COMPLICATIONS OF HIP AND KNEE REPLACEMENT SURGERY

A PHARMACOEPIDEMIOLOGICAL APPROACH

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A PHARMACOEPIDEMIOLOGICAL APPROACH

Complicaties na totale heup- en knievervangingen
een farmaco-epidemiologische benadering

(met een samenvatting in het Nederlands)

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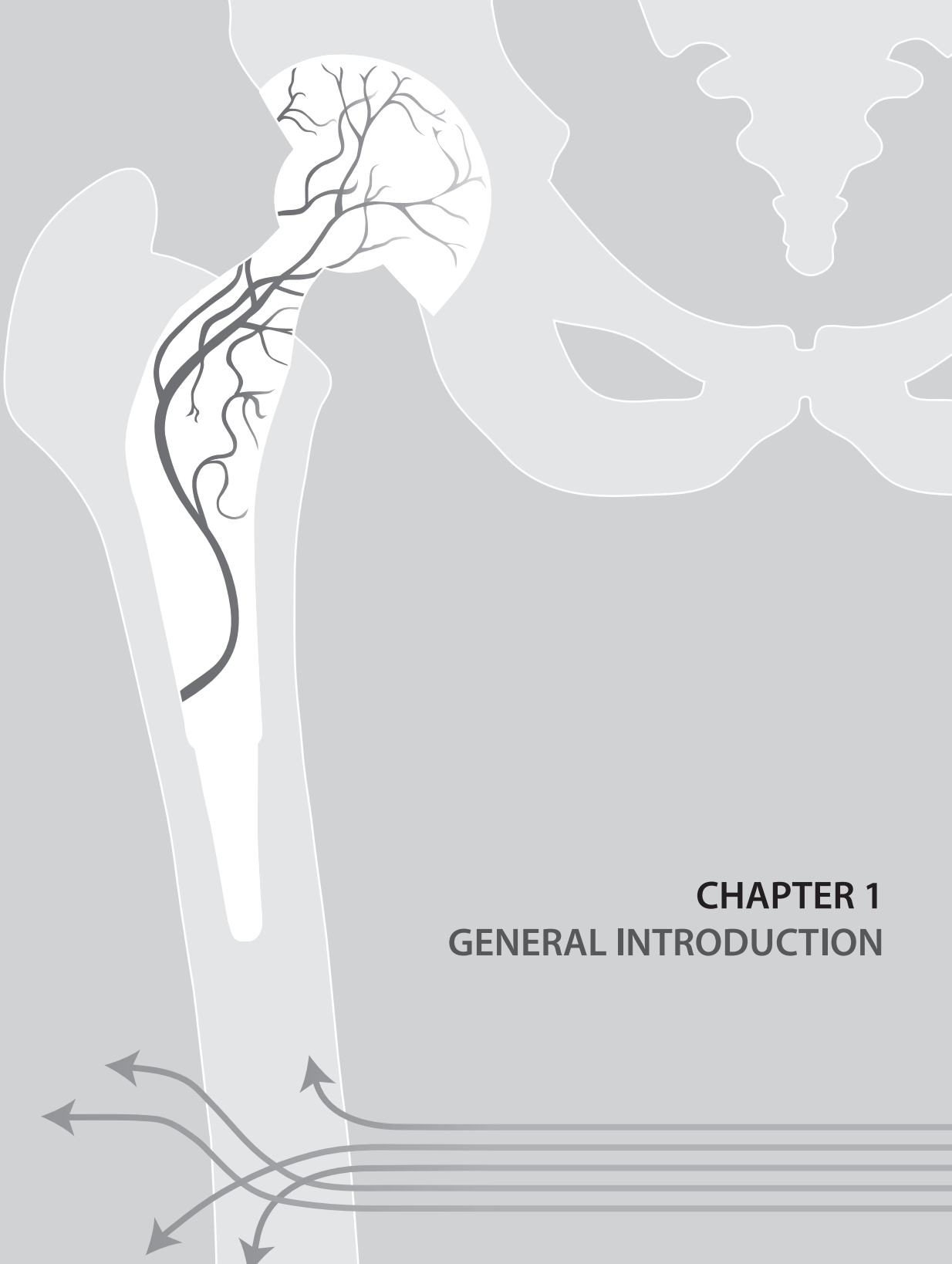


CHAPTER 1
GENERAL INTRODUCTION

OSTEOARTHRITIS AND TOTAL HIP / KNEE REPLACEMENT SURGERY

Osteoarthritis is the most common form of joint disorders, and is the leading cause of pain and physical disability in older individuals.[1] In 2007, 19% of the Dutch population aged 65 years and older suffered from osteoarthritis.2 By the year of 2040, the prevalence is expected to have increased by 52%, due to ageing of the population and an increase in body weight.[2] Osteoarthritis typically presents at joints related to the knees and hips, besides the hands, spine, and feet.[3] The lifetime probability of developing symptomatic osteoarthritis is 25% for the hip and 45% for the knee.[4,5] Clinical features include pain and stiffness, which severely limits day-to-day activities such as walking, climbing stairs, and sleeping.[6]

In advanced stages of osteoarthritis, patients may require total hip (THR) or knee replacement surgery (TKR). Pharmacological interventions are primarily aimed at symptom relief, but do not slow down the progression of osteoarthritis.[7] Hence, pharmacological interventions may not provide adequate response in these advanced stages of osteoarthritis, and THR / TKR is needed. In short, the surgery is used to replace the damaged bone / cartilage by an artificial joint. The procedure is highly effective in patients with moderate to severe osteoarthritis, resulting into substantial pain relief and improved quality of life.[8,9] Within a few months after surgery, patients transition from being dependent on walking aids to being able to walk well without the help of crutches or a cane.[8] In a British survey study comprising 1,327 patients who received THR for osteoarthritis, pain, stiffness, and function all improved after surgery: the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score improved by 35.9 points (scale of 100 points) 12 months after surgery.[10] Changes in WOMAC scores following TKR surgery show similar trends, although slightly smaller than following THR surgery.[11]

Because of these benefits, the popularity of this surgery has grown tremendously. In 2002, 39 thousand THR / TKR procedures were performed in the Netherlands, which is a 3-fold increase as compared to in 1980.[12] In 2006, it has been estimated that a total of 1.6 million THR / TKR procedures are performed worldwide each year.[13] The numbers of these procedures are expected to continue to grow over the coming years: an American study projected a growth of 174% for THR and 673% for TKR between 2005 and 2030.[14]

ADVERSE OUTCOMES FOLLOWING TOTAL HIP / KNEE REPLACEMENT

Despite the well-established benefits of THR / TKR, these drastic surgical procedures may result into potentially fatal complications. Adverse outcomes include acute myocardial infarction,[15-21] venous thromboembolism (VTE),[22-28] severe infections,[29-32] major bleedings,[33-35] and stroke.[36-39,19] Among all surgeries, occurrence of these severe and expensive outcomes has been reported to be highest among THR / TKR. For example, without adequate prophylaxis, symptomatic DVT occurs in 40%-60% of THR / TKR surgical patients, compared to an incidence of 15%-40% in general surgery.[40]

Although there are some reports on absolute risks of these adverse outcomes following THR / TKR, major knowledge gaps remain for the attending physician. These include:

- TIMING OF ADVERSE OUTCOMES. Little is known about when adverse outcomes occur after THR / TKR surgery, and when the risk diminishes towards baseline levels. This is of particular importance because (1) the physician needs to know when to monitor for certain risks, (2) there needs to be a well-balanced decision on when to discharge the patient after surgery (involving both the physician and patient), (3) timing patterns may reveal the need for prophylactic drug therapies (in particular essential to determine the length of pharmacological prophylaxis), and (4) this information is essential for risk communication between the physician and the patient prior to an elective THR / TKR surgery. Most previous studies could only report adverse outcomes during the hospitalization stay, which is often a limited time of follow-up. Even within this pre-discharge period, they do not provide detailed information on the hazard function. For example, it is unknown whether the risk is increased on the first postoperative day only, or perhaps during the entire hospitalization period.

- SIZE OF EXCESS RISK. The lack of a valid comparison group makes it difficult to interpret the findings from the previous uncontrolled studies. For example, a patient may have a 30-day risk for major bleeds of 1%. However, without a valid comparison, it is unclear whether this is an increased risk or not, compared to similar patients who did not undergo surgery. None of the previous studies included such a reference group. Therefore, it is difficult for the physician to know the added risk of adverse outcomes if the patient undergoes THR / TKR surgery, as compared to when she or he does not.

- INFLUENCE OF PATIENTS CHARACTERISTICS, IN PARTICULAR DRUG USE. Most previous studies could only report adverse outcomes following THR / TKR surgery by hospital rather than by individual patient characteristics. This is of particular interest, as the patients who undergo surgery widely vary in patient characteristics. For example, a young 20-year old athlete without any comorbidities or drug use may undergo knee surgery because of meniscal cartilage tear due to heavy exercise. The next patient for TKR surgery is an 85-year old female with severe osteoarthritis, multiple comorbidities, and who takes 15 different drugs each day. The risk of adverse outcomes following TKR surgery may substantially differ between these two patients. Unfortunately, studies evaluating patient characteristics as determinants for these adverse outcomes are scarce. The limited number of available studies could only evaluate simple baseline characteristics, such as age and sex.[41] The influence of many comorbidities, and importantly, longitudinal drug use, remains unclear. Therefore, we currently rely on aggregate risk estimations, which may neither be true for the 20-year old athlete nor the 85-year old lady suffering from severe osteoarthritis.

The following potential adverse outcomes following THR / TKR surgery will be evaluated in this thesis:

- THROMBOTIC AND HAEMOSTATIC ADVERSE OUTCOMES. Potentially fatal thrombotic / haemostatic complications following THR / TKR surgery have been reported in several studies. These include venous thromboembolism (VTE),[22-28] acute myocardial infarction (AMI),[15-21] and ischaemic stroke,[36-39,19] and typically carry a great health burden in the general population. For example, each year, more than 7 million patients are estimated to sustain an AMI worldwide.[42] Mortality rates following hospitalized AMI are as high as 19% during the first 30 days.[43,44] Previous studies have shown that, among patients undergoing THR / TKR surgery, up to 1.8% sustains an AMI,[15-21] and up to 7% develops symptomatic VTE in the first 90 days.[22-28] These negative outcomes may be the result of an increased activity of haemodynamic stressors associated with the surgery.[45] Some of these stressors include blood loss, fluid shifts, arrhythmias, hypoxia, and the effects of anaesthesia on the cardiovascular system. Moreover, as these patients slowly regain their physical strength in the following months, their physical activity is limited in the initial period and may further contribute to the increased risk of thrombotic events (even weeks or months after surgery).[8] In order to prevent these thrombotic complications, extended thromboprophylaxis (up to 35 days) is now standard of care with THR / TKR surgery.[40,46] In turn, this may however lead to life-threatening bleeds. Data from clinical trials show a perioperative risk of major bleeding of as high as 4%.[33-35] Because of this double-edged sword prophylaxis regimen, there is much debate on the required length and intensity of thromboprophylaxis, and experts call for individualized treatment regimens.[47] This practice is currently limited, as data on timing of these events (including post-discharge) and patient level prognostic factors (e.g. drug use and comorbidities) are scarce. Most studies are limited to a 30-day follow-up, and do not exclude the possibility of an excess risk beyond this period. Identified prognostic factors include age and sex,[41] while the influence of drug use remains largely unknown: these patients typically use various drugs that could theoretically alter the risk of thrombotic events (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]).

- CANCER. International concerns have been raised about certain hip implant devices and the risk of cancer. Over the past few decades, metal-on-metal hip implants gained popularity, and up to recently accounted for approximately 14% of all THR implant devices in England and Wales.[48,49] Data from in vitro and in vivo studies have shown that metal particles (including cobalt and chromium) from these implants may spread throughout the entire body.[50] The observed blood levels of these metals have previously been associated with the development of carcinomas in animal models.[51] No data are available on the actual risk of cancer in patients who received these full-metal hip prostheses. Hence, there is a huge demand from regulatory agencies to study the association between metal-on-metal hip implant devices and the risk of cancer in large epidemiological studies.

- FRACTURE. Risk of hip fracture may either be decreased or increased in patients with TKR surgery. In frail elderly patients, TKR may protect against hip fracture by reducing

the occurrence of falls. On the other hand, within the first month after TKR, muscle strength is often decreased, which can elevate fracture risk.[52] Hip fracture in the general population is accompanied by substantial morbidity and mortality: one in five patients will die within the first year after the hip fracture, whilst one in three of those surviving needs assistance with walking.[53,54] Actual data on the association between TKR surgery and hip fracture are lacking.

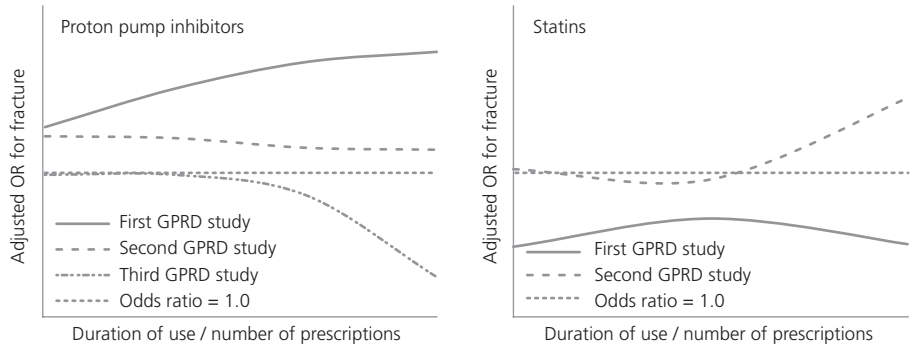
- IMPLANT FAILURE. Up to 8.3% of patients with a THR / TKR surgery needs their joint implant revised in the first 10 years.[55] A revision surgery is associated with poorer clinical outcome compared to primary THR / TKR surgery.[56,57] Consequently, there is an urgent need for interventions including drug therapies that may reduce implant failure rates, but no drugs have been assessed in clinical trials up to date. In vitro and in vivo studies suggested that bisphosphonates and statins may reduce the chance of implant failure.[58,59] Both act on the mevalonate pathway, and have been on the market for other clinical indications for decades. By reducing the formation of mevalonic acid, bisphosphonates and statins are thought to inhibit osteoclast-mediated bone resorption.[60] This may reduce the resorption of bone surrounding the joint implant, and thereby preventing implant failure. Although this was shown in preclinical studies, clinical data on implant failure are currently lacking. Pharmacoepidemiology may be an efficient tool to identify possible drug candidates, which may be further studied in randomized clinical trials.

PHARMACOEPIDEMIOLOGY VERSUS CLINICAL TRIALS

Adverse outcomes following THR / TKR surgery cannot be easily studied using conventional randomized clinical trials. Foremost, it is not ethical to withhold patients from THR / TKR surgery (as is the case in the comparison arm [i.e., no surgery] in clinical trials) while the surgery is already standard of care in the same patient population. Furthermore, despite its clear advantages, clinical trials are limited in that (1) they often have to deal with strict in- and exclusion criteria (thereby excluding the more critically ill patients), (2) they typically comprise a sample size too small to detect rare, but severe adverse reactions, (3) their duration of follow-up is often too short to detect adverse reactions with a long latency period (such as cancer), and (4) they represent the "ideal" patient (e.g. high drug adherence and no use of interacting co-medication), which does not always reflect the "real-life" situation.[61] Nowadays, there is a trend towards performing THR / TKR surgery in more complex patients (e.g. older individuals with multiple comorbidities), who were originally excluded from clinical trials.[62,63] Some of the described adverse outcomes following THR / TKR are rare (< 1%), which would require thousands of patients to be included in clinical trials. Moreover, studying the relationship between specific types of hip implants and the risk of cancer would require these patients to be followed up for at least five to ten years. Because of the homogeneity in most clinical trials, identification of predictors for adverse outcomes becomes troublesome given the low variety in baseline patient characteristics. All of these issues require a methodology that is much more suitable and efficient than conventional clinical trials.

To overcome these difficulties, pharmacoepidemiology is crucial to study adverse outcomes following THR / TKR surgery and its associated predictors. Pharmaco-epidemiology studies the use and clinical effects of drugs in millions of people. Because of the large and unselected study population compared to randomized clinical trials, pharmacoepidemiological studies are most useful to detect (rare) adverse drug reactions in "real-life" settings after market authorization of a new drug. Well established associations include the risk of bone fracture with the use of systemic glucocorticoids,[64] antidepressants,[65] and benzodiazepines,[66] and the risk of AMI in patients taking NSAIDs.[67] Because of the rare nature of these adverse drug reactions, they were initially not detected in clinical trials. Pharmacoepidemiology acted as an essential and efficient tool to identify these severe adverse drug reactions.

FIGURE 1.1 | Risk of fracture with proton pump inhibitor (left) and statin use (right) in relation with the duration of use / number of prescriptions. All presented studies were conducted within the British General Practice Research Database (GPRD).



DISCREPANCIES IN PHARMACOEPIDEMIOLOGICAL STUDIES

Because of the richness and complexity of many pharmacoepidemiological databases, the study design often depends on countless micro-decisions on how to deal with specific parts of the study. As studies are rarely repeated within the same database, it is often impossible to know the impact of these micro-decisions. An illustrative example of repeat studies includes the risk of fracture with proton pump inhibitors (Figure 1.1, left). It has been hypothesized that proton pump inhibitors may reduce calcium absorption, and thereby increase the risk of fracture.[68,69] This was supported by the first observational study, conducted within the British General Practice Research Database (GPRD), currently known as the Clinical Practice Research Datalink (CPRD).[70] The authors found an overall increased hip fracture risk of 44% with the use of proton pump inhibitors. Moreover, the association became stronger with a longer duration of use, which is supportive for a causal relationship. In contrast, the second GPRD study could not demonstrate such a time relationship,[71] and the third GPRD study even reported a decrease in risk of fracture with a prolonged use of proton pump inhibitors.[72] In a second example, the first GPRD study showed a 45% decreased risk of fracture with statin use,[73] whereas the second GPRD study could not find such an effect (odds ratio of 1.01,

95% confidence interval [CI] 0.88-1.16).[74] Interestingly, in the second GPRD study, the risk even tended to increase with a longer duration of use (Figure 1.1, right). These rare examples illustrate that micro-decisions in the study design may have a substantial influence on the key findings, even when the analyses are conducted within the same database.

Despite the enormous growth of pharmacoepidemiology, there is no gold standard on how to conduct these types of studies. As a result, a large number of different study designs are used, which are for a large part based on personal preferences of the study team. Some important differences in study design are summed in Figure 1.2, and, in short, include the following parameters:

- NATURE OF DATA SOURCE.There is a growing use of automated electronic health records in the field of pharmacoepidemiology. As exposure data are populated regardless of a future outcome, the collection of this information is not prone to recall bias (as opposed to with patient interviews). Popular sources for drug exposure include pharmacy dispensing data and prescription records from general practices (GP). There may be some differences in validity of the data between these two potential sources as patients (1) may get a prescription from the GP, but do not collect their medication at the pharmacy (or do not get their drug dispensed because of drug-drug interactions), (2) collect their medication at a pharmacy that is not in the area coverage of the database, and (3) got their prescriptions from a GP out of the coverage area, but collected their medication at a pharmacy that was included in the database. Inpatient drug use (i.e. medication use while hospitalized) is typically not available using these data sources, as the drug is prescribed by a specialist and is dispensed by the hospital pharmacy. In terms of study outcomes (which generally is a disease or death), various registries are used, including GP records, hospitalization registries, disease specific databases (mostly prospectively collected), and death certificates. All of these data sources come with their own set of strengths and limitations. For example, GPs may collect (primary care) symptoms that are not easily caught by hospitalization registries (e.g. common cold). On the other hand, GPs partially rely on hospital discharge letters to receive information on in-hospital events. To illustrate this difference in numbers, a British retrospective cohort study explored rates of different types of cancer in diabetic patients using GP based registers and hospitalization data.[75] On one hand, hospitals tended to have higher registration rates for colorectal cancer (rate per 100 person years: 0.24), as compared to GPs (rate: 0.18). On the other hand, GPs captured non-melanoma skin cancers more readily (rate: 0.41) than hospitals (rate: 0.22). This nicely reflects the types of cancer that are typically seen by hospital specialists and GPs, and illustrates the potential strengths and weaknesses of both data sources.

- TYPE OF ANALYTICAL STUDY DESIGN. Traditionally, two major types of non-experimental studies are used in the field of pharmacoepidemiology. Cohort studies compare two groups with different exposure statuses and follow them for a disease. Case-control

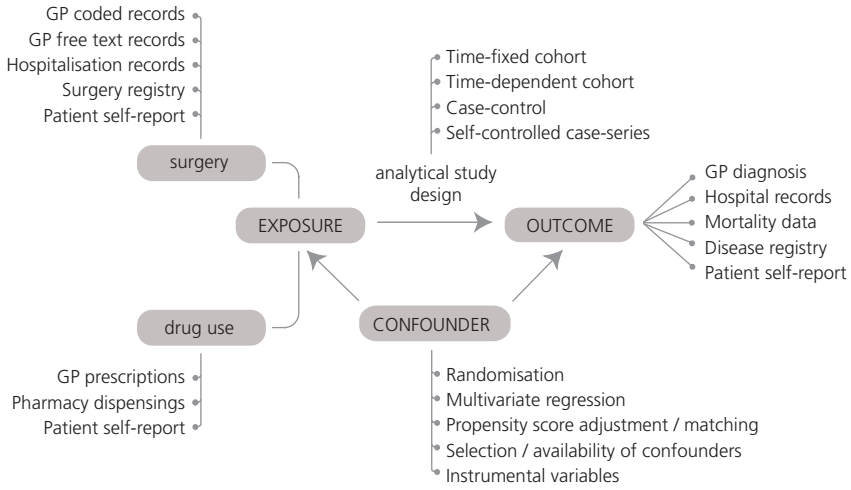
studies compare incident cases with (a sample of) individuals who did not get the outcome, and look back in time to determine the distribution of exposure statuses. Hence, case-control studies are, in general, more prone to biases such as selection bias and recall bias. Using automated electronic health care records, however, these limitations are less likely, as previous diagnoses / events are recorded unconditional on a future event. Moreover, cohort studies come with their own set of difficulties. As cohort studies deal with person time, careful allocation of person years is essential to obtain unbiased risk estimates. A prime example of person time misclassification is immortal time bias.[76] This may occur when a patient has a "wait period" to become exposed, i.e. a patient becomes exposed some time after start of follow-up (e.g. a first beta blocker prescription one year after his or her COPD diagnosis). In order to become exposed, the patient has to survive the "wait period", thereby falsely lowering the risk of getting a disease. This is in particular a problem when the cohort study is analysed in a time fixed manner (i.e. a patient is either exposed or unexposed), which is a widely used analytical technique to analyse cohort studies. Time-dependent techniques that explicitly classify immortal time (i.e., the exposure status is dependent on the time of follow-up) may effectively deal with this type of bias.[77]

- TIMING OF FOLLOW-UP. The risk of certain adverse outcomes may substantially depend on when patients were followed up. For example, in patients with multiple sclerosis (MS), the start of follow-up largely influenced the risk of hip fracture. In a British MS study, the risk of hip fracture was 2.8-fold increased as compared to patients without MS.[78] Using the same methodology, in Danish MS patients, no significantly increased risk of hip fracture could be observed.[79] The most important difference between these studies was that the Danish study followed MS patients at the onset of the disease, whereas the British study included a mix of incident and prevalent MS patients. Analogously, the risk of adverse outcomes following THR / TKR surgery may largely depend on when patients were followed up and for how long. Moreover, the risk may nowadays be vastly different as compared to the risk 2 decades ago, making calendar time an important methodological aspect.

- TECHNIQUES TO DEAL WITH CONFOUNDING. As observational etiologic studies are not randomized, there may be an imbalance in determinants of the outcome between exposed and unexposed individuals, i.e. confounding. This is the most important limitation of observational studies, and, hence, many efforts have been made to develop techniques that minimize confounding bias. A popular method to deal with confounding is multivariate regression, in which the individual confounders are all entered into the model. However, often the number of confounding variables is larger than what the specific model can handle. There needs to be a selection of the most important confounders to lower this number of variables, but there is much debate on how to select these confounders.[80] Popular methods include (1) change in effect estimate (e.g. determine the influence of a single confounder on the relative risk of interest), (2) stepwise elimination of confounders (based on p-values), (3) best model

fits (e.g. only keep the covariates that contribute to a better model), and (4) purely on the basis of prior knowledge. All of these methods come with their own strengths and limitations, and hence, are all used without consensus on the best technique. At the same time, new techniques, such as propensity score techniques (either adjusted for or matched by) and instrumental variables are introduced.[81,82] Studies comparing all of these techniques in real life data are however scarce, and it is therefore difficult to describe the "gold standard".

FIGURE 1.2 | Summary of frequently used variations in pharmacoepidemiological study designs.



THESIS OBJECTIVE

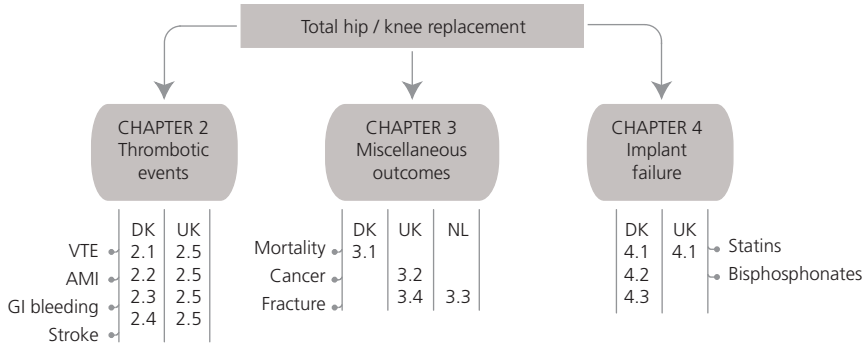
The overall thesis aim was to evaluate adverse outcomes following total hip / knee replacement surgery, and to explore the impact of various differences in the methodological design. More specifically, our aims were:

- To evaluate timing of adverse outcomes following total hip and knee replacement surgery versus matched controls
- To determine the influence of drug use on adverse outcomes following total hip / knee replacement surgery
- To study pharmacological interventions in order to prevent joint implant failure
- To investigate the impact of differences in methodological design in pharmaco-epidemiological studies
- To describe the robustness of study results using various epidemiological data sources

THESIS OUTLINE

Figure 1.3 displays the general outline of the thesis. Chapter 2 focuses on thrombotic / cardiac adverse events following THR / TKR surgery, and the influence of drug use. In this chapter, the outcomes will be evaluated in both Denmark and in the United Kingdom. As data sources from these two countries have their own set of characteristics (with its own strengths and weaknesses), this is a unique opportunity to study the impact of using epidemiological data sources from two different countries. Chapter 3 studies non-cardiac outcomes, including cancer, fracture, and overall mortality. In the case of cancer, the impact of using various epidemiological data sources will be further explored (e.g. the use of GP based registries, hospitalization data, death certificates, and the use of prospective dedicated hip / knee joint registries). Chapter 4 describes the influence of drug use on improved implant survival in patients with hip / knee prostheses. Chapter 4.1 focuses on statin use in both Denmark and the United Kingdom, and will thoroughly explore the influence of (1) the nature of utilized data source, (2) different analytical study designs [e.g. time-dependent versus time fixed], and (3) techniques to deal with confounding. Chapters 4.2 and 4.3 repeat this process for bisphosphonates as the exposure of interest.

FIGURE 1.3 | Schematic thesis outline. AMI = acute myocardial infarction, DK = Denmark, GI = gastrointestinal, NL = Netherlands, UK = United Kingdom, VTE = venous thromboembolism.



