Total hip replacement surgery

- occurrence and prognosis

Doctoral dissertation

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This thesis is based on the previously published eleven papers listed below, which will be referred to in the text by their Roman numerals. Papers I and II were included in my PhD thesis: "Studies based on the Danish Hip Arthroplasty Registry", Aarhus University, 2006. Papers III–XI have not been previously submitted in order to achieve an academic degree.

I. Pedersen AB, Johnsen SP, Overgaard S, Soballe K, Sorensen HT, Lucht U. Total hip arthroplasty in Denmark. Incidence of primary operations and revisions 1996-2002 and estimated future demands. Acta Orthopaedica 2005; 76: 182-9.

II. Johnsen SP, Sorensen HT, Lucht U, Soballe K, Overgaard S, Pedersen AB. Patient-related predictors of implant failure after primary total hip replacement in the initial, short- and long-terms. A nationwide Danish follow-up study including 36,984 patients. J Bone Joint Surg Br 2006; 88: 1303-8.

III. Pedersen AB, Mehnert F, Havelin LI, Furnes O, Herberts P, Karrholm J, et al. Association between fixation technique and revision risk in total hip arthroplasty patients younger than 55 years of age. Results from the Nordic Arthroplasty Register Association. Osteoarthritis Cartilage 2014; 22: 659-67.

IV. Pedersen AB, Svendsson JE, Johnsen SP, Riis A, Overgaard S. Risk factors for revision due to infection after primary total hip arthroplasty. A population-based study of 80,756 primary procedures in the Danish Hip Arthroplasty Registry. Acta Orthop 2010; 81: 542-7.

V. Pedersen AB, Mehnert F, Johnsen SP, Sorensen HT. Risk of revision of a total hip replacement in patients with diabetes mellitus: a population-based follow up study. J Bone Joint Surg Br 2010; 92: 929-34.

VI. Pedersen AB, Mehnert F, Overgaard S, Johnsen SP. Allogeneic blood transfusion and prognosis following total hip replacement: a population-based follow up study. BMC Musculoskelet Disord 2009; 10: 167.

VII. Pedersen AB, Baron JA, Overgaard S, Johnsen SP. Short- and long-term mortality following primary total hip replacement for osteoarthritis: a Danish nationwide epidemiological study. J Bone Joint Surg Br 2011; 93: 172-7.

VIII. Pedersen AB, Sorensen HT, Mehnert F, Overgaard S, Johnsen SP. Risk Factors for Venous Thromboembolism in Patients Undergoing Total Hip Replacement and Receiving Routine Thromboprophylaxis. J Bone Joint Surg Am 2010; 92: 2156-64.

IX. Pedersen AB, Johnsen SP, Sorensen HT. Increased one-year risk of symptomatic venous thromboembolism following total hip replacement: A nationwide cohort study. J Bone Joint Surg Br 2012; 94: 1598-603.

X. Pedersen AB, Mehnert F, Sorensen HT, Emmeluth C, Overgaard S, Johnsen SP. The risk of venous thromboembolism, myocardial infarction, stroke, major bleeding and death in patients undergoing total hip and knee replacement: a 15-year retrospective cohort study of routine clinical practice. Bone Joint J 2014; 96: 479-85.

XI. Pedersen AB, Sorensen HT, Mehnert F, Johnsen SP, Overgaard S. Efficacy and safety of short and extended thromboprophylaxis in 16,865 unselected hip replacement patients from routine clinical practice. Thrombosis Research 2015 Feb; 135 (2): 322-8.

PREFACE

This thesis is based on studies performed during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

First of all, I wish to express my deep gratitude to Professor Henrik Toft Sørensen—Head of the Department of Clinical Epidemiology, Aarhus University Hospital—for giving me the opportunity to conduct research in the field of orthopedic surgery, and for permitting to put my daily departmental tasks and duties aside to complete this thesis. Henrik Toft Sørensen's never-failing enthusiasm, positive attitude, comprehensive epidemiological knowledge, and constructive scientific advice helped lay the cornerstone of this thesis and hopefully paved the way to future collaboration.

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CONTENTS

1. INTRODUCTION

Total hip replacement (THR) is a common major surgical procedure (1) involving the removal of a severely impaired hip joint and its replacement with an artificial joint. Hip joint damage is caused most frequently by primary hip osteoarthritis (OA) (2), giving rise to persistent pain and interfering with daily activities. THR surgery is offered to patients after other treatments, such as medication, exercise, and walking aids, fail to result in clear improvement (3). An aging population is creating an increasing need for this type of surgery (4).

THR is a successful procedure that substantially reduces hip pain, leads to recovery of hip function and mobility, and improves quality of life (5-7). Analyses assessing the value of THR on the basis of cost, adverse outcomes, and quality of life relative to other treatment therapies, including knee replacement, have shown that THR is more cost-effective (8;9). Although THR surgery is considered safe, as with all surgeries, it carries risk of peri-operative and post-operative complications or adverse outcomes (10), including death (11). Research regarding the adverse outcomes of THR surgery has focused mainly on revision surgery (12-17), a new procedure performed to remove or replace part of or the whole primary THR, and how the surgical intervention and the technique used affect the need for revision. As new implants and changes in implant design and materials are introduced over time, it is important to continue examining the risk of revision surgery.

Few investigations have focused on other adverse outcomes. The risks of venous thromboembolism (VTE) and bleeding have been described primarily in randomized clinical trials (18-20). Only limited data on these risks are available from non-randomized studies (21-23) and very few investigations have focused on other cardiovascular complications (*i.e.*, myocardial infarction (MI) and stroke) (24;25) or death (26;27).

Adverse outcomes may be affected by factors such as patient characteristics (including comorbidities), choice of surgical treatment, performance of the surgeon/hospital, and patient compliance with post-operative treatment. Knowledge about the effect of these factors on adverse THR outcomes remains limited, particularly for comorbidities (defined as presence of co-existing diseases at or after THR surgery, unrelated to the surgery itself (28)) and type of surgical treatment (29;30).

Unanswered questions also exist regarding excess mortality risk in patients who undergo THR compared to persons in the general population who have not had this surgical procedure (26;27). Excess risk of most other adverse outcomes compared to a general population cohort has not been examined (31).

Over the past two decades, THR surgery has substantially changed and improved in terms of surgical technique, anesthesia, and preventive medication use (32;33). However, before study X, few published time-trend studies have provided information about the impact of these changes on adverse outcomes among patients undergoing THR (17;34-36).

The overall aim of this thesis was to improve our understanding of the long-term clinical course of patients undergoing THR surgery from the time a patient undergoes surgery until the development of specific outcomes (37). Therefore, we examined the occurrence of a broad range of adverse outcomes, including revision surgery, VTE, MI, stroke, bleeding, infection, and death, and factors associated with these outcomes within the entire population of Danish THR patients. The work reported in this thesis extends current knowledge about the prognosis of patients undergoing this surgery, making it possible to alter pre-operative and operative management to improve outcomes (37).

The thesis is divided into 13 chapters. The "Background" chapter defines the THR procedure and describes the history of THR, THR occurrence (study I), the symptoms and clinical presentation of patients for whom THR is indicated, the performance of THR surgery, risk factors for hip diseases leading to THR, and the prognostic factors and possible clinical outcomes of patients undergoing THR surgery. The chapters on "Revision surgery (studies II–VI) ", "Venous thromboembolism (studies VI and VIII–XI)", "Myocardial infarction and stroke (studies VI, X, and XI)", "Bleeding (studies X and XI)", and "Mortality (studies VI, VII, and XI)" discuss the current literature regarding the risks and prognostic factors for revision surgery, VTE, MI, bleeding, and mortality, including findings from studies II–XI. These chapters also highlight methodological issues that may have influenced prognostic studies in THR patients in general or specific investigator's analyses. The chapter "Other outcomes after THR surgery" briefly presents current knowledge on the risks of THR surgery not included in the specific aims of this thesis. Finally, the chapter "Conclusions" summarizes my conclusions based on the current literature. These chapters are followed by the "Danish summary", "References", and an "Appendix" containing the literature search algorithm.

2. AIMS OF THE THESIS

In order to achieve the overall aim of this thesis, several specific aims were set.

The specific aims of this thesis were to examine:

1. The rates of THR surgery and to predict future demands for THR surgery (study I),
2. The risk of revision surgery after primary THR and to identify related prognostic factors (studies II–VI),
3. The risk of developing post-operative VTE and to identify related prognostic factors (studies VI, VIII, X, and XI),
4. The excess risk of developing post-operative VTE (study IX),
5. The risks of post-operative MI and stroke (studies VI, X, and XI),
6. The risk of post-operative bleeding and to identify related prognostic factors (study X),
7. Mortality following THR (studies VI and X) and excess mortality (study VII),
8. The time-trend development of revision surgery, cardiovascular events, bleeding, and death after THR (study X).

3. BACKGROUND

3.1. Definition and history of THR surgery

THR involves the surgical removal of diseased cartilage and bone from the femoral head and acetabulum and its replacement with an artificial ball joint comprising a stem inserted into the femur bone with a ball on the top and an artificial socket with a plastic liner inside the acetabulum (38). The history of THR began in 1925 with the invention of the "mold arthroplasty", a ball-shaped hollow hemisphere of glass that could fit over the ball of a patient's hip joint to stimulate cartilage regeneration on both sides of the molded glass joint (39). Problems with the fragility of glass led to the use of other materials, such as plastic and steel. However, these materials did not provide a smooth surface, and movement remained limited for some patients. Years later, hemiarthroplasty, also called partial hip replacement, was introduced (40). In this procedure, the femoral head was replaced with a metal ball, while the acetabulum was left unaltered. Hemiarthroplasty remains a common procedure for managing a displaced fracture of the femoral neck, particularly among elderly patients (41). However, hemiarthroplasty is associated with several problems, including concomitant thigh and groin pain, protrusion, stem loosening and subsidence, and progressive destruction of the normal acetabulum surface (42;43).

These concerns led to the development of total hip arthroplasty in 1960 by the English surgeon John Charnley (44;45). He replaced the acetabulum component with high-molecular-weight polyethylene with high-wear properties and used a metal femoral component. Charnley also suggested the use of methyl-methacrylate bone cement to fix the artificial components to the bone (45) and introduced the clean-air operating technique to reduce the risk of infection (46). These practices ushered in the modern era of THR. The Charnley prosthesis remains one of the most commonly used prostheses in Western countries (2;17;47).

3.2. Symptoms and presentation of patients suitable for THR

Pain around the hip joint is typically the most important symptom motivating a patient to undergo surgery (48). Possible differential diagnoses vary depending on the patient's age, build, and activity level. For example, in a thin 20-year-old runner, the likely diagnoses may be tendinitis, bursitis, or gynecological and back problems. However, in an overweight and sedentary 70-year-old patient, such pain is due to primary or idiopathic hip OA disease in more than 75% of cases (2). OA damages the joint cartilage and bone and is clinically characterized by stiffness, instability, and limited range of motion, as well as occasional joint inflammation and/or joint deformity (49). Pain at rest or during the night is an indication of severe hip disease affecting the joint capsule, synovial membrane, periarticular ligaments and muscles, periosteum, or subchondral bone (50).

Hip joint damage and pain can be caused by a variety of other diseases (14;51). Atraumatic necrosis occurs as a result of an insufficient blood supply to the bone, leading to bone death, with 90% of cases

associated with corticosteroid treatment or alcohol consumption (52). The most frequent pediatric hip disorders are slipped capital femoral epiphysis, developmental dysplasia of the hip, and Perthes' disease (53). Slipped capital femoral epiphysis is displacement of the capital femoral epiphysis from the rest of the femur through the pliable cartilaginous growth plate, known as the proximal femoral epiphysis. In developmental dysplasia of the hip, the femoral head is too large relative to the acetabulum and moves in and out of the acetabulum (54). In Perthes' disease, reduced blood flow to the femoral head makes it susceptible to collapse and small fractures, eventually flattening its spherical shape (55). In general, these patients do not have disabilities during childhood; however, the conditions requires proactive surgical measures to forestall the development of severe hip arthritis and permanent hip deformation (56). Rheumatoid arthritis (RA) is a chronic, erosive inflammatory disease characterized by synovitis, tenosynovitis, and destruction of multiple joints, including the hip and knee (57). RA is initially treated non-operatively, but approximately 30% of patients with RA will eventually undergo THR (58). Decisions regarding treatment interventions to offer patients and the timing of treatment strongly depend on the underlying hip disease.

3.3. THR occurrence (study I)

From 1995 to 2012, the number of primary THR procedures in Denmark increased from 3,824 to 8,787. These numbers correspond to overall crude THR incidence rates (*i.e.,* the number of new THR procedures divided by the total number of individuals at risk by calendar year) of approximately 75 per 100,000 inhabitants in 1996 and 155 per 100,000 inhabitants in 2012 (59). THR rates must be studied to estimate the THR burden in a population; guide the planning of health care services, including the allocation of sufficient economic resources and staff; monitor changes over time; detect variations in health care; and identify reasons for THR surgery (60).

The overall rates of THR procedures vary greatly worldwide (4;12;17;61-70). However, comparing the reported THR rates can be complicated by differences in study periods, data collection methods, and data reporting formats. In addition, because crude rates are influenced by the age composition of a population, they cannot be used to evaluate differences in THR burden among countries. Applying the age distribution of a standard population to determine age-standardized THR rates (known as the direct method of standardization) enables the calculation of standardized incidence rates in a number of countries, allowing valid and direct comparison of THR rates (71). Several standard populations are available (*e.g.,* European, World Health Organization's world population, or United States standard population), and this method is commonly practiced when comparing cancer incidences worldwide (72). To the best of our knowledge, study I was one of the first published studies of THR rates that examined the Danish THR incidence rates standardized to both the Danish population in 1996 and the European standard population (including 18 age

groups), enabling a comparison between Danish and international rates. Several subsequent studies estimated THR rates using similar methods (12;73;74).

