by others [18], which could reflect the method of collecting and classifying data. Some researchers use a decrease in hemoglobin greater than 2 g/dL in the definition of major bleeding [11], and the rate of major bleeding frequently is reported as a safety outcome in trials of thromboprophylaxis [9, 13, 16, 23]. We found such a decrease in hemoglobin for the majority of patients until the first postoperative injection (83% versus 90%) and the day after surgery (93% versus 90%), which indicates a decrease in hemoglobin is a poor parameter for defining major bleeding in patients undergoing THA.

Many patients undergoing major orthopaedic surgery receive blood transfusions (Table 6). A transfusion frequency of 30% to 40% has been reported in a publication regarding new anticoagulants [16], and a review on transfusion decision-making reported between 16% and 50% of patients who had THAs received transfusions [1]. We found similar percentages: 30% with preoperative and 12.5% with postoperative thromboprophylaxis. Our study was not powered to show differences in transfusions and we observed no differences in total units transfused, frequency of transfusions, or number of patients who had transfusions. Parameters known to affect transfusion requirements, such as preoperative and postoperative hemoglobin level, American Society of Anesthesiologists physical status classification, weight, and age [1], were similar in both groups and should not influence the results. However, fewer patients received blood transfusions and the number of RBC units transfused was less in the postoperative group.

Thrombosis formation begins at the time of surgery in THA, and it follows that efforts to prevent the formation of thrombi should begin as early as possible. The timing of initiation of pharmacologic prophylaxis is a clinical decision that should consider the risk of venous thromboembolism and bleeding associated with antithrombotic therapy. We found no differences in blood loss when 5000 IU dalteparin was initiated 12 hours before or 6 hours after primary THA. However, we observed a trend toward fewer transfusions with postoperative start.

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Paper III

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Clinical Study

Biomarkers of Coagulation and Fibrinolysis during Cemented Total Hip Arthroplasty with Pre- versus Postoperative Start of Thromboprophylaxis

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Venous thrombosis is common in elective hip surgery, and prophylaxis is recommended. Clinical trials suggest that the drug dose and timing of initiating prophylaxis significantly influence antithrombotic effectiveness and safety. We studied the time course and gradient of plasma coagulation and fibrinolysis during total hip arthroplasty (THA) in twenty patients that were randomly assigned to have the first dose of 5000 IU dalteparin subcutaneously (sc) injected 12 hours before or 6 hours after surgery. Baseline characteristics were similar in both groups. Specific biomarkers on coagulation (prothrombin fragment 1+2 (F1+2)) and fibrinolytic activity (plasmin/α2-antiplasmin complex (PAP) and D-dimer) were collected at six events during hospitalization and analysed. There were no significant group differences in the biomarkers at any time point. The highest concentrations were measured 6 hours after surgery and before the first postoperative injection. A marked decrease followed at the first postoperative day, and then a second increase in plasma concentrations was observed 6 days after surgery. This study showed that activation of coagulation and fibrinolysis by the operative trauma was the same when the first dose of dalteparin was injected 12 hours before or 6 hours after surgery.

1. Introduction

Thrombosis formation begins during joint replacement surgery [1, 2], and a few patients may develop nonfatal or fatal pulmonary embolism (PE) [3]. It has been suggested that it is easier to prevent thrombus formation than to arrest thrombus growth once it has been established. Preoperative initiation of thromboprophylaxis therefore has been recommended [4, 5]. However, most thrombi develop postoperatively [6, 7], and, because anticoagulants have the potential to increase bleeding, some surgeons and anesthesiologists prefer postoperative initiation to reduce blood loss, need for transfusion, and bleeding complications [8–10]. Low-molecular-weight heparins (LMWHs) are widely used as antithrombotic because of their favorable efficacy-to-safety profiles and the absence of accumulated postmarketing reports on severe adverse events. Trials on timing of thromboprophylaxis have been designed to detect thrombotic events, and venographically detected DVT has been the primary end point. Bleeding has been a secondary underpowered outcome, and trials have been criticized for underestimating the risk of bleeding and related complications [11]. From surgeons point of view, blood loss and bleeding complications are important and pharmaceutical prophylaxis has remained controversial [12, 13].

There are no head to head comparisons with different regimens using the same drug; therefore, both preoperative and postoperative initiations of prophylaxis are still recommended in recent guidelines [14], and the need for further investigations has been emphasized. In a retrospective study on patients undergoing total hip arthroplasty (THA), we found reduced bleeding when dalteparin prophylaxis was started after surgery [15]. This was not confirmed in

a prospective, randomized double blind clinical study where an identical dose of dalteparin administered 12 hours before or 6 hours after THA caused the same volume of blood loss and bleeding related events in both groups [16]. This finding was newly substantiated in another study on knee replacement patients [17]. The biochemical rationale for this finding is uncertain and needs to be clarified.

Several biomarkers have been used to study haemostatic response to surgery [18, 19]. Furthermore, they have been proposed as surrogate endpoints of bleeding and venous thromboembolism (VTE) and to be of prognostic value to assess clinical outcome [20, 21]. F1+2 fragment is produced when prothrombin is converted to thrombin which acts on fibrin to form blood clots [22], while plasmin/α2-antiplasmin complex (PAP) and D-dimer have been found to be valuable markers of fibrinolytic activity during THA [23].

In this present study, we measured changes in these haemostatic markers to assess potential alterations when thromboprophylaxis was initiated with 5000 IU dalteparin injected 12 hours before versus 6 hours after THA surgery. Based on our clinical randomized study with no recorded differences in blood loss, bleeding events, and thromboembolic events, we hypothesized that activation of these haemostatic markers is the same in pre- versus postoperative start of prophylaxis. The results of these plasma analyses are presented here.

2. Material and Methods

The material consisted of THA patients included in a clinical prospective randomized double blind study on safety and efficacy of preoperative versus postoperative initiated thromboprophylaxis conducted at Martina Hansens Hospital between March and June 2008. The study was approved by the Regional Ethics Committee (08012d), registered in the Norwegian Biobank register (2058), and performed in accordance with the ethical standards of the Declaration of Helsinki.