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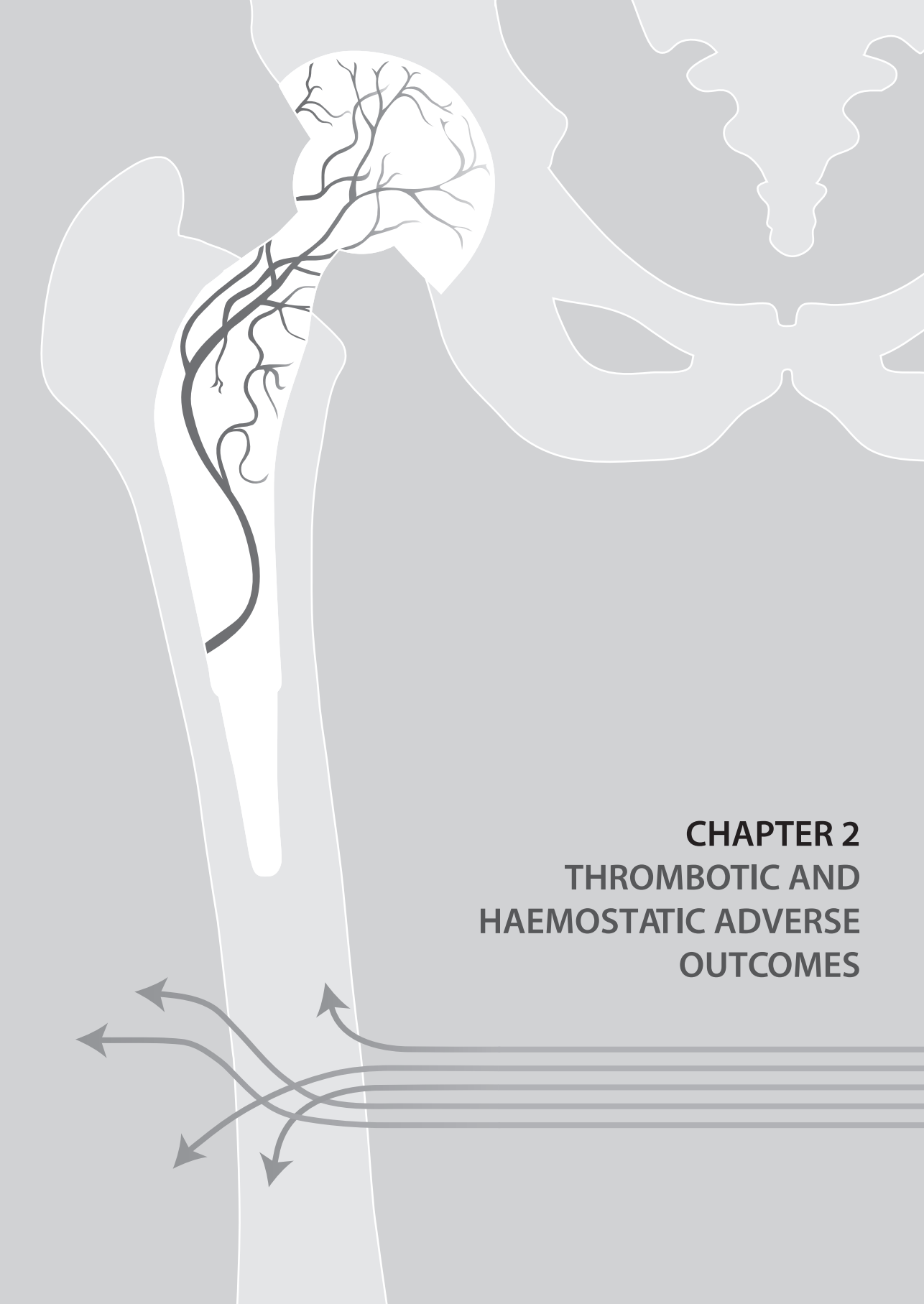

CHAPTER 2
THROMBOTIC AND HAEMOSTATIC ADVERSE OUTCOMES

CHAPTER 2.1

Prolonged outpatient vitamin K antagonist use and risk of venous thromboembolism in patients undergoing total hip or knee replacement

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ABSTRACT

BACKGROUND: Long-term risk of venous thromboembolism (VTE) following total hip or knee replacement (THR/TKR) compared with controls has not been studied extensively, and the long-term influence of outpatient anticoagulant use on VTE risk remains unknown. The objectives were to evaluate long-term VTE risk following THR/TKR compared with matched controls, and to investigate effect modification by prolonged outpatient vitamin K antagonist use.

METHODS: A Danish retrospective nationwide cohort study was conducted. All patients undergoing primary THR/TKR (n = 95,227) between 1998 and 2007 were selected, each matched by age, sex and region with three controls (no THR/TKR). Patients were stratified by prolonged outpatient vitamin K antagonist use in the previous 3 months (in a time-dependent manner). All subjects were followed for VTE, and Cox models were used to calculate disease and medication history adjusted hazard ratios (HRs).

RESULTS: Within 6 weeks following surgery, a 13-fold increased risk of VTE was found for THR (adj. HR 12.9; 95% CI 11.2–14.7), and a 14-fold elevated risk for TKR (adj. HR 13.6; 95% CI 11.0–16.7), compared with matched controls. The risk remained substantially increased for at least 4 months following THR/TKR. Within this period, prolonged outpatient vitamin K antagonist use reduced the increase in VTE risk by 69% for THR and 54% for TKR.

CONCLUSIONS: The risk of VTE remains substantially elevated for at least 4 months following THR/TKR; this is well beyond the recommended duration of anticoagulant use. The increase in VTE risk is less pronounced in prolonged outpatient vitamin K antagonist users.

INTRODUCTION

Elective total hip and knee replacements (THR/TKR) substantially improve quality of life in patients with osteoarthritis[1] and, each year, an estimated 1.8 million procedures are performed worldwide.[2,3] Venous thromboembolism (VTE) is the most common cause of emergency hospital readmission following THR and TKR.[4] Importantly, symptomatic VTE has been reported in 1–7% of THR/TKR patients within 90 days after surgery despite routine use of thromboprophylaxis.[5-11]

Controversy exists regarding the optimal duration of thromboprophylaxis in THR/TKR patients.[12] The American College of Chest Physicians (ACCP) guidelines recommend that extensive VTE prophylaxis (with low-molecular-weight heparins [LMWH], vitamin K antagonists [VKA] or fondaparinux) is used for 10–35 days after surgery.[13] The underlying evidence for this treatment period is based on clinical trials restricted by a follow-up time of only 5 weeks after discharge.[14,15] Evidence on the risk of VTE exceeding 5 weeks (compared

with control subjects) is scarce. One study compared VTE rates in THR/TKR patients beyond the first 35 days with controls, but was conducted in a selected cohort of relatively young women (mean age 56 years) and frequent users of hormone replacement therapy (32%).[16] The authors reported a 221-fold increased risk of VTE during the first 6 weeks following THR/TKR and the risk of VTE remained elevated even beyond 1 year after THR/TKR. Despite this finding, prolonged outpatient use of anticoagulants (> 35 days) has not been studied in these patients before.

Individual risk factors for VTE in these patients have not been studied extensively. Previous epidemiological studies have examined only a limited number of risk factors, such as body mass index, prior VTE history, age, sex and a history of cancer.[7,8,17–21] Potential risk factors, such as major surgery, length of hospitalization, socioeconomic status and outpatient medication use, have not been thoroughly evaluated.

Accordingly, the objectives of this study were (i) to evaluate the time course of VTE occurrence after THR/TKR surgery compared with healthy matched control subjects, (ii) to investigate the (long-term) influence of prolonged outpatient anticoagulant/antithrombotic use on the risk of VTE, and (iii) to identify effect modification by potential VTE risk factors.

METHODS

DATA SOURCE

A nationwide retrospective cohort study was conducted on the basis of Danish national databases, including information on all Danish residents (5.5 million). These nationwide databases included the National Hospital Discharge Register (including data on hospital admissions, outpatient clinics and emergency visits; from 1977 onwards), the National Pharmacological Database (drugs sold at retail pharmacies; from 1996 onwards), the Danish Civil Registry (vital status, date of death, residence, migration and socioeconomic status; from 1968 onwards) and the Danish Registry of Causes of Death (cause of death [one underlying cause, and up to three additional immediate causes] recorded by the last physician attending the patient; from 1970 onwards).

These databases have been used in numerous recent epidemiological studies, and the completeness (as high as 100%), quality and validity have been described previously.[22] For VTE, the sensitivity has been reported to be 80–90%.[23-25]

STUDY POPULATION

The study population consisted of all patients aged ≥ 18 years of age with a primary THR or primary TKR between 1 January 1998 and 31 December 2007, as recorded in the National Hospital Discharge Register (International Classification of Diseases, ICD, 10th revision: ICD10 procedure codes NFB.XX [THR] and NGB.XX [TKR]). The index date was defined as the hospital admission date for the primary THR/TKR. We excluded patients with a record of VTE within 6

weeks before the index date, and those with a record of pregnancy within 44 weeks before or during follow-up, and delivery within 6 weeks before or during follow-up. Each THR/TKR patient was matched to three control subjects of the same age, gender and geographical region with no history of primary or secondary THR/TKR. Control subjects were assigned the same index date as their matched THR/TKR patient.

Danish guidelines recommend thromboprophylaxis (primarily LMWH) for all THR/TKR patients during hospitalization, and for up to 35 days after surgery.[26] Previous Danish data showed that 99.1% of THR/TKR patients received thromboprophylactic agents (of which 93% included LMWHs).[27]

OUTCOME ASSESSMENT

All patients were followed from the index date until death, migration, THR/TKR revision, end of study period (31 December 2007) or VTE, whichever came first. Patients were followed-up for deep-vein thrombosis (DVT) and pulmonary embolism (PE) separately. DVT and PE were assessed using the National Hospital Discharge Register and the Danish Registry of Causes of Death (both using ICD10 codes: I80.1-I80.9, I82.1-I82.9 for DVT; I26 for PE).

POTENTIAL CONFOUNDERS / EFFECT MODIFIERS

General (potential) risk factors[13,28] considered in this study included age (continuous variable), sex, socioeconomic status (quintiles), indication for surgery, length of hospital stay related to THR/TKR (time-dependent, continuous variable), and a history of VTE, heart failure or chronic obstructive pulmonary disorder (COPD). Malignancies and varicose veins were considered risk factors if recorded within the previous year, and acute myocardial infarction, stroke and pneumonia were assessed within 6 weeks before. The use of pain relievers, estrogen containing drugs, tamoxifen and antithrombotic agents (stratified by type: vitamin K antagonists [VKAs], antiplatelet drugs, heparins and others), and use of cardiovascular drugs, was assessed in the previous 6 months. In addition, we created a proxy for immobility by calculating the number of bed days due to major surgery (non-superficial surgery between neck and hip, orthopedic and obstetric surgery) or major trauma/fracture (non-superficial; head, neck, thorax, abdomen, lower back, spinal cord, pelvis, hip, lower leg or knee) in the previous 6 weeks. All other hospitalizations were used to calculate the number of bed days due to other causes in the previous 6 weeks. We treated the number of bed days as categorical variables (0 days, 1–7 days, 8–14 days and > 14 days).

STATISTICAL ANALYSIS

The PHREG procedure from SAS 9.2 (SAS Institute, Cary, North Carolina, USA) was used to derive hazard ratios (HRs) for DVT/PE risk among THR/TKR patients vs. age- and gender-matched controls. Total follow-up time was divided into 6-week periods, and for the first 6 weeks into 1-week periods. Information on potential confounders/risk factors/outpatient anticoagulant use was collected before the start of each period (before or during follow-up). Potential confounders were included in the final model if they independently changed the beta coefficient for THR/TKR by at least 5%.

In order to assess timing of VTE following THR/TKR, we included time period interaction terms (time period * surgery) in the model for the following time periods: < 2 weeks, 2–6 weeks, 7–12 weeks, 4–6 months, 7–12 months and ≥ 1 year after surgery. For each period, the risk of VTE was plotted against the median time since THR/TKR, and visualized using smoothing spline regression.[29–32]

For potential effect modifiers, we evaluated two time periods by restricting follow-up to: < 6 weeks or 6–52 weeks following surgery. Potential effect modifiers were screened by entering an interaction term (risk factor * surgery) into the model.

To evaluate the influence of prolonged outpatient anticoagulant/antithrombotic use (within the previous 3 months) on the risk of VTE following THR/TKR, we included an interaction term for anticoagulants. Types of outpatient anticoagulants included: (i) VKA only, (ii) antiplatelet drugs (e.g. low-dose aspirin) only, (iii) mixed use/other antithrombotic agents (e.g. LMWHs and fondaparinux), and (iv) no outpatient anticoagulant use within the previous 3 months (assessed in a time-dependent manner). Direct inhibitors of factor (F) IIa (dabigatran) and FXa (rivaroxaban and apixaban) were not yet available at the time of data collection. HRs were calculated for the 6 time periods described above, and visualized using smoothing spline regression. This study was approved by the National Board of Health and the Danish Data Protection Agency.

RESULTS

BASELINE CHARACTERISTICS

Table 2.1.1 shows baseline characteristics of THR/TKR patients and controls. We enrolled a total of 95 255 patients undergoing primary THR (66 594) or TKR (28 661), and 285 935 matched control subjects of equal age (THR 71.9 years; TKR 67.2 years) and the same sex (THR 36.9% male; TKR 37.6% male). In general, THR/TKR patients were comparable to the matched control subjects in terms of socioeconomic status, co-morbidities and drug use. THR/TKR patients were more likely to be diagnosed with osteoarthritis or rheumatoid arthritis, had a higher incidence rate for hip/knee fractures and were more likely to have used pain relievers.

In the 30 days after THR discharge, 1.3% of the patients were dispensed vitamin K antagonists, 6.9% received an antiplatelet drug, and 0.1% collected a different type of antithrombotic agent at an outpatient pharmacy (data not shown). Outpatient antithrombotic dispensing patterns were similar in the first 30 days after TKR discharge. Although LMWH use is recommended for up to 35 days, these drugs are most likely dispensed by the hospitals, and could therefore not be captured. During the first 12 weeks after surgery, rates for gastrointestinal bleeding were 0.52% for THR and 0.18% for TKR. We have previously reported rates for hemorrhagic stroke among THR surgical patients, which seemed to be relatively low (during the first 6 weeks: 0.06% hemorrhagic stroke, 0.42% unspecified stroke).

TABLE 2.1.1 | Baseline characteristics of THR / TKR patients and matched controls.

	THR		TKR	
Characteristic	THR n = 66,594	No THR n = 199,843	TKR n = 28,661	No TKR n = 86,092
Mean follow-up time (years, SD)	3.9 (2.8)	4.1 (2.7)	3.9 (2.6)	3.7 (2.6)
Males	36.9%	36.9%	37.6%	37.6%
Mean age (years, SD)	71.9 (12.5)	71.9 (12.5)	67.2 (10.8)	67.2 (10.8)
Mean THR / TKR hospital stay (days, SD)	10.8 (9.4)		9.3 (6.3)	
Disease history (ever before, unless specified otherwise)				
Osteoarthritis	69.6%	8.0% ‡	98.3%	7.4% ‡
Rheumatoid arthritis	3.1%	1.4% ‡	5.7%	1.4% ‡
Hip / knee fracture (1 month)	6.3%	0.7% ‡	0.7%	0.6%
Malignancies (1 year)	3.2%	2.3% ‡	1.8%	2.1% *
Prior VTE	3.3%	2.5% ‡	4.3%	2.2% ‡
Heart failure	8.0%	6.5% ‡	5.1%	4.6% ‡
COPD	6.9%	5.4% ‡	4.6%	4.8%
Medication use 6 months before				
Paracetamol	34.6%	14.2% ‡	30.0%	10.3% ‡
NSAIDs	50.7%	16.4% ‡	60.9%	16.6% ‡
Opioids (tramadol or stronger)	30.8%	7.7% ‡	25.7%	6.5% ‡
Estrogen-containing drugs	6.9%	6.7% *	10.3%	8.4% ‡
Outpatient antithrombotic agents				
Vitamin K antagonists	3.3%	3.0% ‡	3.1%	2.8% *
Antiplatelet drugs	22.4%	20.9% ‡	19.5%	17.2% ‡
Other antithrombotic agents	0.1%	0.0% *	0.1%	0.0% *

* $p < 0.05$, † $p < 0.005$, ‡ $p < 0.0005$.
Data are presented as means (SD) or percentages (among THR / TKR cases or controls), unless stated otherwise.
Abbreviations: COPD = chronic obstructive pulmonary disorder; NSAIDs, non-steroidal anti-inflammatory drugs; SD = standard deviation; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism.

TIMING OF VTE FOLLOWING THR / TKR

The risk of VTE in THR/TKR patients was substantially increased for at least 4 months postoperatively when compared with matched controls (Figure 2.1.1). We found similar time trends comparing DVT risk with the risk of PE: during the first 2 weeks after THR, an 18-fold increased risk of DVT (adjusted [adj.] HR 17.9 [95% confidence interval (CI) 14.7–21.9]) and a 15-fold increased risk of PE (adj. HR 15.4 [95% CI 11.6–20.4]) was found (Table 2.1.2). Within 4 to 6 months postoperatively, the risk remained substantially increased (adj. HR 3.09 [95% CI 2.49–3.84] for DVT; adj. HR 1.61 [95% CI 1.12–2.32] for PE). Similar time patterns were found in TKR patients and matched controls (Table 2.1.2).

PROLONGED OUTPATIENT VKA USE

Prolonged outpatient use of VKAs (in the previous 3 months) significantly lowered the HR for VTE by 69% in the first 4 months following THR, and by 54% within 4 months after TKR (Figure 2.1.1, Table 2.1.3). Within 6 weeks following THR, the HR was 15.3 (95% CI 13.1–18.0) in non-users, and 4.28 (95% CI 2.37–7.73) in VKA users. After 4 months following THR/TKR, no differences were observed between non-users and VKA users. Outpatient use of aspirin (in the previous 3 months) did not affect the HR among TKR patients, whereas a small reduction in HR was seen in the first 4 months following THR compared with no outpatient use of anticoagulants. Atrial fibrillation was the primary indication for outpatient

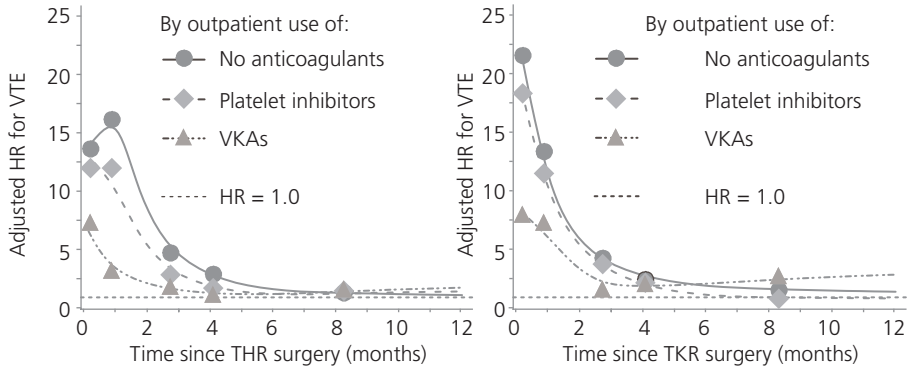
VKA use among THR/TKR surgical patients (recorded prevalence of 66%). It is unlikely that VKA patients were also on LMWHs, as Danish guidelines recommend against this practice.

TABLE 2.1.2 | Risk of DVT / PE following THR / TKR surgery versus age- and gender-matched controls.

	DVT		PE	
Time since surgery	IR *	Adj. HR (95% CI) †	IR *	Adj. HR (95% CI) †
THR-surgery				
< 2 weeks	51.6	17.9 (14.7-21.9)	25.4	15.4 (11.6-20.4)
2 - 6 weeks	59.1	19.8 (16.8-23.2)	19.1	10.6 (8.21-13.6)
7 - 12 weeks	17.0	6.52 (5.35-7.95)	5.5	2.84 (2.02-4.00)
4 - 6 months	7.3	3.09 (2.49-3.84)	2.4	1.61 (1.12-2.32)
6 - 12 months	3.4	1.47 (1.16-1.87)	1.7	1.17 (0.84-1.63)
≥ 1 year	2.4	1.06 (0.92-1.22)	1.2	0.80 (0.65-0.97)
TKR-surgery				
< 2 weeks	70.9	26.2 (19.8-34.6)	20.2	16.3 (10.0-26.4)
2 - 6 weeks	50.7	16.6 (12.8-21.4)	15.7	10.8 (7.05-16.5)
7 - 12 weeks	13.6	5.22 (3.75-7.27)	4.0	2.69 (1.49-4.86)
4 - 6 months	7.4	3.49 (2.52-4.83)	2.0	1.79 (0.98-3.29)
6 - 12 months	3.1	1.51 (1.02-2.22)	1.5	1.34 (0.77-2.35)
≥ 1 year	3.1	1.47 (1.18-1.83)	1.6	1.35 (0.99-1.82)

Abbreviations: CI = confidence interval; DVT = deep-vein thrombosis; PE = pulmonary embolism; THR = total hip replacement; TKR = total knee replacement; HR = hazard ratio; IR = incidence rate (per 1000 person years).
* Incidence rate (per 1000 person years) calculated for each time interval as the number of events divided by the person time that contributed to the given time interval.
† Adjusted for previous VTE, number of bed days in the previous 6 weeks, malignancies in the previous year, and vitamin K antagonists in the previous 6 months.

FIGURE 2.1.1 | Spline regression plot of time since THR (left) and TKR surgery (right) and the risk of VTE in THR/TKR patients vs. matched controls, within prolonged outpatient users of (i) no anticoagulants, (ii) platelet inhibitors only, and (iii) vitamin K antagonists only. HRs are adjusted for confounders as shown in Table 2. HR = hazard ratio; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism.



EFFECT MODIFIERS

We found a strong effect modification by age, indication for surgery, prior VTE and malignancies in the previous year (Table 2.1.4). The association between THR and VTE was strongest in younger patients: the 6-week risk of VTE was 31-fold increased in patients < 60 years of age (adj. HR 31.1; 95% CI 16.8–57.8), while an 11-fold increase was found in the oldest patients (≥ 80 years old; adj. HR 10.9; 95% CI 7.85–15.0). During the first 6 weeks,

the association was weaker among those who required THR for hip fracture (adj. HR 6.80; 95% CI 5.14–8.99), as compared with those with osteoarthritis as the underlying disease (adj. HR 17.8; 95% CI 15.3–20.5). Effect modification was not observed for any of the other investigated risk factors.

TABLE 2.1.3 | Incidence rates (per 1000 person years) for VTE, stratified by follow-up time and peri-operative use of anticoagulants / antithrombotics.

	IR for VTE with THR surgery * THR vs. controls		IR for VTE with TKR surgery * TKR vs. controls	
Stratum	6-week risk	6-52 week risk	6-week risk	6-52 week risk
All patients	64.3 vs 3.3 (IRR 19.2)	8.3 vs 3.0 (IRR 2.78)	59.5 vs 3.3 (IRR 18.1)	7.7 vs 2.4 (IRR 3.15)
By perioperative use of anticoagulants / antithrombotic agents				
No use	65.2 vs 2.9 (IRR 22.5)	7.5 vs 2.6 (IRR 2.80)	52.1 vs 2.7 (IRR 19.1)	6.2 vs 2.0 (IRR 3.40)
Platelet inhibitors only	56.8 vs 3.1 (IRR 18.5)	6.8 vs 2.7 (IRR 2.55)	67.8 vs 2.9 (IRR 23.3)	6.7 vs 2.7 (IRR 2.38)
VKAs only	84.7 vs 13.3 (IRR 6.28)	30.8 vs 8.7 (IRR 3.51)	146.3 vs 23.3 (IRR 6.27)	35.8 vs 6.5 (IRR 5.53)
Combined use / other	127.7 vs 11.9 (IRR 10.5)	37.6 vs 15.9 (IRR 2.32)	-	41.2 vs 13.5 (IRR 3.03)

Abbreviations: IR = incidence rate, IRR = incidence rate ratio, PY = person years, THR = total hip replacement, TKR = total knee replacement, VKA = vitamin K antagonist, VTE = venous thromboembolism.
* Adjusted for confounding factors: IRs and IRRs are calculated for a 70-year old female, without any evidence of prior VTE or a malignancy in the previous year.

DISCUSSION

In this large-scale nationwide study, we found a significantly increased 6-week risk of VTE among THR (13-fold) and TKR patients (14-fold) compared with matched controls. The risk remained substantially elevated for at least 4 months following surgery. During these 4 months, prolonged outpatient use of VKAs lowered the HR by 69% after THR and by 54% after TKR. Finally, the association was strongest among patients aged < 80 years old and those who required surgery for osteoarthritis rather than hip fracture.

COMPARISON WITH OTHER STUDIES

To our knowledge, this is the first study evaluating the risk of VTE following THR/TKR in a nationwide population. Furthermore, this is the only study with detailed information on outpatient prescriptions and matched controls. The only previous study comparing risk of VTE following THR/TKR with controls, was conducted in a selected population of middle-aged women (mean age 56 years) with a relatively frequent use of hormone replacement therapy (32%).[16] In line with our results, the authors found a substantially increased risk of VTE in the first 6 weeks following THR/TKR (221-fold increase), which remained elevated far beyond this period. All other studies did not have information on the risk of VTE in matched controls, and most of them were limited by a short follow-up (90 days).[7–10,27,28,33]

To the best of our knowledge, no other study has evaluated long-term VKA use (> 35 days) for preventing VTE following THR/TKR, compared with control subjects. Our findings suggest a beneficial role of prolonged outpatient VKA use for up to 4 months following THR/TKR. For short-term use, the efficacy of warfarin in THR/TKR patients has been demonstrated previously.[13] In line with our findings, aspirin was shown to be inferior to warfarin in clinical trials.[34,35] Consequently, the ACCP does not recommend the use of aspirin as the preferred therapeutic for the prevention of VTE after surgery.[13]

TABLE 2.1.4 | Effect modifiers of VTE risk following THR / TKR versus matched controls.

	Adjusted hazard ratio (95% confidence interval *			
	Risk of VTE with THR surgery		Risk of VTE with TKR surgery	
Stratum	6-week risk	6-52 week risk	6-week risk	6-52 week risk
All patients	17.8 (13.8-23.0)	2.69 (2.32-3.11)	17.3 (11.6-25.9)	2.85 (2.25-3.61)
By age				
18 - 59 years	31.1 (16.8-57.8)	4.50 (3.12-6.49)	20.6 (9.85-43.1)	4.44 (2.81-7.00)
60 - 79 years	36.4 (19.1-69.4)	2.76 (2.08-3.66)	14.7 (7.71-28.0)	3.73 (2.52-5.53)
≥ 80 years	10.9 (7.85-15.0)	2.28 (1.88-2.77)	17.6 (8.69-35.5)	1.54 (1.03-2.31)
By surgery indication †				
Osteoarthritis	17.8 (15.3-20.5)	2.20 (1.91-2.53)	-	-
Rheumatoid arthritis	14.3 (3.56-57.4)	3.27 (1.36-7.86)	-	-
Hip / knee fracture	6.80 (5.14-8.99)	2.52 (1.31-4.88)	-	-
Unknown / multiple	7.05 (5.28-9.42)	1.83 (1.50-2.22)	-	-
By history of diseases ever before				
No previous VTE	21.5 (16.1-28.6)	2.80 (2.39-3.29)	25.4 (15.5-41.4)	3.06 (2.36-3.97)
Previous VTE	5.05 (2.73-9.34)	2.17 (1.52-3.11)	3.78 (1.80-7.93)	2.09 (1.22-3.59)
No malignancies ‡	19.0 (14.6-24.9)	2.73 (2.35-3.18)	17.8 (11.7-26.9)	2.87 (2.26-3.66)
Malignancies ‡	5.23 (2.04-13.4)	2.05 (1.15-3.67)	11.8 (2.49-55.5)	2.31 (0.70-7.57)
No varicose veins ‡	17.9 (13.8-23.2)	2.67 (2.31-3.09)	17.4 (11.6-26.2)	2.90 (2.29-3.69)
Varicose veins ‡	9.61 (1.12-82.3)	7.47 (0.83-66.8)	10.4 (1.28-84.7)	1.20 (0.29-5.01)
By statin use in the previous 6 months				
No	19.7 (15.2-25.5)	2.73 (2.36-3.15)	18.5 (12.3-27.8)	3.04 (2.38-3.89)
Yes	15.1 (7.61-30.1)	3.30 (2.07-5.27)	16.3 (6.26-42.2)	3.96 (2.16-7.28)

Abbreviations: Adj = adjusted; CI = confidence interval; HR = hazard ratio; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism; HR = hazard ratio.
* Adjusted for confounders as shown in Table 2.1.2.
† For TKR patients, the number of observations was too low to calculate HRs for surgery indication strata.
‡ At least one record in the year before.

Our finding of a prolonged elevated risk of VTE following THR/TKR suggests that a longer duration of thromboprophylaxis than currently recommended in international guidelines may be warranted. The ACCP recommends thromboprophylaxis for 10–35 days (with LMWHs, VKAs or fondaparinux) after surgery in patients undergoing elective THR/TKR.[13] Similarly, the National Institute for Health and Clinical Excellence (NICE) guidelines recommend a duration of 28–35 days with dabigatran, fondaparinux, LMWH, rivaroxaban or unfractioned heparin.[36] These time windows are based on clinical trials with a relatively short duration of thromboprohylaxis (at most 39 days after discharge).[14,15] These trials demonstrated an added value of prolonged thromboprophylaxis (e.g. with rivaroxaban [up to 39 days] or dalteparin [up to 35 days]). Although prolonged thromboprophylaxis (up to 39 days) did not appear

to be associated with an increased risk of bleeding in individual studies,[14,15] a meta-analysis demonstrated an excess of minor bleeding when thromboprophylaxis is continued beyond the first 7–10 days.[37] A Canadian cost-utility analysis has demonstrated acceptable economic value of extended dalteparin use (35 days post-discharge; costs for each quality-adjusted life-year [QALY] gained ranged from $Can 31,200 to $Can 46,500).[38]

However, efficacy, safety and cost-effectiveness remain unknown beyond 35 days of thromboprophylaxis and need to be studied in long-term randomized clinical trials. Interestingly, our findings suggest an added value of outpatient VKA use in the first 4 months following THR/TKR. This may imply that THR/TKR patients could benefit from prolonged thromboprophylaxis (up to 4 months), although this needs to be confirmed in randomized clinical trials (along with its safety profile).

Our findings suggest that patients with osteoarthritis should receive special attention regarding VTE risk assessment in the first 6 weeks following THR. We found a 2.6-fold higher risk of VTE in these patients compared with those requiring surgery for hip fracture. This finding is in line with a study by Sweetland and colleagues, and may be partly explained by differences in physical activity levels following elective THR/TKR.[16] Further, with elective joint replacements, patients generally require two crutches in the first 12 weeks, and then slowly regain their walking ability over the next 2 months.[1] Because of the known complications following hip fracture, intense physical activity is often part of the rehabilitation process; rehabilitation is initiated within 1 day after surgery.[39]

We found that patients with a previous VTE, malignancies and varicose veins had lower relative risks of VTE during the first 6 weeks than those without these risk factors. Presumably this relates to the use of thromboprophylaxis, although we did adjust for outpatient antithrombotic drug use. It seems that these patients are less susceptible to surgery-induced VTE. A possible explanation is that individuals with a previous VTE are on warfarin on a continuous basis (i.e. well before surgery, and then lifelong instead of just 10–35 days after surgery). This may be a possible explanation for the lower relative risks (i.e. the surgery has less of an impact) among patients with a previous VTE.

STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this study include the nationwide population-based design, large sample size, detailed information on matched controls and completeness of follow-up. Unlike most other studies, we had access to outpatient prescription data and information from outpatient clinics. An important limitation is the lack of information on body mass index (BMI), because a higher BMI is associated with an increased risk of VTE[40] and osteoarthritis[41] – the main indication for THR/TKR. Although this may have overestimated our HRs, the magnitude of our association was not larger than that found in a study including data on BMI.[16] Furthermore, we could not assess in-hospital use of antithrombotic agents. However, this is unlikely to have influenced our findings on risk factors: Danish guidelines recommend prophylaxis

for all THR/TKR patients for 7–10 days with an option to extend treatment up to 35 days postoperatively.[26] With a mean hospital stay of 9 to 11 days following THR/TKR, this implies that most patients would have received medical thromboprophylaxis during their hospital stay. Moreover, previous Danish data have shown that up to 99.1% of those undergoing THR/TKR did receive medical thromboprophylaxis (primarily subcutaneous LMWHs).[27] We did not have information on the length of (hospital-initiated) thromboprophylaxis, which may have had an impact on VTE rates up to the first 35 days after surgery. A treatment duration of 35 days may have underestimated VTE rates, whereas any shorter duration could have overestimated these rates. However, VTE rates beyond this period are unlikely to be affected because guidelines do not recommend treatment beyond the first 35 days. We were not able to create a proxy for length of prophylaxis use as: (i) almost all patients are discharged home after hospitalization (rather than to a rehabilitation ward), and (ii) post-discharge LMWHs are most likely to be prescribed by the attending hospital clinicians (and this could not be captured in the Danish registries).

CONCLUSIONS AND IMPLICATIONS

This study shows that the risk of VTE remains substantially elevated for at least 4 months following THR/TKR, which is well beyond the currently recommended duration of anticoagulant use. Our findings suggest that prolonged outpatient VKA use may lower VTE risk during the first 4 months following THR/TKR surgery. Future randomized controlled clinical trials should investigate extended anticoagulant use.

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CHAPTER 2.2

Timing of acute myocardial infarction in patients undergoing total hip or knee replacement: a nationwide cohort study

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ABSTRACT

BACKGROUND: Limited evidence suggests that the risk of acute myocardial infarction (AMI) may be increased shortly after total hip replacement (THR) and total knee replacement (TKR) surgery. However, risk of AMI in these patients has not been compared against matched controls who have not undergone surgery. The objective of this study was to evaluate the timing of AMI in patients undergoing THR or TKR surgery compared with matched controls.

METHODS: Retrospective, nationwide cohort study within the Danish national registries. All patients who underwent a primary THR or TKR (n=95 227) surgery from January 1, 1998, through December 31, 2007, were selected and matched to 3 controls (no THR or TKR) by age, sex, and geographic region. All study participants were followed up for AMI, and disease- and medication history–adjusted hazard ratios (HRs) were calculated.

RESULTS: During the first 2 postoperative weeks, the risk of AMI was substantially increased in THR patients compared with controls (adjusted HR, 25.5; 95% CI, 17.1-37.9). The risk remained elevated for 2 to 6 weeks after surgery (adjusted HR, 5.05; 95% CI, 3.58-7.13) and then decreased to baseline levels. For TKR patients, AMI risk was also increased during the first 2 weeks (adjusted HR, 30.9; 95% CI, 11.1-85.5) but did not differ from controls after the first 2 weeks. The absolute 6-week risk of AMI was 0.51% in THR patients and 0.21% in TKR patients.

CONCLUSIONS: Risk of AMI is substantially increased in the first 2 weeks after THR (25-fold) and TKR (31-fold) surgery compared with controls. Risk assessment of AMI should be considered during the first 6 weeks after THR surgery and during the first 2 weeks after TKR surgery.

INTRODUCTION

Total hip replacement (THR) and total knee replacement (TKR) are highly effective in patients with moderate to severe osteoarthritis.[1] These surgical procedures are frequently performed, yielding an estimated annual number of 1.8 million procedures worldwide.[2,3] Among patients undergoing THR or TKR surgery, acute myocardial infarction (AMI) has been identified as an important perioperative complication.[4,5] In the general population, AMI is a major cause of morbidity and mortality worldwide,[6] and each year more than 7 million patients are estimated to sustain an AMI.[6] In THR or TKR patients, the risk of AMI may be decreased or increased shortly after surgery. On one hand, the surgery itself may result in ischemic complications caused by marrow embolization.[7,8] On the other hand, antithrombotic agents are commonly used in these patients during hospitalization and have the potential to decrease the risk of AMI.[9] Epidemiologic studies[4,10-15] have reported 90-day AMI rates of up to 1.8%, of which most occurred within the first week.

Timing of AMI after THR or TKR surgery has become of increasing interest.[14] Although early hospital discharge has been promoted in these patients, perioperative complications, including AMI, may argue against this practice.[16] Because no previous studies included a large control cohort for reference, it is thus difficult to interpret the magnitude of increased AMI risk after THR or TKR surgery compared with the general population. Differences in baseline characteristics among the studies further add to this difficulty. More important, previous studies have only focused on short-term AMI risk (ie, >90 days) and did not investigate long-term risk for AMI.

Furthermore, data are limited on individual risk factor for AMI after THR or TKR surgery. This drawback is of particular importance given the number of comorbidities often present in these elderly patients. Previous studies[4,10-15] were limited by several design issues, such as small sample sizes and lack of matched control cohorts who did not undergo THR or TKR surgery. Moreover, none of these studies provided analyses adjusted for medication. For example, use of pain relievers (in particular, nonsteroidal anti-inflammatory drugs NSAIDs]) is common among THR and TKR patients and might increase the risk of AMI.[17,18] The objectives of this study were to evaluate the timing of AMI after THR and TKR surgery, to evaluate potential effect modifiers of this relationship, and to identify determinants of AMI in THR and TKR patients.

METHODS

DATA SOURCES

Using Danish national registries, we conducted a nationwide retrospective cohort study. The total population from which the study participants were drawn was 5.5 million. Detailed information was available for all Danish residents, including data on second-line visits (hospitals, outpatient clinics, and emergency departments; from 1977 onward), drugs sold at retail pharmacies (from 1996 onward), citizen status (vital status, date of death, residence, migration, and socioeconomic status; from 1968 onward), and causes of death (1 underlying cause and up to 3 additional immediate causes; from 1970 onward). In Denmark, all residents have free access to health services, including hospital services and visits to general practitioners (tax funded). Previous reports demonstrated high quality, completeness, and validity rates, and these registries have been used in numerous recent epidemiologic studies.[19]

STUDY POPULATION

All patients aged 18 years or older who underwent a primary THR or primary TKR from January 1, 1998, through December 31, 2007, were included in the study. Both THR and TKR were identified using hospital discharge records and were classified by the International Classification of Diseases, 10th revision (ICD-10)[20] (ICD-10 code NFB.XX for THR and ICD-10 code NGB.XX for TKR). Each THR and TKR patient was matched with 3 controls of the same age and sex without a history of THR and TKR. The index date was defined as the date of primary THR and TKR hospital admission for THR and TKR patients and similarly for matched

controls. We excluded individuals with a prior AMI within 6 weeks before or on the index date.

Danish guidelines recommend thromboprophylaxis (mostly low-molecular-weight heparin [LMWH]; started 12 hours before surgery or 12-24 hours after surgery) for all THR and TKR patients while in the hospital, which can be extended up to 35 days.[21] Previous Danish data revealed that 99.1% of THR and TKR patients had indeed received thromboprophylactic agents (of which 93% included LMWHs).[22]

OUTCOME ASSESSMENT

All patients were followed up from the index date until death, migration, THR or TKR revision, or the end of the study period (December 31, 2007) or AMI, whichever came first. Acute myocardial infarction was assessed using the National Hospital Discharge Registry and the Danish Causes of Death Registry (both classified using ICD-10 code I21). Acute myocardial infarction was divided into fatal and nonfatal events based on death certificates.

POTENTIAL RISK FACTORS

We reviewed the literature to define potential (general) risk factors and confounders for this study.[23,24] These factors included age, sex, socioeconomic status, indication for surgery, a history of AMI (stratified by time between most recent AMI and THR or TKR surgery), history of other ischemic heart disease, heart failure, and cerebrovascular disease. Furthermore, a drug dispensing for beta blockers, renin-angiotensin-aldosterone system inhibitors, thiazide diuretics, calcium channel blockers, organic nitrates, statins, nonselective NSAIDs (including high-dose aspirin), cyclooxygenase 2 (COX-2) selective inhibitors, antiplatelet drugs, vitamin K antagonists, estrogen-containing drugs, antidiabetic drugs, and inhaled beta-2 agonists within 6 months were considered as potential confounders for AMI.

STATISTICAL ANALYSIS

Using the PHREG procedure from SAS statistical software, version 9.2 (SAS Institute, Inc), we calculated hazard ratios (HRs) for the risk of AMI with THR and TKR and compared them with age- and sex-matched controls (stratified on matched pairs). Total follow-up time was divided into 6-week periods and the first 6 weeks into 1-week periods. Information on potential confounders and risk factors was collected during follow-up; before the start of each period, we evaluated the presence of these covariates. Potential confounders were included in the final model if they independently changed the beta coefficient for THR or TKR by at least 5%.

To assess the timing of AMI after THR and TKR surgery, we included period interaction terms (period × surgery) in the model for the following periods: less than 2 weeks, 2 to 6 weeks, 7 to 12 weeks, 4 to 6 months, 7 to 12 months, and 1 year or more after surgery. For each period, AMI risk was plotted against the median time since THR or TKR surgery and visualized using smoothing spline regression,[25-28] which has been advocated as an alternative to categorical analysis.[29] In addition, we used Kaplan-Meier plots to present the cumulative incidence rates

of AMI over time (divided into fatal and nonfatal events).

To compare AMI risk after THR or TKR surgery with other elective operations, we performed a sensitivity analysis. Within THR matched controls, we selected patients who underwent hernia surgery. For these controls, the index date was reset at time of elective surgery hospital admission. The THR patients whose matched controls did not undergo these elective operations were excluded, and the analyses were further adjusted for calendar year, sex, and age at surgery.

For potential effect modifiers and determinants, we evaluated 2 periods by restricting follow-up to less than 6 weeks or 6 to 52 weeks after surgery. Potential effect modifiers were screened by entering an interaction term (risk factor × surgery) into the model. To identify determinants of AMI within THR and TKR patients only, we excluded controls and used stepwise backward elimination to determine the final regression model after entering all previously mentioned risk factors ($P < .05$) into the model. This study was approved by the National Board of Health and the Danish Data Protection Agency.

RESULTS

TABLE 2.2.1 | Baseline characteristics of THR / TKR patients and matched controls.

	THR		TKR	
Characteristic	THR n = 66,524	No THR n = 200,001	TKR n = 28,703	No TKR n = 86,164
Mean follow-up time (years, SD)	3.9 (2.8)	4.1 (2.7)	3.9 (2.6)	3.7 (2.6)
Males	36.9%	36.9%	37.6%	37.6%
Mean age (years, SD)	71.9 (12.5)	71.9 (12.5)	67.2 (10.8)	67.2 (10.8)
Mean THR / TKR hospital stay (days, SD)	10.8 (9.4)		9.3 (6.3)	
Disease history (ever before, unless specified otherwise)				
Ischaemic heart disease	12.5%	10.5%	11.8%	9.4%
Heart failure	7.9%	6.5%	5.0%	4.5%
Drug use (within 6 months before)				
NSAIDs	50.7%	16.4%	60.9%	16.6%
RAAS inhibitors	19.1%	16.6%	24.8%	16.7%
Beta blockers	13.2%	12.1%	14.9%	11.9%
Antiplatelet drugs	22.3%	20.9%	19.5%	17.1%
Vitamin K antagonists	3.3%	3.0%	3.1%	2.8%
Thiazide diuretics	17.9%	14.2%	20.4%	12.6%
Calcium channel blockers	14.4%	12.6%	16.0%	11.4%
Antidiabetic drugs	5.6%	5.5%	7.1%	5.4%
Statins	8.7%	8.7%	13.1%	11.0%

Values are means (SD) or percentages (among THR / TKR patients or controls), unless stated otherwise. Abbreviations: NSAIDs = non-steroidal anti-inflammatory drugs; RAAS inhibitors = renin-angiotensin-aldosterone blockers; SD = standard deviation; THR = total hip replacement; TKR = total knee replacement.

After exclusion of 437 patients with an AMI in the 6 weeks before or on the index date, 66,524 THR patients, 28,703 TKR patients, and 286,165 matched controls were enrolled in the study (Table 2.2.1). Because of matching, patients had a similar distribution of age (THR:

mean age, 71.9 years; TKR: mean age, 67.2 years) and sex (THR: 36.9% male; TKR: 37.6% male) compared with matched controls. The THR and TKR patients were more likely to have used NSAIDs compared with controls and had slightly more often been diagnosed as having ischemic heart disease before surgery.

FIGURE 2.2.1 | Adjusted hazard ratios (HRs) for acute myocardial infarction (AMI).

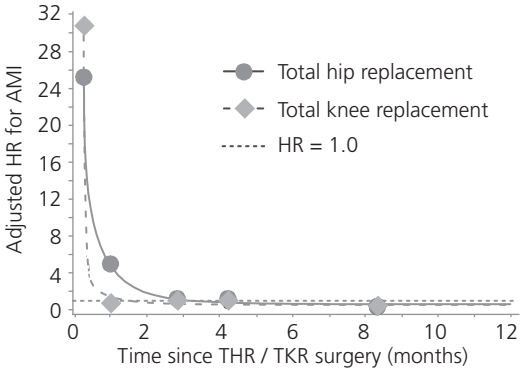
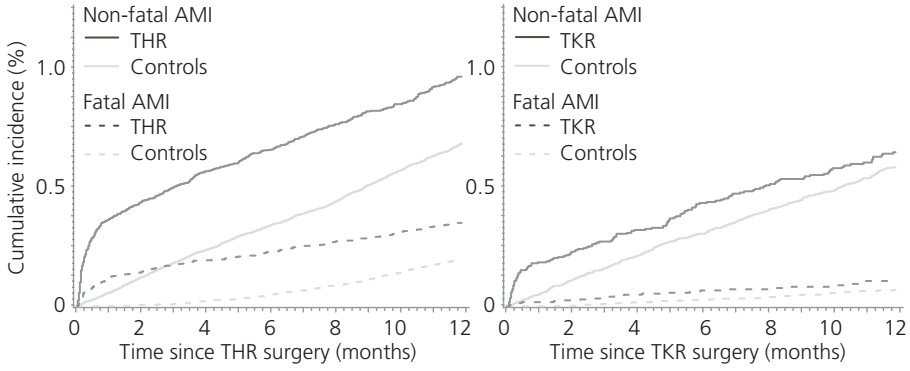


Figure 2.2.1 shows that the risk of AMI was substantially increased during the first 2 weeks after THR or TKR surgery compared with controls. Adjusted HRs were 25.5 (95% CI, 17.1-37.9) for THR and 30.9 (95% CI, 11.1-85.5) for TKR. Compared with patients who underwent hernia surgery, the 2-week AMI risk remained significantly elevated (adjusted HR, 21.9; 95% CI, 2.94-163.2). In TKR patients, the risk reached baseline levels after the first 2 weeks (3-6 weeks: adjusted HR, 0.81; 95% CI, 0.37-1.77), whereas in THR patients, the risk remained elevated during the first 6weeks after surgery (3-6 weeks: adjusted HR, 5.05; 95% CI, 3.58-7.13). Kaplan-Meier plots revealed the same timing patterns (Figure 2.2.2). Absolute 6-week rates of AMI were 0.51% for THR patients and 0.21% for TKR patients.

FIGURE 2.2.2 | Cumulative incidence rates of acute myocardial infarction (AMI). Left, Patients undergoing total hip replacement (THR); Right, patients undergoing total knee replacement (TKR).



For both THR and TKR, we found a strong effect modification by age (Table 2.2.2). During the first 6 weeks, the effect of THR on AMI risk was highest in the oldest patients (≥80 years

old; adjusted HR, 25.3; 95% CI, 17.7-36.2), whereas we could not detect a significantly increased risk in patients younger than 60 years (adjusted HR, 2.41; 95% CI, 0.68-8.57). We found a similar, albeit less substantial, age trend with TKR surgery. No other significant effect modifiers for the relationship between THR or TKR and AMI during the first 6 postoperative weeks were identified.

TABLE 2.2.2 | Effect modifiers of AMI risk following THR / TKR versus matched controls.

	Adjusted hazard ratio (95% confidence interval) *			
	Risk of AMI after THR		Risk of AMI after TKR	
Stratum	6-week risk	6-52 week risk	6-week risk	6-52 week risk
All patients	17.8 (13.5-23.4)	0.95 (0.82-1.10)	8.69 (4.73-16.0)	0.70 (0.53-0.92)
By age				
18 - 59 years	2.41 (0.68-8.57)	1.14 (0.56-2.30)	2.26 (0.45-11.3)	2.68 (1.27-5.67)
60 - 79 years	12.4 (8.35-18.5)	0.95 (0.78-1.17)	9.20 (4.13-20.5)	0.60 (0.42-0.84)
≥ 80 years	25.3 (17.7-36.2)	0.94 (0.76-1.15)	11.2 (4.83-25.8)	0.58 (0.34-1.01)
By sex				
Males	12.8 (8.56-19.3)	0.98 (0.79-1.23)	7.86 (3.59-17.2)	1.02 (0.70-1.46)
Females	21.7 (15.4-30.4)	0.93 (0.77-1.12)	9.50 (4.47-20.2)	0.45 (0.30-0.69)
By history of diseases ever before, unless stated otherwise				
No previous AMI	18.8 (13.9-25.5)	1.00 (0.85-1.17)	8.63 (4.44-16.7)	0.68 (0.50-0.92)
Previous AMI	12.5 (5.54-28.4)	0.72 (0.48-1.09)	9.03 (1.89-43.1)	0.84 (0.37-1.88)
No heart failure	14.9 (10.9-20.4)	1.03 (0.87-1.21)	6.51 (3.28-12.9)	0.85 (0.63-1.15)
Heart failure	37.2 (17.8-78.0)	0.64 (0.45-0.93)	29.9 (6.25-144)	0.23 (0.11-0.48)
No cerebrovascular disease	15.7 (11.6-21.2)	1.04 (0.89-1.21)	9.73 (4.96-19.1)	0.82 (0.62-1.10)
Cerebrovascular disease	30.3 (12.8-71.6)	0.49 (0.30-0.79)	2.35 (0.45-12.2)	0.12 (0.04-0.36)
By outpatient use of antithrombotic drugs 6 months before †				
None of the below	13.8 (9.49-20.1)	1.13 (0.94-1.36)	-	0.81 (0.58-1.15)
VKA only	25.3 (4.41-146)	1.36 (0.58-3.18)	-	1.31 (0.33-5.15)
Antiplatelets only	24.9 (15.4-40.3)	0.67 (0.51-0.88)	-	0.51 (0.31-0.87)
Combined / other	-	1.00 (0.31-3.16)	-	0.16 (0.01-2.48)

Abbreviations: Adj = adjusted; AMI = acute myocardial infarction; CI = confidence interval; HR = hazard ratio; THR = total hip replacement; TKR = total knee replacement.
* Adjusted for ischaemic heart disease ever before, and use of antithrombotic drugs, loop diuretics, non-selective NSAIDs, or SSRIs within 6 months before.
† For TKR patients, number of observations was too low to calculate 6-week HRs for antithrombotic drug use strata.

In the THR patients, the 6-week risk of AMI was higher among older patients; men; patients with a previous AMI, heart failure, or cerebrovascular disease; and users of NSAIDs, beta blockers, potassium-sparing diuretics, organic nitrates, and antiplatelet drugs during follow-up compared with THR patients without these characteristics (Table 2.2.3). The elevated risk caused by a previous AMI before THR or TKR surgery diminished with an increasing time since most recent AMI before surgery (Table 2.2.3).

DISCUSSION

This study demonstrated an increased risk of AMI during the first 2 weeks after THR (25-fold) and TKR (31-fold) surgery compared with matched controls. The risk of AMI sharply

decreased after this period, although it remained significantly elevated in the first 6 weeks for THR patients. The association was strongest in patients 80 years or older, whereas we could not detect a significantly increased risk in patients younger than 60 years. Furthermore, a previous AMI in the 6 months before surgery increased the risk of new AMI during the first 6 weeks after THR and TKR (4-fold increase) surgery but did not modify the relationship between THR or TKR and AMI.

TABLE 2.2.3 | Determinants of AMI risk within THR / TKR patients

	Adjusted hazard ratio (95% confidence interval) *			
	Risk of AMI in THR patients		Risk of AMI in TKR patients	
Determinant	6-week risk	6-52 week risk	6-week risk	6-52 week risk
By age (reference = 18 - 59 years)				
60 - 79 years	5.46 (2.22-13.4)	3.26 (1.85-5.76)	2.55 (0.77-8.42)	1.27 (0.73-2.22)
≥ 80 years	11.1 (4.48-27.4)	5.04 (2.80-9.07)	8.20 (2.38-28.2)	2.35 (1.21-4.57)
Females (reference = males)	0.70 (0.55-0.88)	0.70 (0.56-0.88)	0.57 (0.33-0.98)	0.28 (0.18-0.44)
By history of diseases ever before, unless stated otherwise (reference = no history)				
Previous AMI †	2.12 (1.59-2.83)	2.72 (2.02-3.66)	1.15 (0.55-2.42)	2.79 (1.60-4.86)
1.5 - 6 months before	4.25 (2.24-8.05)	5.23 (2.51-10.9)	4.14 (0.91-18.9)	2.55 (0.34-19.2)
6 - 12 months before	3.82 (1.90-7.67)	3.32 (1.34-8.24)	2.18 (0.28-16.8)	
> 12 months before	1.91 (1.40-2.59)	2.56 (1.88-3.49)	0.96 (0.43-2.17)	2.92 (1.66-5.11)
Heart failure	2.47 (1.90-3.20)	2.76 (2.11-3.61)	3.75 (2.01-6.98)	2.34 (1.37-4.02)
Cerebrovascular disease	2.06 (1.57-2.70)	1.26 (0.92-1.74)	2.09 (1.05-4.15)	0.82 (0.35-1.91)
By use of drugs 6 months before (reference = no use 6 months before)				
NSAIDs ‡	1.80 (1.31-2.47)	3.37 (2.43-4.67)	1.64 (0.78-3.42)	2.39 (1.31-4.37)
By cumulative DDD exposure ever before				
< 30 DDDs	1.33 (0.66-2.71)	3.33 (1.81-6.13)	2.61 (1.09-6.24)	2.06 (0.83-5.16)
30 - 180 DDDs	2.22 (1.45-3.41)	3.20 (1.97-5.19)		
> 180 DDDs	1.63 (0.99-2.68)	3.62 (2.17-6.05)	1.29 (0.39-4.20)	3.91 (1.86-8.22)
Beta blockers	1.45 (1.11-1.88)	1.00 (0.75-1.32)	1.49 (0.82-2.67)	1.53 (0.96-2.44)
Potassium sparing diuretics	1.61 (1.10-2.36)	1.49 (1.01-2.22)	0.60 (0.14-2.55)	0.81 (0.29-2.30)
Organic nitrates	2.68 (2.02-3.55)	1.64 (1.19-2.27)	1.45 (0.68-3.10)	2.60 (1.45-4.64)
By outpatient use of anticoagulant drugs 6 months before (reference = no use 6 months before)				
VKA only	0.83 (0.46-1.49)	0.83 (0.49-1.40)	1.86 (0.65-5.36)	1.03 (0.43-2.49)
Platelet inhibitors only	1.33 (1.03-1.73)	0.92 (0.71-1.19)	2.30 (1.21-4.37)	1.11 (0.67-1.83)
Combined use / other	0.23 (0.06-0.94)	0.90 (0.45-1.81)	-	0.33 (0.04-2.42)

Abbreviations: Adj = adjusted; AMI = acute myocardial infarction; CI = confidence interval; DDD = daily defined dosage; HR = hazard ratio; NSAID = non-steroidal anti-inflammatory drug; THR = total hip replacement; TKR = total knee replacement; VKA = vitamin K antagonist.

* The following covariates were retained in the final model after stepwise backward elimination: age, sex, previous AMI, a history of heart failure, and cerebrovascular disease ever before, use of NSAIDs in the previous three months, and use of beta blockers, potassium sparing diuretics, organic nitrates, and antithrombotic agents in the previous 6 months.

† For TKR patients (6-52 week risk), previous AMI recency categories were merged (too few observations): 1.5 - 12 months before, and > 12 months before.

‡ At least one prescription in the previous three months; reference = no use three months before. For TKR patients, cumulative DDD categories < 30 DDDs and 30 - 180 DDDs were merged (too few observations).

To our knowledge, this is the first study comparing AMI risk after THR or TKR surgery with the risk of matched controls not undergoing surgery. Previous studies were limited to reports on (primarily perioperative) incidence rates only and showed somewhat conflicting results. For example, Khatod et al[11] demonstrated a 0.1% incidence rate of AMI within 90 days after TKR surgery, whereas Gandhi et al[14] found a 1.8% incidence rate in the first 18 days after THR or TKR surgery. This discrepancy may partially be explained by differences in diagnosing AMI because the latter study used serum troponin levels in addition to electrocardiogram changes for diagnosis. Most other studies[4,12,13,15] found an AMI incidence rate of 0.3% to 0.8%, which is well in line with our findings. Because most of these studies included perioperative events only (typically <20 days), our incidence rates tended to be more toward 0.8% rather than the lower end. Alternatively, the discrepancy may be explained by differences in baseline characteristics among the studies, including comorbid cardiovascular disease and characteristics of the orthopaedic center performing the surgical procedure. An American study[30] thus showed that high-volume hospitals had a lower 30-day mortality rate after major orthopedic surgery, although no adjustments were made for comorbidities or surgical complexity.

Evidence on timing of AMI after THR and TKR surgery is scarce. Previous studies have only found an elevated risk during the first 4 to 5 postoperative days. Gandhi et al[14] found that within 5 days after THR or TKR surgery, 91% of all in-hospital AMI events had occurred. Similarly, Parvizi et al[13] found that perioperative AMIs were most likely to occur within 4 days after THR or TKR surgery. Our findings confirm this increased risk of AMI and suggest that the risk is actually increased for an even longer period (THR: first 6 weeks; TKR: first 2 weeks).

The biological mechanism explaining the increased risk of AMI may be related to marrow embolization because surgical invasion of the medullary canal of the femur potentially causes marrow embolization and cardiac stress.[14] This embolization process occurs primarily with THR and to a lesser extent with TKR.[7,8] This fact may explain the differences in AMI risk between THR and TKR observed in our study. Among THR patients, the increase in AMI risk lasted for a longer period compared with TKR patients. Furthermore, hemodynamic stressors associated with the surgery (eg, effects of anesthesia on the cardiovascular system, blood loss, fluid shifts, arrhythmias, and hypoxia) can further contribute to the observed increased risk of AMI after THR and TKR surgery.

It is unlikely that the use of inpatient antithrombotic agents will explain the observed elevated risk of AMI after THR and TKR surgery. Most Danish THR and TKR patients are treated with LMWHs,[22] which have been shown to lower the risk of death and myocardial infarction during the first 6 days of therapy in patients with unstable coronary artery disease.[9] This finding would imply that we may have underestimated the risk of AMI and that the actual association between THR or TKR and risk of AMI would be even stronger. There is conflicting evidence about the association between dabigatran etexilate and an increased risk of AMI.[31] However, dabigatran was not available during the entire study period and should therefore not have influenced our results. As a further note, patients taking (outpatient) antithrombotic agents

may represent a higher-risk population (eg, use of low-dose aspirin to prevent secondary events). This may have cancelled our effect modification and is most likely the reason why antiplatelet drugs were identified as a significant determinant of AMI during the first 6 weeks after THR and TKR surgery.

Our study implies that a recent AMI (within 1 year) should be a contraindication for those undergoing elective THR surgery. Previous literature confirmed AMI as a risk factor for a new AMI in these patients.[14] However, no other study has evaluated the time since most recent AMI, but this is important when planning the performance of THR. We were able to show a sharp decrease in risk of a new AMI when the previous AMI had occurred more than 1 year before surgery. However, even beyond this period, the risk remained elevated compared with those without a previous AMI. These findings are indirectly supported by a Swedish retrospective cohort study[32] in patients with ST-elevation myocardial infarction. The authors of that study reported that the risk of reinfarction was highest within the first year of AMI.

Strengths of this study include the nationwide population-based design, the large sample size, information on matched controls, and completeness of follow-up. Unlike most other studies, we had access to outpatient prescription data (such as NSAIDs) and information from outpatient clinics. Because we had highly valid data on mortality, we were able to identify out-of-hospital fatal AMI events. The major drawback is the lack of information on other risk factors for AMI, such as smoking, blood pressure, biochemical variables, and body mass index. A higher body mass index is associated with an increased risk of coronary artery disease[33] and osteoarthritis, the main indication for THR and TKR. However, in a previous study[34] on patients undergoing THR, body mass index at the time of surgery was not associated with short- or long-term mortality. Furthermore, we did not have information on inpatient anticoagulant use. Because warfarin and LMWHs have been shown to reduce AMI incidence, this could have distorted our study findings.[9,35] As explained, this would mean an underestimation of our observed increased AMI risk. We cannot exclude the possibility that hospitalized patients may have been more likely to be diagnosed as having an AMI. However, we did not look at silent myocardial infarctions (which are more likely to be recorded as silent ischemic events rather than AMIs). Moreover, we also found an increased risk of fatal AMIs, for which the detection rate should be equal. Finally, we did not have information about general anesthesia, which may well be the cause of the increased risk of AMI after THR and TKR surgery. However, a previous study[36] that evaluated the influence of general anesthesia in surgical patients vs those who received regional anesthesia showed a trend toward only a 1.4-fold increased risk of AMI. This is well below the excess risk we observed in our study, suggesting that the increased risk in THR/TKR patients might not be fully explained by general anesthesia only. Furthermore, our sensitivity analysis demonstrated that the increased risk of AMI after THR surgery remained elevated when compared with other elective operations.