Despite worldwide variation in THR rates, a continuous overall increase of 5% to 70% has been reported consistently over the last 20 years (4;12;62;63;65;75;76). In Denmark from 1996 to 2002, the overall incidence rates of primary THR (standardized to the European standard population) increased by 30%, from 86.7 to 113.0 per 100,000 inhabitants (study I), mirroring worldwide trends. Across all calendar periods studied, the highest overall incidence rates of primary THR were among persons aged 70–79 years (65;74;76-78) (study I). However, the highest increases in overall THR rates were reported among persons aged 50–59 years between 1996 and 2002 in Denmark (study I) and 2001 and 2007 in the United States (69); among persons aged 60–69 years between 1989 and 2008 in Norway (12); among persons aged 75–85 years between 1991 and 2004 in the United Kingdom (66); and among persons aged 30–34 years between 1988 and 1998 in Australia (76).

The increase in THR rates is attributable to population aging, changes in clinical criteria for performing THR (*e.g.,* increased willingness to perform THR on younger (62;76) and older patients (59) and those with severe comorbidities (79)), changes in patients' preferences and demands, improved surgical techniques, the availability of private clinics, and the establishment of more specialized and efficient clinics with high operating volumes. Overall, THR rates are higher in women than in men (12;65;74;75) (study I). Howker et al. (80) estimated that the THR rates among women would be even higher than presently indicated if the data accounted for them being less willing to undergo surgery than men. THR rates increased more among women than men in some countries (66;81), but not in Denmark (study I).

However, during the same time period, THR rates among RA patients have declined in many countries (82-87). In Denmark (study I), the THR rates among RA patients peaked in the 1990s and have since declined in all age groups (88). This decline is likely related to improvements in diagnostic tools, which enable early RA identification and therapy, gradually turning it into a milder disease (89;90). In addition, international treatment guidelines introduced in 2000 recommend more aggressive RA treatment with a combination of two or more disease-modifying anti-rheumatic drugs (DMARDs) (85;91-93), and biological anti-rheumatic drugs are now commonly administered early in the course of the disease (90). However, only sparse epidemiological evidence from large population-based studies is available to support these hypotheses (85;89;94). Therefore, we recently initiated a study designed to examine time trends in the consumption of anti-rheumatic drugs, C-reactive protein levels as a marker of disease activity, and the use of orthopedic procedures among THR patients with RA. Despite the observed improvements in RA outcomes as measured by the need for joint surgery, there is no evidence of a contemporaneous decrease in mortality among these patients (95).

Future demands for THR surgery may exceed the current capacity for its performance (96-100). Based on the expected changes in the age distribution of the Danish population, the rates of primary THR will be 22% higher in 2020 compared to 2002. However, assuming that THR rates will continue to increase with the same acceleration as observed from 1996 to 2002, the THR rate will increase by 210% in Denmark by 2020 (96) (study I). In the United States, the latest study predicted that the annual number of THR procedures will increase by 174% from 2005 to 2030 (100). These estimates depend on the accuracy of the demographic projections and the future preferences of surgeons and patients. Interestingly, the most recent data from the Danish Hip Arthroplasty Register (DHR) indicate that the demands for THR may have been met (59), as the THR rates peaked in 2009 and have decreased since.

3.4. How is THR surgery performed?

The THR procedure is performed with the patient under general or regional/epidural anesthesia and lasts, on average, approximately 2 hours (101) (study IV). The surgery begins with an incision along the side of the hip to reveal the hip joint. The surgeon detaches the muscles that support the hip joint and cuts and removes the femoral head from the top of the femur. The hip socket area of the pelvic bone is cleaned out to remove the remaining cartilage and the damaged or arthritic bone. The acetabulum component of the prosthesis (also called the cup) is then inserted into the prepared socket. Similarly, the hollow center of the femur is cleaned and the femoral component of the prosthesis inserted into the femur (10). Both components can be secured in the bone using different fixation techniques, including the uncemented technique (both the femur and acetabulum components are inserted without cement), the cemented technique (both the femur and acetabulum components are cemented), the hybrid technique (cement is used for the femoral component but not the acetabulum component), and the inverse hybrid technique (cement is used for the acetabulum component but not the femoral component) (59). Next, the artificial head is placed on top of the femoral component and fitted together with the acetabulum component. The bearing surface (*i.e.,* articulating surface) between the femoral head and acetabulum is most commonly composed of metal-on-polyethylene (70%), followed by ceramic-on-ceramic and metal-on-metal (102).

Following complete assembly of the replacement hip, the surgeon repairs the muscles and tendons around the new joint and closes the surgical incision. Antibiotics are usually given pre-operatively, peri-operatively, or post-operatively to prevent infection (103). For over 20 years, pharmacological thromboprophylaxis treatment for up to 14 days from the date of surgery has been the standard of care for preventing thromboembolic complications (32). A blood transfusion is often required (104). The patient is mobilized within 2 hours if following the fast-track program (105), and no later than 24 hours following surgery, using the full support of the operated hip under the guidance of post-operative physiotherapy. The mean hospital stay for THR in Denmark is 3 days (105).
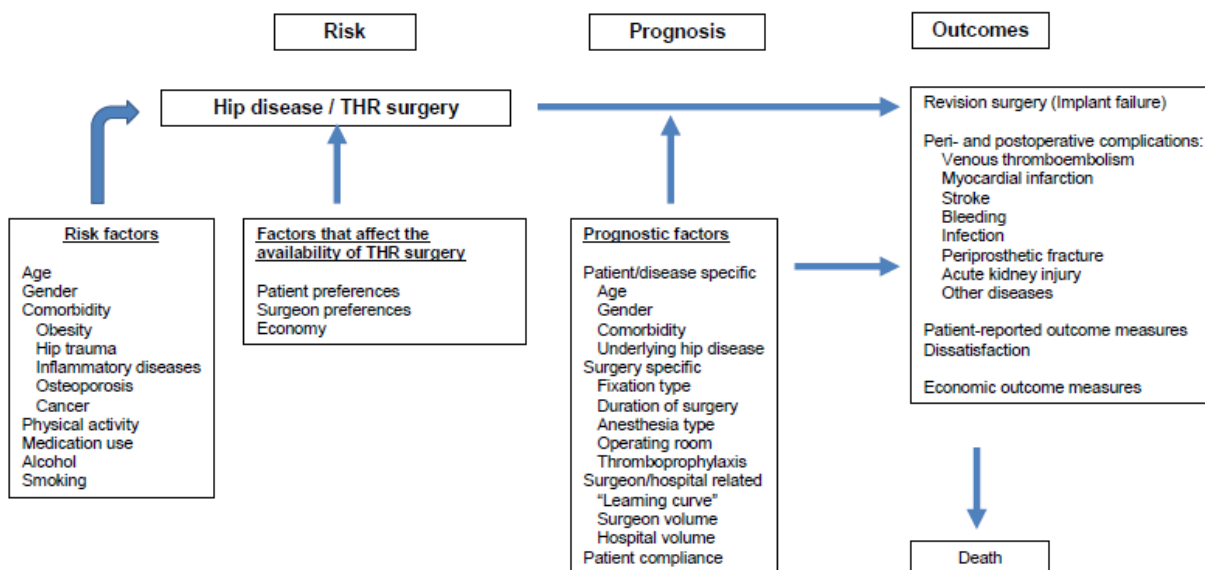
3.5. Risk factors for hip disease leading to THR surgery

Factors associated with an increased risk of hip disease are referred to as risk factors (106) (Figure 1). Knowledge of risk factors can improve our understanding of the causes of hip disease and our ability to prevent the occurrence of hip disease (50). Though the presence of a given risk factor does not necessarily translate into the development of hip disease in an individual (106), on the population level, increasing prevalence of a risk factor (*e.g.,* obesity) is likely to be accompanied by increasing THR rates.

Studies have examined several risk factors for radiographically confirmed OA, including advanced age (49). However, radiographic evidence of OA of the hip is present in approximately 5% of the population over the age of 65 years (107), and more than 90% of persons with radiographic OA do not have symptoms (108). On the other hand, early painful OA may not be accompanied by radiographic changes because such changes tend to become visible only relatively late in the disease course after many pathological changes have occurred in the joint (49). Therefore, many studies of risk factors for OA have investigated symptomatic OA, using THR surgery due to OA as a surrogate and easily quantifiable measure of severe and painful OA. For example, a body mass index of more than 27 kg/m^2 increases the risk of THR due to OA roughly 2-fold compared to persons with a body mass index below 23 kg/m^2 (109). Similarly, persons who perform intensive physical activity at work have a 2-fold increased risk of THR due to OA compared to those with sedentary jobs (109).

Several important issues must be taken into consideration when studying risk factors for THR due to OA rather than radiographic OA in the hip joint (irrespective of surgery), including the patients' and surgeons' preferences. These preferences can substantially alter or completely remove the importance of a risk factor. For example, alcohol consumption is a well-known risk factor for atraumatic necrosis of the femoral head (52). If surgeons avoid surgery in patients with extensive alcohol consumption due to fear of complications (110), then we may draw the incorrect conclusion that extensive alcohol consumption is not a risk factor for THR due to atraumatic necrosis when relying on surgery to measure the occurrence of atraumatic necrosis.

Figure 1. The risk and prognosis of THR surgery

| Risk | Prognosis | Outcomes |

Hip disease / THR surgery

Risk factors

Age
Gender
Comorbidity
　Obesity
　Hip trauma
　Inflammatory diseases
　Osteoporosis
　Cancer
Physical activity
Medication use
Alcohol
Smoking

Factors that affect the availability of THR surgery

Patient preferences
Surgeon preferences
Economy

Prognostic factors

Patient/disease specific
　Age
　Gender
　Comorbidity
　Underlying hip disease
Surgery specific
　Fixation type
　Duration of surgery
　Anesthesia type
　Operating room
　Thromboprophylaxis
Surgeon/hospital related
　"Learning curve"
　Surgeon volume
　Hospital volume
Patient compliance

Revision surgery (Implant failure)

Peri- and postoperative complications:
　Venous thromboembolism
　Myocardial infarction
　Stroke
　Bleeding
　Infection
　Periprosthetic fracture
　Acute kidney injury
　Other diseases

Patient-reported outcome measures
Dissatisfaction

Economic outcome measures

Death

3.6. Prognostic factors for the outcome of THR surgery

Factors associated with the outcome of THR surgery are referred to as prognostic factors (106) (Figure 1). A prognostic factor for one THR outcome may not be a prognostic factor for another THR outcome (*e.g.,* diabetes (studies V and VIII) or duration of surgery (study X)). Prognostic factors for THR outcomes also differ from the risk factors for hip disease leading to THR surgery. Some factors, such as age, obesity, or physical activity, may be associated with both the risk of surgery and prognosis following surgery (111). Prognostic factors can be classified as non-modifiable (*i.e.,* those that cannot be changed, including age, gender, race, family history, and genetics) or modifiable (*i.e.,* those that can be treated or controlled, including lifestyle factors, medication use, immobilization, occupational and/or recreational physical activity, and treatment interventions related to THR surgery) (112). Alternatively, prognostic factors may be classified as patient- or disease-specific (*e.g.,* underlying hip diseases, age, and comorbidities at the time of THR), surgery-specific (*e.g.,* type of implant, fixation, and anesthesia), surgeon- or hospital-related (*e.g.,* hospital or surgeon volume, and "learning curve"), or patient compliance with treatment (113) (Figure 1).

　　The "gold standard" design for investigating the prognostic effect of THR surgery or other treatment factors is a randomized clinical trial (114) in which the researcher randomly assigns patients to receive THR surgery or other treatment interventions. In such an investigation, patients can be randomly assigned to certain modifiable prognostic factors, such as different THR fixation techniques or different durations of thromboprophylaxis. Non-modifiable prognostic factors of THR surgery cannot be studied in randomized clinical trials because it is not feasible to randomize patients to have different underlying hip diseases or ages. In addition, some outcomes require long-term follow-up, in which case a randomized clinical trial

would be prohibitively expensive in regards to money and other resources. A non-randomized cohort design enables the simultaneous study of several prognostic factors alone or in combinations, and of several outcomes, reflecting the "real life" setting. Compared to randomized clinical trials, a major drawback of non-randomized cohort studies is an impeded causal interpretation of the observed association because of possible uncontrolled or unknown confounding (114). One option under these circumstances is an observational non-randomized cohort study design using a multivariate approach to achieve comparability of the study groups (115). One prognostic factor that can be studied almost exclusively in non-randomized cohort studies is the presence of comorbidities before THR surgery.