International Normalization Ratio (INR) without thromboprophylaxis is normally approximately 1.0. In patients on anticoagulants, a level of 1.8 (which is 80% higher) is generally accepted for performing spinal anesthesia and major orthopedic surgery. Without previous data on the effect of dalteparin versus placebo on these biomarkers, we calculated the sample size using previously published data on F1+2 during THA surgery [24]. To detect an 80% difference in the increase in F1+2 with or without dalteparin, 10 patients in each group would have the power of 80% with an alpha of 0.05.

After signing informed consent, 20 patients above 50 years that underwent primary cemented THA due to osteoarthritis were randomly allocated to either 12 hours preoperative or 6 hours postoperative start with 5000 IU dalteparin (Fragmin, Pharmacia and Upjohn, Stockholm, Sweden). All patients received spinal anesthesia without hypotensive effect with 5 mg/mL bupivacaine (Marcain; AstraZeneca, Södertälje, Sweden) injected at the lumbar level. Cephalothin (Keflin; EuroCept Pharmaceuticals BV, Kortenhoef, The Netherlands) at 2 g × 4 was given intravenously as prophylaxis against infection. Voluven and Ringer's acetate (Fresenius KABI, Bad Homburg, Germany) were used as plasma substitutes.

The operation was performed in the lateral position, using a standardized posterior approach where only the piriform muscle was detached and with capsular repair at the end of the procedure. Postoperative analgesia was administered according to a standard protocol consisting of paracetamol + codeine sulfate (Paralgin forte; Weifa AS, Oslo, Norway) and ketobemidone (Ketorax; Jenahexal Pharma, Jena, Germany). Closed postoperative drainage was used for 24 hours. All patients were mobilized on the first postoperative day. We did not allow concomitant mechanical prophylaxis against DVT.

Patients with allergy to LMWH, bleeding disorders, renal failure, hepatic disease, active treatment for malignancy, ongoing antithrombotic treatment, and history of DVT or PE and patients experiencing major operations, traumas, stroke, or cardiac infarction the last 3 months before surgery were excluded. In the hospital's written patient information, patients were advised to stop antiplatelet medication, that is, NSAIDs and high-dose aspirin, 1 week before surgery.

We assigned patients to either 5000 IU dalteparin subcutaneously or placebo (saline) injected 12 hours before surgery. All patients had 5000 IU dalteparin subcutaneously 6 hours after surgery and each day until the 35th postoperative day. The syringes with 5000 IU dalteparin and placebo with the same volume in each syringe were prepared by a study nurse who otherwise was not engaged in the study, according to randomized strata. The injection was blinded to the investigator, hospital staff, and the patient. The study blinding was broken after all patients had completed 6 months' follow-up. No patients were lost to follow up.

Haemoglobin (Hgb.), haematocrit (Hct.), white blood counts (WBC), platelet counts (PLT), C-reactive protein (CRP), creatinine (Cr), and liver enzymes were analysed the day before surgery.

Blood samples for biomarkers were obtained from peripheral veins at the following time points: (T1) day before surgery, (T2) before induction of anaesthesia, (T3) at the end of surgery, (T4) 6 hours after surgery and before injection of dalteparin, (T5) the day after surgery, and (T6) 6 days after surgery. Blood sample was kept on ice until it was separated by centrifugation at 2500 g for 20 min at 18 degrees C and stored at −80 degrees C until assayed.

2.1. Laboratory Analyses. Prothrombin fragment F1+2 was measured in citrated plasma by ELISA using a commercial kit (Enzygnost F1+2 micro, Dade Behring, Marburg, Germany), following manufacturer's instructions. Plasmin/α2-antiplasmin (PAP) complex was measured in citrated plasma by ELISA using a commercial kit (Enzygnost PAP micro, Dade Behring, Marburg, Germany) following manufacturer's instructions. D-dimer was determined in citrated plasma using a commercial kit (STA-Liatest D-Di, Diagnostica Stago, Asnières s/Seine, France) following the manufacturer's instructions.

2.2. Statistical Analyses. Statistical analyses were performed using SPSS II software Version 19 (IBM Inc., USA). Data

Table 1: Patient characteristics (mean ± standard deviation) and *P* value.

Characteristic	Preoperative group	Postoperative group	*P* value
Number of patients	10	10	
Sex (% males)	30	50	
Age (years)	65.6 ± 6.9	71.2 ± 6.6	0.083
Height (cm)	168.0 ± 8.7	171.5 ± 9.4	0.397
Weight (kg)	73.8 ± 16.8	81.9 ± 15.8	0.282
BMI (kg/m^2)	26.1 ± 5.3	28.0 ± 0.6	0.453
ASA classification	1.9 ± 0.6	2.0 ± 0.7	0.722
Preop. hemoglobin	14.3 ± 0.9	14.0 ± 0.7	0.495
Preop. hematocrit	41.9 ± 3.5	40.7 ± 2.5	0.395
Preop. C-reactive protein	2.6 ± 3.0	3.9 ± 5.6	0.540
Preop. creatinine	58.6 ± 10.6	66.0 ± 11.0	0.142
Preop. blood plates	246 ± 93.1	246 ± 56.6	1.0

Table 2: F1+2 (pmol·mL^{-1}). Time points are the day before surgery (1), after anaesthesia but before surgery (2), at the end of wound closure (3), at 6 hours after surgery (4), at the first day after surgery (5), and at 6 days after surgery (6). Values are mean ± standard deviation (SD) and 95% confidence interval (CI).

Time point	Preop. group	Postop. group	*P* value (ANOVA)
T1	214 ± 63 (131–297)	212 ± 99 (129–295)	0.799
T2	184 ± 56 (101–267)	148 ± 67 (65–231)	0.799
T3	532 ± 148[a] (449–615)	567 ± 187[e] (484–649)	0.799
T4	594 ± 173[b] (512–677)	549 ± 131[f] (466–632)	0.799
T5	250 ± 140[c] (167–333)	310 ± 194[g] (227–393)	0.799
T6	335 ± 115[d] (252–418)	362 ± 113[h] (279–445)	0.799
P value (ANOVA)	<0.001	<0.001	

[a]$P < 0.001$; [b]$P < 0.001$; [c]$P = 0.240$; [d]$P = 0.009$; [e]$P < 0.001$; [f]$P < 0.001$; [g]$P = 0.012$; [h]$P = 0.001$, all in relation to time point 2 (before surgery).

are presented by mean and standard deviation. Independent samples *t*-test is used to compare descriptive variables. Time dependent changes were performed by two-way analysis of variance (ANOVA). If significant differences were indicated, we used the LSD post hoc test. $P \leq 0.05$ was considered significant.