To our knowledge, this is the first study that found that THR (25-fold) and TKR patients (31-fold) are at increased risk of AMI during the first 2 weeks after surgery. The elevated risk was sustained for 6 weeks after THR and for 2 weeks after TKR. The effect of surgery on AMI

risk was strongest in patients 80 years or older. The relationship was not more pronounced in those with well-known risk factors of AMI (such as heart failure, cerebrovascular disease, and previous AMI), although they increased the risk of AMI within THR and TKR patients. Finally, our data suggest that elective THR surgery should be contraindicated in patients with a previous AMI in the last 12 months before surgery.

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CHAPTER 2.3

Risk of gastrointestinal bleeding in patients undergoing total hip or knee replacement compared with matched controls: a nationwide cohort study

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ABSTRACT

BACKGROUND: Gastrointestinal (GI) bleeding may impose a serious threat in patients undergoing total hip and knee replacements (THR/TKR). However, timing of GI bleeding in these patients versus matched controls, and the influence of proton pump inhibitors (PPIs) have not been studied. To evaluate the timing of GI bleeding following THR/TKR and to determine effect modification by PPI use.

METHODS: In a nationwide Danish cohort study, we selected all patients with a primary THR/TKR between 1998 and 2007 (n=95,115). Three control subjects without THR/TKR were matched by age, sex, and region. We calculated disease and medication adjusted (adj.) HRs for GI bleeding with THR/TKR versus controls. PPI use was assessed in the previous three months (in a time-dependent manner).

RESULTS: We identified a 6.0-fold increased risk of GI bleeding during the first 2 weeks following THR (adj. HR 6.02; 95% CI 4.06-8.92), and a 2.3-fold increased risk for TKR patients (adj. HR 2.30; 95% CI 1.17-4.54), both versus matched controls. The elevated risk lasted longer in THR patients (12 weeks), as compared with TKR patients (6 weeks). PPI use lowered the HR for GI bleeding by 74% during the first 6 weeks following THR, but not TKR.

CONCLUSIONS: This study demonstrated an increased risk of GI bleeding during the first 2 weeks following THR (6.0-fold), and TKR (2.3-fold), and remained increased for up to 6 (TKR) to 12 weeks (THR) after surgery. PPI use substantially lowered this elevated risk in THR patients, but not in TKR patients.

INTRODUCTION

Total hip and knee replacements (THR / TKR) are effective major orthopaedic procedures that are in particular considered in patients with moderate to severe osteoarthritis.[1] The surgery is performed in large numbers, yielding a total annual estimate of 1.8 million replacements worldwide.[2,3] With venous thromboembolism (VTE) being the leading cause of emergency hospital readmission, THR / TKR patients are intensively treated with antithrombotics while hospitalized.[4] Fine-tuning of antithrombotic therapy is essential, as overtreatment may result into an additional risk of major bleedings (including potentially life-threatening gastrointestinal [GI] haemorrhages). Clinical trials reported a perioperative risk of major bleeding of as high as 4%, depending on the definition of major bleeding.[5-7] Moreover, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is common among patients with osteoarthritis, and may further increase the risk of GI bleeding.[8,9]

Some studies advocate prolonged antithrombotic therapy in patients undergoing THR / TKR.6,7 To balance benefits and risks using this approach, it is important to understand long-

term risk of GI bleeding in these surgical patients as well (in particular with the ongoing extensive use of NSAIDs). At the moment, most studies are limited to short-term evidence (up to 35 days after surgery) only, and looked at major bleeding as a whole.[5-7,10] Furthermore, the rates have not been compared against matched control subjects who did not have surgery.

Optimal fine-tuning of antithrombotic treatment is focused on balancing the benefits (reducing VTE incidence) and risks (maintaining a low bleeding risk). In patients at high risk for developing VTE, prolonged antithrombotic therapy may be indicated, and thereby possibly increasing the risk for GI bleeding. These patients may theoretically benefit from acid suppressant drugs (such as proton pump inhibitors [PPIs] and histamine-2 receptor antagonists [H2RAs]) that are commonly used to prevent GI bleeds. However, the effect of these drugs on risk of GI bleeding following THR / TKR is poorly studied. Evidence remains limited to one observational study that found a decreased risk of upper GI bleeding with use of 300 mg ranitidine in patients undergoing THR / TKR (treated with 150 mg aspirin for 6 weeks postoperatively).[11] However, the authors could not adjust for age, sex, comorbidities, and co-medication, and took late occurring bleeding (i.e. bleeding after 1 year) into account as well. Consequently, the aims of this study were to evaluate the timing of GI bleeding in patients undergoing THR / TKR versus matched control subjects, and to assess the influence of acid suppressants on this association.

METHODS

DATA SOURCES

A retrospective cohort study was conducted using the Danish national registries covering the entire country of Denmark (5.5 million residents). The registries provides detailed information on hospital / emergency room / outpatient clinic visits, dispensed drugs at community pharmacies, death (including cause of death), geographical residence, migration status, and information on socioeconomic status. Overall high completeness and validity have been reported previously, and the Danish national registries have been used in numerous epidemiological studies.[12]

STUDY POPULATION

The patient cohort comprised all patients aged ≥ 18 years old who had undergone a primary THR (International Classification of Diseases, ICD, 10th revision: ICD10 procedure code NFB.XX) or TKR (ICD10 procedure code NGB.XX) between January 1, 1998, and December 31, 2007. THR / TKR patients were matched to three control subjects without a record of THR / TKR during the entire study period, based on age, gender, and geographical location. The index date was defined as the date of the patient's THR / TKR hospital admission, and was similar for matched controls. We excluded subjects who had a record for GI bleeding within the 6 weeks before the index date.

OUTCOME ASSESSMENT

Patients were followed for the occurrence of GI bleeding (recorded in the hospitalization registry [including emergency rooms and outpatient clinics] or on death certificates). GI bleeding was identified using the following ICD10 codes: K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K920-K922, and I850. We censored the patients if they had died (not GI bleeding related), migrated, underwent THR / TKR revision, or if the study period had ended (December 31, 2007), whichever came first.

POTENTIAL RISK FACTORS

Data on risk factors were collected in a time-dependent manner: total follow-up time was divided into 6-week periods, and for the first 6 weeks into one-week periods. At baseline, we determined age, sex, socioeconomic status, indication for surgery, and a history of GI bleeding, non-bleeding GI ulcers, oesophagitis, gastritis, and malignancies.[13] In the 6 months before the start of each interval, we further evaluated use (at least one prescription) of outpatient antithrombotic agents (stratified by drug type: vitamin K antagonists [e.g. warfarin], antiplatelet drugs [e.g. low-dose aspirin], and other [e.g. enoxaparin]), non-steroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids, selective serotonin reuptake inhibitors (SSRIs), organic nitrates, beta blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, thiazide diuretics, statins, loop diuretics, calcium channel blockers, antidiabetics, and antiarrhythmics.[9,14-17] Current acid suppressant use (PPIs or H2RAs) was assessed in the three months before the start of each interval (i.e. in a time-dependent manner, before and after surgery). In Denmark, chronic medication is typically prescribed for three months, and a current user is therefore likely to have been dispensed a drug in the previous three months. Current acid suppressant users were further stratified according to the last prescribed daily dose (calculated as omeprazole equivalent dosage), and the cumulative amount of daily-defined dosages (DDDs) prescribed in the previous year.

STATISTICAL ANALYSIS

Using the PHREG option from SAS 9.2 (SAS Institute, Cary, North Carolina), we calculated disease and drug use adjusted (adj.) hazard ratios (HRs) for GI bleeding in THR / TKR patients compared with age- and gender-matched controls. Potential confounders were only included into the final model if they independently changed the beta coefficient for THR / TKR surgery by at least 5% (change-in-estimate method, advocated by Greenland).[18]

We used time interaction terms (surgery * time period) to estimate HRs for the following time periods: < 2 weeks, 2 – 6 weeks, 7 – 12 weeks, 4 – 6 months, 7 – 12 months, and ≥ 1 year after surgery. Timing of GI bleeding was plotted against the median time of follow-up and visualized using smoothing spline regression.[19]

For effect modifiers and determinants, we restricted the total follow-up to either < 6 weeks or 6 – 52 weeks following surgery. Interaction terms (risk factor * surgery) were included into

the model to assess statistically significant effect modifiers (at a significance level of 5%). For determinants, we ran a full Cox model (including all potential risk factors), and identified significant determinants at a level of $p < 0.05$. This study was approved by the National Board of Health and the Danish Data Protection Agency.

RESULTS

Table 2.3.1 summarizes the baseline characteristics of patients who underwent THR (n = 66,428) or TKR (n = 28,687), and their matched controls (n = 286,024). We found a mean age at index date of 71.9 years for THR, and 67.2 years for TKR, and a proportion of males of 36.9% for THR, and 37.6% for TKR. Age and sex distribution was similar among matched controls. Mean follow-up time ranged between 3.7-4.1 years, and we found a mean duration of arthroplasty related hospital stay of 10.8 days for THR, and 9.3 days for TKR. Prior GI events were slightly more prevalent among THR / TKR patients as compared with control subjects, and they were more likely to have used acid suppressants as well. As expected, NSAID use was higher among THR / TKR patients, in comparison with control subjects.

TABLE 2.3.1 | Baseline characteristics of THR / TKR patients and matched controls.

Characteristic	THR patients n = 66,428	Controls n = 199,888	TKR patients n = 28,687	Controls n = 86,136
Mean follow-up time (years, SD)	3.9 (2.8)	4.1 (2.7)	3.9 (2.6)	3.7 (2.6)
Males	36.90%	36.90%	37.60%	37.60%
Mean age (years, SD)	71.9 (12.5)	71.9 (12.5)	67.2 (10.8)	67.2 (10.8)
Mean THR hospital stay (days, SD)	10.8 (9.4)		9.3 (6.3)	
Surgery indication				
Osteoarthritis	69.6%		93.6%	
Hip / knee fracture	6.3%		0.7%	
Other / unknown	24.1%		5.7%	
Disease history (ever before, unless specified otherwise)				
GI bleeding	2.8%	2.0%	2.2%	1.6%
Non-bleeding ulcers	3.3%	2.4%	3.3%	2.2%
Drug use (within 6 months before)				
NSAIDs	50.7%	16.4%	60.9%	16.6%
Systemic glucocorticoids	7.6%	4.7%	10.2%	3.9%
SSRIs	11.0%	7.4%	6.7%	6.3%
Antidiabetics	5.6%	5.5%	7.1%	5.4%
Statins	8.7%	8.7%	13.1%	11.0%
Loop diuretics	14.5%	11.5%	10.8%	7.6%
Proton pump inhibitors	11.4%	7.9%	13.0%	7.4%
H2 receptor antagonists	3.0%	2.5%	3.3%	2.0%
Vitamin K antagonists	3.3%	3.0%	3.1%	2.8%
Antiplatelet drugs	22.3%	20.9%	19.5%	17.1%

Values are means or percentages (among THR patients or controls), unless stated otherwise. Abbreviations: GI, gastrointestinal; H2, histamine-2; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; THR, total hip replacement; TKR, total knee replacement.

We found a considerably increased risk of GI bleeding during the first 2 weeks after THR (adj. HR 6.02; 95% CI 4.06-8.92), and TKR (adj. HR 2.30; 95% CI 1.17-4.54), as compared with matched control subjects (Table 2.3.2, Figure 2.3.1). For THR, the risk remained significantly

elevated during the first 12 weeks, whereas for TKR, the risk reached baseline levels after the first 6-12 weeks. During the first 12 weeks after surgery, we were able to identify 343 GI bleeding events in THR patients (0.52%), and 53 events in TKR patients (0.18%). The association was not modified by the indication for surgery.

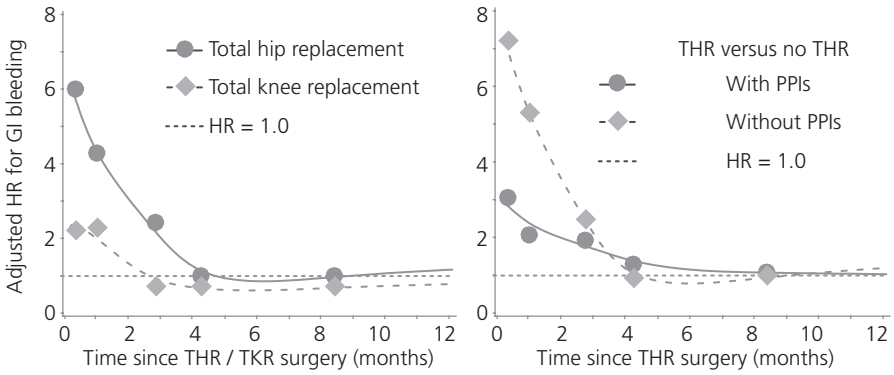
TABLE 2.3.2 | Risk of GI bleeding following THR / TKR surgery versus age- and sex-matched controls, stratified by time after surgery.

	Total hip replacement		Total knee replacement		P-value
Time since surgery	Events	Adj. HR (95% CI) *	Events	Adj. HR (95% CI) *	†
< 2 weeks	102	6.02 (4.06-8.92)	19	2.30 (1.17-4.54)	0.03
2 - 6 weeks	150	4.31 (3.27-5.68)	24	2.31 (1.27-4.19)	0.07
7 - 12 weeks	91	2.39 (1.79-3.20)	10	0.77 (0.37-1.60)	0.01
4 - 6 months	80	1.01 (0.78-1.31)	24	0.76 (0.47-1.21)	0.52
7 - 12 months	130	1.03 (0.85-1.26)	31	0.72 (0.48-1.07)	0.14
≥ 1 year	505	0.90 (0.82-0.99)	106	0.60 (0.49-0.75)	<0.01

Abbreviations: Adj, adjusted; CI, confidence interval; GI, gastrointestinal; H2, histamine-2; HR, hazard ratio; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors; THR, total hip replacement; TKR, total knee replacement.
* Adjusted for GI bleeding, and non-bleeding ulcers ever before, and use of NSAIDs, SSRIs, antithrombotic agents, systemic glucocorticoids, PPIs, and H2 receptor antagonists in the previous 6 months.
† P values represent statistical differences in risk of GI bleeding between THR and TKR patients.

FIGURE 2.3.1 | Spline regression plot of time since THR / TKR surgery and the risk of gastro-intestinal bleeding among THR (solid line, dots) and TKR patients (dashed line, circles) compared to age- and gender-matched controls. HRs are adjusted for confounders as shown in Table 2.3.2. Abbreviations: Adj, adjusted; HR, hazard ratio; THR, total hip replacement; TKR, total knee replacement.

FIGURE 2.3.2 | Spline regression plot of time since THR surgery and the risk of gastrointestinal bleeding among THR patients compared to age- and gender-matched controls, stratified by current PPI use. HRs are adjusted for confounders as shown in Table 2.3.2. Abbreviations: Adj, adjusted; HR, hazard ratio; THR, total hip replacement; PPIs, proton pump inhibitors; TKR, total knee replacement.



During the first 6 weeks after surgery, we found a strong effect modification by current PPI use with THR surgery, but not with TKR surgery (Table 2.3.3, Figure 2.3.2). Within this time period after THR, PPI users had a significantly 74% lower excess risk of GI bleeding (adj. HR 2.38; 95% CI 1.50-3.76), as compared with subjects who had not recently used PPIs (adj. HR 6.27; 95% CI 4.81-8.18). This trend was not modified by current use of antiplatelet drugs / NSAIDs (data not shown). A higher daily dose or a higher cumulative dose of PPIs in the previous year (time-dependent) was not associated with a further reduction in risk of GI bleeding. A somewhat similar trend was seen with H2RA use, although the difference

did not reach statistical significance. Furthermore, we found a substantial rise in excess risk of GI bleeding with a higher age: the increase in GI bleeding risk was greatest with patients aged > 80 years (adj. HR 5.94; 95% CI 4.46-7.90), while the risk was no longer significantly elevated among patients who were younger than 60 years (adj. HR 1.58; 0.59-4.28). Among individuals who underwent THR surgery, 66.2% were diagnosed with osteoarthritis and 4.8% had a hip fracture (29.0% other / unknown indication). Those with traumatic hip fracture had a higher excess risk of GI bleeding during the first 6 weeks (adj HR 7.26, 95% CI 5.57-9.47), as compared to individuals with osteoarthritis (adj HR 3.13, 95% CI 2.30-4.28). For individuals with osteoarthritis, there was no longer an increased risk beyond the first 6 weeks (6-52 weeks: adj HR 0.71, 95% CI 0.58-0.87), whereas the risk remained significantly increased in

TABLE 2.3.3 | Effect modifiers of GI bleeding risk following THR / TKR versus matched controls.

	Adjusted hazard ratio (95% confidence interval) *			
	Total hip replacement		Total knee replacement	
Effect modifier	< 6 weeks	6-52 weeks	< 6 weeks	6-52 weeks
All patients	5.07 (4.03-6.39)	1.19 (1.04-1.37)	2.44 (1.52-3.94)	0.67 (0.49-0.90)
By age				
40 - 59 years	1.58 (0.59-4.28)	1.19 (0.68-2.07)	-	0.68 (0.29-1.58)
60 - 79 years	4.22 (2.81-6.33)	0.93 (0.74-1.16)	2.49 (1.40-4.41)	0.73 (0.51-1.05)
≥ 80 years	5.94 (4.46-7.90)	1.41 (1.18-0.68)	2.96 (1.30-6.73)	0.51 (0.27-0.95)
By surgery indication				
Osteoarthritis	3.13 (2.30-4.28)	0.71 (0.58-0.87)	2.84 (1.53-4.04)	0.62 (0.45-0.85)
Hip / knee fracture	7.26 (5.57-9.47)	2.94 (1.81-4.76)	20.1 (2.67-150)	-
Other / unknown	4.36 (3.19-5.96)	1.71 (1.45-2.03)	1.75 (0.53-5.75)	1.11 (0.58-2.14)
By history of diseases ever before				
No previous GI bleeding	6.80 (5.32-8.69)	1.34 (1.16-1.55)	3.82 (2.18-6.68)	0.78 (0.56-1.07)
Previous GI bleeding	5.27 (2.67-10.4)	1.05 (0.69-1.59)	1.33 (0.48-3.72)	0.66 (0.29-1.47)
By use of acid suppressant drugs three months before				
No PPIs	6.27 (4.81-8.18)	1.16 (0.99-1.35)	2.15 (1.26-3.67)	0.74 (0.53-1.04)
PPIs	2.38 (1.50-3.76)	1.31 (0.99-1.73)	3.82 (1.41-10.4)	0.48 (0.26-0.87)
By cumulative DDDs in the year before †				
< 30 DDDs	0.79 (0.27-2.36)	1.19 (0.59-2.39)	-	0.23 (0.05-1.22)
31 - 180 DDDs	1.04 (0.48-2.28)	1.28 (0.74-2.21)	-	0.13 (0.03-0.59)
> 180 DDDs	6.58 (2.62-16.5)	1.18 (0.77-1.81)	-	0.44 (0.16-1.16)
By last prescribed daily dosis (omeprazole equivalents) †				
< 40 mg	3.27 (1.21-8.85)	1.82 (0.97-3.43)	-	0.15 (0.02-1.12)
≥ 40 mg	2.05 (1.16-3.65)	1.16 (0.82-1.64)	-	0.46 (0.20-1.02)
No H2RAs	5.25 (4.14-6.66)	1.22 (1.06-1.40)	2.61 (1.60-4.27)	0.64 (0.47-0.88)
H2RAs	2.65 (1.02-6.89)	0.68 (0.33-1.42)	0.65 (0.07-6.29)	0.96 (0.38-2.41)
By outpatient use of antithrombotic drugs 6 months before				
No outpatient use	5.69 (4.11-7.88)	1.22 (1.01-1.47)	2.11 (1.12-3.98)	0.63 (0.43-0.93)
VKA use only	9.79 (2.79-34.4)	0.56 (0.26-1.21)	0.98 (0.18-5.41)	0.19 (0.02-1.46)
Antiplatelet use only	4.32 (3.07-6.08)	1.27 (1.03-1.57)	5.97 (2.44-14.6)	0.83 (0.50-1.39)
Mixed / other use	2.83 (0.83-9.69)	0.56 (0.22-1.42)	0.27 (0.03-2.35)	0.49 (0.17-1.42)

Abbreviations: Adj, adjusted; DDD = daily-defined dosage, H2RA, histamine-2 receptor antagonist; THR, total hip replacement, VKA = vitamin K antagonist.
* Adjusted for confounders as shown in Table 2.3.2.
† Number of TKR patients exposed to PPIs was too low to further stratify into cumulative DDDs or daily dose.

those with hip fracture (adj HR 2.94, 95% CI 1.81-4.76). When we compared osteoarthritic THR patients directly to osteoarthritic TKR patients, we could not find any difference GI bleeding risk for any of the time interval (6-week GI bleeding adj. HR 1.15; 95% CI 0.78-1.70). We were not able to detect effect modification for any of the other investigated risk factors.

TABLE 2.3.4 | Determinants of GI bleeding within THR / TKR patients.

	Hazard ratio (95% confidence interval) *			
	Total hip replacement		Total knee replacement	
Determinant	< 6 weeks	6-52 weeks	< 6 weeks	6-52 weeks
By age (reference = 18 - 59 years)				
60 - 79 years	1.94 (0.97-3.90)	1.17 (0.73-1.89)	-	1.69 (0.78-4.65)
80+ years	4.95 (2.45-10.0)	2.34 (1.43-3.82)	-	2.41 (0.95-6.13)
Females (reference = males)	0.56 (0.43-0.73)	0.80 (0.62-1.02)	0.62 (0.34-1.16)	0.61 (0.37-1.01)
Previous GI bleeding	2.08 (1.35-3.20)	2.11 (1.41-3.14)	3.13 (1.21-8.11)	3.22 (1.41-7.34)
Non-bleeding ulcers	4.16 (2.87-6.03)	3.24 (2.27-4.62)	3.75 (1.57-8.97)	4.15 (2.00-8.64)
By use of drugs 6 months before (reference = no use)				
Non-selective NSAIDs	1.07 (0.81-1.41)	1.50 (1.18-1.92)	0.93 (0.50-1.71)	2.07 (1.23-3.47)
COX-2 selective NSAIDs	1.85 (1.27-2.70)	1.62 (1.12-2.34)	0.97 (0.37-2.51)	1.07 (0.46-2.49)
Loop diuretics	1.40 (1.05-1.87)	1.52 (1.17-1.97)	1.34 (0.62-2.91)	1.75 (0.95-3.22)
RAAS inhibitors	1.49 (1.11-1.99)	1.05 (0.78-1.42)	2.22 (1.16-4.23)	1.82 (1.06-3.12)
PPIs	0.75 (0.52-1.07)	1.47 (1.11-1.94)	1.32 (0.64-2.72)	0.93 (0.50-1.76)
H2RAs	1.07 (0.55-2.08)	0.93 (0.48-1.81)	0.57 (0.08-4.14)	3.40 (1.54-7.52)
By outpatient use of antithrombotic drugs 6 months before (reference = no use)				
VKA only	1.79 (1.00-3.22)	1.03 (0.50-2.11)	1.59 (0.36-7.04)	0.46 (0.06-3.38)
Antiplatelet drugs only	1.54 (1.16-2.04)	1.86 (1.44-2.41)	2.10 (1.04-4.23)	1.39 (0.75-2.57)
Mixed / other use	2.55 (1.17-5.56)	1.83 (0.80-4.21)	1.61 (0.21-12.5)	4.30 (1.55-11.9)

Abbreviations: HR, hazard ratio; CI, confidence interval; THR, total hip replacement; VKA, vitamin K antagonist.
* All covariates described in the methods section were entered into the full model; Table displays all statistically significant determinants.

Table 2.3.4 displays a selection of the potential determinants (before and after surgery, in a time-dependent manner) for GI bleeding within THR and TKR patients, stratified by time of follow-up. A higher age, male gender, previous GI bleeding, non-bleeding GI ulcers, use of COX-2 selective NSAIDs, loop diuretics, RAAS inhibitors, and outpatient antithrombotic use (regardless of type) were associated with a higher risk of GI bleeding during the first 6 weeks after THR. For TKR, we could only identify previous GI bleeding, non-bleeding GI ulcers, RAAS inhibitors, and antiplatelet drugs as significant determinants for risk of GI bleeding during the first 6 postoperative weeks.

Table 2.3.5 shows the 90-day cumulative incidence of GI bleeding for specific patient groups who underwent THR or TKR surgery. A 30-year old female with no history of GI bleeding who underwent THR surgery would have a 90-days GI bleeding risk of 0.1%. The risk increases to 1.0% if it concerned an 85-years old female. Adding a history of GI bleeding as a risk factor would further elevate the 90-day risk to 2.1%. If she was a male instead of a female, the 90-day risk would be further inflated to 3.7%.

TABLE 2.3.5 | Cumulative incidence of GI bleeding following THR / TKR surgery.

	90-day cumulative risk of GI bleeding (%)											
	Total hip replacement						Total knee replacement					
	Males			Females			Males			Females		
	Age (years):			Age (years):			Age (years):			Age (years):		
Determinant	18 - 59	60 - 79	80+	18 - 59	60 - 79	80+	18 - 59	60 - 79	80+	18 - 59	60 - 79	80+
All patients	0.3	0.4	1.4	0.1	0.3	1.0	<0.1	0.3	0.4	-	0.1	0.3
History of GI bleeding												
No	0.2	0.3	1.4	0.1	0.3	1.0	-	0.3	-	-	0.1	0.2
Yes	2.3	2.4	3.7	1.5	2.5	2.1	-	1.6	-	-	0.5	3.3
Use of NSAIDs in the previous 6 months												
No	0.2	0.3	1.3	0.1	0.3	0.8	-	0.2	0.1	-	0.1	0.1
Yes	0.3	0.6	1.9	0.1	0.4	1.5	-	0.5	0.9	-	0.2	0.6
Outpatient use of anticoagulants in the previous 6 months												
None	0.2	0.3	1.4	-	0.2	0.9	-	0.2	0.3	-	0.1	0.3
VKAs	1.5	0.3	2.1	-	0.8	1.3	-	0.6	1.3	-	-	-
Antiplatelets	0.7	0.5	1.5	-	0.6	1.1	-	0.5	0.5	-	0.3	0.4
Combined	1.5	0.9	1.9	-	0.5	1.0	-	1.3	-	-	-	-

Abbreviations: GI = gastrointestinal, NSAID = non-steroidal anti-inflammatory drug, VKA = vitamin K antagonist.

DISCUSSION

The risk of GI bleeding was increased 6.0-fold during the first 2 weeks after THR, and 2.3-fold during the first 2 weeks after TKR, both compared with matched control subjects who did not have surgery. Outpatient antithrombotic treatment (before and after surgery) did not significantly influence risk of GI bleeding. The risk remained elevated for 12 weeks after THR, while after TKR, risk of GI bleeding reached baseline levels after 6 weeks following surgery. Furthermore, during the first 6 weeks after THR surgery, current use of PPIs significantly lowered the HR for GI bleeding by 74%, as compared to subjects not taking PPIs, regardless of co-medication of outpatient antiplatelet drugs or NSAIDs. The excess risk of GI bleeding following THR rose with a higher age and was higher for those with traumatic hip fracture as compared to individuals with osteoarthritis.

This is the first study that compared rates of GI bleeding in THR / TKR patients with age-sex matched controls. Our findings are in line with evidence from clinical trials, which reported an increased rate of major clinical bleedings.[5-7] However, these trials were subject to a limited time of follow-up (at most for 35 days after surgery), and aggregated GI bleedings together with other major bleedings, which makes it difficult to compare rates of haemorrhages in the GI tract. Moreover, these trials often had strict inclusion and exclusion criteria. These major orthopaedic surgeries have substantial benefits in the treatment of osteoarthritis. Therefore, the procedures are now performed in patients who were not included in these original clinical trials.[20] This is confirmed by our finding of a mean age of 72 years at THR surgery, which was

10 years older than the patients in the RCTs by Eriksson et al and Kakkar et al.[5,6] The difference in age at surgery may suggest that clinical trials potentially underestimate these rates, as compared to true rates in real life: our results demonstrated an excess risk of GI bleeding briefly after THR surgery, which further increased with age.

We found a difference in the magnitude and duration of GI bleeding risk between THR and TKR surgery. This may partially be driven by some patients having THR surgery for traumatic hip fracture (rather than elective surgery). These patients may have more comorbid conditions, are more frequent drug users, and mobilize less faster, which may all have contributed to the increased risk of GI bleeding following THR surgery. Osteoarthritic THR patients had an excess and duration of GI bleeding risk that closely resembled TKR surgical patients. This further implies that comorbid conditions in patients with hip fracture may partially have driven the difference in GI bleeding risk patterns between THR and TKR surgery.

Our results emphasize the need for fine-tuning individualized antithrombotic treatment in terms of target dose, type of agent, and length of therapy in patients undergoing THR / TKR. This requires validated clinical risk scores to estimate an individual's risk for both VTE and GI bleeding. Currently, guidelines do not differentiate between high or low risk patients. For example, the American ACCP and British NICE guidelines recommend anticoagulant treatment for a period of at least 10 days in all patients undergoing THR / TKR (with LMWHs, vitamin K antagonists, dabigatran, fondaparinux or rivaroxaban), regardless of the individual's risk profile.[4,21] According to these guidelines, the duration of treatment may be extended to up to 35 days, but data is lacking to determine which specific patients should be candidates for this prolonged treatment.