3.7. Comorbidity

The clinical characteristics of THR patients have changed over the last 25 years (36). The mean age at the time of THR surgery has increased (59;79), particularly among patients who undergo uncemented THR (from 58 years in 1995 to 66 years in 2014 among Danish women, and from 51 years in 1995 to 64 years in 2014 among Danish men). In addition, a greater number of THR patients have comorbidities; for example, the proportions of THR patients with diabetes, obesity, and congestive heart failure increased 1.4 to 3-fold from 1991 to 2008 (36), whereas the proportion of THR patients with renal failure increased 9.7-fold (79). The prevalence of metabolic syndrome, a group of co-occurring metabolic conditions (116), has increased substantially in various populations across all age groups and in both genders (117), as well as among THR patients (118). Furthermore, the percentage of patients with multimorbidity (*i.e.,* the coexistence of two or more chronic conditions) has been estimated to range from roughly 50% for persons under 65 years of age to 62–82% among those over 65 years of age (119). The presence of one or several comorbidities at the time of THR may delay and alter treatment; lead to adverse outcomes, poor functional status, and reduced quality of life; and worsen patient survival (118;120-122) due to the disease itself or to polypharmacy-associated side effects.

In the studies comprising this thesis, comorbidity was used as both a prognostic factor and a potential confounding factor, *i.e.,* a factor that distorts the association between an exposure and an outcome due to its strong relationship with both (111). For example, in studying the association between age and peri-prosthetic fracture after THR, comorbidity is a confounding factor because it is associated with both the exposure (persons with comorbidities are more likely to be old) and the outcome (persons with comorbidities have a greater risk of falls and associated fractures).

Comorbidity can be measured with comorbidity indices. The Charlson comorbidity index (CCI) is one of the more frequently used comorbidity indices in epidemiological and clinical research (123;124). Originally developed and validated for predicting short- and long-term mortality in patients admitted to internal medicine departments (123), the CCI includes 19 major disease categories, including cardiovascular, cerebrovascular, chronic pulmonary, liver, renal and ulcer disease, diabetes, and solid and hematological

tumors. Admissions related to each category are given a weight of 1, 2, 3, or 6, and then summed to calculate the total score, which can be categorized into two or more levels of comorbidity (125). However, the CCI has several limitations (28;126). The index is an imperfect measure of the severity of several conditions and does not include psychiatric diseases or disease duration; therefore, patients' true comorbidity status may be misclassified based on the CCI. Furthermore, the index sensitivity and specificity are less than 100% because comorbid disease registration is never complete or fully accurate (126), regardless of whether the data are obtained from medical records or administrative medical databases (studies II and IV–XI). An imperfect measure of comorbidity by the CCI impedes our ability to detect the effect of comorbidities on the prognosis of THR patients and may lead to residual confounding due to a failure to fully account for comorbidity in multivariate analyses (126).

Other comorbidity indices widely used in studies of orthopedic patients include the Charnley classification and the American Society of Anesthesiologists physical function classification (ASA) (127). The Charnley classification categorizes patients into class A if they have single-joint arthroplasty and no significant medical comorbidity; class B if they have one other joint in need of arthroplasty or have an unsuccessful or failing arthroplasty; and class C if they have multiple joints that require arthroplasty and/or have failing arthroplasties, or have substantial medical or psychological impairment (128). A proposed modified Charnley classification takes bilateral THR into consideration (129). The ASA was published in 1941 and designed to pre-operatively assess a patient's physical status. This index has been widely used almost unaltered since 1961 (130) and ranks patients into five groups based on disease severity: 1, a normally healthy patient; 2, a patient with mild systemic disease; 3, a patient with severe systemic disease that limits activity but is not incapacitating; 4, a patient with an incapacitating systemic disease that is a constant threat to life; and 5, a moribund patient who is not expected to survive 24 hours with or without treatment. The simplicity of both the Charnley and ASA classification may mask the true complexity of comorbidities, and both include categories that are not precisely defined; thus, both may suffer from inter-observer variation to a larger extent than, for example, the CCI (126).

Although a comorbidity index may be a useful overall summary of a patient's health status, it can only play a limited role in elucidating the impact of and mechanisms through which specific diseases affect patient outcome. However, patients with different combinations of medical diseases may have similar CCI scores. Therefore, the prognostic effects of specific diseases or groups of diseases that may arise from a common cause must be studied.

One specific disease of interest is diabetes, which had a global prevalence of 6.4% in 2010 and is projected to increase by 20% before 2030 (131). Diabetes is closely related to obesity, with over 50% of all patients with type 2 diabetes being currently or formerly obese (132). There is an established association between diabetes and a number of cardiovascular complications in the general population (133;134) and a

possible impact of diabetes on bone remodeling (135) has been demonstrated in experimental settings. The few small studies investigating the subject to date have found no association between obesity and poor prognosis after THR (136;137). Our understanding of the clinical course of THR may be improved by additional investigations of how THR prognosis is impacted by other serious chronic medical diseases, such as psychiatric diseases, cardiovascular diseases, cancer, chronic obstructive lung diseases, and infectious diseases (138).

Given the high volume of THR procedures and the ongoing change in patient demographics, attaining a better understanding of the association between comorbidities and postsurgical outcomes to improve the quality of THR treatment is an important public health priority. The studies included in this thesis are some of the first population-based studies to examine comorbidity as a prognostic factor for a variety of clinical outcomes following THR surgery instead of just death. The following chapters will present a review of the current literature on the prognostic effect of CCI, as well as several single diseases and disease groups, including the findings of studies II, IV, V, and VIII–X.

3.8. Overview of outcomes in patients undergoing THR surgery

Measuring THR surgical outcomes is important for improving the quality of patient care. In this section, I will walk you through the possible outcomes following THR surgery. The subsequent chapters (4–8) will present a review of the current literature on the risks and prognostic factors for specific outcomes, including the findings of studies II–XI, and the possible mechanisms for these post-operative events.

Important clinical or health outcomes are patient-relevant and broadly agreed upon, and measurable changes in a patient's health status arise as a consequence of treatment (139). Health outcomes for patients undergoing THR surgery may include patient survival (mortality); the occurrence of diseases, complications, or adverse events; patient-reported quality of life and functional status; and the patient's experience with treatment (106). In addition, economic outcomes have been used, to some extent, to evaluate THR success (*e.g.,* cost-effectiveness analyses; Figure 1) (140).

Implant failure is one possible post-primary-THR-surgery complication that occurs when the patient experiences clinical and symptomatic implant failure (141). Only a subset of these patients will subsequently require revision surgery (6) to remove or exchange a part of or the whole THR. Revision surgery is the most common clinical outcome used to describe the prognosis of patients undergoing THR surgery. The overall 10-year risk of revision for any cause following primary THR (*i.e.,* the number of patients with primary THR who undergo revision during a 10-year period over the number of THR patients followed for the same time period) (71) is reported between 3% and 10%, but can be even higher (14;51;142-144). During a median follow-up of approximately 5 years, 3.1% of all Danish primary THR patients underwent revision due to any cause (study II), and 0.7% due to joint infection (study IV). Aseptic loosening of the femur and/or acetabulum component is the main cause of revision (14;51;142;145), accounting for approximately 50% of

all revisions (study II). Aseptic loosening usually occurs during the long-term period after surgery, secondary to the formation of debris from prosthetic wear, which can mediate inflammatory osteolysis and loosen the bond between the implant and bone (146). Among patients younger than 55 years, aseptic loosening accounts for roughly 23% of revisions, whereas 45% of revisions in this age group are due to dislocation and peri-prosthetic joint infection (study III). Across all age groups, dislocation and peri-prosthetic joint infection account for approximately 40% of all revisions (75;101) and are the main cause for revision within 1–2 years post-operatively (study II). The remaining revisions are performed due to peri-prosthetic fracture of the femur, pain, or miscellaneous reasons (14;51;142) (study II).

The revision risk is closely related to the cause of revision and the length of follow-up and can further be explained by the presence of different prognostic factors. A number of studies have examined prognostic factors for revision with the aim of identifying patients at high risk. To the best of my knowledge, studies II–VI were the first to examine the association between comorbidities and revision surgery and the time-dependency of the effect associated with a number of prognostic factors, as suggested in other settings (147;148).

Less than 1% of THR patients die during or immediately after THR surgery for reasons mostly related to the treatment itself (149) (studies VII and X). Long-term mortality is most likely related to the presence of comorbid diseases at the time of surgery or the occurrence of other outcomes, such as peri- and post-operative diseases or complications, which can change the risk of dying and the clinical course of THR patients (10). Study VII of this thesis was the first to consider comorbidity as a confounding factor when examining post-THR long-term mortality in Scandinavian settings, in which the health care system differs from that of the United States (26).

Cardiovascular peri- and post-operative complications, including VTE, MI, and stroke, constitute the leading causes of post-operative morbidity and short-term mortality in THR patients (149-151) (study VII). VTE is a disease or complication that comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) (32), referring to the formation of a blood clot (thrombus) in the deep veins of the legs, pelvis, or arteries of the lung. VTE may be associated with increased risk of recurrent VTE (152) and post-thrombotic venous stasis syndrome (153), and a long-term risk of subsequent arterial cardiovascular events (154). Mortality within 3 months of VTE onset is 8% for DVT and 37% for PE (155). MI refers to a coronary artery occlusion in which an abrupt and mostly unpredictable plaque rupture and thrombosis play a central role (156). The World Health Organization defines stroke as a "focal or global neurological deficit of rapid onset and vascular origin with symptoms lasting 24 hours or longer or leading to death" (157). Prior to studies VI–XI, very few investigations examined the prognostic factors for these outcomes in population-based THR settings. In addition, previous studies may have been inadequately powered to detect significant prognostic factors. Peri- and post-operative bleeding complications following THR procedures have been studied, mostly in

relation to thromboprophylaxis (studies X–XI). Sparse data exist on other prognostic factors for bleeding in these patients.

Other complications of THR include infection around the implant, urinary tract infection, pneumonia, and peri-prosthetic fractures (10). Few studies have examined the occurrence of acute kidney injury after femoral neck fracture treated primarily with THR (158;159), which is a complication associated with increased risk of immediate post-operative mortality (160;161) and long-term mortality (161-164) in other clinical settings. One continuously monitored and feared, but seldom encountered, post-THR clinical outcome is the long-term occurrence of cancer and genetic damage due to the effects of "metal debris" from the hip implant (165).

The adverse outcomes described above are reported by healthcare providers. The evaluation of THR results by providers may not be consistent with patient evaluations. Therefore, patient-reported outcome (PRO) data have been increasingly used to measure the prognosis of THR surgery (166-170), providing a means of attaining insight into how patients perceive their health and the impact of THR surgery on their quality of life.

The occurrence of these other post-THR outcomes is highly relevant to comprehensively understanding the clinical course of THR surgery and should be studied further. In chapter 9, I will briefly present the current knowledge related to other outcomes, which are otherwise not part of this thesis.

4. REVISION SURGERY (STUDIES II–VI)

4.1. Prognostic factors for revision surgery

4.1.1. Age and risk of revision surgery

Although age categorization varies across studies, a decline in the overall long-term risk of revision with increasing age has been reported in several study populations (141;171), including Denmark (study II) (143). Body weight and physical activity substantially decrease with advancing age (172;173), reducing the stress on components and the risk for revision due to aseptic loosening, which is the main cause of revision in the long-term period. Most studies have focused primarily on the long-term risk of revision (144), although the mechanisms and measures for preventing revision may differ between the short- and long-term follow-up periods. Study II is the first report of a tendency of increased relative risk for revision with increasing age less than 30 days after surgery. For patients of ≥80 years of age, the adjusted relative risk (RR) for THR failure was 1.6 (95% confidence interval (CI): 1.0–2.6) compared to patients 60–69 years of age (study II). This finding can be explained by the increased risk of falls among elderly individuals (174;175). Furthermore, the risk of fracture increases (176) as bone mineral density declines, which occurs at a rate of 1–2% per year after 35 to 40 years of age (177). In the long-term, older age does not appear to

be associated with an increased risk of THR revision. Some studies have investigated revision due to deep infection alone and recognized age as a prognostic factor (75;178), but most large studies have found no association between age and revision risk due to infection, irrespective of the follow-up period (study IV) (179-181).

4.1.2. Gender and risk of revision surgery

There is broad agreement that male gender is a risk factor for any revision (141;171). Compared to women, men had a 20–50% increased risk of THR failure from any cause in both the short- and long-term follow-up (study II). This finding was explained by a higher risk of dislocations (182) and infections (180) (study IV) in men compared to women. However, two newly published studies indicate that femoral head size and bearing surfaces may substantially reduce the risk of post-THR revision in women, but not in men (183;184). The effect of gender may be further complicated by the effect of age and may depend on the cause of revision and follow-up time. Among THR patients younger than 55 years, no gender-related difference has been evident in revisions due to aseptic loosening. However, women in this age group had a 10–20% higher risk of revision due to causes other than aseptic loosening (*e.g.,* dislocation, infection, and peri-prosthetic fractures) (study III), even after adjusting for femoral head size and bearing surfaces.

4.1.3. Underlying hip joint diseases and risk of revision surgery

Overall, the results of THR for pediatric hip disease have been reported to be inferior to the results of THR for primary OA (13;185;186). In study II, we observed for the first time that pediatric diseases are associated with an increased 30 day and 31 day-6 month risk of failure due to any cause compared to primary OA (adjusted RR 1.9, 95% CI: 0.4-3.3 and adjusted RR 2.6, 95% CI: 1.4–4.8, respectively), but there was no increased risk beyond 6 months post-THR (adjusted RR 1.0, 95% CI: 0.6–1.4). These findings were later confirmed in two studies that reported a clearly increased risk of revision due to dislocation within 6 months of THR in pediatric patients vs. OA patients but no difference in the long-term risk of revision due to any cause (53;187).