3. Results

Baseline patient characteristics were similar in the two groups (Table 1).

There were no significant group differences of F1+2, PAP, and D-dimer at any time point (Tables 2, 3, and 4). No significant changes in biomarkers were demonstrated from 12 hours before until start of surgery. Surgery caused marked increases in F1+2, PAP, and D-dimer synchronously in both groups. The highest concentrations were measured 6 hours after surgery before the first postoperative dalteparin injection where after they declined to lowest level on day 1. Between postoperative day 1 and 6, modest increases in F1+2 and D-dimer were recorded, while the level of PAP was significantly increased ($P = 0.006$ and 0.001 in preoperative and postoperative group).

Clinically, one patient in the preoperative group experienced hematoma which was evacuated during hospitalization. There were no thromboembolic events.

4. Discussion

In this study based on a prospective randomized double blind study with pre- versus postoperative initiation of the same dose of dalteparin, markers on coagulation and fibrinolysis showed that intravascular thrombin formation (F1+2,) and plasmin activity (PAP and D-dimer) increased almost simultaneously during surgery, reached maximum 6 hours postoperatively, and declined the next 12 hours. All the biomarkers were significantly higher at the end of the first postoperative week than those before surgery (Tables 2, 3, and 4). Preoperative or postoperative dalteparin administration did not change this hemostatic pattern. This variation in pro- and anticoagulant activities over time is in accordance with other studies [2]. It also confirmed the primary endpoint, that is, the bleeding parameters in our clinical trial that showed the same bleeding whether 5000 IU dalteparin was injected 12 hours before or 6 hours after surgery [16]. The results are also in accordance with a recent study by Llau [17] and colleges who injected 40 mg enoxaparin at the same timepoints after total knee arthroplasties (TKA).

There are some limitations to this study. At all time points, there were marginal differences in F1+2 between the two groups, and we are aware that with a small number of patients these differences might have been significant if the patient number was increased. However, to reach statistical

Table 3: D-dimer ($\mu g \cdot mL^{-1}$). Time points are the day before surgery (1), after anaesthesia but before surgery (2), at the end of wound closure (3), at 6 hours after surgery (4), at the first day after surgery (5), and at 6 days after surgery (6). Values are mean ± standard deviation (SD) and 95% confidence interval (CI).

Time point	Preop. group	Postop. group	*P* value (ANOVA)
1	0.76 ± 0.47 (0.02–1.51)	0.69 ± 0.49 (−0.6–1.4)	0.965
2	0.75 ± 0.56 (0.001–1.49)	0.79 ± 0.87 (0.04–1.53)	0.965
3	3.71 ± 1.22[a] (2.97–4.46)	4.24 ± 1.72[e] (3.49–4.98)	0.965
4	5.15 ± 2.19[b] (4.40–5.89)	4.80 ± 1.78[f] (4.05–5.54)	0.965
5	2.61 ± 1.15[c] (1.87–3.35)	2.41 ± 0.89[g] (1.66–3.15)	0.965
6	1.97 ± 0.42[d] (1.19–2.76)	2.09 ± 0.69[h] (1.3–2.87)	0.965
P value (ANOVA)	<0.001	<0.001	

[a]$P < 0.001$; [b]$P < 0.001$; [c]$P = 0.001$; [d]$P = 0.029$; [e]$P < 0.001$; [f]$P < 0.001$; [g]$P = 0.004$; [h]$P = 0.021$, all in relation to time point 2.

Table 4: PAP ($\mu g \cdot L^{-1}$). Time points are the day before surgery (1), after anaesthesia but before surgery (2), at the end of wound closure (3), at 6 hours after surgery (4), at the first day after surgery (5), and at 6 days after surgery (6). Values are mean ± standard deviation (SD) and 95% confidence interval (CI).

Time point	Preop. group	Postop. group	*P* value (ANOVA)
1	627 ± 153 (510–744)	511 ± 172 (394–628)	0.110
2	616 ± 149 (499–733)	478 ± 106 (361–595)	0.110
3	917 ± 257[a] (800–1034)	936 ± 255[e] (819–1053)	0.110
4	1084 ± 326[b] (967–12019)	1033 ± 204[f] (916–1151)	0.110
5	588 ± 124[c] (471–705)	539 ± 97[g] (422–656)	0.110
6	846 ± 90[d] (729–963)	851 ± 135[h] (734–968)	0.110
P value time (ANOVA)	<0.001	<0.001	

[a]$P = 0.002$; [b]$P < 0.001$; [c]$P = 0.756$; [d]$P = 0.013$; [e]$P < 0.001$; [f]$P < 0.001$; [g]$P = 0.429$; [h]$P < 0.001$, all in relation to time point 2.

significant differences between these treatment groups, the number of patients had to be over 400 in each group, which indicate that this difference is of no clinical significance, and, from an ethical point of view, an expansion of the study population would have been questionable.

We collected blood from peripheral veins. Earlier studies have demonstrated a more moderate expression of the level of biomarkers in peripheral venous blood compared to arterial blood or mixed venous blood, which may be due to passage of the arteriovenous filter or dilution [25]. Furthermore, several biomarkers are available to analyze coagulation and fibrinolysis and they reflect activity from different parts of these processes. The selected biomarkers might not be the optimal ones to measure the influence of dalteparin on hemostasis during surgery.

The various LMWHs differ in their pharmacokinetic properties and anticoagulant activity [26], and, even if others have shown the same clinical pattern [16], the results of this study should not be generalized for other compounds.