The causation of GI bleeding following THR / TKR surgery is complex. Our results suggest a direct effect of in-hospital antithrombotic use (and any prolonged outpatient drug use that may have been dispensed by the hospital pharmacy) as the excess risk was not caused by concomitant NSAID use (or any other drug that has been associated with a higher risk for GI bleeding). However, the majority of these patients received subcutaneous LMWHs while in hospital,[22] which, in general, are not associated with an increased risk of GI bleeding. A meta-analysis of 33 randomized controlled trials showed that GI bleeding incidence is rare with LMWH use, and is not higher as compared with placebo injections.[23] The mean age of patients in the systematic review was, however, relatively low (59 years), and the results therefore do not necessarily apply to older individuals. A Spanish study evaluating risk factors for major bleeds in patients aged ≥ 80 years old found a 2-fold increased risk of major bleeds with long-term LMWH therapy.[24] As our patients were older at time of surgery (mean age 72 years for THR and 67 for TKR) compared to individuals in the systematic review, they may reflect a population that is more susceptible to GI bleeding caused by LMWHs. Moreover, concomitant use of NSAIDs may potentiate the detrimental effect of LMWHs on bleeding,[25] although our results do not directly support this hypothesis. The lack of short-term association with NSAIDs may be because of the following reasons: (1) postoperative NSAID use in the first

2 weeks is likely to be very high which limits the possibility of showing an excess risk related to concomitant NSAID use, (2) some patients may have used NSAIDs over-the-counter for which we did not have information, and (3) those with a high risk of GI bleeding may have been put on acetaminophen or opioids instead of NSAIDs. Outpatient aspirin users are likely to be switched over to prophylactic LMWH treatment regimens while hospitalized, which could explain the lack of observed effect modification with aspirin. A previous study reported a prevalence of anticoagulant use of 99.1% (primarily LMWH). This implies that virtually all surgical patients were on some type of thromboprophylaxis, which limits the evaluation of additional excess GI bleeding risk by outpatient anticoagulant use.

Our results demonstrate that PPIs may be beneficial in lowering risk of GI bleeding among patients undergoing THR. PPIs lower acid levels in the stomach, thereby optimizing the protective mucus function surrounding the gastric wall. Our finding is in line with a retrospective study in THR / TKR patients that found a significantly lower rate of GI bleeding in patients receiving low-dose aspirin and ranitidine, as compared with subjects that received low-dose aspirin only.[11] No other study evaluated the effect of acid suppressants in patients undergoing THR / TKR. Our findings are however indirectly supported by clinical trials that investigated use of PPIs in patients at increased risk of GI bleeding. For example, a meta-analysis revealed that PPIs are superior to both H2RAs and placebo in preventing rebleeding in patients with prevalent GI bleeding.[17] The potential benefit of PPIs in patients undergoing THR surgery should be confirmed in randomized controlled trials. Alternatively, the observed inverse association could have been the result of healthy user bias (i.e. those who adhere to PPI medication may be those who are more aware of their health and are in general healthier). We could not find a protective effect of PPI use in TKR surgical patients. This may be the result of confounding or the low number of events among individuals who underwent TKR surgery.

Major strengths of our study include the nationwide population-based design, large sample size, detailed information on matched controls, and completeness of follow-up. Access to outpatient prescription data enabled us to study the effect of PPIs, and adjust for commonly used drugs that are associated with GI bleeding (such as NSAIDs and antiplatelet drugs). In particular the time-dependent manner of adjustments is a major strength, as NSAID use typically decreases over time after THR / TKR surgery. For example, at time of surgery, 50.7% of THR patients were exposed to NSAIDs, whereas the proportion of NSAID use halved to 25.3% at one year after THR surgery. An important limitation is the lack of information on some important risk factors, such as over-the-counter NSAID use. However, most of these patients are diagnosed with osteoarthritis, and are more likely to be dispensed with a prescription from their physician. Furthermore, we could not assess in-hospital use of antithrombotic agents (and prolonged drug use that may have been dispensed by the hospital pharmacy), which would have been useful to assess different bleeding profiles between types of thromboprophylactic regimens. Previous Danish data showed that up to 99.1% of those undergoing THR / TKR received medical thromboprophylaxis, and that type of anticoagulant drug use is fairly homogenous: 92.9% of these patients received subcutaneous LMWHs.[22]

This study shows that risk of GI bleeding is substantially elevated during the first 2 weeks following THR (6.0-fold increase), and TKR (2.3-fold increase) surgery. The excess risk of GI bleeding disappeared after 12 weeks following THR, and after 6 week following TKR. The increase in GI bleeding risk was not influenced by current outpatient antithrombotic drug use, and PPIs lowered the 6-week risk of GI bleeding following THR, regardless of concomitant NSAID use. These results emphasize the importance of GI bleeding risk assessment, fine-tuning in-hospital antithrombotic therapy, and the potential benefit of prescribing PPIs.

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CHAPTER 2.4

Timing of stroke in patients undergoing total hip replacement and matched controls: a nationwide cohort study

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ABSTRACT

BACKGROUND: Stroke is a potentially fatal complication of total hip replacements (THR). However, timing of stroke in THR patients compared with matched controls and influence of drug use remain unknown. The objective of this study was to determine timing of stroke in patients with THR compared with matched control subjects.

METHODS: A nationwide cohort study was conducted within the Danish registers (1998-2007). Included patients were those with a primary THR in the study period (n=66,583), and were matched by age, sex, and region to three referent subjects without THR or total knee replacements. Time-dependent cox models were used to derive hazard ratios (HR), and were adjusted (adj.) for disease history and drug use.

RESULTS: A 4.7-fold increased risk of ischaemic stroke (adj. HR 4.69; 95% CI 3.12-7.06), and a 4.4-fold increased risk of haemorrhagic stroke (adj. HR 4.40; 95% CI 2.01-9.62) were found within 2 weeks following THR, compared with matched controls. The risk remained elevated during the first 6 postoperative weeks for ischaemic stroke, and the first 12 weeks for haemorrhagic stroke. Outpatient antiplatelet drug use lowered the 6-week HR for ischaemic stroke by 70%, while not affecting risk of haemorrhagic stroke.

CONCLUSIONS: This study shows, that THR patients have a 4.7-fold increased risk of ischaemic stroke, and a 4.4-fold increased risk of haemorrhagic stroke during the first 2 weeks post-surgery. Risk assessment of stroke in individual patients undergoing THR (i.e. evaluate other risk factors for stroke) should be considered during the first 6 to 12 weeks.

INTRODUCTION

Stroke is a major cause of death and long-term disability in most industrialized populations.[1] The majority of these events occur among patients older than 75 years of age, and incidence rates of stroke are increasing given the ageing of the population.[1,2] Stroke has been recognized as a serious perioperative complication after total hip replacements (THR).[3] These orthopaedic procedures effectively reduce pain and increase quality of life in patients with moderate to severe osteoarthritis.[4] Epidemiological studies demonstrated perioperative stroke incidence rates of as high as 0.6%.[3,5-8] This complication has become of particular interest, given the fact that THRs are performed in large numbers (approximately one million annually worldwide) and the surgery is offered to older patients more often.[9,10]

Although incidence rates of perioperative stroke following THR have been described reasonably well, the rates have not been compared with control subjects who did not have

surgery. Furthermore, the timing of these events has not been thoroughly evaluated, in particular the period after THR discharge. None of the previous studies were able to evaluate effect modification by comorbidities and drug use. This is of particular interest, as THR patients widely use pain relievers, which have been associated with both an increased and decreased risk of stroke.[11-13] Other drugs that may be associated with a decreased or increased risk of stroke include antiplatelet drugs, anticoagulants, statins, thiazide diuretics, estrogen containing drugs, selective serotonin reuptake inhibitors (SSRIs), and antipsychotics.[1,14-18] Its use in THR patients in relation with perioperative stroke, however, remains unknown.

The objectives of this study were to evaluate timing of stroke after THR compared with matched control subjects who did not have surgery, and to assess effect modification by comorbidities and drug use.

METHODS

DATA SOURCES

We carried out a nationwide retrospective cohort study using Danish national registries. These registries include all 5.5 million Danish residents, and contain detailed information on hospitalizations (including emergency room visits), outpatient clinic visits, drugs sold at retail pharmacies, vital status, date / cause of death (underlying cause, and up to three additional immediate causes), geographical residence, migration status, and socioeconomic status. The Danish national registries have been the source of numerous recent epidemiological studies, and previous studies have reported high completeness and validity.[19] Positive predictive values of 81% to 86% have been demonstrated for stroke in the Danish national registries.[20]

STUDY POPULATION

All patients aged ≥ 18 years old who had undergone a primary THR (International Classification of Diseases, ICD, 10th revision: ICD10 procedure codes NFB.XX) between January 1, 1998, and December 31, 2007 were included in the study cohort. Patients with primary or secondary knee replacement (TKR) during the study period were excluded. The date of hospital admission for the primary THR was defined as the index date. Each THR patient was matched to three control subjects by year of birth, gender, and geographical location, and had not undergone a primary or secondary THR / TKR at any time during the study period. Control subjects were assigned the same index date as their matched THR patient. Patients with a record for stroke within 6 weeks before the index date were excluded.

OUTCOME ASSESSMENT

All patients were followed up from the index date until death, migration, THR revision, end of study period (December 31, 2007), or stroke, whichever came first. Stroke was assessed using the National Hospital Discharge Register and the Danish Registry of Causes of Death (both classified using ICD10 codes: haemorrhagic stroke I60-I62, ischaemic stroke I63, unspecified stroke I64). In Denmark, almost all hospitalized individuals suspected of stroke undergo at

least computed tomography [CT] (and in many cases magnetic resonance imaging [MRI]) within 24 hours (due to national requirements). For deceased individuals, the diagnosis will be made postmortem using imaging techniques. To assess the potential for diagnosis recording bias (i.e. a higher recording rate shortly after THR), we additionally followed all patients for cancer (which should yield a hazard ratio [HR] close to 1; ICD10 codes C).

POTENTIAL RISK FACTORS

Total follow-up time was divided into 6-week periods, and for the first 6 weeks into 1-week periods. Risk factors considered at baseline (i.e. before surgery) in this study included sex, socioeconomic status, indication for surgery, and a history of cerebrovascular disease (ICD10-codes I60-I69, including carotid stenosis / occlusion), heart failure, atrial fibrillation, malignancies, and falls ever before.[1,14] Age and current drug use was assessed in a time-dependent manner (before and during follow-up), i.e. age was calculated at the start of each 6-week interval, and drug prescribing was evaluated in the 6 months before the start of each 6-week interval. We chose an exposure window of 6 months, because this is likely to reflect current use (in Denmark, drugs are generally prescribed for 3 months, and most of these drugs are used on a chronic basis). Drugs that were assessed using this time-dependent approach included: pain relievers (stratified by drug type: paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], and opioids [tramadol or stronger]), estrogen-containing drugs, antithrombotic agents (stratified by type: vitamin K antagonists [e.g. warfarin], antiplatelet drugs [e.g. low-dose aspirin], and others [e.g. enoxaparin]), systemic corticosteroids, antipsychotics, SSRIs, tricyclic antidepressants (TCAs), statins, thiazide diuretics, organic nitrates, beta blockers, renin angiotensin aldosterone system (RAAS) inhibitors, loop diuretics, calcium channel blockers, and oral antidiabetics / insulin.[14,15,17]

STATISTICAL ANALYSIS

Disease and drug use adjusted hazard ratios (HRs) for stroke were derived among THR patients versus age- and gender-matched control subjects (SAS 9.2). Potential confounders were included in the final model if they independently changed the beta coefficient for THR / TKR by at least 5% (i.e. change-in-estimate method using univariate analyses).[21]

Timing patterns were evaluated using time interaction terms (time period * surgery) into the Cox model. HRs were estimated for the following time periods: < 2 weeks, 2 – 6 weeks, 7 – 12 weeks, 4 – 6 months, 7 – 12 months, and ≥ 1 year after surgery. Smoothing spline regression was used to visualize the time trend of stroke following THR in the first postoperative year.[22-25] The 6-week relative risk was stratified by the presence of risk factors to determine effect modification. This study was approved by the National Board of Health and the Danish Data Protection Agency.

RESULTS

Baseline characteristics of THR patients (n = 66,583), and age- and gender-matched control

subjects (n = 199,995) are shown in Table 2.4.1 (after exclusion of 102 patients with a stroke event in the 6 weeks before or on the index date, or without at least one day of follow-up). For both patients and controls, the mean age was 71.9 years, and 36.9% of the study population was male. Within each matched set, THR patients and matched controls were of same sex, exact same age, and originated from the same geographical region. In general, THR patients and controls were comparable in terms of socioeconomic status and comorbidities, although THR patients were slightly more likely to have used cardiovascular drugs, and had a modestly higher prevalence of prior cerebrovascular disease. Pain reliever use was substantially more frequent among THR patients as compared with matched controls.

TABLE 2.4.1 | Baseline characteristics of THR patients and matched controls.

Characteristic	THR patients n = 66,583	Controls n = 199,995
Mean follow-up time (years, SD)	3.9 (2.8)	4.1 (2.7)
Males	36.9%	36.9%
Mean age (years, SD)	71.9 (12.5)	71.9 (12.5)
Mean THR hospital stay (days, SD)	10.8 (9.4)	
Disease history (ever before, unless specified otherwise)		
Cerebrovascular disease	7.7%	6.4%
Carotid stenosis / occlusion	0.5%	0.4%
Stroke	0.7%	0.6%
Drug use (within 6 months before)		
NSAIDs	50.7%	16.4%
SSRIs	11.0%	7.4%
Antidiabetics	5.6%	5.5%
Beta blockers	13.3%	12.1%
RAAS inhibitors	19.1%	16.6%
Thiazide diuretics	17.9%	14.2%
Statins	8.7%	8.7%
Vitamin K antagonists	3.3%	3.0%
Antiplatelet drugs	22.4%	20.9%

Values are means or percentages (among THR patients or controls), unless stated otherwise.
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone-system; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; THR, total hip replacement.

TABLE 2.4.2 | Risk of stroke following THR surgery versus age- and gender-matched controls, stratified by type of stroke and time after surgery.

Time since	Ischaemic stroke		Haemorrhagic stroke		P value
THR surgery	Rate *	Adj. HR (95% CI) †	Rate *	Adj. HR (95% CI) †	‡
< 2 weeks	26 v 5.6	4.69 (3.12-7.06)	6.7 v 1.6	4.40 (2.01-9.62)	0.917
2 - 6 weeks	14 v 6.2	2.12 (1.53-2.93)	3.8 v 1.7	2.16 (1.14-4.06)	0.909
7 - 12 weeks	7.0 v 5.7	1.12 (0.80-1.58)	4.3 v 1.7	2.17 (1.32-3.57)	0.025
4 - 6 months	6.4 v 5.7	1.06 (0.82-1.38)	3.1 v 2.0	1.45 (0.99-2.13)	0.147
7 - 12 months	5.4 v 5.9	0.87 (0.71-1.08)	3.1 v 2.4	1.26 (0.95-1.68)	0.035
≥ 1 year	5.6 v 5.8	0.82 (0.75-0.90)	2.4 v 2.5	0.81 (0.70-0.94)	0.788

Abbreviations: Adj, adjusted; HR, hazard ratio; CI, confidence interval; THR, total hip replacement; INR, international normalized ratio.
* Rates display the number of events per 1000 person years for THR patients versus matched controls.
† Adjusted for use of a history of cerebrovascular disease, and druge use of NSAIDs, antithrombotic agents, SSRIs, and warfarin interacting drugs / INR increasing drugs 6 months before.
‡ P value represents statistical difference between HRs for ischaemic and haemorrhagic stroke in each stratum of time since THR surgery.

FIGURE 2.4.1 | Spline regression plot of time since THR surgery and the risk of ischaemic (solid line, dots) and haemorrhagic (dashed line, circles) stroke among THR patients compared to age- and gender-matched controls. HRs are adjusted for confounders as shown in Table 2.4.2. Abbreviations: HR, hazard ratio; THR, total hip replacement.

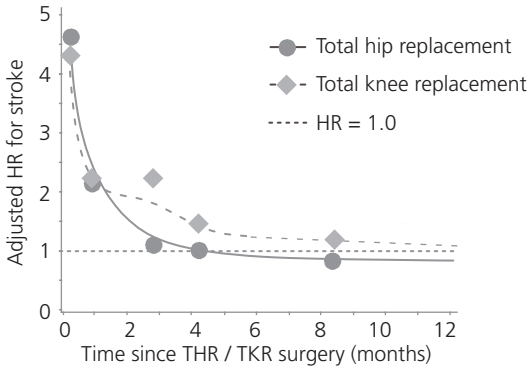

Table 2.4.2 and Figure 2.4.1 demonstrate a substantially increased risk of ischaemic stroke (adjusted [adj.] HR 4.69; 95% confidence interval [CI] 3.12-7.06), and haemorrhagic stroke (adj. HR 4.40; 95% CI 2.01-9.62) during the first 2 weeks after THR. This is probably not the result of higher diagnosis recording rates shortly after THR: for cancer, the HR during the first 2 weeks was 0.90 (95% CI 0.64-1.27). For both types of stroke, the risk dropped steadily afterwards, but remained significantly elevated during at least the first 6 postoperative weeks for ischaemic stroke, and the first 12 weeks for haemorrhagic stroke. The association tended to be stronger for fatal events, although this difference did not reach statistical significance (Table 2.4.3).

TABLE 2.4.3 | Risk of stroke during the first 6 weeks following THR, stratified by type of stroke.

	Rate *	Adj. HR (95% CI) †
Ischaemic stroke	22 v 7.0	3.13 (2.46 - 3.97)
Non-fatal events	19 v 6.5	2.84 (2.22 - 3.63)
Fatal events	2.1 v 0.5	3.91 (1.71 - 8.91)
Haemorrhagic stroke	5.6 v 2.0	2.91 (1.84 - 4.60)
Non-fatal events	4.0 v 1.5	2.19 (1.31 - 3.64)
Fatal events	1.6 v 0.5	3.34 (1.36 - 8.22)
Intracerebral	3.4 v 0.9	3.69 (1.96 - 6.92)
Subdural	2.2 v 0.6	4.04 (1.84 - 8.91)
Subarachnoid	0.0 v 0.4	-
Epidural	0.0 v 0.1	-
Unspecified stroke	36 v 10	3.55 (2.94 - 4.30)

Abbreviations: Adj, adjusted; HR, hazard ratio; CI, confidence interval; THR, total hip replacement.
* Rates display the number of events per 1000 person years for THR patients versus matched controls.
† Adjusted for confounders as shown in Table 2.4.2.

Table 2.4.4 shows that current outpatient antiplatelet drug use substantially lowered the 6-week HR for ischaemic stroke (70% decrease, calculated as a synergy index, i.e. 1-RR1 / 1-RR2). These results did not change when we used an exposure time window of 2 weeks (adj. HR 2.08; 95% CI 0.95-5.06) instead of the original 6 months (adj. HR 1.81; 95% CI 1.24-2.66). Among THR patients using aspirin, 15.7% were concomitantly using ibuprofen

(adj. HR 2.37; 95% CI 0.22-26.2), 29.9% were on any other NSAID (adj. HR 1.46; 95% CI 0.56-3.79), but the association was not stronger as compared to aspirin users who did not concomitantly use NSAIDs (adj. HR 2.46; 95% CI 1.55-3.91). Antiplatelet users were in general less healthy than non-users, and this could therefore not explain the seemingly protective effect (Table 2.4.5). No other effect modification was observed for any of the other investigated covariates (including pain relievers, statins, thiazide diuretics, antipsychotics, and SSRIs). For haemorrhagic stroke, statistical power was too low to detect significant effect modification.

TABLE 2.4.4 | Effect modifiers of the 6-week stroke risk following THR versus matched controls.

Effect modifier	Ischaemic stroke Adj. HR (95% CI) *	Haemorrhagic stroke Adj. HR (95% CI) *
All patients	2.78 (2.18-3.56)	3.00 (1.81-4.96)
By THR surgery indication		
Osteoarthritis	2.20 (1.21-3.98)	-
Hip fracture	4.59 (0.64-33.1)	-
Multiple / other indications	2.35 (1.57-3.50)	-
By history of diseases ever before, unless stated otherwise		
No previous stroke	3.35 (2.49-4.52)	3.73 (2.04-6.79)
Previous stroke	3.82 (2.31-6.32)	2.76 (1.11-6.84)
No carotid stenosis / occlusion	2.69 (1.95-3.73)	-
Carotid stenosis / occlusion	3.00 (0.31-28.8)	-
By use of drugs 6 months before		
Statins No	3.02 (2.31-3.95)	3.02 (1.79-5.10)
Yes	1.87 (1.03-3.40)	2.77 (0.55-13.9)
By outpatient use of antithrombotics		
No outpatient use	3.73 (2.65-5.24)	2.53 (1.34-4.79)
Vitamin K antagonist use only	3.78 (1.41-10.2)	5.76 (0.52-63.6)
Antiplatelet drug use only	1.81 (1.24-2.66)	3.72 (1.62-8.58)
Mixed / other use	-	-

Abbreviations: Adj, adjusted; HR, hazard ratio; CI, confidence interval; THR, total hip replacement.
* Adjusted for confounders as shown in Table 2.4.2.

DISCUSSION

This nationwide study demonstrated a substantially increased risk of ischaemic (4.7-fold) and haemorrhagic stroke (4.4-fold) during the first 2 weeks after THR. The risk remained significantly elevated for at least the first 6 postoperative weeks for ischaemic stroke, and the first 12 weeks for haemorrhagic stroke. Furthermore, current outpatient antiplatelet drug use reduced the 6-week HR for ischaemic stroke by 70%.

To the best of our knowledge, this is the first study that evaluated risk of stroke in THR patients compared with matched controls who did not undergo surgery. Previous epidemiological studies have not compared rates to that in control subjects, and the majority took only perioperative periods into consideration.[3,5-8] For example, Bateman and colleagues reported a perioperative stroke rate of 0.2% among 201,235 American THR patients.[3] In line with our findings, the two studies that looked beyond discharge as well, showed a 1-year incidence rate of as high as 1.5% (compared with 1.4% in our study).[5,7]

TABLE 2.4.5 | Baseline characteristics of THR patients and matched controls, stratified by antiplatelet drug use.

	THR patients, n = 66,583		Controls, n = 199,995	
Characteristic	Antiplatelets n = 14,889	No antiplatelets n = 51,694	Antiplatelets n = 41,868	No antiplatelets n = 158,127
Mean follow-up time (years, SD)	3.8 (2.8)	3.9 (2.8)	4.0 (2.7)	4.1 (2.7)
Males	35.9%	37.2%	36.3%	37.1%
Mean age (years, SD)	77.7 (9.4)	70.3 (12.8)	78.2 (9.1)	70.3 (12.8)
Mean THR hospital stay (days, SD)	11.5 (10.4)	10.7 (9.2)		
Disease history (ever before, unless specified otherwise)				
Cerebrovascular disease	21.9%	3.5%	20.4%	2.7%
Stroke	1.0%	0.6%	0.8%	0.5%
Drug use (within 6 months before)				
NSAIDs	45.5%	52.2%	19.2%	15.7%
SSRIs	17.7%	9.0%	12.9%	6.0%
Antidiabetics	10.6%	4.1%	11.1%	4.0%
Beta blockers	26.7%	9.4%	27.6%	8.0%
RAAS inhibitors	32.7%	15.2%	33.8%	12.0%
Thiazide diuretics	25.4%	15.7%	24.0%	11.7%
Statins	23.3%	4.5%	25.0%	4.3%
Vitamin K antagonists	3.6%	3.3%	3.2%	2.9%

Values are means or percentages, unless stated otherwise. Abbreviations: THR, total hip replacement; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

The underlying mechanism for the increased risk of stroke shortly after THR is thought to be related to cerebral hypoperfusion and marrow embolization. Intraoperative hypotension may result into hypoperfusion, and the decreased blood flow may slow down the washout of embolic material in the cerebral blood vessels.[26] Marrow embolization may be caused by surgical invasion of the medullary canal of the femur, as shown previously.[27,28] In particular individuals with right-to-left shunts may be at increased risk, as these shunts may facilitate the entrance of larger fat particles into the systemic circulation.[29] Furthermore, intraoperative arrhythmias and effects of anaesthesia on the cardiovascular system may further explain the increased risk of stroke following THR.[6]

This study shows a potential beneficial effect of antiplatelet drugs on ischaemic stroke occurrence in patients undergoing THR. Patients who had currently used antiplatelet drugs experienced a 70% reduction in HR of ischaemic stroke during the first 6 weeks after THR, compared with subjects who had not been dispensed any antithrombotic agent. Antiplatelet drugs, such as low-dose aspirin, are widely used for secondary prevention of ischaemic stroke, and its benefits have been demonstrated in several randomized controlled clinical trials.[30] A meta-analysis revealed a 15% risk reduction of any secondary stroke event with aspirin, and the magnitude of benefit was consistent among doses between 50 and 1500 mg / day.[30,31] Randomized clinical trials should further investigate our finding of a potential beneficial effect in patients who require THR surgery.

The nationwide population-based design, large sample size, detailed information on matched controls, and completeness of follow-up are the major strengths of this study. We had access to outpatient prescription data, which is particularly important given the relationship of the

widely used NSAIDs (the majority of our THR patients) and stroke. Furthermore, we had the ability to differentiate between haemorrhagic and ischaemic stroke. An important limitation is the lack of information on body mass index (BMI), since a higher BMI is associated with an increased risk of stroke[32,33] and osteoarthritis[34] – the main indication for THR. However, the relationship between body mass index and osteoarthritis seems to be stronger for knee osteoarthritis, and a large cohort study could not demonstrate a relationship with hip osteoarthritis.[35] Furthermore, we could not assess in-hospital use of antithrombotic agents. Previous Danish data have shown that up to 99.1% of those undergoing THR / TKR received medical thromboprophylaxis (primarily subcutaneous low-molecular-weight heparins [LMWHs]).[36] Several authors proposed that LMWHs may lower risk of stroke,[18] although a meta-analysis could not confirm this beneficial effect.[37] We cannot exclude the possibility of ascertainment or recording bias towards the diagnosis of stroke soon after THR. However, we could not find an increased risk of cancer during the first 2 weeks, which implies that the presence of this Berkson-type bias is unlikely. Unfortunately, we were not able to differentiate between lacunar and territorial infarctions, which may well have different rates following THR. Controls were not chosen from hospitalization or other surgery. The increased risk of stroke may therefore not be exclusive for THR only, but may apply to other surgeries or hospitalizations as well.

This study showed an increased risk of ischaemic (4.7-fold) and haemorrhagic stroke (4.4-fold) during the first 2 weeks after THR surgery. The risk remained significantly elevated for at least 6 weeks for ischaemic stroke and 12 weeks for haemorrhagic stroke. Current use of antiplatelet drugs lowered the increased risk of ischaemic stroke by 70% during the first 6 weeks. This seemingly protective effect should be interpreted with caution, given the observational design and the lack of information on inpatient antithrombotic use. Risk assessment of stroke in individual patients undergoing THR (i.e. evaluate other risk factors for stroke) should be considered during the first 6 to 12 weeks.

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CHAPTER 2.5

The pattern of risks over time and secular trends of cardiovascular outcomes following total hip or knee replacement: a British population based cohort study

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Submitted.

ABSTRACT

BACKGROUND: Cardiovascular events are severe potential complications following total hip (THR) and knee (TKR) replacements. The objectives of this study were to assess timing patterns of cardiovascular events following THR/TKR and to evaluate secular trends of these events over the past 25 years.

METHODS: In this British retrospective cohort study, we selected 130,790 THR/TKR surgical patients (January 1987 – October 2012), and an equal number of control patients without surgery (matched by year of birth, sex, and practice). Using Cox regression, we estimated the risk of cardiovascular events (acute myocardial infarction [AMI], venous thromboembolism [VTE], stroke, and gastrointestinal [GI] bleed) following THR/TKR, compared to matched controls.

RESULTS: During the first 2 weeks following THR, risk of VTE (HR 38.9, 95% CI 17.2-88.0), AMI (HR 4.11, 95% CI 2.35-7.18), stroke (HR 2.11, 95% CI 1.40-3.19), GI bleed (HR 5.00, 95% CI 2.34-10.7) were substantially elevated. Most of these excess risks diminished within a few weeks, with the exception of VTE (which persisted even beyond the first postoperative year). Trends were similar for TKR surgery, although we could not find an elevated risk of stroke. Sixty-day rates of VTE had declined by 64% in 2008-2012 compared to 1987-1991.

CONCLUSIONS: THR/TKR surgery briefly boosts the risk of cardiovascular events, while VTE risk remains significantly elevated even beyond the first postoperative year. Nevertheless, the substantial drop in VTE rates over the past 25 years – and relatively low absolute rates in the more recent years – are reassuring for patients undergoing THR/TKR surgery.

INTRODUCTION

Cardiovascular events are a major cause of morbidity and mortality worldwide.[1] In 2008, an estimated global number of 17.3 million patients died from cardiovascular diseases, of which 45% represented ischaemic heart disease (including acute myocardial infarction [AMI]), and 29% represented stroke.[2,3] It constitutes one of the most important potentially fatal outcomes following total hip (THR) and knee replacements (TKR). This surgical procedure is performed in approximately 1.8 million individuals worldwide each year,[4,5] and is considered a highly efficacious and safe operation in patients with moderate to severe osteoarthritis.[6] Nevertheless, haemodynamic stressors induced by the surgery may result into potentially fatal cardiovascular adverse outcomes, including AMI (up to 1.8% during the first 90 days),[7-13] VTE (up to 7.0% during the first 90 days),[14-20] and stroke (up to 0.6% peri-operatively).[21-24,11] To prevent in particular VTE, long-term thromboprophylaxis (mostly low-molecular-weight heparins [LMWHs] for 10-35 days) is now standard of care, but may subsequently increase the risk of gastrointestinal (GI) bleeds.[25-27]

Data on timing of the risks of cardiovascular adverse events following THR / TKR are scarce (i.e. when the risk is increased and when it returns to baseline risk levels). The only controlled evidence comes from a series of Danish nationwide cohort studies, which showed that rates of VTE were substantially increased during at least the first four months,[28] whereas risk of AMI,[29] stroke,[30] and GI bleed[31] was only briefly, but significantly, elevated during the first 2 weeks, compared to matched controls. The authors could, however, not adjust for important prognostic factors, such as body mass index and smoking status. No other study included a matched control cohort, which makes it difficult to interpret the magnitude and course of increased cardiovascular risk following THR / TKR compared with the general population.