Comparisons between THR patients with avascular necrosis of the femoral head and those with OA have had contradictory results (13;188;189). Compared to OA patients, patients with avascular necrosis of the femoral head have shown an almost 3-fold (95% CI: 1.7–5.0) and 2.3-fold (95% CI: 1.1–4.6) increased risk of any revision within 30 days and 6 months of THR, respectively, whereas the long-term risk for any revision was similar in these two groups (study II). However, a large Nordic study by Bergh et al. (188) reported that patients with avascular necrosis of the femoral head are at increased risk of any revision compared to OA patients, irrespective of follow-up time. In addition, THR patients operated on due to avascular necrosis have a higher risk of revision due to infection (study IV), dislocation, and peri-prosthetic fracture (188), indicating that efforts to reduce early revisions should be a top priority in these patients. Avascular necrosis has been linked with steroid therapy, trauma, renal disease, and alcohol consumption

(52;190), which may lead to reduced bone quality, impaired growth and remodeling, and higher risk of falls, dislocations, and infection. Unfortunately, studies II and IV or later studies in this patient population were not able to account for these potential confounding factors.

In summary, the effects of age, gender, and underlying hip diseases on the risk of revision are closely related to the follow-up period and reasons for revision.

4.1.4. Comorbidities and risk of revision surgery

We observed that a higher CCI score is associated with a significantly higher risk of revision due to any cause within 30 days of THR (adjusted RR 2.3, 95% CI: 1.6-3.5) and within 6 months of THR (adjusted RR 3.0, 95% CI: 2.1-4.5) (study II), particularly with the early risk of revision due to deep infection (study IV) and dislocation, which corroborates results from several other studies (29;30;75). Furthermore, for the first time, we observed that a higher CCI is associated with long-term risk of any revision (adjusted RR 2.8, 95% CI: 2.3-3.3) (study II). The mechanism underlying these associations is not yet fully understood. However, a number of diseases included in the CCI, such as liver disease, cancer, and chronic lung disease, can influence bone resorption and implant ingrowth (191-193), promoting implant failure.

Two recently published studies reported an association between high CCI and late risk of dislocation and infection (29;30). To better understand the clinical course of revision due to infection, Bozic et al. (194) studied 29 comorbid conditions and found that rheumatic disease, obesity, coagulopathy, and pre-operative anemia increase the risk of infection within 90 days. Jamsen et al. (195) reported that cardiovascular and psychotic comorbidities, cancer, and depression are also important predictors of long-term revision after primary THR.

The risk of post-THR revision due to infection has been reported to be similar (194-199) or higher (study V) in patients with diabetes compared to non-diabetic patients. In study V, we reported an increased risk of revision due to infection among patients with diabetes less than 5 years pre–THR, those with complications due to diabetes, and those with cardiovascular comorbidities prior to surgery. Another study recently confirmed these findings (198). The type of diabetes medication and pre-operative glucose levels were not associated with the risk of revision due to infection (198). However, the effect of glycemic control on the risk of revision due to infection has not been examined in detail. Some studies have indicated that the risk of revision due to infection depends on the type of diabetes, with an increased risk in patients with type 2 diabetes but not those with type 1 diabetes (study V) (200), but other studies have not reported this association (198;201).

In summary, the current data clearly illustrate that a high comorbidity level before surgery has a profound impact on the risk of implant failure. Diabetes has a detrimental effect on the risk of post-THR revision due to infection, possibly due to insufficient control of glucose levels.

4.1.5. Fixation technique and risk of any revision

Over the last two decades, preferences regarding THR fixation have changed, with a worldwide increase in the use of uncemented implants over cemented implants (202). Uncemented implants were introduced to avoid aseptic loosening, which occurs with cemented implants (203), as well as wearing of the acetabular bearing side (204), particularly in younger patients. Porous- and HA-coated uncemented femoral components and circumferentially porous- and HA-coated uncemented acetabular components allow bone to grow into or on the implants, reduce loosening, and are associated with better survival, supporting the use of uncemented implants (205-208). Some countries, including Australia, Denmark, Finland, Canada, and the United States, now predominantly use uncemented implants irrespective of patient age, whereas roughly 80% of all THR surgeries in Norway and Sweden are still cemented (51;59;142;145;209;210).

A systematic review and meta-analysis of nine randomized clinical trials found no difference between uncemented and cemented implants in terms of the long-term risk of any revision (>5 years of follow-up) (211). However, several observational studies (141;212-214) have reported an association between uncemented implants and a higher risk of any revision among all THR patients. An analysis of all THR patients from the New Zealand registry found that, compared to cemented implants, uncemented implants are associated with a higher revision rate more than 90 days post-operatively due to dislocations, pain, peri-prosthetic femoral fractures, and other causes, except deep infections (214).

The effects of fixation technique on implant survival have been suggested to differ according to age (102). A recent study showed that uncemented and cemented implants are associated with similar 10-year risks for any revision among 55 to 64-year-old THR patients (implant survival: 91.8% and 92.2%), whereas patients 65 to 74 years of age had an almost 50% higher risk of any revision with uncemented vs. cemented implants (implant survival: 92.9% vs. 93.8%), and patients older than 75 years of age had 110% higher risk of any revision with uncemented vs. cemented implants (implant survival: 93.0% vs. 95.8%), particularly during the first 6 months after surgery (15). Among THR patients younger than 55 years of age, we found no major differences in revision rates between patients receiving uncemented vs. cemented fixation (study III), which is in agreement with the literature (34;51;77;213-216). In study III, we observed that uncemented implants were associated with a 50% reduced risk of revision due to aseptic loosening, which is in line with the results of a Finnish study (216). However, compared to cemented implants, uncemented implants were associated with a greater than 2-fold elevated risk of revision due to causes other than aseptic loosening and revision due to any cause within 2 years of the surgery.

Changes in implant design and materials over the years have influenced the risk of revision of uncemented implants, which have undergone design and material changes more frequently than cemented implants. For example, a metal-on-metal bearing surface and large femoral head size are known to be associated with increased risk of early revision (184), and they have been used almost exclusively in

uncemented implants. The Australian Hip Registry (37) showed for the first time that uncemented implants are associated with a significantly lower risk of revision compared to cemented implants after the exclusion of implants with a large head size. In contrast, in study III, the differences in femoral head size and bearing surfaces between cemented and uncemented implants could not entirely explain the association of uncemented implants with revision risk.

The hybrid fixation technique was associated with a 30% higher risk of any revision among patients younger than 55 years (study III) and those older than 65 years (15) compared to the cemented technique. Study III also found that hybrid and cemented implants did not differ with regard to revision due to aseptic loosening in patients younger than 55 years in Nordic countries. This is in agreement with findings from New Zealand and Australia, which have a much longer tradition of using the hybrid implant (142;214). On the other hand, compared to cemented implants, hybrid implants in patients younger than 55 years led to a 2.1-fold increased risk of revision due to causes other than aseptic loosening (study III), particularly within 2 years of surgery, probably due to problems related to the uncemented cup component. This problem is not only a short-term concern because similar trends have been reported in analyses among patients younger than 55 years with complete 5- and 10-year follow-ups (study III). As the younger patients are less likely to die than to require a revision (144), it is important to assess and optimize the outcomes of younger patients in both short- and long-term follow-up.

Compared to cemented implants, inverse hybrid implants in younger patients seem to confer a lower risk of any revision and of revision due to aseptic loosening, but a higher risk of revision for other causes (study III). In addition, increased risks of early peri-prosthetic fractures and infections have been reported with the use of inverse hybrid implants (180;217).

In summary, uncemented, hybrid, and inverse hybrid implants may be associated with less long-term revisions due to their improved durability and resistance to aseptic loosening. However, the issues with short-term revision due to mechanical and technical problems have not yet been solved.

4.1.6. Fixation technique and risk of revision due to infection

Despite advances in surgical techniques, operating theater design, and the prophylactic use of antibiotics systematically and in cement, recent registry-based THR studies in the United States and Scandinavia have found increasing rates of revision due to deep infection (180;218). The risk of first time revision due to infection increased in Scandinavian countries from 0.5% to 1% from 1995 to 2009 (180). This increase may represent an artefact, improved diagnostic techniques, or improved registration of infections in hip registries, but may also reflect a true increase in infection rates over time. The burden of infections may be even higher than previously estimated; the latest report shows that relying only on hip registry data to identify revisions due to infections leads to an underestimation of the true incidence, and that the use of multiple data sources is preferable (219). Furthermore, revisions due to prosthetic joint infection incur greater

hospital costs than other revisions (220). Thus, the problem of deep infections following THR has not yet been solved and constitutes a considerable burden for health care systems.

The current literature examining the association between type of fixation and risk of revision due to infection is sparse and contradictory. Compared to cemented implants, uncemented implants have been associated with both increased (179) and reduced risks of revision due to infection (study IV) (180;214). Study IV found no difference in the risk of revision due to infection between hybrid and cemented implants (study IV). Another study found that the risk of infection was similar across all types of fixation (181).

Although several studies have adjusted analyses for a number of patient- and surgery-related prognostic factors for infection, information regarding potential confounders, including patient body mass index, smoking, alcohol intake, use of body exhaust suites and helmets, surgical approach, number of persons in the operating room, and injection of bacteria from the environment, is generally lacking (221). Roughly 30% of all hip infections have been suggested to be caused by bacteria that enter the operation wound during surgery, carried through the air as epithelial scales are shed from operating room personnel or dust (222). Skin and hair are the main sources of airborne bacteria. The remaining infections may be due to surgical gloves, instruments, and the implants themselves (222). Surgery lasting more than 2 hours is associated with an elevated risk of revision due to infection compared to surgery lasting less than 1 hour (adjusted RR 2.01, 95% CI: 1.49-2.75 in study IV) (30;223). Some researchers have suggested that each additional minute of operating time leads to a 3% increase in peri-operative complications (224). Because the operation time is longer in cemented implants compared to uncemented implants (223), residual confounding by operation time may partly contribute to the reported differences. Cemented implants are associated with a higher risk of receiving blood transfusions, which increases the risk of infections, such as pneumonia, but surprisingly not the risk of revision due to deep infection (study VI). Besides confounding, the lack of a generally accepted definition of deep infection of the THR can hamper international comparisons (225-227).

In summary, evidence regarding the association between the type of fixation and risk of revision due to deep infection is contradictory.

4.1.7. Operating theater and risk of revision due to infection

National and international standards specify that THR poses a high risk of infection and should be performed in ultraclean air in the surgical field, defined as ≤10 microorganisms (*e.g.,* bacteria) per cubic meter of air (228). Operation room ventilation systems are designed to provide ultraclean air (229), which can be accomplished by using diffuse and turbulent streams of filtered air, creating conventional mixed ventilation in the whole operating room (230). Alternatively, laminar air flow can be used, with streams moving in parallel layers at identical speeds to avoid turbulence, which produces centrally located streams of ultraclean air over the patient with less clean mixed air in the rest of the room (230). Ninety percent of THR

procedures in Denmark in the last 10 years have been performed in laminar air flow rooms (101), whereas approximately 50% and 60% of these procedures have been performed in laminar air flow rooms in Norway and Germany, respectively (179;231), and even fewer in the United States (181). Compared to the conventional operating room, the laminar air room is much more expensive in terms of both capital investment and maintenance (221). No clear evidence indicates that the use of a laminar air operating room reduces the risk of revision due to infection according to the 2011 Health Technology Assessment report published by the Danish Health Board and other available studies (study IV) (179;221;231).

4.2. Methodological issues with a potential impact on analyses of revision surgery

The validity of our analyses depends on the completeness and data validity of the clinical databases used (232). A validation study of the DHR demonstrated high completeness for primary THR surgery registration, compared to the Danish National Registry of Patients (DNRP) as a gold standard, and high validity of underlying hip diagnosis registration for individual patients compared to medical records (233). Database completeness regarding revision surgery registration is between 80% and 90% (233), which could reduce our ability to identify prognostic factors if the likelihood of missing revisions is associated with prognostic factors of interest. However, this is hardly the case due to prospective registration of data. The completeness of registration for revisions was reported to be similarly "low"/suboptimal in other Scandinavian hip registries (234-236). Few recent studies have examined the completeness of other national hip arthroplasty registries (234-236). Less information is available regarding the validity of data on prognostic factors (*e.g.,* fixation technique, operating room, and duration of surgery).

Primary THR in the right and left hip of the same patient are not independent observations, which may theoretically influence the validity of revision studies (71). For example, a patient with two implants may develop a deep infection in both hips after having one episode of sepsis. A recent systematic review showed that orthopedic publications commonly disregard the non-dependence (237). However, the inclusion of bilateral primary THR in analyses of arthroplasty registry data has been shown to have no or minimal impact on the estimated risk of revision (238-240).

A number of implants are commercially available (14;241), and the vast majority of available implant combinations have been used in fewer than 100 operations (241;242) (study III). The introduction of new implants is associated with worse outcomes (243), partly because the introduction of new implants involves aspects that cannot be accounted for in drug trials (244), such as surgeons needing to acquire new practical skills going through the "learning curve period" for performing the surgery. Furthermore, the efficacy of implants inserted under ideal conditions may not necessarily equal the effectiveness of the same implant inserted in real-world settings. This issue may have introduced unmeasured confounding in our analyses because we were not able to adjust for various implant combinations. Because uncemented implants have been subject to changes in design and materials more often than cemented implants, we included caput size

and articulation in adjusted sub-analyses. These adjusted relative risk estimates were not different from those calculated without taking caput size and articulation into account. In study III, we excluded implants with well-known low performance.