The levels of biomarkers were similar at baseline and before surgery although only one group had preoperative dalteparin. This could be expected, as hemostasis was not yet activated. However, lack of group differences during and after surgery was not anticipated since preoperative administered dalteparin was thought to neutralize thrombin activity [4, 19]. An explanation might be that the substantial thrombin generation (F1+2) caused by the operation masked the remaining effect of dalteparin injected 12 hours before surgery due to its bioavailability with a half-life of 3-4 h [26, 27].

The sharp increase in all biomarkers recorded during surgery reflects that THA surgery, which involves mechanical obstruction of veins in the lower extremities, endothelial damage, and destruction of bone marrow, is a strong signal for hemostatic activity. These observations harmonize with others [1]. The level of quantified biomarkers continued to increase after surgery and peaked at 6 hours which probably is the result of haemostatic amplification when the blood passes the lung circulation [2]. After the first postoperative dalteparin injection 6 hour postoperatively and until the day after surgery, we recorded a rapid decrease in this activity in both groups. These observations concur with previous findings that fibrinolytic activity is enhanced intraoperatively with a shutdown after surgery [2, 28].

During major surgery, there is a complex interaction of cellular components and pro- and anticoagulant factors, to form stable clots. The dynamic of blood loss, dilution, and consumption of these haemostatic factors may lead to the observed reduction of biomarkers on day 1 after surgery. Natural variations during the day and increased plasminogen activator inhibitor (PAI) activity have also been proposed as explanations for this "fibrinolytic shut-down." Alternatively it may simply be dalteparin inhibition of Factor Xa and thrombin. Plasma PAP reflects clot formation and fibrin degradation and is regarded as an index of recent fibrinolytic activity [29]. Results from previous investigations with other

biomarkers indicated that decreased fibrinolytic activity was associated with thromboembolism after surgery [20, 21]. The data from these studies are consistent with the PAP pattern in our study. These authors have also showed that the referred biomarker plasma levels were unaffected by anticoagulation during THA surgery, which is in line with our findings. F1+2 activity in the present study paralleled the fibrinolytic activity and was also unaffected of LMWH.

The observed profile of high or increasing levels of these biomarkers both from baseline and from the first postoperative day until the 6th postoperative day in our series harmonizes with others and indicates a continuing procoagulant state even beyond hospital discharge in several patients [18, 30].

Increased plasma concentrations of F1+2 and D-dimer are found to correlate with thrombosis, but with relative low specificity and predictability [31, 32]. Previously, we have reported the same amount of bleeding with the two regimens [16]. LMWHs have repeatedly been shown to be effective against postoperative thrombosis after THA, and our findings therefore support the view that dose and the interval between surgery and the first administration of prophylaxis are important [9, 33].

The results from clinical investigations on timing of prophylaxis have been divergent. Bergqvist [4] and colleges showed reduced incidence of DVT and increased bleeding when 5000 IU dalteparin compared to half the dose was injected before surgery and pointed out that effect of dalteparin was dose dependent even if it was administered the day before surgery. The majority of his patients had abdominal procedures known to stimulate less thrombotic activity than THA, which can explain why our laboratory results do not concur with his observations.

Hull et al. [33] observed increased protocol defined major bleeding when dalteparin was injected within 2 hours preoperatively, compared to administration 12 hour preoperatively or warfarin 24 hours postoperatively. However, the recorded perioperative volume of blood loss did not differ markedly. In our prospective controlled clinical trial, we could not demonstrate difference in blood loss or bleeding events when dalteparin was initiated 12 hour before or 6 hours after surgery. The present observation with no difference in hemostatic biomarkers is in harmony with our clinical observations.

5. Conclusion

Our hemoanalyses confirms that activation of thrombin generation and fibrinolysis starts during THA surgery. No difference in activation pattern was demonstrated comparing pre- versus postoperative initiation of thromboprophylaxis with dalteparin.

Ethical Approval

Each author certifies that all investigations were conducted in conformity with ethical principles of research.

Conflict of Interests

Each author certifies that he has no commercial associations (e.g., consultancies, stock ownership, equity interest, and patent/licensing) that might pose a conflict of interests in connection with the submitted paper.

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Paper IV

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CLINICAL RESEARCH

Similar Clinical Outcomes with Preoperative and Postoperative Start of Thromboprophylaxis in THA: A Register-based Study

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Abstract

Background Elective THA is associated with a high risk of thromboembolic events. Although these events may be less common now than they were in the past, they can be serious, and most patients undergoing the procedure therefore still receive thromboprophylaxis. However, controversy remains regarding whether to begin thromboprophylaxis before THA or after to best balance the risks of clotting and bleeding.

Questions/purposes We asked the following questions: (1) Is there a difference in bleeding events with pre- versus postoperative thromboprophylaxis? (2) Is there a difference in thromboembolic episodes after THA between the two regimens? (3) How do the two approaches of thromboprophylaxis influence mortality, readmissions, and other complications?

Methods We used a population-based followup design with predefined data based on international health codification to assess clinical effects of LMWH prophylaxis initiated before or after THA. We took data limited to primary THAs done in Norway between January 1, 2008, and December 31, 2011, from the Norwegian Arthroplasty Register and the National Patient Register to have necessary data elements to complete the study. The two registers were merged after identifying patients with their 11-digit personal identification number (Social Security number). We obtained data regarding demographics, administrative and surgical details, and episode histories for prophylaxis-related events within 180 days of surgery. A total of 25,163 patients undergoing THA were included for analysis, and

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Each author certifies that his or her institution approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
This work was performed at Martina Hansens Hospital, Gjettum, Norway.

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9977(40%) versus 15,186 (60%) patients received pre- and postoperative LMWH, respectively. We performed statistical adjustment for differences in baseline characteristics using multivariate logistic regression.

Results After adjustment for age, sex, operation time, year of surgery, and American Society of Anesthesiologists class, we could not show major differences in bleeding events; (odds ratio [OR], 1.04; 95% CI, 0.88–1.22; p = 0.660), thromboembolic episodes; (OR, 1.03; 95% CI, 0.84–1.27; p = 0.786), or other postoperative clinical complications; (OR, 0.86; 95% CI, 0.76–0.99; p = 0.034), with the two regimens. Six-month mortality was similar, (OR, 0.76; 95% CI, 0.56–1.05; p = 0.093), and the readmission rate was higher in the preoperative group; (OR, 0.92; 95% CI, 0.85–0.97; p = 0.016).