As a further important knowledge gap, it is unclear how these rates for cardiovascular adverse events have developed over the past 25 years. Several surgical advances (e.g. a transition towards non-cemented implants) and pharmacological treatments (e.g. the widespread use of LMWHs) have been introduced over the course. Although this may have theoretically led to improved clinical outcome following THR / TKR, this has not been evaluated thoroughly. Therefore, the objectives of this study were to (1) evaluate the timing of cardiovascular adverse outcomes following THR / TKR surgery, and (2) to investigate secular trends of these adverse events over the past 25 years.

METHODS

DATA SOURCE

We conducted a retrospective cohort study using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD). CPRD collates the computerised medical records of general practitioners (GPs). The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987 [www.CPRD.com].

STUDY POPULATION

We selected all individuals aged 18+ years who had undergone primary THR / TKR surgery between 1 January 1987 and 31 October 2012 (CPRD READ codes). Patients with a previous AMI, VTE, stroke or GI bleed in the 6 weeks before surgery were excluded. To each THR / TKR patient, one control patient (no THR / TKR) was selected using incidence density sampling, and was matched by year of birth, sex, and GP practice. The index date for THR / TKR patients was the date of the surgery, and was similar for the matched control patient. All included patients were followed up from the index date until the end of data collection, date of transfer of the patient out of the practice area, the patient's death, a new primary TJR, or implant revision surgery, whichever came first.

OUTCOMES

In four separate analyses, the outcomes of interest were postoperative AMI, VTE, stroke,

and GI bleed (CPRD READ codes). The events were not mutually exclusive, e.g., in the analysis for AMI, patients were allowed to sustain other cardiovascular events before the first postoperative AMI occurrence.

COVARIATES

We reviewed the literature to identify risk factors for AMI, VTE, stroke, and GI bleed. Time-varying potential confounders were assessed in a time dependent manner, with the exception of sex, smoking status, body mass index, and alcohol use. For the time dependent approach, we divided total follow-up into 30-day intervals. Time dependent potential confounders were collected at the start of each time interval. These covariates included: age, a history of AMI (for in the previous year, and prior to that separately), other ischaemic diseases, heart failure, atrial fibrillation, GI bleeds, chronic obstructive pulmonary disease, malignancies, varicose veins, hypertension, hypercholesterolaemia, cerebrovascular disease, and drug use in the previous 6 months of the following agents: beta blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, thiazide diuretics, calcium channel blockers, organic nitrates, statins, non-selective non-steroidal anti-inflammatory drugs (NSAIDs, including high-dose aspirin), COX-2 selective inhibitors, antiplatelet drugs, vitamin K antagonists, estrogen containing drugs, antidiabetics, proton pump inhibitors, histamine-2 receptor antagonists, and inhaled beta-2 agonists. All variables were treated as categorical variables (including age and body mass index), and we used dummy indicator variables to account for missing data on smoking status, body mass index, and alcohol use.

STATISTICAL ANALYSIS

We calculated adjusted (adj.) rate ratios (RRs) for risk of AMI, VTE, stroke, and GI bleed following THR / TKR surgery versus matched controls using Cox proportional hazards models (PHREG procedure of SAS 9.2). Time interaction terms were included in the model to derive RRs for each specific period (surgery * time period; < 2 weeks, 2 – 6 weeks, 7 – 12 weeks, 4 – 6 months, 7 – 12 months, and ≥ 12 months after surgery. Timing of these cardiovascular events was visualized using smoothing spline regression.[32,33] In our secular calendar time trend analysis, we calculated the 60-day adverse outcome risk following THR / TKR (1992-1996, 1997-2002, 2003-2007, and 2008-2012), and compared these rates to those during 1987 and 1991. This was done using Cox proportional hazards models, and the analyses were fully adjusted for all potential confounders.

RESULTS

A total of 74,895 THR and 55,895 TKR patients were identified, along with an equal number of age- and sex-matched controls (Table 2.5.1). Due to matching, there were no substantial differences between THR/TKR patients and matched controls in age (mean age THR 70.3 years, TKR 69.7 years) and sex (proportion females THR 63.2%, TKR 57.6%). On average, THR patients had a mean follow-up time of 5.5 years, and TKR patients were followed for a mean time of 5.2 years. Overall, THR / TKR patients and matched controls were similar in terms of

smoking status, disease history and medication use. TKR patients had a slightly higher BMI at baseline (29.9 kg/m2) compared to matched controls (26.9 kg/m2). Furthermore, both THR and TKR patients were more likely to have used NSAIDs in the 6 months before surgery.

TABLE 2.5.1 | Baseline characteristics of THR / TKR patients and matched control subjects.

	THR surgery		TKR surgery	
Characteristic	THR n = 74,895 (%)	No THR n = 74,895 (%)	TKR n = 55,895 (%)	No TKR n = 55,895 (%)
Follow-up (mean, y [SD])	5.6 (4.3)	5.3 (4.2)	5.4 (3.9)	4.9 (3.8)
Age (mean, y [SD])	70.3 (11.9)	70.3 (11.9)	69.7 (9.6)	69.7 (9.6)
Females (%)	63.2	63.2	57.6	57.6
Body mass index (mean,kg/m^2 [SD])	27.1 (5.1)	26.6 (5.1)	29.5 (5.3)	26.9 (5.1)
< 20.0 kg/m^2	5.0	5.6	1.5	4.8
20.0 – 24.9 kg/m^2	26.8	29.6	16.5	29.0
25.0 – 29.9 kg/m^2	34.8	33.0	37.2	34.7
≥ 30.0 kg/m^2	23.4	19.0	39.2	21.0
Outpatient drug use in the previous 6 months (%)				
VKA use	3.4	3.4	3.4	3.5
Antiplatelet use	21.4	21.1	23.3	21.9
NSAIDs	48.0	17.4	52.8	17.5
Beta blockers	15.6	14.4	17.5	15.2
Antidiabetics	5.3	6.4	7.4	7.2
Statins	20.1	19.9	27.1	26.6
Comordities (%)				
Ischaemic heart disease	13.2	13.9	14.3	14.2
Heart failure	3.9	4.2	3.2	3.7
Gastrointestinal bleed	2.2	1.8	2.3	1.6
Venous thromboembolism	2.6	1.8	3.0	1.7
Stroke (any type)	6.4	6.8	5.5	6.3

Abbreviations: NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation, THR = total hip replacement, TKR = total knee replacement, VKA = vitamin K antagonist.

Compared with matched controls, we found a substantially increased risk of VTE (adj. RR 38.9, 95% CI 17.2-88.0), AMI (adj. RR 4.11, 95% CI 2.35-7.18), stroke (adj. RR 2.11, 95% CI 1.40-3.19), and GI bleed (adj. RR 5.00, 95% CI 2.34-10.7) during the first 2 weeks following THR surgery (Table 2.5.2). The increased excess risk of VTE persisted even beyond the first postoperative year, whereas the risk of GI bleed was not significantly elevated after the first 12 weeks. For AMI, the excess risk lost its significance after the first 6 weeks, and for stroke, the risk was only significantly elevated during the first 2 weeks. Similar trends were found for TKR surgery, although we could not detect an increased risk of stroke.

As compared with the rate between 1987 and 1991, the 60-day risk of VTE following THR / TKR significantly decreased by 64% in 2008-2012 (Table 2.5.3, Figures 2.5.1A / 2.5.1B). Similar secular trends were observed for AMI and stroke, although these patterns failed to reach statistical significance. In contrast with the trends for these three cardiovascular events, the risk of GI bleed did not (tend to) decrease over the past 25 years.

TABLE 2.5.2 | Risk of adverse outcomes following THR/TKR surgery versus age- and sex-matched controls, stratified by time after surgery.

	Adjusted hazard ratio (95% confidence interval) * Time since THR / TKR surgery					
	< 2 weeks	2-6 weeks	7-12 weeks	4-6 months	7-12 months	≥1 year
Total hip replacement versus matched controls By adverse outcome						
Venous thromboembolism	38.9 (17.2-88.0)	28.8 (16.8-49.3)	11.6 (7.00-19.3)	4.29 (2.91-6.32)	1.55 (1.13-2.15)	1.39 (1.24-1.55)
[IR (per 1000 PYs)]	[92.3 vs 2.1]	[82.3 vs 2.5]	[27.4 vs 2.0]	[9.3 vs 1.8]	[3.6 vs 2.2]	[3.1 vs 2.0]
Acute myocardial infarction	4.11 (2.35-7.18)	2.63 (1.45-4.77)	1.58 (0.96-2.61)	0.77 (0.52-1.13)	1.04 (0.81-1.33)	1.10 (1.01-1.20)
[IR (per 1000 PYs)]	[24.4 vs 7.0]	[9.7 vs 3.5]	[6.2 vs 4.6]	[3.7 vs 4.7]	[5.1 vs 5.2]	[5.2 vs 4.8]
Stroke	2.11 (1.40-3.19)	1.01 (0.73-1.40)	0.93 (0.71-1.21)	1.10 (0.92-1.31)	0.90 (0.78-1.04)	1.05 (0.99-1.10)
[IR (per 1000 PYs)]	[23.7 vs 11.9]	[12.5 vs 12.7]	[12.4 vs 13.6]	[13.3 vs 12.4]	[11.0 vs 12.4]	[10.6 vs 10.2]
Gastrointestinal bleed	5.00 (2.34-10.7)	3.28 (1.87-5.74)	1.90 (1.12-3.22)	1.11 (0.76-1.62)	1.06 (0.80-1.41)	1.25 (1.14-1.37)
[IR (per 1000 PYs)]	[12.2 vs 2.8]	[9.5 vs 2.8]	[4.9 vs 2.5]	[3.2 vs 2.7]	[3.1 vs 2.7]	[3.0 vs 2.3]
Total knee replacement versus matched controls By adverse outcome						
Venous thromboembolism	24.0 (11.1-52.1)	19.4 (10.9-34.6)	10.5 (5.42-20.1)	2.35 (1.54-3.60)	2.26 (1.55-3.30)	1.52 (1.32-1.74)
[IR (per 1000 PYs)]	[99.2 vs 3.0]	[78.1 vs 3.1]	[22.7 vs 1.7]	[7.1 vs 2.9]	[5.4 vs 2.0]	[3.6 vs 1.8]
Acute myocardial infarction	5.78 (2.44-13.7)	1.88 (0.87-4.05)	1.58 (0.85-2.93)	1.23 (0.78-1.94)	1.09 (0.79-1.51)	1.09 (0.98-1.21)
[IR (per 1000 PYs)]	[26.2 vs 3.7]	[7.3 vs 4.5]	[5.7 vs 4.9]	[4.6 vs 4.7]	[4.8 vs 5.1]	[5.1 vs 4.7]
Stroke	1.12 (0.63-1.97)	0.64 (0.42-0.97)	1.14 (0.82-1.60)	0.73 (0.57-0.94)	0.89 (0.75-1.05)	1.09 (1.03-1.15)
[IR (per 1000 PYs)]	[10.7 vs 10.8]	[8.7 vs 13.9]	[11.4 vs 10.3]	[7.5 vs 10.4]	[9.5 vs 10.9]	[10.7 vs 9.7]
Gastrointestinal bleed	9.28 (2.82-30.5)	3.15 (1.54-6.47)	1.52 (0.84-2.77)	0.72 (0.46-1.13)	1.47 (1.00-2.14)	1.18 (1.05-1.32)
[IR (per 1000 PYs)]	[12.6 vs 1.4]	[7.3 vs 2.4]	[4.6 vs 2.9]	[2.5 vs 3.0]	]2.8 vs 1.7]	[3.1 vs 2.4]

Abbreviations: AMI = acute myocardial infarction, PY = person year, THR = total hip replacement, TKR = total knee replacement.

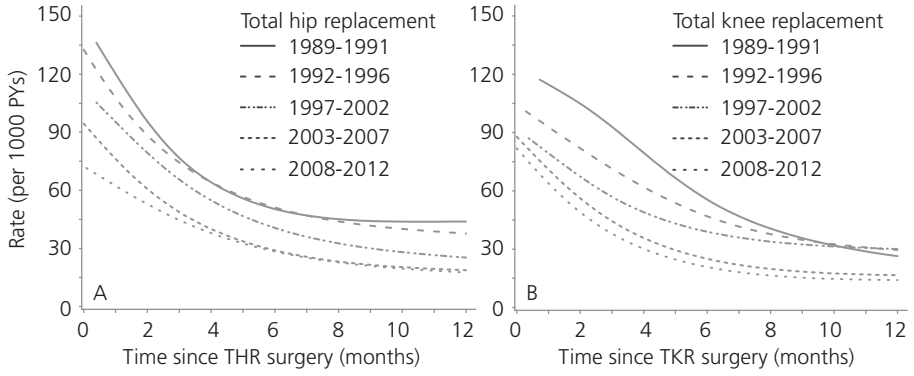
* Fully adjusted for age, sex, smoking status, body mass index, alcohol use, and indication for surgery, a history of AMI (for in the previous year, and prior to that separately), other ischaemic heart diseases, heart failure, atrial fibrillation, gastrointestinal bleeds, chronic obstructive pulmonary disease, malignancies, varicose veins, hypertension, hypercholesterolaemia, cerebrovascular disease, and drug use in the previous 6 months of the following agents: beta blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, thiazide diuretics, calcium channel blockers, organic nitrates, statins, non-selective non-steroidal anti-inflammatory drugs (NSAIDs, including high-dose aspirin), COX-2 selective inhibitors, antiplatelet drugs, vitamin K antagonists, estrogen containing drugs, antidiabetics, proton pump inhibitors, histamine-2 receptor antagonists, and inhaled beta-2 agonists.

TABLE 2.5.3 | Sixty-day risk of adverse outcomes following THR/TKR surgery versus matched controls, stratified by year of surgery.

	Adjusted 60-day hazard ratio (95% confidence interval) * Excess 60-day risk (THR/TKR vs controls) (%) Year of surgery				
	1987-1991	1992-1996	1997-2002	2003-2007	2008-2012
Total hip / knee replacement					
By adverse outcome					
VTE					
HR (vs 1987-1991)	1	0.62 (0.42-0.92)	0.56 (0.38-0.80)	0.45 (0.31-0.64)	0.36 (0.25-0.52)
Excess risk	2.3 (2.4 vs 0.1)	1.5 (1.6 vs 0.1)	1.4 (1.4 vs 0.0)	1.1 (1.2 vs 0.0)	0.9 (0.9 vs 0.0)
AMI					
HR (vs 1987-1991)	1	0.84 (0.25-2.84)	0.94 (0.29-3.02)	0.57 (0.18-1.85)	0.53 (0.16-1.74)
Excess risk	0.2 (0.2 vs 0.1)	0.1 (0.2 vs 0.2)	0.2 (0.3 vs 0.1)	0.1 (0.2 vs 0.1)	0.1 (0.2 vs 0.0)
Stroke					
HR (vs 1987-1991)	1	0.77 (0.30-1.99)	0.75 (0.30-1.85)	0.48 (0.20-1.18)	0.41 (0.17-1.02)
Excess risk	0.1 (0.4 vs 0.3)	0.0 (0.3 vs 0.3)	0.0 (0.3 vs 0.3)	0.0 (0.2 vs 0.2)	0.0 (0.2 vs 0.2)
GI bleeding					
HR (vs 1987-1991)	1	2.44 (0.33-18.4)	1.98 (0.27-14.5)	1.60 (0.22-11.7)	1.64 (0.22-11.9)
Excess risk	0.1 (0.1 vs 0.0)	0.1 (0.2 vs 0.1)	0.1 (0.2 vs 0.1)	0.1 (0.1 vs 0.0)	0.1 (0.1 vs 0.0)

Abbreviations: AMI = acute myocardial infarction, GI = gastrointestinal, THR = total hip replacement, TKR = total knee replacement, VTE = venous thromboembolism.
* Fully adjusted for confounders as shown in Table 2.5.2.

FIGURE 2.5.1 | Absolute incidence rates (per 1000 person years) of cardiovascular adverse outcomes (acute myocardial infarction, venous thromboembolism, gastrointestinal bleed, stroke) following (A) THR surgery and (B) TKR surgery, in relation with the time since THR / TKR surgery, stratified by year of surgery.



DISCUSSION

This study demonstrated that the risk of VTE (39-fold), AMI (4.1-fold), stroke (2.1-fold), and GI bleed (5.0-fold) was substantially increased during the first 2 weeks following THR surgery.

For TKR, similar excess risks were found, although the risk of stroke was not significantly elevated. The increased rate of VTE persisted even beyond the first year of surgery, while the occurrence of the other cardiovascular events diminished within a few weeks. Sixty-day rates of VTE have dramatically declined over the past 25 years. Similar secular trends were seen for AMI and stroke, although these did not reach statistical significance. No secular trend was observed for GI bleed.

In line with our findings, previous Danish nationwide cohort studies found a substantially increased risk of VTE, AMI, stroke, and GI bleed following THR / TKR surgery during the first 2 postoperative weeks.[28-31] This Danish study could, however, not adjust for some important prognostics factors (e.g. smoking status). This may partially explain the difference in magnitude of increased AMI risk between the Danish (25- to 31-fold increase) and the present study (4.1- to 5.8-fold increase). On one hand, this may be explained by biological etiologic reasons. For example, cemented procedures are more commonly performed in Scandinavian countries, as compared to the United Kingdom.[34,35] Bone cement has been hypothesized to induce hypoxia, hypotension, and arrhythmias, which may contribute to the excess risk of AMI.[36,37] On the other hand, methodological differences may partially explain the discrepant findings. The Danish study utilized hospitalization registries (including data from outpatient clinics) and death certificate data, whereas our study used GP based electronic health records. As GP data partially rely on discharge letters from the hospital for the recording of AMI events, this may have resulted into a differential under recording between the two data sources. For the other cardiovascular outcomes, the RRs were comparable between the Danish and our study.

There are limited data on the timing of cardiovascular events following THR / TKR surgery. Similar to the Danish studies, our study found the highest excess risk during the first 2 postoperative weeks, and, for most cardiovascular events, diminished shortly afterwards.[29-31] For VTE on the other hand, the increased risk remained for several months post-surgery, which is longer than what was previously thought.[28] This finding suggests that a longer duration of thromboprophylaxis than currently recommended in international guidelines may be warranted. However, no randomized clinical trial has evaluated the added benefits of thromboprophylaxis beyond the first 39 days of surgery.[26,38] Hence, most international guidelines only recommend a thromboprophylaxis duration of 10-35 days.[39,40]

There are several proposed biological mechanisms for the observed excess risk of cardiovascular events following THR / TKR surgery. The surgery activates haemodynamic stressors (such as blood loss, fluid shifts, arrhythmias, and hypoxia) that contribute to the risk of postsurgical cardiovascular adverse outcomes.[41] In addition, cemented procedures may further trigger these haemodynamic stressors.[36,37] Surgical invasion of the medullary canal of the femur may lead to marrow embolisation and cardiac stress.[42,43,12] Other explanations may include better control and correction of haemoglobulin levels, bellovac drains in which a patient's blood loss in the first 6 postoperative hours is readministered, and better pre- and peri-operative blood pressure control.

Several aspects may contribute to our observed decrease over the past 25 years in short-term VTE following THR / TKR surgery. Firstly, the introduction of LMWHs in the early 90s may explain the drop, and may have contributed to the declining trend in AMI and stroke as well. A meta-analysis including 9 clinical trials showed a 62% reduction in the frequency of symptomatic VTE with extended use of heparins (mainly LMWHs), as compared to placebo after THR or TKR surgery.[44] Furthermore, LMWHs have been shown to lower the incidence of myocardial reinfarction in patients receiving fibrinolysis for ST-elevation AMI.[45] These drugs also reduce the rates for recurrent ischaemic stroke in individuals with acute ischaemic stroke, albeit with an increase in risk of major bleeding.[46] This latter finding may explain our observed secular trend towards an increase in GI bleeding risk, although the trend failed to reach statistical significance. As a second explanation for the decline in cardiovascular adverse outcomes, there has been an increasing focus on aggressive accelerated rehabilitation programs.17 Multimodal anaesthesia and new surgical technical advances may have further improved clinical outcome and physical function after THR / TKR surgery.[47]

The major strengths of this study include the large sample size, information on matched controls, and the data on important prognostic factors (such as smoking status, body mass index, and hypertension). An important limitation is the lack of information on inpatient anticoagulant use. A report from the National Joint Registry showed that 96% of the British THR / TKR patients received a form of chemical thromboprophylaxis (primarily low-molecular-weight heparins or direct thrombin inhibitors).[34] It is therefore likely that these patients are rather homogenous in terms of thromboprophylaxis. We cannot exclude the possibility of under recording of cardiovascular events, although this is likely to be non-differential (and should therefore not affect the RRs and timing patterns). Finally, we did not have data on anaesthesia, prognostic factors for VTE (such as family history and Factor V Leiden), surgical characteristics (such as cemented procedures), and postoperative blood loss.

In conclusion, THR / TKR surgical patients are at substantially increased risk of cardiovascular events, particularly during the first 2 weeks. The occurrence of these cardiovascular events has dramatically declined over the past 25 years, in particular for VTE. Despite the increase in relative risk, absolute risks remained low on an overall level. While this is reassuring for most patients undergoing THR / TKR surgery, we recommend cardiovascular risk assessment to identify high-risk patients (as for them, such an increased risk may be substantial).

ACKNOWLEDGEMENT
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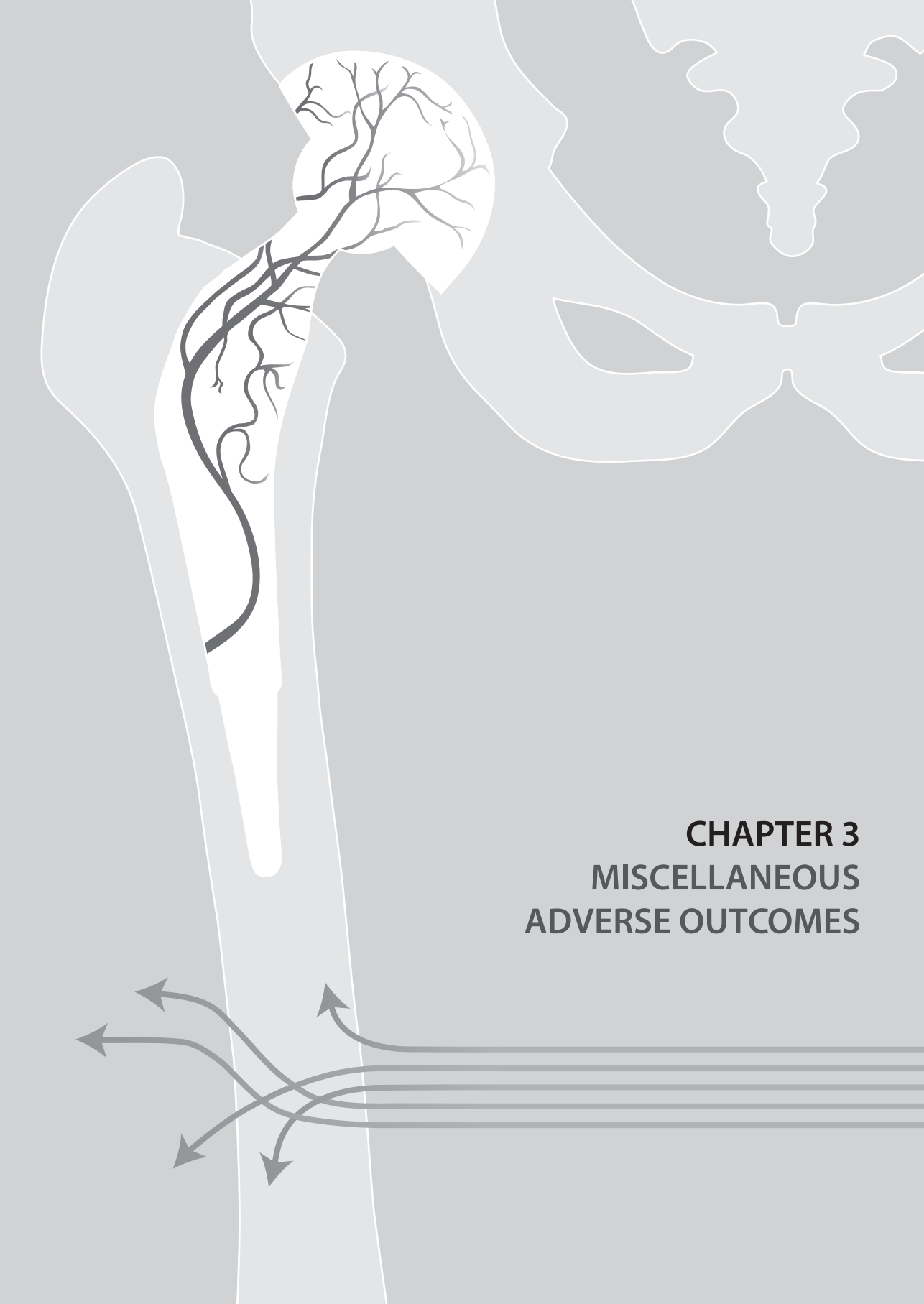

CHAPTER 3
MISCELLANEOUS ADVERSE OUTCOMES

CHAPTER 3.1

Changes in mortality patterns following total hip or knee replacement over the past two decades: a nationwide cohort study

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Arthritis Rheum. 2013; in press.

ABSTRACT

BACKGROUND: THR / TKR surgery are effective procedures for patients with moderate-to-severe osteoarthritis. Mortality rates after THR and TKR may have changed because of new surgical techniques, improvement of peri- and postoperative care, and patients having more comorbidity. Data on secular mortality trends are however scarce. The objective was to evaluate mortality patterns between 1989 and 2007 in patients undergoing elective total hip (THR) and knee (TKR) surgery.

METHODS: In a Danish retrospective nationwide cohort study, 71,812 THR and 40,642 TKR patients were identified between January 1989 and December 2007. Mortality (all-cause and disease-specific) was assessed, stratified by calendar time. Using Cox proportional hazards models, relative rates (RRs) for mortality were calculated between different calendar time periods, adjusted for age, sex, and comorbid diseases.

RESULTS: Since the early 90s, short-term survival following elective THR and TKR surgery has greatly improved. As compared to 1989-1991, 60-day mortality rates were substantially lower between 2004 and 2007 for THR (RR 0.40, 95% CI 0.28-0.58) and TKR patients (RR 0.37, 95% CI 0.21-0.67). This trend was far more superior to what was seen in the general population. The decrease in mortality was greatest for deaths from myocardial infarction, venous thromboembolism, pneumonia, and stroke. Patients tended to have more comorbidity over time and the length of hospital stay roughly halved.

CONCLUSIONS: Mortality rates following elective THR and TKR have decreased substantially since the early 90s, despite operated patients having more comorbidity. These findings are reassuring for patients undergoing elective THR or TKR.

INTRODUCTION

Total hip (THR) and knee replacements (TKR) are considered safe and effective surgical procedures in patients with moderate to severe osteoarthritis.[1] Given its effectiveness, the number of procedures has substantially increased over the past decades. Estimations indicate an annual number of 1.8 million procedures performed worldwide.[2,3] Nevertheless, studies have shown an excess mortality rate shortly after THR and TKR surgery,[4-7] in particular caused by venous thromboembolism (VTE) and acute myocardial infarction (AMI).[8] All-cause mortality rate during the first 90 days following these orthopaedic surgeries has been estimated at 0.7%.

Improvements in surgical technique and the introduction of new therapeutic agents may have improved survival following THR and TKR over the past 20 years.[9] For example, uncemented femoral components and multimodal anaesthesia has been reported to improve outcome

after THR.[10,11] The introduction of low-molecular-weight heparins (LMWHs) in the early 90s,[12,13] the trend towards shorter hospital stays, and aggressive accelerated rehabilitation programs might further contribute to lower mortality.[14] On the other hand, the surgery is now being performed in older patients and often with multiple comorbidities. This is of particular interest, as it has been shown that adverse outcomes increase with a higher number of comorbid conditions.[15,16] Despite these secular trends in THR and TKR over time, data on direct comparisons in mortality between different calendar times are scarce.[17] Furthermore, there is little evidence about the timing of mortality, and how this might have changed over the past 20 years. Both issues should help in understanding how much we have improved THR and TKR and perioperative care in daily practice, and to comprehend the possibility of further decreasing postsurgical death in the near future. Therefore, the primary objective was to study trends in mortality rates following elective THR and TKR surgery over the past two decades.

METHODS

DATA SOURCES

A retrospective cohort study was conducted within the full country of Denmark (5.5 million residents). We used nationwide registries to obtain information about data on second line visits (hospitals, outpatient clinics, emergency rooms), citizen status (vital status, date of death, residence, migration), and causes of death (one underlying cause, and up to three additional immediate causes). All Danish residents are entitled to free (tax-funded) health services including hospital services and visits to general practitioners. Independents studies have demonstrated high-quality, completeness of follow-up and high validity rates, and these registries have been used in numerous recent epidemiological papers.[18]

STUDY POPULATION

We selected all patients with a primary THR or TKR surgery between January 1, 1989, and December 31, 2007. In order to study elective procedures only, eligible patients should have a recorded history of osteoarthritis. We excluded individuals with a history of rheumatoid arthritis, those who had sustained a hip / knee fracture in the month before surgery, and individuals with a previous acute myocardial infarction (AMI), venous thromboembolism (VTE), gastrointestinal bleeding, pneumonia or stroke in the 6 weeks before surgery. The index date was defined as the date of THR or TKR hospital admission. In a sensitivity analysis, we further excluded individuals with a record for hip / knee fracture or infection in the three months before surgery, or a history of cancer.