Surgery-specific prognostic factors are typically not assigned randomly. Patients may be offered a specific implant or regimen of peri- and post-operative treatment because they are low-risk and will most likely benefit from the treatment (*e.g.,* patients who are not offered blood transfusion are more healthy and at lower risk of infection than those for whom transfusion is indicated). "Confounding by indication" refers to such situations of channeling treatment depending on patient characteristics whereby, for example, the indication for transfusion is a confounder affecting prognosis (106). The resulting imbalance in the underlying risk profile between comparison groups can generate biased results, which we tried to account for in study VI by using the propensity matching method (71).

In studies of revision, competing risk is present because a patient is at risk of more than one mutually exclusive event, such as revision and death, and the occurrence of death will prevent the revision event from ever happening (245). Thus, the Kaplan-Meier method (which is widely used for reporting revision risk) overestimates the risk of revision compared to estimates obtained using analytic approaches that account for competing risks, including the cumulative incidence function (246;247). Very few orthopedic papers have applied competing risk analyses in revision studies, most of them from the Australian Hip Registry (246;248). The Nordic Arthroplasty Register Association (NARA) has recognized this problem and elaborated on this issue in the guidelines for statistical analysis of arthroplasty data (239).

5. VENOUS THROMBOEMBOLISM (STUDIES VI AND VIII–XI)

5.1. Risk of developing VTE

VTE is caused by a combination of hereditary (249) and acquired risk factors, including major surgery, trauma, cancer, inflammation, and various comorbidities (250). Three factors described by Rudolf Virchow over a century ago remain the basis of our understanding of thrombosis: vessel wall damage, venous stasis or reduced blood flow through veins, and increased activation of clotting factors triggered by the release of tissue debris, collagen, or fats into the veins during surgery (251). THR patients are especially vulnerable to developing VTE because the surgery is performed on the lower extremities, because of the persistent venous stasis due to prolonged immobility during the post-operative period (252;253), and because of activation of the coagulation-fibrinolysis system during surgery, which may persist for at least 2 months (254;255).

Among THR patients without thromboprophylaxis therapy, the risk of symptomatic and asymptomatic VTE within 90 days of surgery (*i.e.,* the probability that VTE has occurred before a given time) is as high as 60% (256-258). Asymptomatic DVT occurs in more than 50% of all THR patients (259), with an approximate 5:1 ratio of asymptomatic venous thrombi at hospital discharge to symptomatic venous thrombi within 90

days (260). Hence, patients with documented asymptomatic thrombi do not have a higher rate of post-phlebitic stasis than patients without thrombi (261).

Randomized clinical trials have showed that patients receiving thromboprophylaxis have a 1–6% risk of venography-confirmed VTE within 90 days of surgery (262;263). Non-randomized cohort studies have reported a 0.5–4% risk of symptomatic VTE within 90 days of THR (21-23;35;264;265). In Denmark, the cumulative incidence of symptomatic VTE within 90 days of surgery is 1% among THR patients receiving pharmacological thromboprophylaxis (studies VIII and X). Most symptomatic VTE events occur after discharge from the hospital (study X). The reported risk of VTE varies slightly across studies depending on the study design, characteristics of the study population, duration of thromboprophylaxis treatment, and methods of VTE identification.

Few studies have examined the temporal trends (*i.e.,* changes over time) in VTE risk after THR. From 1991 to 2008, the 90-day post-THR VTE risk decreased (36), whereas the risk of in-hospital PE reportedly decreased from 1998 to 2008 (266). In the period from 1994 to 2008, Singh et al. (35) reported an increased occurrence of all cardiac events except VTE within 90 days of surgery. All three of the above-mentioned studies are from the United States. A review of 14 randomized clinical trials published during 1991–2000 found no association between THR and DVT rates (267). We observed a 25% increase in the 90-day risk of VTE from 1995 to 2006 (study VIII), which declined afterwards, but never returned to the initial level (study X). Thus, the net risk of VTE appears to have changed little in Denmark during the 15-year period from 1997 to 2011 (study X). We expected the VTE risk to decrease over time due to major changes in clinical practice, including international guidelines recommending prolonged venous thromboprophylaxis, the launch of new thromboprophylaxis drugs, the introduction of less invasive surgical techniques, and fast-track surgery with early mobilization (263;268;269). These somewhat discouraging results are likely due to several contributing factors that counter the positive effects of innovations in clinical practice. First, the risk profile of THR patients has changed over time; we now include more patients with higher VTE risk (79;270). Second, implementation of extended thromboprophylaxis after THR has proved difficult in many settings (271) due to the short length of hospitalization (272). Third, the diagnostic tests for VTE have improved and some of the observed increase may reflect the detection of VTE events that were previously undiagnosed or misclassified.

In summary, the risk of developing symptomatic VTE within 90 days of THR is as low as 1% among patients receiving pharmacological thromboprophylaxis, and it has not declined during the last 15 years.

5.2. Prognostic factors for developing VTE

5.2.1. Age and gender in relation to VTE risk

VTE risk generally increases with age (273). Although several small studies in THR patients have shown that advanced age is a predictor of the 90-day post-operative risk of VTE (274-276), this association was not observed in other studies (23;35;277-279). Our results showing that patient age does not affect VTE risk in THR patients (studies VIII and X) are the first results obtained from population-based studies with a large sample size while accounting for a number of comorbidities prior to THR. Comorbidities strongly confound the age-VTE association in THR patients (280). Though some evidence suggests that women may have a greater risk of developing VTE after THR compared to men (253;275;281), the majority of studies have not found any association between gender and the 90-day post-operative risk of VTE (23;35;276-279) (studies VIII and X).

In summary, most evidence suggests that neither age nor gender *per se* is associated with the post-operative risk of VTE in THR patients.

5.2.2. Rheumatoid arthritis and VTE risk

A study of 721 RA and 8,859 primary OA THR patients from United States found no difference in the VTE risk between the two groups (282;283). Another study from the United States based on the same data sources found a 56% higher risk of VTE within 90 days of THR among 5,565 patients with RA compared to those without RA (282). On the other hand, in our study in Denmark, we found that the adjusted post-operative VTE risk was 47% lower in 1,841 THR RA patients than in 52,359 THR OA patients (study VIII). A 2012 meta-analysis (284) found no evidence of any difference in the 90-day risk of VTE between THR patients with RA and THR patients with OA, although this conclusion was based on only two studies: White et al. from 1990 (283) and SooHoo et al. from 2010 (282). Interestingly, study VIII was included in the review, but not in the meta-analysis (284). THR may have been offered to RA patients with the best prognosis in our setting. As THR is not the first choice treatment for RA patients, they will likely have been treated conservatively and with anti-rheumatic drugs for years before surgery was discussed. Anti-rheumatic medication, which is more likely to have been received by THR patients with RA, may alter the risk of VTE. Both NSAIDs (285) and corticosteroids (286) have been found to increase VTE risk. On the other hand, several recent studies have suggested that first-line treatment with methotrexate has the beneficial effect of reducing the risk of cardiovascular mortality (287;288).

Recent studies have suggested a higher risk of VTE in RA patients than among the general population without RA (289;290). According to a Danish study, patients with connective tissue disease have a 2-fold increased risk of VTE up to one year after the diagnosis (291). In addition, RA patients are recognized to

have an increased burden of arterial cardiovascular diseases (292), which is believed to be related to silent myocardial ischemia (293).

In summary, Danish THR patients with RA have a reduced risk of post-operative VTE compared to THR patients with primary OA, contrasting the findings from other available studies among THR patients. .

5.2.3. Comorbidities and VTE risk

In our study of approximately 70,000 Danish THR patients, we reported for the first time that a high pre-operative CCI score is associated with a 30–45% increase in the 90-day post-operative risk of VTE compared to a low CCI score (studies VIII and X). Singh et al. (35) later investigated 1195 patients who underwent THR at the Mayo Clinic during 1994–2008 and reported no association between a 1-point increase in the CCI score and the 90-day risk of VTE, regardless of the pre-operative history of VTE. In that study, CCI data were available starting in 1994, and patients enrolled early in the study period may have been misclassified as having no comorbidities or no history of VTE due to left censoring (*i.e.,* if the hospitalization for comorbid diseases occurred before 1994) (71). Such misclassification may have translated into dilution to the null of the estimated association between comorbidity and VTE risk. In a subsequent study from the United States, Huo et al. (22) also reported no association between CCI and VTE risk among 3,109 THR patients operated on from 2004 to 2009. This study did not describe the accessibility of CCI data in detail. In study VIII, comorbidities were detected at least 18 years and up to 29 years prior to surgery. In study X, to reduce misclassification of patients' comorbidity status, we obtained the hospitalization histories for all patients for the 10 years prior to the primary surgery.

Generally, patients with a history of VTE are at a higher risk of sustaining a new VTE than patients without such a history (273). The risk can further increase in the presence of several risk factors, such as major surgery and immobilization (294). THR patients with a history of cardiovascular disease or VTE had a 1.4-fold and 8.1-fold increased risk of VTE, respectively, compared to patients without that history (study VIII). This finding is in agreement with seven of the 10 other studies of THR patients (23;35;253;265;276;278;281).

The higher risk may reflect a higher likelihood of clotting for several reasons. First, endothelial damage may have occurred as a result of previous trauma or new vascular damage. Second, there could be stasis of venous circulation caused by peri-operative immobility, which deprives the deep veins of the legs the pumping action of the calf muscles (251). Third, some patients may have one or more underlying inherited or acquired defects of the coagulation system (249;250). General anesthesia may further decrease vascular tonus and distend veins, causing platelet adhesion and aggregation, triggering the coagulation cascade (295) and contributing to the cumulative risk of VTE (study X). Furthermore, general anesthesia has also been suggested to increase the need for blood transfusion compared to regional anesthesia (296), which may be associated with an increased risk of VTE (study VI). In study X, we observed that VTE risk

increases with the duration of surgery and is 60% higher in patients whose surgery lasted more than 2 hours compared to patients whose operation was completed within 1 hour. The duration of surgery is also a surrogate measure of immobility.

In addition to these possible explanations, recent evidence highlights an association between metabolic syndrome and VTE risk (120). For example, diabetes mellitus is a risk factor for VTE, with a meta-analysis-estimating a 1.4-fold increased risk of VTE among persons with diabetes (297) compared to non-diabetic patients. In study VIII, we found that diabetic THR patients had a 13% increased risk of VTE compared to non-diabetic THR patients. The effect of diabetes on VTE risk is closely related to the presence and co-effects of other cardiovascular conditions common among diabetics, such as obesity, hypertension, and dyslipidemia (297). Obesity is associated with immobility (251), and both obese persons and those with dyslipidemia have higher risks of presenting with elevated levels of procoagulant factors and impaired endogenous fibrinolysis (298-300).

In general, cancer is a well-known risk factor for VTE (301) and would be expected to further increase VTE risk when present in combination with THR. However, study VIII found no difference in VTE risk among the 4,785 THR patients with a history of cancer compared to the THR patients without a history of cancer, which diverges from the current prevailing line of thought in the clinical community (294). To date, no other studies have addressed the effect of malignancy on the risk of VTE after THR surgery performed for reasons other than cancer resection (302). Patient selection may dilute the association, as cancer patients may be less likely to undergo THR than other patients. Selection bias is the most likely explanation in light of the finding of lower mortality among THR patients with a history of cancer than among THR patients without a history of cancer (study VII).

In summary, a high comorbidity level before surgery substantially increases VTE risk. There is clear evidence supporting the association between higher VTE risk in THR patients with prior VTE, a history of cardiovascular disease, and diabetes. However, the association between cancer and VTE, which is well documented in the general population, does not hold for THR patients.

5.2.4. Anesthesia and fixation type in relation to VTE risk

Regional anesthesia has been used in more than 70% of Danish THR patients (215). In a Danish cohort study of more than 51,000 THR patients, general anesthesia was associated with a 20% higher risk of VTE than regional anesthesia (study X). The results of two meta-analyses of clinical trials (296;303) also favor regional anesthesia over general anesthesia due to reduced rates of post-operative thromboembolic events. Many of the trials included in recent meta-analyses were originally published more than 30 years ago and do not reflect current anesthetic and surgical practices. Thus, the beneficial effect of regional anesthesia may be diminished in the presence of modern anticoagulation treatment and modern anesthetic practices (295).

In the early nineties, uncemented implants have been suggested to benefit patients in terms of reducing the risk of fat embolism or VTE disease (304;305), which may occur in conjunction with intramedullary hypertension in the femur during implant insertion in patients undergoing cemented THR. Such intramedullary conjunction does not occur in patients undergoing uncemented THR. However, in a large study (study X) we observed that the risk of VTE did not differ between cemented and uncemented fixation techniques, possibly indicating improvements in the cementation techniques.

In summary, the use of general anesthesia compared to regional anesthesia for THR surgery is associated with an elevated risk of post-operative VTE. The current literature indicates no clear difference in the risk of VTE between the uncemented and cemented fixation techniques.

5.2.5. Duration of thromboprophylaxis

Available guidelines contain some differences regarding recommendations for the duration of thromboprophylaxis after THR surgery. The 2012 American College of Chest Physicians (ACCP) guidelines recommend using anticoagulation drugs for a minimum of 10 to 14 days with grade 1B evidence, and suggests extending prophylaxis for up to 35 days with grade 2B evidence (32). The 2012 guidelines from the National Institute for Health and Care Excellence (NICE) recommend prophylaxis for 28–35 days depending on the summary of product characteristics for the individual agent being used (306). On the other hand, the 2011 guidelines from the American Academy of Orthopedic Surgeons (AAOS) recommend individual assessment of the optimal duration of thromboprophylaxis without any elaboration on the THR patients who may benefit from extended prophylaxis (307). In May 2014, the Danish Council for the Use of Expensive Hospital Medicine (RADS) published the following recommendations: 1) thromboprophylaxis for hip and knee replacement and hip fracture patients should not exceed 10 days, and 2) prophylaxis for hip and knee replacement performed in fast-track settings should not exceed hospitalization time (max 5 days) (308).