Conclusions The risk for postoperative complications seems to be comparable whether LMWH prophylaxis is initiated before or after THA. The postoperative approach reduces costs, decreases risks related to neuraxial anesthesia, and facilitates same-day admissions. Methods for individual risk assessment including laboratory tests would be feasible.

Level of Evidence Level III, therapeutic study.

Introduction

THA is associated with perioperative risks including deep venous thrombosis and pulmonary embolism, both of which are manifestations of venous thromboembolism (VTE) [28, 29]. Substantial progress has been made in reducing the risk of VTE after surgery owing to use of thromboprophylactic drugs [9], but also because of better preoperative preparations, refinement in surgical technique, and earlier mobilization [15, 26]. A trend toward reduced mortality has been observed in recent years despite more patients who are comorbid, and myocardial infarction seems to have replaced pulmonary embolism as the major cause of postoperative deaths [2, 14].

Although a broad consensus for some form of pharmaceutical prophylaxis exists [9, 21], the best timing for initial administration remains unclear. In European countries, low-molecular-weight heparin (LMWH) is frequently used during hip replacement surgery, and it has been initiated preoperatively on the assumption that the operation is the main cause of thrombosis [6, 11, 27, 30]. In the United States and Canada, emphasis traditionally has been placed on the risk of bleeding, and postoperative start of thromboprophylaxis has been the standard [16]. Timing, drug, and dose provided are controversial, and divergent definitions of classifications and outcome measures make it difficult to recommend good evidence-based strategies.

It remains unclear whether LMWH should be started before surgery, or held until surgery has been completed. In this study, we therefore used data from two nationwide population-based registers to compare risks associated with preoperative versus postoperative administration of LMWH. We asked the following questions: (1) Is there a difference in bleeding events with pre- versus postoperative thromboprophylaxis? (2) Is there a difference in thromboembolic episodes after THA between the two regimens? (3) How do the two approaches of thromboprophylaxis influence mortality, readmissions, and other complications?

Patients and Methods

This study has a population-based followup design with data from two national registers. The Norwegian Arthroplasty Register (NAR) receives information on primary and revision joint arthroplasties performed in Norway [12], and registration completeness is high for primary hip arthroplasties [1, 8]. The NAR receives clinical data in a standardized form, identified by the patient's 11-digit personal identification number (Social Security number), and the surgeon completes the form at the time of surgery. The form includes information on age, sex, diagnosis, and operative details. Since 2005, details regarding thromboprophylaxis have been registered. The NAR is linked to Statistics of Norway (https://www.ssb.no/en/) that provides information regarding deaths.

The Norwegian Patient Register (NPR) (http://www.npr.no), established in 1997, is a national health register and contains administrative, medical, and demographic information for all patients waiting for or having received treatment in the specialist health services. The NPR receives information regarding diagnoses using the International Classification of Diseases, 10th Revision (ICD-10), and treatment using the Nordisk medisinalstatistisk kommité (NOMESKO) Classification of Surgical Procedures (NCSP) (http://www.norden.org/en/nordic-council-of-ministers/council-of-ministers/nordic-council-of-ministers-for-health-and-social-affairs-mr-s/institutions-and-co-operative-bodies/co-operative-bodies/nordic-medico-statistical-committee-nomesko). Reporting to the NPR is mandatory for each hospitalization or outpatient visit and is linked to the reimbursement system. From 2008, data regarding each patient's episode histories have been collected by the NPR and linked to the patient's Social Security number, making tracking of particular individuals possible for research purposes. This determined our selection of the cohorts. The regulations of the NAR and NPR allow linkage of the registries. We included patients undergoing primary THA registered with NCSP codes NFB 20 (uncemented THA), 30 (hybrid THA), and 40 (cemented THA), and reported to the NAR between January 1, 2008, and December 31, 2011. The NPR

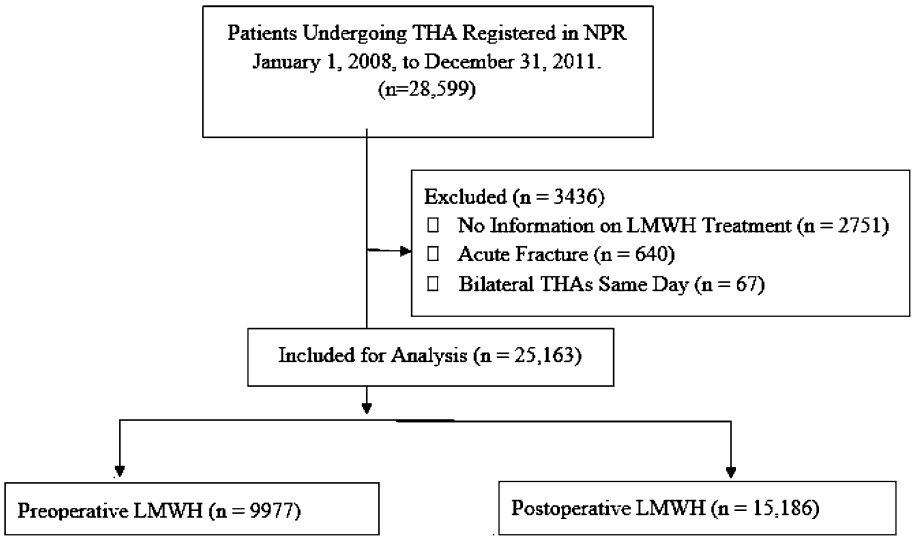

Fig. 1 The flowchart for our study is shown. NPR = Norwegian Patient Register; LMWH = low molecular weight heparin.