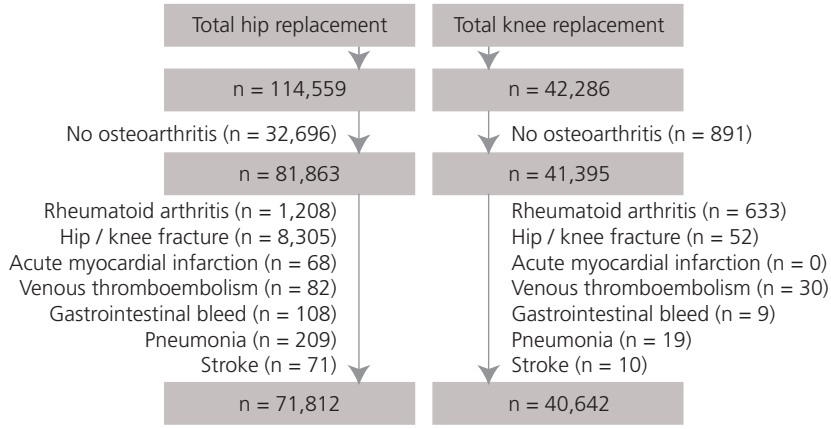
The study population was divided into four categories, based on the individual's index date: (1) 1989 - 1991, (2) 1992 - 1996, (3) 1997 - 2002, and (4) 2003 - 2007. These cut-offs were chosen, because therapeutic interventions are likely to have changed between these periods. The first large-scale Danish LMWH randomised controlled trials were finished in the early 90s (in particular 1991),[19,20] and a nationwide Danish working group further promoted the use

of LMWH in orthopaedic surgery from 1997 onwards.[21] It is therefore likely that the use of LMWHs has increased substantially during the 90s. Recent data from 1995 through 2006 show that use of LMWH in patients undergoing primary THR surgery is as high as 92.1% (7.0% used a different type of thromboprophylaxis).[22]

OUTCOME ASSESSMENT

The primary outcome of interest was all-cause mortality after THR or TKR surgery. Mortality was further stratified by cause of death (using any field of the death certificates), and was grouped into the following categories using the International Classification of Diseases, 8th and 10th revision (ICD8 / ICD10): AMI (ICD8: 410; ICD10: I21, I22), VTE (ICD8: 450, 451; ICD10: I26, I80), pneumonia (ICD8: 480-486; ICD10: J12-J18), gastrointestinal bleeds (ICD8: 530-534; ICD10: K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K92.0-K92.2), ischaemic stroke (ICD8: 432-438; ICD10: I63), haemorrhagic stroke (ICD8: 430, 431; ICD10: I60-I62), cancer (ICD8: 14-20; ICD10: C), and other causes of death. In order to assess timing of mortality, we followed all patients for death by any cause during the first 6 months following THR or TKR surgery. Patients were censored if they had migrated, underwent implant revision surgery or at the end of the study period (whichever came first, and if it occurred before the date of death).

FIGURE 3.1.1 | Population flowchart. Figures outside of boxes represent exclusion numbers.



STATISTICAL ANALYSIS

Cox proportional hazards regression was used to compare 60-day mortality rates following THR or TKR between different calendar time periods (calculated as a relative risk [RR], using the period 1989-1991 as a referent group). These RRs were fully adjusted for age, sex, and a history of AMI, VTE, pneumonia, ischaemic stroke, haemorrhagic stroke, COPD, cerebrovascular disease, diabetes or heart failure (all assessed at baseline), and were calculated using the PHREG procedure from SAS 9.2 (SAS Institute, Cary, North Carolina).[23] The analyses were carried out for all-cause mortality, and further stratified by age, and sex, and cause of

death. Using smoothing spline regression, we visualized the absolute mortality rate (events per 1000 person years) in relation to time since THR or TKR surgery, stratified by calendar period and cause of death.[24-27] Mortality rates were calculated for each week during the first 6 months following THR or TKR surgery. To evaluate the relationship between length of THR/TKR hospital stay and 60-day mortality rates, we evaluated the association using an ecologic design: for each calendar year, the mean length of stay and the 60-day all-cause mortality rates were calculated and visualized using smoothing spline regression. Standardized mortality ratios (SMRs) were calculated by estimating the ratio between observed THR/TKR mortality and the expected age-, sex-, and calendar-year stratified mortality in the Danish general population. This study was approved by the National Board of Health and the Danish Data Protection Agency.

RESULTS

TABLE 3.1.1 | Baseline characteristics of THR patients, stratified by calendar years.

	THR surgery, N = 71,812			
	1989 - 1991 N = 9,841 (%)	1992 - 1996 N = 15,363 (%)	1997 - 2002 N = 22,649 (%)	2003 - 2007 N = 23,959 (%)
Follow-up (mean, y, SD)	12.1 (5.7)	10.7 (4.2)	7.2 (2.4)	2.5 (1.5)
Age (mean, y, SD)	68.8 (10.5)	68.4 (11.0)	68.0 (11.3)	67.8 (11.3)
Males (%)	45.0	44.1	44.1	44.6
THR hospital stay (mean, d, SD)	15.4 (9.1)	14.0 (8.3)	11.6 (5.6)	7.4 (5.0)
Co-morbidities (%, > 6 weeks before)				
Previous AMI	4.4	4.6	4.9	5.2
COPD	3.6	3.8	5.3	7.1
Cerebrovascular disease	3.3	3.7	5.1	6.7
Diabetes	2.2	2.5	2.9	4.5
Heart failure	2.1	2.3	3.0	3.7

Abbreviations: AMI = acute myocardial infarction, COPD = chronic obstructive pulmonary disease, d = days, SD = standard deviation, THR = total hip replacement, y = year.

TABLE 3.1.2 | Baseline characteristics of TKR patients, stratified by calendar years.

	TKR surgery, N = 40,642			
	1989 - 1991 N = 4,009 (%)	1992 - 1996 N = 7,220 (%)	1997 - 2002 N = 10,861 (%)	2003 - 2007 N = 18,552 (%)
Follow-up (mean, y, SD)	11.8 (5.6)	10.5 (4.1)	7.1 (2.2)	2.4 (1.5)
Age (mean, y, SD)	70.2 (9.5)	69.6 (10.0)	68.1 (10.5)	67.2 (10.4)
Males (%)	27.8	30.9	35.6	38.5
TKR hospital stay (mean, d, SD)	17.6 (11.2)	15.7 (7.5)	12.9 (6.9)	7.6 (4.9)
Co-morbidities (%, > 6 weeks before)				
Previous AMI	3.2	4.3	4.4	4.7
COPD	2.7	4.0	5.6	7.8
Cerebrovascular disease	3.6	4.3	5.9	7.1
Diabetes	2.6	3.3	4.0	6.7
Heart failure	2.0	2.5	3.1	3.6

Abbreviations: AMI = acute myocardial infarction, COPD = chronic obstructive pulmonary disease, d = days, SD = standard deviation, TKR = total knee replacement, y = year.

Baseline characteristics of THR and TKR patients, stratified by calendar time, are shown in Tables 3.1.1 and 3.1.2. Overall, we had 112,454 THR/TKR surgical patients (Figure 3.1.1) with an average follow-up time of 6.7 years (standard deviation = 4.9 years). A total of 32.7%

died during the study period, 0.3% was lost to follow-up due to migration, and 3.7% were censored because of a revision surgery. No substantial changes in age and sex distributions were seen over the years. Mean age was relatively constant over time for both THR (68.4 years) and TKR patients (68.2 years). Among THR surgery, the proportion of males stayed constant over time (on average 45%), but slightly increased among TKR surgery (28% in 1989-1991 versus 39% in 2003-2007). The duration of hospital stay roughly halved in 2003-2007 as compared to in 1989-1991, dropping from 15 to 7 days for THR, and from 18 to 8 days for TKR.

TABLE 3.1.3 | 60-day all-cause and disease-specific mortality rate ratios following total hip replacement, stratified by calendar year, age, and sex.

	1989 - 1991 referent category	1992 - 1996 adjusted RR (95% CI) *	1997 - 2002 adjusted RR (95% CI) *	2003 - 2007 adjusted RR (95% CI) *	P for trend †
General population	1.00	1.02 (0.96-1.09)	0.93 (0.87-0.99)	0.72 (0.67-0.77)	< 0.01
Total hip replacement	1.00	0.66 (0.46-0.94)	0.51 (0.36-0.72)	0.40 (0.28-0.58)	< 0.01
By age, y					
18 - 64	1.00	1.07 (0.31-3.67)	0.54 (0.15-1.92)	0.77 (0.24-2.47)	0.45
65 - 79	1.00	0.56 (0.33-0.92)	0.42 (0.25-0.69)	0.28 (0.16-0.48)	< 0.01
≥ 80	1.00	0.72 (0.41-1.27)	0.62 (0.36-1.06)	0.48 (0.27-0.83)	0.24
By sex					
Males	1.00	0.63 (0.39-1.02)	0.53 (0.34-0.84)	0.44 (0.27-0.70)	< 0.01
Females	1.00	0.70 (0.41-1.19)	0.47 (0.28-0.80)	0.36 (0.20-0.62)	< 0.01
By cause of death					
AMI	1.00	0.55 (0.27-1.12)	0.46 (0.23-0.90)	0.27 (0.13-0.58)	< 0.01
VTE	1.00	0.35 (0.13-0.95)	0.25 (0.09-0.67)	0.04 (0.01-0.31)	< 0.01
Pneumonia	1.00	1.02 (0.30-3.50)	0.24 (0.05-1.11)	0.15 (0.03-0.81)	< 0.01
GI bleeding	1.00	-	-	-	-
Ischaemic stroke	1.00	0.09 (0.01-0.75)	0.19 (0.05-0.73)	0.13 (0.03-0.61)	< 0.01
Haemorrhagic stroke	1.00	0.15 (0.02-1.32)	0.18 (0.03-1.01)	0.07 (0.01-0.64)	0.02
None of the above	1.00	1.21 (0.67-2.17)	0.96 (0.55-1.70)	0.93 (0.53-1.63)	0.57

* Adjusted for age, sex, and a history of AMI, COPD, cerebrovascular disease, diabetes or heart failure.
† Tested with the Cochran-Armitage trend test.

Tables 3.1.3, 3.1.4, 3.1.5, and 3.1.6 show a substantially decreasing trend in 60-day mortality for THR or TKR surgery over the years, which was greater than expected from the general population. Compared to 1989-1991, the 60-day mortality rate was lowered by 60% for THR surgery (adj. RR 0.40, 95% CI 0.28-0.58), which was not different in our sensitivity case definition analysis (further exclusion of individuals with a hip / knee fracture or infection in the previous three months or a history of cancer; adj. RR 0.43, 95% CI 0.29-0.62; data not shown). For TKR surgery, the corresponding drop was 63% (adj. RR 0.37, 95% CI 0.21-0.67) in 2003-2007, compared to 1989-1991. For THR surgery, a particular decrease in AMI- (73%), VTE- (96%), pneumonia- (85%), ischaemic stroke- (87%), and haemorrhagic stroke- (93%) related mortality was noted, whereas death from other causes remained stable. A similar pattern was seen for TKR surgery. For THR and TKR surgery, inpatient mortality rates decreased over time: the highest all-cause mortality rates were found between 1989-1991 (54.9 deaths per 1000 person years), followed by 1992-1996 (38.7 deaths per 1000 person years), 1997-2002 (30.3 deaths per 1000 person years), and 2003-2007 (28.4 deaths per 1000 person years).

TABLE 3.1.4 | 60-day all-cause and disease-specific mortality rate ratios following total knee replacement, stratified by calendar year, age, and sex.

	1989 - 1991 referent category	1992 - 1996 adjusted RR (95% CI) *	1997 - 2002 adjusted RR (95% CI) *	2003 - 2007 adjusted RR (95% CI) *	P for trend †
General population	1.00	1.07 (1.01-1.14)	1.01 (0.94-1.07)	0.79 (0.73-0.84)	< 0.01
Total knee replacement	1.00	0.81 (0.45-1.48)	0.44 (0.24-0.82)	0.37 (0.21-0.67)	< 0.01
By age, y					
18 - 64	1.00	0.77 (0.13-4.62)	0.39 (0.07-2.36)	0.07 (0.01-0.75)	< 0.01
65 - 79	1.00	0.96 (0.44-2.10)	0.55 (0.24-1.26)	0.41 (0.18-0.92)	0.01
≥ 80	1.00	0.61 (0.20-1.83)	0.30 (0.09-0.93)	0.43 (0.16-1.14)	0.68
By sex					
Males	1.00	0.81 (0.31-2.08)	0.42 (0.16-1.11)	0.49 (0.21-1.17)	0.16
Females	1.00	0.84 (0.39-1.81)	0.47 (0.21-1.07)	0.27 (0.12-0.64)	< 0.01
By cause of death					
AMI	1.00	0.32 (0.13-0.84)	0.17 (0.06-0.48)	0.03 (0.01-0.16)	< 0.01
VTE	1.00	0.86 (0.24-3.04)	0.20 (0.04-1.09)	0.12 (0.02-0.67)	< 0.01
Pneumonia	1.00	1.68 (0.18-16.2)	1.20 (0.12-11.6)	0.25 (0.02-4.05)	0.04
GI bleeding	1.00	-	-	-	-
Ischaemic stroke	1.00	-	-	-	-
Haemorrhagic stroke	1.00	-	-	-	-
None of the above	1.00	1.37 (0.43-4.38)	0.98 (0.31-3.09)	1.39 (0.48-3.99)	0.47

* Adjusted for age, sex, and a history of AMI, COPD, cerebrovascular disease, diabetes or heart failure.
† Tested with the Cochran-Armitage trend test.

TABLE 3.1.5 | 60-day disease-specific mortality rates following total hip / knee replacement, and distribution of causes of death.

	60-day mortality rate, per 1000 PYs (% of total deaths)							
	1989 - 1991		1992 - 1996		1997 - 2002		2003 - 2007	
Cause of death	IR	(%)	IR	(%)	IR	(%)	IR	(%)
Any cause *	33.5	(100)	23.8	(100)	17.3	(100)	13.8	(100)
Inpatient death †	54.9		38.7		30.3		28.4	
Outpatient death †	18.1		13.8		10.7		9.8	
Acute myocardial infarction	11.9	(35.5)	5.7	(23.9)	4.4	(25.4)	2.0	(14.5)
Venous thromboembolism	6.6	(19.8)	3.2	(13.6)	1.5	(8.4)	0.4	(3.1)
Pneumonia	2.2	(6.6)	2.7	(11.4)	1.1	(6.3)	0.4	(3.1)
Gastrointestinal bleeding	0.9	(2.6)	0.0	(0.0)	0.2	(1.1)	0.3	(2.1)
Ischaemic stroke	3.5	(10.5)	1.1	(4.5)	0.5	(3.2)	0.3	(2.1)
Haemorrhagic stroke	1.8	(5.3)	0.3	(1.1)	0.4	(2.1)	0.1	(1.0)
None of the above	8.4	(25.0)	11.3	(47.6)	9.5	(54.7)	10.2	(73.8)

Percentages represent proportions of disease-specific deaths among all fatal events.
Abbreviations: IR = incidence rate, PY = person years.
* Causes do not precisely add up to 100%, as a patient may have died from multiple causes.
† IRs were calculated as the number of events divided by the person time in each given period (e.g. for inpatient deaths, only the inpatient time was considered for the person time; for outpatient deaths, the inpatient person time was not added to the total person time).

The timing of mortality following THR or TKR, stratified by calendar time and cause of death, is displayed in Figure 3.1.2. Regardless of calendar time, the excess mortality rate was highest during the first 30 days following THR or TKR, and then stabilized in the month thereafter. Over the years, the reduction in mortality seemed to be greatest during the first 30 days, but did not seem to differ substantially at 6 months after surgery. In our ecologic evaluation, 60-day all-cause mortality rates appeared to be stable for the first 13 days of THR/TKR hospital stay, but increased beyond a longer length of stay (Figure 3.1.3).

TABLE 3.1.6 | 60-day all-cause standardized mortality ratio following total hip and knee replacement compared to the general population.

	Standardized mortality ratio (95% confidence interval)				P for trend *
	1989 - 1991	1992 - 1996	1997 - 2002	2003 - 2007	
THR surgery					
General population	1.00	1.00	1.00	1.00	
THR	1.32 (1.00-1.71)	0.91 (0.70-1.16)	0.73 (0.56-0.92)	0.75 (0.57-0.97)	< 0.01
TKR surgery					
General population	1.00	1.00	1.00	1.00	
TKR	1.47 (0.94-2.18)	0.97 (0.65-1.38)	0.78 (0.54-1.09)	0.76 (0.56-1.02)	< 0.01

* Tested with the Cochran-Armitage trend test.

FIGURE 3.1.2 | Mortality rates per 1000 person years in relation to time since total hip / knee replacement, stratified by year of surgery (left) and cause of death (right).

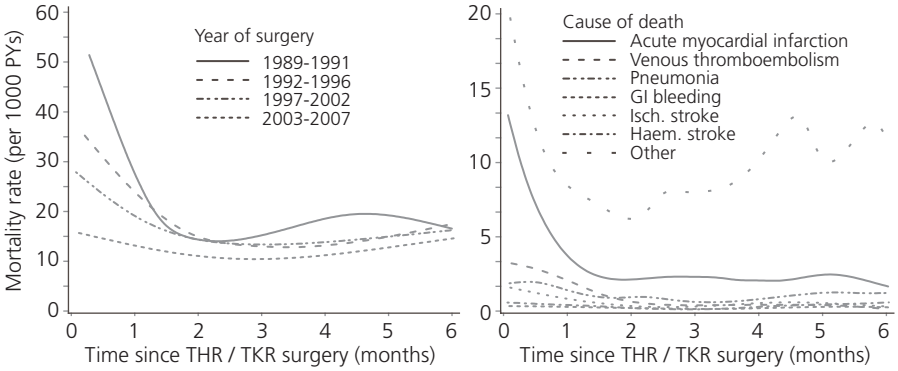
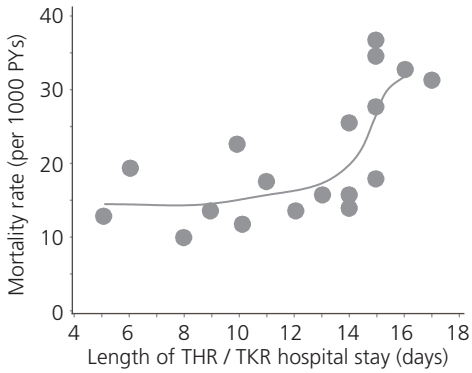


Figure 3.1.3 | Sixty-day all-cause mortality rates per 1000 person years in relation to the mean duration of THR/TKR-associated hospital stay.



DISCUSSION

This study shows that short-term survival following elective THR and TKR surgery has greatly improved since the early 90s. Between 1989 and 2007, all-cause mortality has decreased by 60% - 64%, which is far superior to what was seen in the general population. In particular a drop in deaths from AMI, VTE, pneumonia, and ischaemic / haemorrhagic stroke was noted.

The decreasing trend in mortality was mostly pronounced during the first 30 days following surgery, while mortality rates during the 6th month post-surgery was not significantly altered.

This study is the first to evaluate all-cause and cause-specific mortality rates following THR and TKR in relation to calendar time. Most previous studies among THR patients have focused on post-surgical mortality rates (primarily all-cause), but could not make a direct comparison between different calendar time periods. They reported 30-day mortality rates between 0.24% and 0.95% for THR,[4,7,9,15,28-32] and 0.24% - 0.37% for TKR surgery[6,33-36] in a wide variety of patients who required elective hip / knee surgery. In line with our findings, these studies indirectly support a trend towards a decreasing mortality rate over calendar time. Aynardi et al (population: 2000-2006) found a 30-day mortality rate of 0.24% after THR surgery in US patients undergoing elective surgery (mean age 63 years),[9] while Whittle and coworkers (population: 1983-1985) reported a mortality rate of 0.95% during the first 30 days following THR surgery (albeit in an older population, only US patients of age 65+ years were included).[31] However, differences in study populations, local guidelines, surgical techniques, and quality of data sources limit this indirect comparison, and not all studies were in line with the decreasing trend in mortality. For example, one of the oldest published studies (population: 1969-1973) revealed a 30-day mortality rate (0.4%) in US patients undergoing elective THR surgery (median age 65 years) that was very similar to the more recent studies.[32] Alternatively, under-recording of mortality in this relatively old study may have contributed to the lower observed mortality rate. Adding to these conflicting results, previous studies suggest no decrease in short-term mortality following TKR surgery over calendar time.

Several aspects may contribute to our observed decrease in short-term mortality following THR and TKR surgery. Firstly, the introduction of LMWHs in the early 90s may explain the drop particularly in deaths from VTE, AMI, and ischaemic stroke. A meta-analysis including 9 clinical trials showed a 62% reduction in the frequency of symptomatic VTE with extended use of heparins (mainly LMWHs), as compared to placebo after THR or TKR surgery.[37] Enoxaparin has been associated with a lower incidence of myocardial reinfarction, as compared to unfractionated heparin in patients receiving fibrinolysis for ST-elevation AMI.[38] LMWHs reduce rates for recurrent ischaemic stroke in individuals with acute ischaemic stroke, but subsequently increase the frequency of major bleeding.[39] Interestingly, we could not observe an elevation in risk of fatal haemorrhagic stroke or gastrointestinal bleeding over time, possibly explained by improved perioperative care and the introduction of proton pump inhibitors (for gastrointestinal bleeding). Secondly, there has been an increasing focus on aggressive accelerated rehabilitation programs, typically initiated on the first day after surgery. The trend towards faster ambulation is also reflected by the shorter duration of hospital stay we observed in the present study. White et al showed a 30% reduction in risk of VTE in individuals who were ambulatoryed in the first 2 days after THR surgery, as compared to delayed ambulation.[40] Thirdly, the use of multimodal anaesthesia improves physical function shortly after THR, which may result into fewer adverse outcomes related to immobility.[11] Finally, over the years, several new surgical techniques with improved outcomes have been

introduced. For example, uncemented femoral components have gained popularity over the years, and limited evidence demonstrates lower short-term mortality rates with these implants, as compared to cemented arthroplasty.[9,41]

Data on timing of mortality following THR or TKR surgery are very scarce. Only one previous US study evaluated mortality in relation to time since THR surgery in patients undergoing elective surgery enrolled in the Medicare program (mean age 75 years).[4] In line with our findings, mortality rates were particularly increased during the first postoperative month, and stabilized afterwards. Our results show the same trend for mortality following TKR surgery. The decrease in mortality over the years was most pronounced during the first 30 days. This may imply that the trend is a result of improved surgical survival, rather than lower mortality rates in the general population over time. This is also supported by the fact that we found smaller reductions in mortality rates over calendar time in the general population.

The strengths of this study include the nationwide population-based design, large sample size, and completeness of follow-up. We had a large period of follow-up, which allowed us to make direct comparisons between different calendar times. In Denmark, it is compulsory by law to report deaths to the authorities, i.e. mortality data should be 100% complete.[42] An important limitation is the lack of information on inpatient characteristics, such as administered drugs while in hospital (e.g. thromboprophylaxis, anaesthetics), and surgical techniques. Although this may have helped in further evaluating secular trends over time, we believe this is part of the causal pathway (i.e. changes in patient care over time affecting mortality), and should not be considered as confounders. We did not have information for the year 2008 onwards, which might have been interesting given the introduction of oral direct thrombin inhibitors. However, this is not widely used in Denmark, and is therefore unlikely to substantially change overall mortality trends after 2007. We assessed "elective surgery" by excluding individuals based on a history of trauma-indications. This definition may be incomplete and may have overestimated our mortality rates. However, this overestimation should be similar for all calendar periods, and should therefore not influence the rate ratios. Moreover, the robustness of our sensitivity analysis suggests that this potential limitation only minimally affects the mortality estimates.

In conclusion, short-term survival after elective THR or TKR surgery has greatly improved since the early 90s. These results are reassuring for patients undergoing elective THR or TKR, suggesting that improved patient care, surgical techniques, and novel therapeutics have indeed minimized fatal post-surgical complications over time.

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CHAPTER 3.2

Patterns of risk of cancer in patients with metal-on-metal hip replacements versus other bearing surface types: a record linkage study between a prospective joint registry and general practice electronic health care records in England

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ABSTRACT

BACKGROUND: There are concerns that metal-on-metal hip implants may cause cancer. The objective of this study was to evaluate patterns and timing of risk of cancer in patients with metal-on-metal total hip replacements (THR).

METHODS: In a linkage study between the English National Joint Registry (NJR) and the Clinical Practice Research Datalink (CPRD), we selected all THR surgeries (NJR) between 2003 and 2010 (n=11,540). THR patients were stratified by type of bearing surface. Patients were followed up for cancer and Poisson regression was used to derive adjusted relative rates (RR).

RESULTS: The risk of cancer was similar in patients with hip resurfacing (RR 0.69; 95% Confidence Interval [CI] 0.39 - 1.22) or other types of bearing surfaces (RR 0.96; 95% CI 0.64 - 1.43) compared to individuals with stemmed metal-on-metal THR. The pattern of cancer risk over time did not support a detrimental effect of metal hip implants. There was substantial confounding: patients with metal-on-metal THRs used fewer drugs and had less comorbidity.

CONCLUSIONS: Metal-on-metal THRs were not associated with an increased risk of cancer. There were substantial baseline differences between the different hip implants, indicating possibility of confounding in the comparisons between different types of THR implants.

INTRODUCTION

Total hip replacement (THR) is a highly effective procedure performed in patients with moderate to severe osteoarthritis.[1] It is now ranked among the most common surgical operations performed worldwide, with over one million procedures estimated to be carried out annually.[2,3] Over the past few decades, metal-on-metal hip devices gained popularity, and up to recently accounted for approximately 14% of all THRs in England and Wales.[4,5] The use of these devices, which have been associated with the widespread dissemination of metal ions including cobalt and chromium,[6] has raised a number of health concerns, including the potential risk of cancer.[7,8] The carcinogenic properties of the materials used in these hip devices have been demonstrated previously.[7,9] Cobalt and chromium at similar concentration levels found in post mortem specimens, induce carcinomas in animal models, and in addition may increase the chance of malignant degeneration.[10]

There is limited epidemiological evidence on cancer risk following metal-on-metal THR compared with other bearing surface types. Two recent studies showed no excess risk of any cancer with metal-on-metal hip devices over other hip implants.[8,11] The majority of the epidemiological studies could not differentiate between bearing surface types (or could not make a comparison with non metal-on-metal implants), and reported somewhat conflicting

findings.[12-20] A meta-analysis aggregating nine of these observational studies showed no increased risk of any cancer with any THR prosthesis, although they were able to detect an elevated risk of prostate and skin cancer.[21]

A comparison between bearing surface types has many limitations, as there is a high probability of confounding by indication. Metal-on-metal hip replacements (in particular hip resurfacing) are generally considered in younger and healthier patients. It is important to study which patients are more likely to get certain bearing surface types, as these patient characteristics may also be associated with risk of cancer (and thereby introducing bias). Previous studies have not evaluated these differences in detail. To do so, this would require a linkage between high quality registries providing information on implant details (such as the UK National Joint Registry, NJR), and electronic health records with information on clinical confounders and outcomes (such as the UK Clinical Practice Research Datalink [CPRD]). Consequently, the objectives of this study were to evaluate patterns and timing of risk of cancer in patients with metal-on-metal THR and to identify predictors for bearing surface types, cancer and mortality.

METHODS

DATA SOURCES

Data for this study were obtained from the General Practice Research Database that is part of CPRD. CPRD collates the computerised medical records of general practitioners (GPs). GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Patients are semi-permanently affiliated with a practice that centralises the medical information from the GPs, specialist referrals, and hospitalizations. CPRD now contains computerised records for 650 GP practices, representing 8% of the British population. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987 [www.CPRD.com].

CPRD has now been linked individually and anonymously to other NHS datasets in England. This linkage is done by a trusted third party using information on the NHS number, date of birth, gender and postcode. The majority of patients were linked using their NHS number. At the time of this study, 250 GP practices in England participated in this linkage (about 40% of CPRD). The NHS datasets that were linked to CPRD included the National Joint Registry (NJR), which collects prospectively information on replacement surgeries. Information in this data source includes patient demographics (e.g. date of birth, sex, body mass index), operation details (e.g. hospital, anaesthetics, patient ASA grade), surgeon details (e.g. surgeon grade), procedure details (e.g. side of joint, indication for surgery), surgical approach (e.g. total replacement or resurfacing, cemented, materials used for the implants, minimally invasive techniques, computer guided surgery), intended thromboprophylaxis (both chemical and mechanical), bonegraft used, and intraoperative events. Since April 2003, the NJR has been collecting information on THRs performed in England and Wales. By the end of July 2005, the

mean weekly submission of completed records had reached 2400 operations, with 99% of all hospitals on the joint registry database submitting data. The proportion of all relevant joint replacements performed in England and Wales which was included in NJR was approximately 60%. The NJR collects information for a large number of patient and surgical characteristics. In addition, CPRD was linked to the Hospital Episode Statistics (HES) that records details on the dates of hospital admission, major procedures and admission diagnoses and to death certificates (including primary and secondary cause of death). In the UK, death certificates are filled in upon death of a patient by a registered medical practitioner who has attended the patient during their last period. Death certificates are divided into two parts, containing the original underlying cause of death (part I) and diseases that may have contributed significantly to the death (part II). Diagnoses and causes of death in the HES database and causes of death registry are coded using the international classification of diseases, 10th version (ICD-10). The linkage to CPRD was only available for England. Data were available for the following time periods: CPRD data (January 1987 – December 2011), NJR data (April 2003 – November 2010), HES data (April 1997 – November 2010), death certificate data (December 2000 – November 2011). For the linked datasets, the study period was defined as the latest data entry for any of the linked datasets until the earliest end of data collection. The study protocol was approved by the CPRD Independent Scientific Advisory Committee and by the Research Subcommittee (ISAC) of the NJR.