In study XI, we found that the benefits (*i.e.,* reducing the risk of developing of VTE or VTE/death) and risks (the risk of major bleeding events) did not differ in relation to the duration of thromboprophylaxis in a real life setting. This finding was not in line with randomized clinical trials that showed greater benefits of extended thromboprophylaxis compared to the standard prophylaxis duration of 7–14 days (309-311) without introducing additional harmful effects.

Successive randomized clinical trials have compared the benefits of standard vs. extended and risks of standard vs. extended duration of thromboprophylaxis treatment (312) and reported reductions in the absolute risk of VTE and bleeding. No previous studies directly compared the benefits and risks of different durations of thromboprophylaxis using net clinical benefit analyses, which is a well-described method in other clinical settings (313). In study XI, the direct comparison of benefits and risks did not favor short-term, standard, or extended treatment duration in THR patients. However, fast-track programs are being implemented rapidly in orthopedic departments in Denmark and other countries (314;315). The majority of

patients who received short-term thromboprophylaxis in study XI underwent surgery at hospitals participating in a large cohort study on fast-track patient management (316). Thus, our findings must be interpreted in the context of treatment management changes in Denmark, including multimodal approaches involving anesthesia, analgesia, thromboprophylaxis during admission, minimal surgical stress response, fluid management, minimally invasive surgery, nutrition, and early mobilization within 2 hours, as well as ambulation during the pre-operative, intra-operative, and post-operative periods, none of which have been found to increase VTE risk (105;264). Decisions regarding acceptable durations of thromboprophylaxis should balance the very low absolute VTE risk (study VIII and X), the results regarding net clinical benefits (study XI) and cost-effectiveness, the results from real life settings (study XI), and the current treatment practices with the introduction of fast-track programs (105;264).

In summary, evidence from randomized clinical trials indicates a beneficial effect of extended thromboprophylaxis in terms of reducing VTE risk without introducing harmful effects (*e.g.,* major bleeding) compared to the standard treatment duration of less than 14 days. However, evidence from non-randomized cohort studies based on real life THR patients indicates that the risks of developing VTE, VTE/death, or major bleeding do not differ between extended and short-term thromboprophylaxis. Study XI was used as part of the background literature for the RADS recommendation.

5.3. Excess risk of developing VTE compared to the general population

In study IX, we found that patients undergoing THR had an increased excess 90-day post-operative risk of symptomatic VTE, with an adjusted relative risk of 15.84 (95% CI: 13.12–19.12), compared to the risk expected in the general population without THR. The relative risk was particularly high during the first 30 days after surgery (26.97, 95% CI: 20.19–36.02). In addition, during post-THR days 91 to 365, the adjusted relative risk among patients undergoing THR was 2.41 (95% CI: 2.04–2.85) compared to the general population (study IX). Similar findings of a slightly different magnitude were reported in only one other cohort study, which compared healthy middle-aged women with and without THR (mean age 56 years) (31). Furthermore, study IX suggested for the first time that VTE risk is increased for up to one year post-operatively in all age groups and irrespective of comorbidity level before surgery, although the relative risk was highest in patients younger than 59 years of age and in those without previous comorbidities. This finding indicates that, although THR is considered to be a safe procedure with a high success rate, it imposes a risk that is most evident among patients with a low baseline risk of VTE. The increased relative risk among younger patients may reflect system-related factors, such as a lower level of awareness among health professionals regarding the prevention, detection, and treatment of VTE in patients who are typically considered to be at low risk. THR confers a substantial risk of VTE beyond the current duration of hospitalization (317) and the recommended duration of prophylaxis. Notably, the absolute risks are less than 1% (study IX).

In summary, THR is associated with an increased excess risk of developing symptomatic VTE for up to one year after surgery compared to the general population without THR, regardless of patient gender, age, or level of comorbidity at the time of THR.

5.4. Methodological issues with a potential impact on analyses of the risk of developing VTE and excess VTE

In study XI, we excluded approximately 10% of patients registered in the DHR due to missing data regarding the duration of thromboprophylaxis. Compared to the patients included in the study population, the excluded patients had similar median age, sex, and comorbidity level. In light of the prospective registration of data in the DHR, it is unlikely that missing information regarding thromboprophylaxis duration occurred systematically as a function of its duration and/or later outcomes. Rather than excluding these patients, multiple imputation could be performed based on all available variables (318), a method rarely used in orthopedic studies.

We also found discrepancies between the duration of treatment with specific anticoagulation drugs recommended by the companies and the duration of treatment prescribed by a department as registered in the DHR (study XI). By reviewing the departmental guidelines for thromboprophylaxis and contacting departments by phone, we validated and confirmed the accuracy of data in the DHR regarding the prescribed duration of treatment in all departments.

The DNRP was used to collect data regarding the occurrence of VTE and major bleeding (studies VI and VIII–XI). After reviewing medical records, a VTE diagnosis could be confirmed in 75-95% of the patients in the DNRP (319). Any misclassification of VTE diagnosis is most likely independent of the prognostic factors examined in studies VI, VIII, X, and XI, and non-differential misclassification tends to produce estimates that are diluted values of the actual effect (111).

To examine the effect of the duration of thromboprophylaxis in THR patients, the best study design would be a clinical trial randomly assigning patients to receive short-term or extended prophylaxis. However, clinical trials have been criticized for including younger and healthy patients for randomization, as these patients are not typically seen in clinical practice and because the controlled and ideal conditions maintained in clinical trials are difficult to apply in routine clinical practice (study XI) (105;264). In addition, compliance with extended thromboprophylaxis is reportedly more than 90% in most clinical trials, which is slightly higher than reported in routine clinical practice (320). If lower compliance is related to extended prophylaxis, as in study XI, it could dilute the actual effect of extended prophylaxis on VTE risk. With a non-randomized cohort design, one cannot completely overcome confounding by indication (*i.e.,* the shorter treatment duration being offered to healthier and younger patients at lower risk for VTE and bleeding), unmeasured confounding (*i.e.,* the inability to control for known confounders due to poorly measured or unavailable data, such as body mass index), and unknown confounding (*i.e.,* not controlling for unknown factors that could

distort the association between treatment duration and risk of VTE and bleeding) (study XI), particularly when studying the effects of treatment.

The estimates of the net clinical benefit analyses in study XI must be interpreted with caution due to statistical imprecision. Our estimates of net clinical benefit may provide a useful anchor point for discussing risk stratification in regards to the duration of thromboprophylaxis in THR patients. However, unlike other clinical settings, we were unable to perform net clinical benefit analyses on the subgroup level (321), which would allow us to identify patients who would clearly benefit from extended prophylaxis without sustaining more bleeding events. This issue requires a large sample size, which is an impetus for international collaboration between THR registries.

Some discrepancy in the VTE risk between studies may be due to inherited differences between the International Classification of Diseases (ICD)-10 coding system used in Denmark and the ICD-9 coding system used in some other European countries and the United States. Furthermore, regarding randomized clinical trials, the use of routine venography to identify asymptomatic VTE and confirm symptomatic VTE before randomization and during the follow-up period may lead to overestimation of the risk of symptomatic VTE, as the assessment of symptomatic VTE did not occur independently of the results of routine venography (322).

Furthermore, we cannot entirely exclude the possibility of surveillance bias in study IX, which could include a higher level of physician awareness regarding the prevention and detection of VTE in high-risk THR patients compared to persons from the background population.

6. MYOCARDIAL INFARCTION AND STROKE (STUDIES VI, X, AND XI)

6.1. Risk of developing MI and stroke

Several studies have reported the risk of MI following THR surgery, with estimates of 0.13% (323) and 0.16% (324) in-hospital, 0.5% within 30 days of surgery (274), and 1.2% (35) and 0.5% (325) (study X) within 90 days of surgery. The risk of MI is higher among males than females and increases with age, increasing to approximately 2% in THR patients older than 80 years within 30 days of THR (274).

The median time to hospitalization for MI varies between 3 and 5 days (323;324) and is 8 days in Danish settings (study X), which is much shorter than the median time to hospitalization for VTE. Lalmohamed et al. (325) observed that the risk of MI peaks 2 weeks post-THR, remains increased for 6 weeks (until week 8), and then decreases compared to controls from the general population without THR. One year post-THR, the risk of MI is similar in THR patients and the general population without THR (325). Ravi et al. (326) even found that THR surgery may have a cardio-protective effect after 3 years of follow-up.

Few studies have examined the risk of ischemic stroke following THR surgery. Three studies based on data from the United States reported that THR patients have a 0.2% risk of peri-operative stroke (25;327) and a 3.9% risk of stroke one year after the surgery (328). The risk of stroke within 90 days of surgery is 0.5% (study X). A recent study from Denmark reported that the relative risk of stroke is elevated for up to six post-operative weeks compared to matched controls from the general population (329).

The mechanism underlying post-operative MI and stroke is not completely understood and is clearly multifactorial (156;157). Most post-operative MIs start during the emergence from anesthesia (330;331). The post-operative period is characterized by adrenergic stimulation, inflammatory response, tachycardia, hypertension, high blood viscosity, increased prothrombotic activity, and reduced fibrinolytic activity (156;332). This combination of events may trigger coronary vasospasm, plaque rupture, and coronary occlusion. One of the main triggers of post-operative stroke may be intra-operative hypotension, which often continues unnoticed in the post-operative period (333). The occurrence of MI and stroke shortly after surgery may also be related to fat and bone marrow embolism, which can be prompted by surgical drilling in the medullary canal of the femur, intra-operative hypotension causing reduced blood flow, cerebral blood vessels having a reduced ability to remove eventual thrombi, and cardiac stress (334;335). Furthermore, blood transfusion is widely performed with THR surgery in Denmark and may further contribute to the occurrence of MI and stroke. In study VI we found that blood transfusion is associated with the risk of cardiovascular and cerebrovascular events within 90 days of surgery compared to non-transfused patients (RR 1.42; 95% CI: 0.93–2.15). Finally, the epidemiology of atrial fibrillation is changing, and it is a growing public health problem (336), which is important because patients with atrial fibrillation are at increased risk of stroke and MI (337;338).

Several studies from the United States have observed slight increases in the occurrence of in-hospital MI and stroke between 1991 and 2008 (35;36;266). In Denmark, during the 15-year study period between 1997 and 2011, we observed small variations in the annual rates of MI and stroke within 90 days of surgery (study X), with a peak in 2002–2003; however, in principle, the rates remained unchanged. New diagnostic criteria introduced in 2002 included troponin as the main diagnostic biomarker of MI (339), which may have increased the detection of smaller infarcts and influenced the estimated rate of MI. Data indicate that the incidences of MI and stroke are declining in the general population (340;341) due to better prevention and treatment; thus, our results could suggest that changes in the THR technique may have introduced more MIs and strokes. MI and stroke are associated with high morbidity and mortality (341) and are the main causes of death in THR patients (149-151) (study VII), usually occurring within a few days of surgery (study X).

In summary, it is clinically important, and important to public health, to focus on the prevention and early detection of MI and ischemic stroke among THR patients.

6.2. Methodological issues with a potential impact on analyses of MI and stroke risk

The DNRP was used to collect outcome data on MI and stroke (study VI, X–XI). After reviewing medical records, a diagnosis of MI was confirmed in approximately 94% of patients (342) and the diagnosis of ischemic stroke in approximately 88–94% of patients registered in the DNRP (343;344). Thus, there may have been some misclassification of outcomes, most likely non-differential, producing more conservative estimates of MI and stroke risk.

7. BLEEDING (STUDIES X AND XI)

7.1. Risk of and prognostic factors for post-operative bleeding

Although THR surgery is an elective procedure and there is usually time for pre-operative hemodynamic stabilization of the patient, 30–80% of THR cases are associated with blood loss resulting in a allogeneic blood transfusion during surgery or recovery in the hospital (104;345) (study VI). This despite described association between blood transfusion and adverse prognosis following THR surgery (study VI). Much of the peri-surgical bleeding comes from the bone, muscles, and vessels that were cut and cannot be avoided. Bleeding during surgery can be calculated by measuring the amount of blood removed from the operation field by suction into the container placed outside or weighing the swabs or sponges used during the surgery. Although all types of bleeding can cause complications, more extensive, rapid, and continuous bleeding during and after THR surgery or bleeding into other organs is most likely to cause severe post-operative complications and death. One example of bleeding complication is wound hematoma or bleeding stomach ulcers (346).