received the Social Security numbers for 28,607 patients undergoing THA from the NAR and 28,599 of these patients also were identified in the NPR (99% registration completeness). The Social Security numbers were first encrypted, and then replaced by study allocation numbers generated by the NAR, and the two registers were merged to have the necessary data elements to complete the study. The analyzed files did not at any time contain data identifying individual patients. Most symptomatic cases of VTE and readmissions for other complications occur within 3 months after surgery [3, 20]. We followed the patients for 6 months to be sure that all postoperative complications were registered. To provide information regarding the total disease history of these patients in 6 months after joint arthroplasty, the NPR used the Social Security number to link episodes of treatment registered at all different hospitals from January 1, 2008, to June 30, 2012. This constituted 25,909 patients with registered events, and a total of 67,980 visits available for further analysis. Patients treated for acute fracture (640 patients) were excluded because they present another surgical pathophysiologic challenge. According to NAR, approximately 95% of patients having primary THA received LMWH as thromboprophylaxis during the period studied, and only 0.1% of patients received no chemical prophylaxis [31]. We split patients into five groups according to their thromboprophylactic regimen: (1) first dose preoperative (n = 10,322); (2) first dose postoperative (n = 15,534); (3) no thromboprophylaxis (n = 18); (4) no information regarding prophylaxis (n = 220); and (5) received prophylaxis but no information regarding timing (n = 2513). Patients belonging to Groups 3 through 5 were excluded. Patients undergoing a bilateral one-stage procedure also were excluded owing to difficulty identifying procedure-relevant events. Altogether, 25,163 patients were included in the analyses, and 9977(40%) and 15,186(60%) patients received pre- versus postoperative LMWH (Fig. 1). This investigation was approved by the regional ethics committee (07.11.2012. Ref. 2012/1580/REK sør-øst B).

Assessment of Outcomes

Based on ICD codification, we selected 21 predefined prophylaxis-related events (Table 1). Data recordings of these predefined events were grouped in three categories reflecting possible clinical relevance: (1) bleeding events: anemia, shock, bleeding, hematemesis/melena, and reoperation for bleeding and infection; (2) thromboembolic episodes: pulmonary embolism, phlebitis and thrombophlebitis, other vein thrombosis, postthrombotic syndrome, and arterial embolism/thrombosis; and (3) other clinical complications associated with anticoagulation: angina pectoris, acute myocardial infarction, other acute ischemic heart disease, arrhythmia, disseminated intravascular coagulation, acute respiratory distress syndrome, stroke, fat embolus, and skin infections.

Readmissions and mortality from all causes during the first 180 days after primary THA for the whole population and for the two cohorts also were assessed. Readmission was defined as the first postoperative visit that resulted in hospitalization. Reoperations for dislocation and revision of implants also were recorded.

Statistical Analysis

Patient characteristics are presented as mean (SD) or number of patients (percentage) as appropriate. Differences in patient baseline characteristics between pre- and

Table 1. Predefined events among the assessed patients

Clinical events	ICD-10 and NCSP code	Total event	Preoperative group	Postoperative group
Bleeding events				
Anemia	D64	189 (0.8)	84 (0.8)	105 (0.7)
Shock	R57	13 (0.1)	3 (0.0)	10 (0.1)
Bleeding	R58	7 (0.0)	1 (0.0)	6 (0.0)
Hematemesis/melena	K92	90 (0.4)	39 (0.4)	51 (0.3)
Reoperation for bleeding or infection	NFW	407 (1.6)	159 (1.6)	248 (1.6)
Thromboembolic events				
Pulmonary embolism	I26	124 (0.5)	52 (0.5)	72 (0.5)
Phlebitis and thrombophlebitis	I80	199 (0.8)	75 (0.8)	124 (0.8)
Other vein thrombosis	I82	101 (0.4)	42 (0.4)	59 (0.4)
Postthrombotic syndrome	I87	21 (0.1)	9 (0.1)	12 (0.1)
Arterial embolism/thrombosis	I74	16 (0.1)	8 (0.1)	8 (0.1)
Other clinical complications				
Angina pectoris	I20	631 (2.5)	309 (3.1)	322 (2.1)
Acute myocardial infarction	I21 + I23.0-9	173 (0.7)	78 (0.8)	95 (0.6)
Other acute ischemic heart disease	I24	2 (0.0)	2 (0.0)	0 (0.0)
Stroke	I64 + G45 + G46	71 (0.3)	21 (0.2)	50 (0.3)
Skin infections	L02	21 (0.1)	9 (0.1)	12 (0.1)
Arrhythmia	I49	143 (0.6)	69 (0.7)	74 (0.5)
Disseminated intravascular coagulation	D65	33 (0.1)	13 (0.1)	20 (0.1)
Acute respiratory distress syndrome	J80	0	0	0
Fat embolus	T79	0	0	0
Reposition for dislocation	NFH	477 (1.9)	230 (2.3)	247 (1.6)
Revision of implants	NFC	421 (1.7)	178 (1.8)	243 (1.6)

Number of events (%); ICD-10 = International Classification of Diseases, Version 2010; NCSP = NOMESKO Classification of Surgical and Medical Procedures.

postoperative groups (Table 2) were assessed with independent samples t test or Pearson's chi-squared test for continuous or categorical variables, respectively. Multivariable logistic regression was used to adjust for possible bias in the comparison of pre- and postoperative groups because of differences in baseline characteristics. In the multivariable model, a defined binary event was the dependent variable (outcome). Independent variables were LMWH group (preoperative start as reference), sex, age (in years), year of operation (treated as a categorical variable), American Society of Anesthesiologists (ASA) classification (treated as a categorical variable) and operation time (in minutes). This approach estimated an odds ratio (OR) of the defined event for pre- and postoperative groups adjusted for sex, age, year of operation, ASA classification, and operation time. The adjusted OR is presented with 95% CI and probability value. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics Version 22.0 (IBM Corporation, Armonk, NY, USA). We used Stata SE 14.1 for Windows (StataCorp LLC, College Station, TX, USA) for estimation of statistical power.

Results

After controlling for age, sex, year of operation, ASA score and operation time, we found no difference between pre- and postoperative LMWH administration in terms of bleeding events (OR, 1.04; 95% CI, 0.88–1.22; p = 0.660) (Table 3). The rate of reoperations for bleeding and infection (NCSP code NFW) were comparable (OR, 1.09; 95% CI, 0.88–1.34; p = 0.425). When we analyzed reoperations for bleeding separately, we registered a total of 142 patients equally distributed in the two groups (OR, 1.09; 95% CI, 0.77–1.54; p = 0.618). Only 14 of these bleeding events were classified as hematoma. In-depth analyses of possible bleeding events showed equal distribution of open exploration of the hip (five versus four) at 13 to 122 days after surgery (mean, 43 days).

We recorded 407 (1.6%) patients with thromboembolic episodes, and without differences between the two groups (OR, 1.03; 95% CI, 0.84–1.27; p = 0.786). However, there was a lower frequency of patients with events categorized as other complications in the postoperative group (OR, 0.86; 95% CI, 0.76–0.99; $p < 0.034$), and this difference

Table 2. Patient characteristics

Patient characteristic	Total	Preoperative	Postoperative
Number of patients	25,163	9977 (40)	15,186 (60)
Age - years		68.9 (10.9)	67.8 (11.7)
Sex			
Female	16,409 (65)	6398 (64)	10,011 (66)
Male	8754 (35)	3579 (36)	5175 (34)
Year of operation			
2008	6030 (24)	3034 (30)	2996 (20)
2009	6306 (25)	2531 (25)	3775 (25)
2010	6496 (26)	2280 (23)	4216 (28)
2011	6331 (25)	2132 (21)	4199 (28)
ASA score			
1	5612 (22)	2334 (23)	3278 (22)
2	14,464 (58)	5387 (55)	9077 (60)
3	4678 (19)	2086 (21)	2592 (17)
4	74 (0.3)	41 (0.4)	33 (0.2)
Unknown	335 (1)	129 (1)	206 (1)
Operation time (minutes; SD)		97.9 (31.2)	87.4 (29.3)
Days of thromboprophylaxis (mean, SD)		23.7 (11.7)	22.1 (11.5)
Diagnosis (number and % in group)			
Coxarthrosis	20,095	8039 (81)	12,056 (80)
Rheumatoid arthritis	472	212 (2)	260 (2)
Sequela fracture	1385	661 (7)	724 (5)
Sequela dysplasia	2033	609 (6)	1424 (9)
Sequela dysplasia (luxation)	93	28 (0.3)	65 (0.4)
Sequela Perthes	29	9 (0.1)	20 (0.1)
Sequela epiphysiolysis	12	3 (0.0)	9 (0.1)
Ankylosing spondylitis	80	39 (0.4)	41 (0.3)

Number of patients (%) in group, mean and SD for continuous variables; ASA score = American Society of Anesthesiologists score.

was more pronounced when we analyzed for diagnoses related to myocardial ischemia (OR, 0.83; 95% CI, 0.76–0.99; $p < 0.017$) (Table 3).

One hundred seventy-five patients (0.7%) died, but there was no difference in mortality at 180 days between the two groups (OR, 0.76; 95% CI, 0.56–1.05; $p = 0.093$). However, patients given preoperative medication were more likely to be readmitted to the hospital in that time (OR, 0.92; 95% CI, 0.85–0.97; $p = 0.016$).

Discussion

There is consensus for some form of pharmaceutical prophylaxis owing to the elevated VTE risk in THA [9, 21]. However, optimal timing of the first dose of thromboprophylactic drugs remains unclear, and owing to lack of head to head studies comparing the same compounds, we sought to determine whether there are differences in bleeding events, thromboembolic episodes, and prophylaxis-related clinical complications with preoperative versus postoperative start of LMWH. We also assessed mortality and readmissions, and we followed the patients for 6 months to be sure that all complications after THA were registered. The data in this study indicate a comparable risk of bleeding events, thromboembolic episodes, other complications, readmissions, and deaths with starting LMWH prophylaxis in patients before or after THA. Thus, there was no evidence of important clinical benefits of either of the regimens.

This study is potentially limited in several ways. The major limitation was that the two study groups were dissimilar at baseline in numerous ways that could bias the comparison. Therefore, comparison was done after statistical adjustment for differences in baseline characteristics using multivariable logistic regression. To the best of our knowledge, we adjusted for important observed confounders, such as sex, age, year of

Table 3. Adjusted odds ratio of clinical events within 180 days after pre versus postoperative start of LMWH

Clinical events	Total (%)	Preoperative LMWH (%)	Postoperative LMWH (%)	Adjusted OR	CI	p value
Bleeding events:						
D64 + R57 + R58 + K92 + NFW	686 (2.7)	279 (2.8)	407 (2.7)	1.04	0.88–1.22	0.660
Reoperation for bleeding/infection:						
NFW	407 (1.6)	159 (1.6)	248 (1.6)	1.09	0.88–1.34	0.425
Thromboembolic episodes:						
I26 + I80 + I82 + I87 + I74	411 (1.6)	165 (1.7)	246 (1.6)	1.03	0.84–1.27	0.786
Other complications:						
I20 + I21 + I23 + I24 + I64 + G45 + G46 + L02 + I49 + D65 + J80	981 (3.9)	456 (4.6)	525 (3.5)	0.86	0.76–0.99	<0.034
Myocardial ischemia:						
I20 + I21 + I23 + I24	731 (3.1)	370 (3.7)	401 (2.6)	0.83	0.76–0.99	<0.017
Mortality						
30 days	54 (0.21)	30 (0.3)	24 (0.2)	0.53	0.30–0.94	<0.030
90 days	110 (0.44)	56 (0.6)	54 (0.4)	0.74	0.50–1.10	0.140
180 days	175 (0.70)	88 (0.9)	87 (0.6)	0.76	0.56–1.05	0.093
Readmission						
30 days	2819 (11.2)	1210 (12.1)	1609 (10.6)	1.09	1.00–1.18	<0.044
90 days	3779 (15.0)	1619 (16.2)	2160 (14.2)	1.08	1.00–1.16	<0.042
180 days	5190 (21.6)	2199 (22.1)	2989 (19.7)	0.92	0.85–0.97	<0.016

Preoperative group is reference; number of events (%) in group; LMWH = low-molecular-weight heparin; OR = odds ratio.