The risk of bleeding has been reported as a safety outcome in a number of randomized clinical trials studying the efficacy of new anticoagulation drugs (18-20) or prolonged thromboprophylaxis (310;311) in THR patients, as well as in a few non-randomized cohort studies (21;22;347;348). The bleeding risk was found to range from 0.1% to 3.5% depending on study design, definitions, and the methods of identifying these outcomes. Major bleeding outcomes in randomized clinical trials usually include clinically overt bleeding associated with death, a fall in hemoglobin, or the need for transfusion, assessed daily during hospitalization and at outpatient visits. In contrast, non-randomized cohort studies determine such outcomes based on registry data and ICD codes for bleeding (22;348) (studies X and XI). In a Danish setting, the overall risk of hospitalization for major bleeding within 90 days of surgery was 0.6% (483 patients out of 83,756), and 0.4% and 0.5% within 30 and 60 days, respectively (study X). This is similar to the risks observed in clinical trials (18-20;310;311). Gastrointestinal bleeding accounts for roughly 60% of major bleeding episodes after THR (study X). The median time to hospitalization for major bleeding was 21 days among THR patients in study X, but the THR patients also had an increased risk of gastrointestinal bleeding

for up to 12 weeks after surgery (346). The rates of post-operative major bleeding were stable during 1997–2011 (study X).

Major bleeding occurs less frequently than VTE, suggesting a favorable benefit/risk profile for VTE prophylaxis in THR patients (study XI). However, sparse data are available on patient-, disease-, and surgery-related predictors of bleeding in thromboprophylaxis-treated patients undergoing THR. A longer duration of thromboprophylaxis may slightly increase bleeding risk (20;311), but this procedure has not yet been fully implemented in Denmark. Several new anticoagulation drugs (312), including rivaroxaban, are associated with an increased risk of bleeding compared to enoxaparin. THR patients are at an increased risk of bleeding due to the multiple prescription drugs they may be taking, including non-steroid anti-inflammatory drugs (349), antiplatelet drugs (350), antidepressants (351), and corticosteroids (352). Further research is warranted to determine how the bleeding risk in THR patients is impacted by these drugs, as well as polypharmacy.

In study X, we identified several predictors of major bleeding after THR, including male gender, increasing age, comorbidities, and use of general anesthesia. Huo et al. (22) studied the predictors of post-discharge bleeding in a sample of 3,109 THR patients and reported that age, gender, and comorbidity level prior to surgery are predictors of bleeding. The authors noted that their results based on patients enrolled in a large health care program may not be generalizable to other populations. There is a tendency towards lower bleeding risk with uncemented and hybrid implants compared to cemented implants, which may be explained by the surgical procedure being shorter in duration and less extensive (study X).

In summary, there is a low (0.6%) risk of bleeding in Danish THR patients, which has remained unchanged since 1995. However, this is a serious condition that predicts the risk of death with a relative risk of 6 (347). Several factors increase bleeding risk in THR patients, including male gender, increasing age, comorbidity level, use of general anesthesia, and drug use.

7.2. Methodological issues with a potential impact on analyses of bleeding risk

Studying the risks of and prognostic factors for post-operative bleeding following THR surgery may be challenging due to the low absolute number of events. Individual studies of bleeding must be performed on large study populations and/or with long follow-up periods to detect statistically precise and clinically important differences in prognostic factors.

8. MORTALITY (STUDIES VI, VII, AND XI)

8.1. Short-term excess mortality compared to the general population

In the first 30 days post-surgery, all-cause mortality is approximately 40% higher among THR patients than the general population (study VII) (26;353), but it is similar (26;75) or 20% lower after 90 post-operative days (study VII). A recent Danish study reported that mortality did not substantially differ in patients 6 months after THR compared to a cohort without THR (354). Some studies included both OA and RA patients, which could explain small differences in the duration of excess mortality risk.

THR patients with OA and younger than 60 years had an increased relative all-cause mortality of 2.1 within 90 days of surgery, which clearly contrasts with the relative mortality risk of 0.8 in patients older than 60 years (study VII) and the results of two studies from Norway (27;353), which reported excessive early all-cause mortality in patients older than 70 years of age. We further found that, among those without prior co-morbidity, the relative mortality rates were increased 2.1-fold and 1.4-fold 30 days and 60 days post-operatively, respectively (study VII). Younger patients and patients without comorbidity before surgery had a small absolute risk of death compared to patients who are older or have more comorbidity; thus, the increase in short-term relative mortality is explainable by the low background mortality. Careful selection of patients eligible for surgery results in the THR patients with moderate and high CCI before surgery having lower 90-day mortality than the general population with similar CCI levels (study VII).

In summary, THR surgery was associated with an increased overall short-term risk of dying during the first 30 days after surgery, whereas 90-day mortality among patients undergoing THR for OA was similar to or lower than that of the general population. However, THR still conferred an increased risk of dying within 90 days in patients with a low baseline risk of mortality, such as younger patients and those without prior comorbidity. Target patients for prevention should be those at the highest absolute risk of mortality because attention to the care of older patients and comorbid patients would result in a larger reduction in mortality in the population.

8.2. Long-term excess mortality compared to the general population

THR patients with OA have an approximately 30% lower overall long-term mortality than comparable controls from the general population (26;27) (study VII). Selection bias is the most plausible explanation for the apparent protective effect of surgery. Another possible explanation is unmeasured confounding, though we accounted for the CCI score and for each of the comorbid diagnoses included in the CCI because they also impact mortality in THR patients (26;355;356). Moreover, the surgery itself may introduce a lower risk of long-term mortality compared to the general population due to the optimization of a patient's medication for and after surgery, physical rehabilitation and exercises, changes in home settings (*e.g.,* to reduce falls), and increased attention to symptoms of infection and thrombosis by both patients and their physicians.

In summary, THR surgery is associated with lower long-term mortality among patients with OA, reflecting a combination of the inherently low mortality rate of patients selected for surgery and unmeasured confounding.

8.3. Cause-specific mortality

In study VII, we examined the mortality attributed to specific causes during a specified time interval (*i.e.* cause-specific mortality). THR surgery is associated with increased relative 90-day mortality due to MI and VTE compared to the general population (study VII) (355;357;358). For the first time, relative mortality due to MI and VTE was found to be independent of age, gender, and comorbidity before surgery in study VII. In light of the latest evidence showing declines in in-hospital and 90-day mortality (36;266;354) (study X), but not the risk of cardiovascular events (study X), our results strongly indicate that the prevention and treatment of thromboembolic events should focus on reducing or eliminating preventable deaths following THR surgery. Study VII reported the novel finding that, after the first 90 post-operative days during the long-term period, THR patients have lower relative mortality than the general population for a number of reasons.

In summary, MI and VTE are the leading causes of death in THR patients, particularly during the short-term post-operative period.

8.4. Methodological issues with a potential impact on mortality analyses

Study VII may be impacted by unknown confounding or unmeasured confounding because data were not available regarding possible confounding factors, such as social status, physical activity, and drug use, in THR patients or the general population.

9. OTHER OUTCOMES AFTER THR SURGERY

Peri-prosthetic femoral fracture is an intra-operative or post-operative complication following THR with or without concomitant loosening of the femoral component (359). Our group participated in a large cohort study based on 437,629 THR procedures registered in the NARA database and found that approximately 0.5% of THR patients suffer peri-prosthetic fracture within 2 years of surgery, and that the occurrence of peri-prosthetic fractures has increased since 1995 (360). This complication is closely related to uncemented implants (360), and we expect continued increases in the occurrence of peri-prosthetic fractures over the forthcoming decades in association with the increasing use of uncemented THR and the longer life-expectancy in the population. Some uncemented femoral components are particularly conducive to peri-prosthetic fractures, including the recently recalled Stryker ABG II.

Continuous motion at the metal-on-polyethylene and metal-on-metal surfaces of THR implants can result in the release of metal microparticles from hip implants into the surrounding tissue (361). These metal microparticles can corrode, resulting in the release of metal ions into the circulation, including chromium, cobalt, and titanium. Metal debris can be associated with genetic alterations (362); therefore, the cancer risk after THR has been monitored continuously. To date, no increased risk of cancer has been found after either standard metal-on-polyethylene or metal-on-metal THR (165;363). However, metal-on-metal bearings are associated with an excess risk of revision and several other complications, including the development of pseudo tumors, which destroy bone and muscle around the implant (51;142). Our group participated in a large cohort study based on the NARA dataset, which confirmed the high revision risk associated with metal-on-metal implants, particularly ASR implants (364). Since then, the use of metal-on-metal implants has decreased substantially, and a program has been established for the assessment and follow-up of these patients.

A few studies in hip fracture patients, roughly half of whom underwent THR, reported an 8–24% risk of acute kidney injury while in the hospital or within 72 hours after surgery (158;159). In addition, Bennet et al. (158) reported that patients with acute kidney injury are three times more likely to die within 120 days of surgery than those without acute kidney injury. We initiated several currently ongoing studies to examine the risk of and prognostic factors for acute kidney injury among Danish hip fracture patients.

Several hip-specific and general health (*i.e.,* generic) PRO measurements (PROMs) are available to evaluate the prognosis of THR surgery (166-170). PhD student Paulsen and colleagues (169) assessed the usefulness of two generic PROMs (the EuroQoL-5D and SF-12 health survey measures) and two disease-specific PROMs (the hip dysfunction and osteoarthritis outcome score (HOOS) and the Oxford 12-item hip score (OHS)) in DHR settings. All four PROMs are appropriate for administration in a hip registry. Paulsen's PhD study also identified cut-off points corresponding to minimal clinically important changes in PRO scores and the acceptable post-operative PRO score by estimating minimal clinically important improvements (MCII) and patient-acceptable symptom states (PASSs) one year after THR. Although PROMs have been used for years in many international hip registries to understand how patients perceive their health and the impact of THR surgery on their quality of life, this has not yet been done in Denmark in a systematic way.

Several studies have performed a cost-effectiveness analysis concerning THR surgery, expressing the costs per quality-adjusted life years (QALY) or per disability-adjusted life years (DALY) (8;9;140;365). THR has been found to be cost-effective compared to non-operative treatment. THR had an estimated cost of US$4600 per QALY gained in men aged 85 years and more in one study (8) and of US$12,000 per QALY gained in patients with a mean age of 62 years in another study (366), and has even been found to be cost-saving among 60-year-old white women (8). The cost-effectiveness of THR has been estimated as AU$5000 per DALY gained among OA patients older than 40 years (140), which is more than two times better than a

knee replacement procedure (140;365). Compared to other procedures or treatments, the cost-effectiveness of THR within 3 years of surgery has been reported to be similar to that of a coronary artery bypass procedure for left main disease with angina, more than 4 times better than that of a coronary artery bypass procedure for two-vessel disease with angina, 2–6 times better than that of screening mammography for women aged 50 years and more, 7–8 times better than that of renal dialysis, and 11 times better than treatment with captopril for hypertension (8). In addition, the QALY gained with THR surgery are maintained for 5 years following surgery (366-368). Future research should focus on cost-effectiveness analyses of different treatment interventions, such as different durations of thromboprophylaxis or fixation methods.

10. CONCLUSIONS

This thesis investigated the prognosis of THR patients over the last two decades. Ten studies were based on Danish cohorts of THR patients, whereas one study examined THR patients operated on in four Nordic countries: Denmark, Sweden, Norway, and Finland. As the overall aim of this thesis was to improve our understanding of the long-term clinical course of patients undergoing THR surgery (12), the occurrence of a broad range of adverse outcomes, including revision surgery, VTE, MI, stroke, bleeding, infection, and death was examined. The thesis further identified patients who are at increased risk of developing these outcomes in both the short- and long-term post-operative periods in order to create a basis for preventing adverse outcomes, refine patient selection and treatment, and improve the quality of THR surgery.

THR surgery is now one of the most commonly performed surgical procedures in Western countries, with increasing rates worldwide over the last two decades, including a 30% increase in Denmark from 1996-2002 (study I). Direct comparison of THR rates from different countries is complicated by a lack of generally accepted standardization methods as recognized in study I. In contrast, during the same time period in Denmark, the rate of THR due to RA was reduced by 30% (study I), which is in accordance with reports from other countries (82-87).

Several studies have predicted that the overall demand for THR surgery will further increase based on anticipated changes in patient demographics alone (96-100), as well as on the surgical activity in previous years (study I). On the other hand, the newest data show that the incidence of THR in Denmark has been stable over the years 2010-2013 (102), which may be partly attributable to lower OA disease activity in the general population or more extensive pharmacological treatment, neither of which has been confirmed in the literature.

One feared post-THR complication is revision surgery, which has been studied extensively since the insertion of the first hip implants. A number of factors have been associated with the risk of revision surgery. However, there is a possible contradiction regarding the direction of associations depending on whether

short- or long-term risk was studied, which has not been widely acknowledged before this thesis. For example, we observed that, during the short-term post-operative period, older patients have a higher risk of any revision due to their increased risk of falling and sustaining a fracture or dislocation. On the other hand, younger patients were at a higher risk of revision during the long-term period (study II) due to implant loosening. Similarly, in the short-term post-operative period, pediatric diseases were associated with an increased risk of any revision compared to OA due to the increased risk of dislocations (53;187), but no difference in revision risk was observed in the long-term period (study II) (53;187). During a median follow-up time of approximately 5 years, 3.1% of all Danish primary THR patients underwent revision due to any cause (study II) and 0.7% due to joint infection (study IV).

Two studies observed that a high comorbidity level prior to surgery has a profound impact on short-term revision risk (study II) (75). A novel finding of this thesis was that high comorbidity also affects the long-term revision risk (study II), which has been confirmed by several recent studies (29;30;194;195). Due to the increasing burden of a variety of comorbidities in THR patients, their association with revision risk and the underlying mechanisms merit further research. To offer some possible explanations for how comorbidity affects revision risk, this thesis focused in more detail on THR patients with diabetes, which has a high and increasing prevalence in both the general population and the THR population. Diabetes increased the risk of revision due to infection, particularly in patients with diabetes for less than 5 years prior to THR, those with complications due to diabetes, and those with cardiovascular comorbidities prior to surgery (study V). These findings were also confirmed recently (198). However, the effect of the quality of glycemic control on the risk of revision due to infection has not yet been addressed in detail. Other prognostic factors for revision due to infection remain to be identified, as several reports indicate increasing rates of revision due to deep infection (180;218).

Uncemented implants are supposed to solve the problem of aseptic loosening with cemented implants (203) and wear of the acetabular bearing side (204). Uncemented implants are successful in achieving this goal when they are used in patients younger than 55 years of age (study III), but not in patients over 65 years (15). However, we still need to solve mechanical and technical problems with uncemented implants, which lead to short-term revisions irrespective of age (study III).

The 90-day risk of symptomatic VTE among Danish THR patients receiving pharmacological thromboprophylaxis is only 1% (studies VIII and X). THR was associated with an increased excess risk of developing symptomatic VTE up to one year after surgery compared to the general population without THR, irrespective of gender, age, or comorbidity prior to THR (study IX). There is clear evidence of an association between previous VTE or history of cardiovascular diseases and risk of post-operative VTE in THR patients (study VIII) (23;35;253;265;276;278;281;297). However, only sparse data exist regarding the general effect of comorbidity on VTE risk. A high CCI score before surgery has been shown to substantially increase VTE

risk in Danish settings (study VIII and X), but not in select clinics in the United States (22;35). Study VIII observed that THR patients with RA have a lower 90-day risk of VTE compared to THR patients with primary OA. However, this finding was not confirmed in a recent meta-analysis based on two studies (284) and further research is needed.

Evidence from non-randomized cohort study XI based on real life THR patients indicates that the risks of developing VTE, VTE/death, or major bleeding do not differ between extended and short-term thromboprophylaxis.

Approximately 1 in 200 THR patients develop MI or ischemic stroke within 90 days of surgery (study X) (325). The risk of MI and stoke is elevated for 6 weeks following THR compared to the general population without THR (325;329).

The risk of major bleeding complications associated with THR was stable from 1997 to 2011 (study X), and was approximately 0.5% within 90 post-operative days. Despite more aggressive thromboprophylaxis (study XI), major bleeding still occurred infrequently and was less common than VTE (study X). Study X reported for the first time several prognostic factors for major bleeding in THR patients, including male gender, older age, high comorbidity level, and use of general anesthesia. Approximately 32% Danish THR patients received treatment with allogeneic blood transfusion, although the treatment is associated with an adverse prognosis following THR surgery (study VI).

As expected, THR surgery is associated with an increased risk of any death within the first 30 days after surgery (study VII). However, in general, 90 days after surgery, patients who underwent THR due to OA showed similar (26;75) or even lower any cause mortality (study VII) compared to the general population, which persisted in the long term (study VII) (26;27). A novel finding of this thesis was that THR surgery seems to be associated with increased 90 days mortality, particularly due to MI and VTE, among younger patients and those without comorbidity before surgery compared to matched persons from the general population without THR (study VII). Treatment with THR is overall well optimized, as shown by the decreased in-hospital mortality and 90-day mortality rates in several developed countries (study X) (36;266;354). The steady-state occurrence of cardiovascular complications was observed over the last 15 years, from 1997 to 2011 (study X) suggesting that that there may still be room for clinical improvement.

11. DANISH SUMMARY (DANSK RESUME AF AFHANDLINGEN)

Denne afhandling omhandler prognosen for patienter, som har gennemgået en total hoftealloplastikoperation i løbet af de seneste to årtier. Afhandlingen er baseret på 11 studier, hvoraf de 10 udelukkende omhandler danske patienter, mens et studie er baseret på patienter opereret i fire nordiske lande: Danmark, Sverige, Norge eller Finland. Det overordnede formål med denne afhandling er at forbedre vores forståelse af det fulde kliniske forløb for patienter med total hoftealloplastikoperation, og afhandlingen beskriver derfor forekomsten af en bred vifte af komplikationer, herunder reoperation, venøs tromboemboli (VTE), arteriel tromboemboli inklusiv myokardieinfarkt (MI), apopleksi, blødning, infektion og død. Endvidere identificerer afhandlingen en række patient- og operationsrelaterede faktorer, som har betydning for risikoen for udvikling af disse komplikationer på både kort og lang sigt.

Total hoftealloplastikoperation er i dag en af de hyppigst udførte kirurgiske procedurer i de vestlige lande, og incidensen er steget over hele verden i de seneste to årtier (4;12;62;63;65;75;76). I Danmark steg incidensen af total hoftealloplastikoperationer med 30% i perioden fra 1996 til 2002 (studie I). Antallet af disse operationer, der blev gennemført på grund af reumatoid artritis, faldt dog med 30% i samme periode (studie I), hvilket er i overensstemmelse med rapporter fra andre lande (82-87). Der er foreslået flere mulige forklaringer på dette fald, herunder forbedret diagnostik og bedre behandling af reumatoid artritis. Der eksisterer dog kun få store populationsbaserede studier, som støtter disse hypoteser (85;89;94).

Flere undersøgelser har forudsagt, at efterspørgslen efter total hoftealloplastik vil stige yderligere baseret på de forventede ændringer i patienternes demografi alene (96-100) samt baseret på det kirurgiske aktivitetsniveau i de senere årtier (studie I). Imidlertid viser de nyeste danske data, at incidensen af total hoftealloplastik har været stabil i Danmark i årene 2010-2013 (102). Dette kan muligvis tilskrives mildere sygdomme i hofteleddet i befolkningen generelt eller mere omfattende medicinsk behandling, men ingen af disse forklaringer er blevet bekræftet i litteraturen endnu.

Alvorlige komplikationer efter total hoftealloplastikoperation kan føre til reoperation, som har været undersøgt i mange studier siden indsættelsen af de første proteser. En række faktorer, som har betydning for risikoen for reoperation, er blevet identificeret. Der har imidlertid været modsigende resultater vedrørende en mulig association mellem nogle af disse risikofaktorer og reoperation, alt efter om der blev set på risikoen på kort eller lang sigt – at en association kan være tidsafhængig er et problem, som ikke var almindeligt anerkendt før denne afhandling. Vi har for eksempel påvist, at ældre patienter på kort sigt (0-30 dage efter operation) har en højere risiko for reoperation på grund af fraktur eller dislokation, formentlig relateret til deres øgede risiko for at falde (studie II). Til gengæld har yngre patienter en højere risiko for reoperation på lang sigt (studie II) på grund af løsning af protesen. Ligeledes har patienter, som har gennemgået en total hoftealloplastikoperation på grund af en medfødt hoftesygdom, på kort sigt en højere risiko for reoperation sammenlignet med osteoartrosepatienter, mens der ikke blev fundet nogen forskel i

risikoen for reoperation på lang sigt (studie II) (53;187). Overordnet er risikoen for reoperation uanset årsag 3,1% inden for fem år efter operation (studie II), hvorimod risikoen for reoperation på grund af infektion er 0,7% (studie IV).

Dee er en voksende byrde af komorbiditet blandt total hoftealloplastikpatienter. To studier har vist, at en høj komorbiditet før operation har stor indvirkning på risikoen for reoperation på kort sigt (studie II) (75). Studie II viste yderlige en association mellem høj komorbiditet før operation og risiko for reoperation også på lang sigt, hvilket er bekræftet i flere nyere undersøgelser (29;30;194;195). For bedre at kunne forstå de underliggende mekanismer bag denne association, har afhandlingen fokuseret yderligere på de enkelte komorbide sygdomme, som hoftealloplastikpatienter i stigende grad præsenterer sig med, og på de specifikke årsager til reoperation. Det er vist, at incidensen af reoperationer på grund af infektion er stigende i hele verden (180;218). Studie V viste, at diabetes øger risikoen for reoperation på grund af infektion, især blandt patienter, der havde fået en diabetesdiagnose mindre end fem år før operationen, blandt patienter med komplikationer som følge af diabetes, og blandt diabetespatienter med kardiovaskulære sygdomme før operationen. Disse resultater blev bekræftet for nylig (198).

Uncementerede proteser bliver indsat i cirka 50% af danske hoftealloplastikpatienter. Disse proteser anvendes i stigende grad også i andre lande med det formål at undgå problemer med aseptisk løsning af cementerede proteser (203) og slitage af acetabulum (204). Det ser ud til, at ucementerede proteser virker efter hensigten, når de anvendes til patienter yngre end 55 år (studie III), men ikke blandt patienter over 65 år (15). Til gengæld er ucementerede proteser forbundet med højere risiko for mekaniske og tekniske problemer, der på kort sigt fører til reoperation uanset alder (studie III).

Risikoen for symptomatisk VTE inden for 90 dage efter operation blandt hoftealloplastikpatienter, der får farmakologisk tromboseprofylakse, er kun 1% (studierne VIII og X). Desuden viste studie IX for første gang, at total hoftealloplastikoperation er associeret med en øget risiko for symptomatisk VTE op til et år efter operationen sammenlignet med risikoen i baggrundsbefolkningen, uanset køn, alder og komorbiditet før operation. Hoftealloplastikpatienter med tidligere VTE eller tidligere kardiovaskulære sygdomme har øget risiko for postoperativ VTE (studie VIII) (23;35;253;265;276;278;281;297). Imidlertid er der kun få studier, som har undersøgt associationen mellem komorbiditet i bredere forstand og risiko for VTE. Studierne VIII og X påviste en association mellem en høj komorbiditet før operation og risiko for postoperativ VTE, hvilket dog ikke stemmer med resultater fra udvalgte klinikker i USA (22;35). Hoftealloplastikpatienter med reumatoid artritis har en lavere risiko for VTE inden for 90 dage efter operation sammenlignet med hoftealloplastikpatienter med osteoartrose (studie VIII). Dette kunne dog ikke bekræftes i en nylig metaanalyse baseret på to studier (284). Der er således behov for yderligere forskning på dette område.

Evidensen fra en ikke randomiseret kohorteundersøgelse (studie XI) viste, at risikoen for at udvikle VTE, VTE/dødsfald eller større blødningskomplikationer ikke adskiller sig væsentligt mellem patienter som har fået tromboseprofylaksebehandling i henholdsvis kort og lang tid.

Cirka 1 ud af 200 total hoftealloplastikpatienter udvikler MI eller apopleksi inden for 90 dage efter operation (studie X) (325). Risikoen for postoperativ MI og apopleksi er øget op til seks uger efter operation sammenlignet med baggrundsbefolkning (325;329).

I perioden fra 1997 til 2011 var risikoen for større blødningskomplikationer i forbindelse med total hoftealloplastikoperation stabil på cirka 0,5% inden for 90 dage efter operation (studie X). Trods mere aggressiv tromboseprofylaksebehandling (studie XI) forekom større blødningskomplikationer stadig sjældent og var mindre udbredt end VTE (studie X). Prognostiske faktorer for større blødninger efter hoftealloplastikoperation var det mandlige køn, alder, høj komorbiditet før operation og anvendelse af generel anæstesi under operation (studie X). Omkring 32% af danske hoftealloplastikpatienter fik behandling med blodtransfusion i perioden 1999-2007 (studie VI), selvom behandlingen er associeret med øget mortalitet og risiko for infektion, VTE, MI og apopleksi (studie VI).

Studie VII viste, at der er en association mellem hoftealloplastikoperation og øget total mortalitet inden for de første 30 dage efter operationen. Blandt patienter, som blev opereret på grund af osteoartrose, var den totale mortalitet imidlertid på niveau med (26;75) eller endog lavere (studie VII) end i baggrundsbefolkningen 90 dage efter operation (studie VII). Hoftealloplastikpatienter har en øget 90-dages mortalitet især på grund af VTE og MI. Endvidere viste studie VII for første gang, at de yngre patienter og patienter uden komorbiditet før operationen har højere 90-dages total mortalitet i forhold til baggrundsbefolkningen, også på grund af VTE og MI. På længere sigt har hoftealloplastikpatienter overordnet lavere mortalitet sammenlignet med baggrundsbefolkningen (studie VII) (26;27).

Behandlingen med total hoftealloplastikoperation er blevet overordnet forbedret, idet vi kan se et fald i mortaliteten inden for de første 90 dage efter operation både i Denmark og i andre vestlige lande (studie X) (36;266;354). Forekomsten af kardiovaskulære komplikationer har imidlertid været uændret i de seneste 15 år (studie X). Der er således stadig plads til forbedring af kvaliteten af behandling med total hoftealloplastikoperation.

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13. APPENDIX 1: LITERATURE SEARCH

Literature searches were performed based on papers I–XI up to the time of acceptance for publication. In addition, I conducted an updated PubMed search to identify studies written in English that were published after papers I–XI were accepted for publication. For this search, I combined PubMed hip arthroplasty MeSH term keywords with search terms related to surgical outcomes, producing the following search query: "Arthroplasty, Replacement, Hip" AND "Prognosis, Risk factors, Predictor" OR "Postoperative complications" OR "Venous thromboembolism" OR "Myocardial infarction" OR "Stroke" OR "Bleeding" OR "Reoperation, Revision" OR "Mortality". From the search results, I reviewed the titles, screened abstracts for all papers potentially eligible for review based on the titles, and reviewed all full papers deemed eligible for inclusion in the final review. Meta-analyses and systematic reviews were prioritized. The reference lists of these papers were used to identify additional papers not captured by the electronic search. We prioritized large population-based studies based on national databases and reviewed the results published in the annual reports of national hip arthroplasty registries.

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