operation, ASA classification, and operation time, which could influence the results using this regression approach. Adjustment of differences in baseline characteristics using multivariable regression models is a common statistical methodology in cohort studies. Data also were assessed with alternative statistical methods, including multivariable Cox regression and Poisson regression, taking into account time at risk, but with no substantial difference in results. Multivariable logistic regression therefore was used in all assessments for ease of presentation. We also performed power analysis to detect differences using the sample size of the current study. There was more than 80% statistical power to detect 0.5%, 1%, and 1.5% differences between post- and preoperative groups for events with rates of 2%, 10%, and 20%, respectively. Although we performed multivariate analyses, unmeasured and residual confounding remains a general threat to all observational studies. Second, postoperative start of thromboprophylaxis became more common during the study period, which may have influenced balancing of the two cohorts. Therefore, statistical adjustment of relevant confounders was conducted as previously described, but this did not change our results. Third, there are inherent pitfalls of extracting data from national administrative databases. Registration completeness is high for primary THA in the NAR (98%) [1, 8], and for stroke diagnoses in the NPR (sensitivity, 86.1%; specificity, 99.9%; and positive predictive value, 93.5%) [33]. Completeness and quality of other risk factors collected in Scandinavian health registers are high because of regular quality controls [19, 23, 25], but we found no publications regarding the quality of the input to the NPR of other diagnosis and procedure codes. However, there is reason to believe that misclassifications would be independent of the two prophylaxis groups. Furthermore, because the NPR uses the ICD-10 coding standard of diagnoses, deaths in hospitals were defined as having occurred when the patient's last contact was registered at the date of death. Because a large number of patients died outside the institutions reporting to the NPR, analyses of reason for death were excluded. Fourth, we did not have detailed information regarding concomitant medication and comorbidities, which are known confounders in such a study, except ASA classes. Data also were assessed with alternative statistical methods including Cox regression

and Poisson regression, taking into account time at risk but with no substantial difference in results. Logistic regression therefore was used in all assessments for ease of presentation.

Classification and reporting of bleeding in randomized controlled trials varies widely [7]. In this study, we relied on the ICD-10-coded clinical events reported by all Norwegian hospitals. Estimations of "Major bleeding," a term frequently used in hip arthroplasty trials, have been reported from 0.1% to 3.1% [7], and vary even more with other bleeding definitions [4, 5, 13]. Although the criteria to report on this term vary substantially and affect trial results, by using the ICD-10 codification, we found a bleeding rate of 2.7%, which is within this range, and with no difference between the two cohorts. In a case-control study, Parvizi et al. [22] reported an influence of anticoagulation on postoperative hematoma, transfusion requirements, and infection comparing warfarin prophylaxis and controls. We found no differences in hematoma formation or infections between the two approaches of LMWH prophylaxis. One hundred forty-two patients had reoperations caused by bleeding, and these were equally distributed between groups. Even when we analyzed each subgroup for possible bleeding complications, we found very few and a similar number of patients with early postoperative surgical exploration, which could be associated with hematoma formation. We found no differences between the groups.

We found a frequency of symptomatic VTE of 1.6%, symptomatic deep venous thrombosis of 1.3%, and pulmonary embolism of 0.5% after 180 days, in the pre- and postoperative groups, respectively. These frequencies are similar and in accordance with an earlier study which showed incidences of VTE (symptomatic and nonsymptomatic) within 3 months of THA ranging from 1.4% to 6%, symptomatic deep venous thrombosis ranging from 0.2% to 4.4%, and fatal and nonfatal pulmonary embolism ranging from 0.1% to 0.3%, in patients receiving thromboprophylaxis [25]. Our rate of postthrombotic syndrome was only 0.1%, but comparable to those in another study (0.2%) [10], and we believe that only postthrombotic syndrome with pronounced symptoms is reported to the registers. Again, there were no differences between the groups, and the similarities between the groups indicate the same protective benefit against symptomatic VTE with starting LMWH before or after surgery. There were slightly more patients in the preoperative cohort with other complications. When we looked at cardiac-related events separately, this difference was even greater. Myocardial ischemia is a major cause of early postoperative death after THA [17, 18, 24]. Hunt et al. [14] reported that the 90-day death rate for patients having THA in the UK steadily decreased from 0.56% in 2003 to 0.29% in 2011. This could explain why we observed a tendency for more deaths during the first 30 days and more readmissions in the preoperative group during the 6-month followup. The mortality for the total study population was higher than reported by Hunt et al., however, Pedersen al. [25] performed a review of death certificates in Denmark for patients who underwent surgery between 1995 and 2006, and found an overall death rate after 90 days of 1.0%. The quality of reporting on date of deaths in the Scandinavian registers is high, owing to a homogeneous and stable population, which may explain this difference. We have not analyzed data regarding reasons for death, because numerous patients died outside the institutions reporting to the NPR.

Some studies report the predictors of, and complications associated with THA readmissions, usually within 30 days and typically at a rate of approximately 5% [20, 35]. Weinberg et al. [34] reported a 90-day readmission rate of 6%, and proposed this as a threshold for expected readmission rates after THA. In a Canadian multicenter prospective cohort study including patients having THA, van Walraven et al. [32], found a 180-day readmission rate of 13.5%. They called for preoperative risk stratification not only for VTE. The rate of readmissions in our study was 21%, and highest in the preoperative group even after the statistical adjustment. The preoperative group had more patients in ASA Classes 3 and 4, which may contribute to these findings, although we adjusted for ASA class in the statistical model. This subset of patients with premorbid conditions might possibly need specific protection and attention to minimize and avoid thrombin-driven and other postoperative complications. Analyzing rare events after THA using a randomized controlled study design is difficult owing to the large number of patients needed to show differences. A population-based register study, including all patients treated during a specified period, may provide assessment of a causal relationship, although there might be unmeasured confounding or other biases.

We could not show any consistent differences in efficacy and similar safety between pre- and postoperative start of LMWH prophylaxis for patients undergoing THA. Therefore, postoperative start with LMWH appears acceptable for the majority of patients, taking into account the reduced costs, decreased risk of anesthesiology complications, and same-day admissions. Methods to identify patients at high risk and tailoring thromboprophylaxis are needed.

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