STUDY POPULATIONS, MOTIVATION STUDY COHORTS

A retrospective cohort study was conducted using CPRD, NJR and HES. Three study cohorts were identified based on a record of THR in CPRD, NJR or HES. Data on bearing surface type was only available in NJR (the coding in HES and CPRD was non-specific with respect to surface type and an analysis of anonymised free-text in CPRD only yielded limited information). The main analyses (i.e. those evaluating bearing surface type) were therefore conducted using the NJR cohort. Analyses not concerning bearing surface type were conducted using the CPRD cohort, as this data source had the largest sample size. For the latter cohort, we compared THR patients (regardless of bearing surface type) to matched referent subjects without THR surgery (see below). As this was our largest cohort, this was the only feasible way to evaluate cancer type specific rates among THR surgical patients versus matched controls. Any increase in cancer rate among this full THR cohort would be supportive that some hip implant devices may elevate the risk for cancer. To assess the consistency between these three databases, the overall risk of cancer following any THR was evaluated in all three databases.

SELECTION OF THR PATIENTS AND MATCHED REFERENT SUBJECTS

For each data source (i.e. CPRD, NJR, and HES), we selected all patients aged 18+ years who had a primary THR record in the corresponding data source within the study period. To each THR patient, up to 6 referent subjects without a history of THR were selected and they were matched to each THR patient by calendar time, age, sex, and practice. The index date for THR patients and matched referent subjects was the date of the primary THR. All patients had at least one year of valid data collection prior to the index date. We excluded patients with a recording of any cancer prior to the index date.

FOLLOW-UP

All patients were followed up from the index date until the end of the study period (i.e. the earliest end of data collection for any of the linked data sets), date of patient's transfer out of the practice or death, whichever came first. In addition, THR patients in the NJR cohort with a bearing surface type other than metal-on-metal were censored if they had undergone conversion arthroplasty to a metal-on-metal hip device during follow-up. Not censoring these patients would lead to misclassification of the exposure (i.e. metal or non-metal), and may therefore dilute the association. We did not censor patients with the converse situation (i.e. non-metal to metal-on-metal). These patients were already exposed to metal hip implants and mutagenic processes may irreversibly lead to carcinomas, even after the conversion to non-metal hip implants.

OUTCOMES

All patients were followed up for an incident record of cancer (excluding in situ and non-melanoma skin cancer) after the index date. We used three sources for cancer outcomes, including CPRD, HES and national death certificates. The analyses requiring HES or death certificates were restricted to practices participating in the linkage. Types of cancer were divided according to the possibility of being related to metal ions and included any cancer, haematological cancer (e.g. lymphoma, leukaemia, or myeloma), malignant melanoma, prostate cancer, renal cancer (bladder, ureter or kidney), or other types of cancer. Cancer was analysed using the three data sources separately, as none of these data sources were viewed to be 'gold standard' without any imperfections. However, findings that are consistent across the different sources are more likely to concern validated outcomes.

CONFOUNDERS

We reviewed the literature to identify potential confounders that were associated with cancer. These confounders were assessed at the index date and included the following: age, sex, calendar year, small-area socioeconomic status (for linked practices), smoking status, use of alcohol, body mass index, a history of hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and a prescribing in the 6 months before of NSAIDs or aspirin, oestrogen containing drugs, oral glucocorticoids, calcium / vitamin D supplements, glucose lowering agents, statins, immunosuppressive agents, bisphosphonates, renin-angiotensin-aldosterone-system (RAAS) inhibitors, platelet inhibitors, beta blockers, calcium channel blockers, diuretics and organic nitrates. Small-area socioeconomic status, smoking status, use of alcohol and body mass index were handled as categorical variables, with a separate category for missing data.

ANALYSES

The following statistical analyses were conducted:

1) Predictors of bearing surface type (NJR cohort), cancer (CPRD cohort) and all-cause mortality (CPRD cohort): In order to assess confounding by indication, we identified

predictors of bearing surface type (using the NJR cohort), in which we modelled all of the potential confounders in a logistic regression model. The outcome of interest was metal-on-metal bearing surface type (stratified by stemmed or resurfacing), compared with hip devices of other materials. In the second analysis, we identified predictors of cancer and all-cause mortality within control subjects, by modelling all potential confounders in a Poisson regression model.

2) Bias-analysis (NJR cohort): We evaluated risk of cancer within 6 months following THR surgery versus matched referent subjects, stratified by type of implant. Any altered cancer risk in this period is unlikely to be causally related to THR and most likely represents confounding by indication.

3) Association between hip replacement (any type) and cancer risk (all three cohorts): Poisson regression was used to estimate adjusted relative rates (RRs) for cancer incidence in the hip replacement cohorts to the referent cohorts. This analysis was performed for all three study cohorts and repeated for the three cancer data sources.

4) Cumulative incidence of cancer (NJR cohort): A competing risk model was used to estimate long-term risk of cancer, stratified by type of bearing surface, gender, and age. Death was considered the competing risk.

5) Patterns and timing of cancer risk (CPRD cohort / NJR cohort): For the first pattern analysis (CPRD cohort), we calculated RRs to compare cancer incidence in the 6-24, 25-60, and 60+ months after the index date with that in the first 6 months. This analysis was conducted within THR surgery patients, as well as in referent subjects, in order to compare timing and patterns. In the second analysis (NJR cohort), we analysed cancer risk over time in patients with metal-on-metal THR versus patients with other hip implant devices.[22-25]

RESULTS

BASELINE CHARACTERISTICS AND PREDICTORS OF BEARING SURFACE TYPES

Demographical information of THR patients in NJR and matched referent subjects is shown in Table 3.2.1 (11,540 THR patients). Patients with metal-on-metal THR were considerably younger (stemmed: 62.6 years, resurfacing: 54.5 years) compared to those with other hip implants (69.4 years). Similarly, the proportion of females was lower in individuals with metal-on-metal hip implants. Multivariate logistic regression demonstrated substantial differences in drug use and comorbidities between metal-on-metal hip replacements and non-metal hip devices. Predictors that were associated with both the bearing surface type and cancer (and / or all-cause mortality) included age, gender, smoking status, socioeconomic status, COPD, and use of oestrogen containing drugs, platelet inhibitors, and beta blockers. The mean age and gender distribution of THR cases were similar throughout all databases (46,425 THR patients in CPRD and 19,034 in HES).

TABLE 3.2.1 | Baseline characteristics of patients with different types of hip replacements and matched controls (NJR cohort).

	Any bearing surface type				Stemmed metal-on-metal				Hip resurfacing				Other bearing surface			
	THR		Controls		THR		Controls		THR		Controls		THR		Controls	
Characteristic	n = 11,540		n = 69,218		n = 988		n = 5,926		n = 838		n = 5,028		n = 9,714		n = 58,264	
Follow-up time (mean, SD)	3.2	(2.1)	3.0	(2.1)	3.7	(1.7)	3.6	(1.7)	4.0	(2.0)	3.9	(2.0)	3.1	(2.1)	2.9	(2.1)
Females (%)	6,862	(59.5)	41,161	(59.5)	436	(44.1)	2,614	(44.1)	278	(33.2)	1,668	(33.2)	6,148	(63.3)	36,879	(63.3)
Age (mean, SD)	67.9	(11.0)	67.9	(11.0)	62.6	(10.9)	62.6	(10.9)	54.5	(8.2)	54.5	(8.2)	69.4	(10.4)	69.4	(10.4)
BMI (mean, SD)	28.3	(5.2)	27.4	(5.4)	28.5	(5.5)	27.5	(5.4)	28.5	(4.5)	27.8	(5.4)	28.3	(5.2)	27.3	(5.4)
Smoking status																
Non-smoker	5,647	(48.9)	30,805	(44.5)	455	(46.1)	2,417	(40.8)	416	(49.6)	1,887	(37.5)	4,776	(49.2)	26,501	(45.5)
Ex-smoker	3,193	(27.7)	17,347	(25.1)	281	(28.4)	1,425	(24.0)	170	(20.3)	1,008	(20.0)	2,742	(28.2)	14,914	(25.6)
Current smoker	1,431	(12.4)	9,931	(14.3)	151	(15.3)	1,008	(17.0)	106	(12.6)	872	(17.3)	1,174	(12.1)	8,051	(13.8)
Unknown	1,269	(11.0)	11,135	(16.1)	101	(10.2)	1,076	(18.2)	146	(17.4)	1,261	(25.1)	1,022	(10.5)	8,798	(15.1)
Medical history (%)																
Hypertension	4,963	(43.0)	26,805	(38.7)	356	(36.0)	1,86	(31.4)	172	(20.5)	949	(18.9)	4,435	(45.7)	23,996	(41.2)
COPD	462	(4.0)	3,62	(5.2)	20	(2.0)	263	(4.4)	9	(1.1)	84	(1.7)	433	(4.5)	3,273	(5.6)
Coronary artery disease	959	(8.3)	6,182	(8.9)	49	(5.0)	395	(6.7)	30	(3.6)	194	(3.9)	880	(9.1)	5,593	(9.6)
Recent prescriptions (%)																
NSAIDs	4,991	(43.2)	8,006	(11.6)	428	(43.3)	614	(10.4)	339	(40.5)	469	(9.3)	4,224	(43.5)	6,923	(11.9)
Oestrogens	380	(3.3)	1,995	(2.9)	29	(2.9)	159	(2.7)	41	(4.9)	139	(2.8)	310	(3.2)	1,697	(2.9)
Corticosteroids	550	(4.8)	2,944	(4.3)	55	(5.6)	196	(3.3)	16	(1.9)	96	(1.9)	479	(4.9)	2,652	(4.6)
Calcium / vitamin D	968	(8.4)	4,443	(6.4)	68	(6.9)	263	(4.4)	15	(1.8)	73	(1.5)	885	(9.1)	4,107	(7.0)
Antidiabetics	636	(5.5)	5,105	(7.4)	43	(4.4)	395	(6.7)	14	(1.7)	198	(3.9)	579	(6.0)	4,512	(7.7)
Statins	3,143	(27.2)	19,1	(27.6)	205	(20.7)	1,437	(24.2)	105	(12.5)	704	(14.0)	2,833	(29.2)	16,959	(29.1)
Immunosuppressants	198	(1.7)	631	(0.9)	23	(2.3)	48	(0.8)	11	(1.3)	31	(0.6)	164	(1.7)	552	(0.9)
Bisphosphonates	743	(6.4)	3,365	(4.9)	49	(5.0)	188	(3.2)	7	(0.8)	56	(1.1)	687	(7.1)	3,121	(5.4)
RAAS inhibitors	3,492	(30.3)	18,668	(27.0)	265	(26.8)	1,329	(22.4)	130	(15.5)	712	(14.2)	3,097	(31.9)	16,627	(28.5)
Platelet inhibitors	2,449	(21.2)	15,283	(22.1)	127	(12.9)	960	(16.2)	49	(5.8)	394	(7.8)	2,273	(23.4)	13,929	(23.9)
Beta blockers	2,08	(18.0)	11,79	(17.0)	125	(12.7)	747	(12.6)	77	(9.2)	433	(8.6)	1,878	(19.3)	10,61	(18.2)
Calcium channel blockers	2,356	(20.4)	12,12	(17.5)	179	(18.1)	854	(14.4)	73	(8.7)	410	(8.2)	2,104	(21.7)	10,856	(18.6)
Diuretics	3,345	(29.0)	17,24	(24.9)	212	(21.5)	1,086	(18.3)	82	(9.8)	445	(8.9)	3,051	(31.4)	15,709	(27.0)
Organic nitrates	488	(4.2)	3,388	(4.9)	20	(2.0)	183	(3.1)	7	(0.8)	82	(1.6)	461	(4.7)	3,123	(5.4)

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; NJR = National Joint Registry; NSAID = non-steroidal anti-inflammatory drug; RAAS = renin-angiotensin-aldosterone-system; SD = standard deviation; THR = total hip replacement.

BIAS ANALYSIS (NJR COHORT)

Table 3.2.2 shows a healthy user effect during the first 6 months after THR surgery. During the period of time immediately after the THR, we observed a decreased risk of any cancer in patients with THR (adjusted RR 0.74; 95% CI 0.57 – 0.95) compared with matched referent subjects. There was a trend of differences in cancer risk between the different types of bearing surfaces during the first 6 months after THR surgery.

TABLE 3.2.2 | Bias-analysis: Relative rates of types of cancer (recorded in the CPRD) < 6 months after total hip replacement (recorded in NJR, stratified by bearing surface type), compared with matched controls without THR surgery, and patients with stemmed metal-on-metal total hip replacements (NJR cohort).

	THR patients		Control patients		Compared with no THR Adjusted relative
	n cases	rate	n cases	rate	rate (95% CI) *
All total hip replacements					
Any cancer	75	1.33	611	1.82	0.74 (0.57-0.96)
By bearing surface type					
Stemmed metal-on-metal	3	0.84	29	0.94	0.80 (0.23-2.76)
Resurfacing	1	0.26	17	0.62	0.39 (0.05-3.12)
Other bearing surfaces	71	1.51	565	1.99	0.75 (0.59-0.96)
Haematological cancer	10	0.18	39	0.12	1.41 (0.67-2.98)
Malignant melanoma	1	0.02	19	0.06	0.26 (0.03-1.99)
Prostate cancer	12	0.21	62	0.18	1.14 (0.59-2.20)
Renal cancer	5	0.09	39	0.12	0.82 (0.31-2.16)
Other cancer	47	0.83	452	1.34	0.63 (0.46-0.86)

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink; n = number; NJR = National Joint Registry; THR = total hip replacement.
Rates are number of events per 100 person years.
* Adjusted for small-area socioeconomic status, smoking status, use of alcohol, body mass index, a history of hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and a prescribing in the 6 months before of NSAIDs or aspirin, oestrogen containing drugs, oral glucocorticoids, calcium / vitamin D supplements, glucose lowering agents, statins, immunosuppressive agents, bisphosphonates, renin-angiotensin-aldosterone-system (RAAS) inhibitors, platelet inhibitors, beta blockers, calcium channel blockers, diuretics, and organic nitrates.

ASSOCIATION BETWEEN HIP REPLACEMENT AND CANCER RISK

The risk of cancer was not increased in THR patients (any bearing surface type) compared with matched referent subjects in any of the three study cohorts and using any of the sources for cancer outcomes (Table 3.2.3). In the CPRD THR cohort, the adjusted RR was 0.76 (95% CI 0.73 – 0.79) using the CPRD for cancer outcomes, 0.73 (95% CI 0.68 – 0.77) using HES for cancer outcomes and 0.70 (95% CI 0.64 – 0.75) using national death certificates. These results closely resembled those of the bias analysis. This implies that patients undergoing THR surgery are healthier at baseline, probably reflecting the selection for surgical fitness. This emphasizes the need for careful timing analyses, rather than overall associations. Similar trends were seen across all databases. Compared with stemmed metal-on-metal hip replacements (NJR cohort), risk of cancer was similar with hip resurfacing (adjusted RR 0.69; 95% CI 0.39 – 1.22) or other types of bearing surfaces (adjusted RR 0.96; 95% CI 0.64 – 1.43).

Table 3.2.4 displays the cumulative incidence rates of cancer over time, stratified by bearing surface type, gender and age (NJR cohort). Overall, we did not find an increased excess rate

TABLE 3.2.3 | Relative rates of cancer (any type as recorded in the CPRD, HES or ONS) during the total follow-up period in patients with and without total hip replacements (as recorded in the CPRD, HES or NJR).

Data sources		THR		Controls		Adj RR
Exposure	Outcome	n cases	rate	n cases	rate	(95% CI) *
CPRD	CPRD	3,752	1.62	25,786	2.11	0.76 (0.73-0.79)
	HES	1,417	1.26	10,166	1.73	0.73 (0.68-0.77)
	ONS	794	0.69	6,058	1.00	0.70 (0.64-0.75)
HES	CPRD	1,64	1.69	10,614	1.99	0.84 (0.80-0.89)
	HES	1,135	1.37	7,488	1.64	0.81 (0.76-0.87)
	ONS	640	0.75	4,469	0.95	0.78 (0.72-0.85)
NJR	CPRD	721	1.69	4,563	1.89	0.89 (0.82-0.97)
	HES	399	1.34	2,701	1.59	0.83 (0.74-0.93)
	ONS	190	0.63	1,395	0.80	0.80 (0.68-0.94)

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; n = number; NJR = National Joint Registry; ONS = Office for National Statistics (death certificates).
Rates are number of events per 100 person years.
* Adjusted for confounders as shown in Table 3.2.2.

TABLE 3.2.4 | Cumulative incidence (%) of any cancer (as recorded in CPRD) after total hip replacement by bearing surface type, sex, and age categories (NJR cohort).

	Cumulative incidence of any cancer (95% confidence interval)				
	≤ 1 years	≤ 2 years	≤ 3 years	≤ 4 years	≤ 5 years
Males					
Age 18 - 59					
Any bearing surface	0.6 (0.3-0.9)	1.2 (0.8-1.6)	1.7 (1.3-2.1)	2.4 (2.0-2.8)	3.0 (2.6-3.4)
Resurfacing	0.4 (0.0-1.4)	0.8 (0.0-1.9)	1.3 (0.1-2.5)	1.7 (0.4-3.0)	2.2 (0.8-3.6)
Stemmed full metal	0.8 (0.0-2.1)	1.6 (0.2-3.0)	2.4 (0.9-3.9)	3.5 (1.8-5.2)	4.2 (2.4-6.0)
Other surfaces	0.6 (0.2-1.0)	1.3 (0.9-1.7)	1.9 (1.5-2.3)	2.6 (2.1-3.1)	3.3 (2.8-3.8)
Age 60 - 79					
Any bearing surface	1.7 (1.2-2.2)	3.4 (2.9-3.9)	5.1 (4.5-5.7)	6.9 (6.3-7.5)	8.7 (8.0-9.4)
Resurfacing	1.4 (0.0-3.1)	3.0 (1.2-4.8)	4.5 (2.6-6.4)	6.3 (4.2-8.4)	8.0 (5.7-10.3)
Stemmed full metal	1.6 (0.0-3.2)	3.3 (1.5-5.1)	4.9 (3.0-6.8)	7.2 (5.1-9.3)	8.4 (6.2-10.6)
Other surfaces	1.8 (1.2-2.4)	3.5 (2.9-4.1)	5.2 (4.6-5.8)	7.0 (6.3-7.7)	8.8 (8.1-9.5)
Age 80+					
Any bearing surface	2.3 (1.0-3.6)	4.6 (3.3-5.9)	6.6 (5.2-8.0)	8.7 (7.2-10.2)	10.7 (9.1-12.3)
Resurfacing	2.8 (0.0-8.1)	5.9 (0.3-11.5)	8.2 (2.5-13.9)	12.1 (5.7-18.5)	15.2 (8.3-22.1)
Stemmed full metal	2.6 (0.0-7.2)	5.2 (0.3-10.1)	7.6 (2.5-12.7)	10.7 (5.1-16.3)	12.5 (6.7-18.3)
Other surfaces	2.4 (1.0-3.8)	4.6 (3.1-6.1)	6.7 (5.2-8.2)	8.7 (7.1-10.3)	10.7 (8.9-12.5)
Females					
Age 18 - 59					
Any bearing surface	0.4 (0.1-0.7)	0.8 (0.5-1.1)	1.2 (0.9-1.5)	1.7 (1.4-2.0)	2.1 (1.7-2.5)
Resurfacing	0.4 (0.0-1.4)	0.8 (0.0-1.9)	1.2 (0.1-2.3)	1.7 (0.4-3.0)	2.2 (0.8-3.6)
Stemmed full metal	0.6 (0.0-1.7)	1.3 (0.1-2.5)	1.9 (0.6-3.2)	2.8 (1.3-4.3)	3.3 (1.7-4.9)
Other surfaces	0.4 (0.1-0.7)	0.9 (0.6-1.2)	1.3 (1.0-1.6)	1.8 (1.4-2.2)	2.3 (1.9-2.7)
Age 60 - 79					
Any bearing surface	1.2 (0.8-1.6)	2.4 (2.0-2.8)	3.6 (3.1-4.1)	4.9 (4.4-5.4)	6.2 (5.6-6.8)
Resurfacing	1.4 (0.0-3.1)	3.1 (1.3-4.9)	4.6 (2.6-6.6)	6.4 (4.3-8.6)	8.1 (5.8-10.4)
Stemmed full metal	1.3 (0.0-2.8)	2.6 (1.0-4.2)	4.0 (2.3-5.7)	5.8 (3.9-7.7)	6.8 (4.8-8.8)
Other surfaces	1.2 (0.7-1.7)	2.4 (1.9-2.9)	3.6 (3.1-4.1)	4.8 (4.2-5.4)	6.1 (5.5-6.7)
Age 80+					
Any bearing surface	1.7 (0.6-2.8)	3.3 (2.2-4.4)	4.8 (3.6-6.0)	6.4 (5.1-7.7)	7.9 (6.5-9.3)
Resurfacing	-	-	-	-	-
Stemmed full metal	2.0 (0.0-6.1)	4.2 (0.0-8.6)	6.2 (1.6-10.8)	8.8 (3.7-13.9)	10.3 (4.9-15.7)
Other surfaces	1.6 (0.4-2.8)	3.1 (1.9-4.3)	4.6 (3.3-5.9)	6.1 (4.7-7.5)	7.6 (6.1-9.1)

Abbreviations: CPRD = Clinical Practice Research Datalink.

of cancer in patients with metal-on-metal hip devices as compared to other bearing surface types. Although there were higher excess rates in specific patient groups (e.g. 80+ years males), the excess rates did not increase over time, suggesting confounding rather than a true causal relationship.

PATTERNS AND TIMING OF CANCER RISK

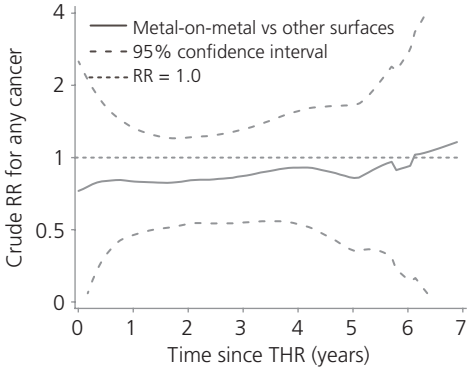
Table 3.2.5 shows the risk of cancer over time within THR patients and matched referent subjects, stratified by type of cancer (CPRD cohort). The risk of cancer increased over time in both THR patients and referent subjects. Figure 3.2.1 shows that risk of cancer in patients with metal-on-metal hip devices remained constant over time compared to individuals with hip implants of other bearing surface types (NJR cohort).

TABLE 3.2.5 | Relative rates of types of cancer (recorded in CPRD) over time (CPRD cohort).

Time period	THR		Adjusted	Controls		Adjusted
(months)	n cases	rate	RR (95% CI)	n cases	rate	RR (95% CI)
Any cancer						
< 6	290	1.31	reference	2,722	2.06	reference
6 - 24	870	1.48	1.13 (0.99 -1.29)	6,903	2.04	0.97 (0.93 -1.02)
25 - 60	1,26	1.56	1.17 (1.03 -1.33)	9,191	2.13	0.96 (0.92 -1.01)
> 60	1,332	1.90	2.10 (1.84 -2.41)	6,97	2.18	1.31 (1.25 -1.38)
Haematological cancer						
< 6	32	0.14	reference	203	0.15	reference
6 - 24	82	0.14	0.95 (0.63 -1.43)	496	0.15	0.93 (0.79 -1.10)
25 - 60	77	0.10	0.63 (0.42 -0.96)	638	0.15	0.88 (0.75 -1.03)
> 60	94	0.13	1.31 (0.85 -2.04)	462	0.14	1.08 (0.91 -1.29)
Malignant melanoma						
< 6	4	0.02	reference	91	0.07	reference
6 - 24	31	0.05	2.89 (1.02 -8.19)	238	0.07	1.01 (0.79 -1.28)
25 - 60	52	0.06	3.38 (1.22 -9.38)	270	0.06	0.86 (0.67 -1.09)
> 60	46	0.07	4.02 (1.41 -11.5)	236	0.07	1.06 (0.82 -1.37)
Prostate cancer						
< 6	42	0.19	reference	294	0.22	reference
6 - 24	116	0.20	1.04 (0.73 -1.48)	707	0.21	0.92 (0.81 -1.06)
25 - 60	142	0.18	0.91 (0.64 -1.29)	969	0.22	0.96 (0.84 -1.10)
> 60	163	0.23	1.93 (1.34 -2.80)	777	0.24	1.64 (1.42 -1.90)
Renal cancer						
< 6	23	0.10	reference	180	0.14	reference
6 - 24	61	0.10	0.99 (0.61 -1.60)	538	0.16	1.15 (0.97 -1.37)
25 - 60	93	0.11	1.06 (0.67 -1.67)	712	0.16	1.15 (0.98 -1.36)
> 60	88	0.13	1.68 (1.03 -2.76)	501	0.16	1.53 (1.28 -1.84)
Other cancer						
< 6	189	0.86	reference	1,954	1.48	reference
6 - 24	580	0.99	1.16 (0.98 -1.36)	4,924	1.45	0.97 (0.92 -1.02)
25 - 60	896	1.11	1.28 (1.09 -1.50)	6,602	1.54	0.96 (0.91 -1.01)
> 60	941	1.34	2.30 (1.94 -2.72)	4,994	1.57	1.29 (1.22 -1.36)

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink; RR = relative rate, THR = total hip replacement.
Adjusted relative rates over time compared to cancer rates during the first 6 months within the same stratum (i.e. within THR patients or within control subjects).

FIGURE 3.2.1 | Crude RR of cancer over time in CPRD (and 95% CI) in patients with a metal-on-metal THR compared to patients with another bearing surface THR (as recorded in NJR



DISCUSSION

This study found that patients with metal-on-metal THR were not at increased risk of cancer compared to individuals with hip implants of other bearing surface types. The results of the patterns of cancer risk over time did not find increases of cancer risk over time. There were substantial differences in baseline characteristics between patients who received metal-on metal hip implants and those with other bearing surfaces. Elderly patients and patients with chronic conditions were less likely to receive a metal-on-metal THR and these factors were found to be associated with the risk of cancer.

Our findings are in line with two recent observational studies investigating the risk of cancer in patients with metal on metal hip replacement.[8,11] Similar to our study, these British and Finnish studies could not find an increased risk of cancer and reported incidence rates that were consistent with our study. However, these previous studies did not have detailed information on risk factors, with only a limited comparison of baseline characteristics between the different types of THR. The present study found that there is strong evidence for confounding between the different types of THR. A Finnish cohort study, comprising 2,164 patients with a mean follow-up of 17 years, showed an increased cancer-related mortality rate in patients with metal-on-metal hip implants (standardised mortality ratio [SMR] of 0.97) compared to individuals with metal-on-polyethylene prostheses (SMR of 0.76).[26] However, as they did not look at incident cancer events, this may well represent confounding by contraindication: individuals with metal-on-polyethylene prostheses are in general older (and may already have developed cancer) and cancer is a relative contraindication for THR. Moreover, life expectancy may be shortened in (prevalent) cancer patients and surgeons may therefore decide not to perform a major elective surgery (such as THR) in these patients. An alternative explanation of the discrepant results is that the length of follow-up (up to 7 years) was shorter in the present study than that in the Finnish study. It has been shown in animal studies that there may be a long latency in the development of tumours following exposure to metal compounds, which may translate to a latency of 10 years in humans.[27] Most other observational studies could

not differentiate between bearing surface types.[7] A meta-analysis including nine of these studies compared risk of cancer in patients with total joint arthroplasty with age- and gender-specific expected cancer rates.[21] In line with our findings, the authors could not find an overall increased risk of any cancer.

This study demonstrates the importance of linkages between different electronic health records for health surveillance monitoring. Whilst the NJR has excellent data on the type of prosthesis, it contains limited data on clinical patient related variables and co-morbidities. In our study, we have shown substantial differences in these clinical variables between prosthesis types, and need to be considered as confounding factors. CPRD does have very extensive information on these variables, as well as comprehensive data on drug and health service utilisation but does not contain detailed surgical information. The linkage of NJR and CPRD does provide an efficient tool for long-term safety monitoring of joint replacements.

The major strength of this study is the linkage between NJR and CPRD which provided detailed information on bearing surface type (NJR) as well as clinical risk factors for cancer (CPRD). Our study had a reasonable sample size and cancer outcomes were obtained through three independently collected databases. A limitation is the lack of information on underlying disease severity (which may have influenced cancer risk) and other potential confounders. Referent subjects were not matched on osteoarthritis (the main indication for THR), which is associated with a decreased risk of cancer.[28] Although this may have underestimated our observed relationship, this is likely to be constant over time and should not have had an impact on the patterns of cancer risk over time. Moreover, this should not have influenced our comparison between bearing surface types, as they should be more or less homogenous with respect to osteoarthritis. We may not be able to extrapolate our findings to long-term situations as some cancers are known to have a prolonged latency since start of exposure. In addition, as explained above, there may be a long latency in the development of tumours following metal exposure, although this has only been based on animal studies.[27]

This study provides reassuring results with respect to the possible signal of increased risks of cancer with metal-on-metal hip replacements. We could not find an elevated risk of cancer with metal-on-metal hip implants and the analyses of cancer risk over time did not support a causal relationship. There were substantial differences in baseline characteristics between the different types of THR complicating the interpretation of a direct comparison between bearing surfaces. The analyses in this study will need to be repeated in the future longer follow-up data, in particular as cancer latency may be prolonged for specific cancer types and following metal exposure.

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CHAPTER 3.3

Knee arthroplasty and risk of hip fracture: a population-based, case-control study

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ABSTRACT

BACKGROUND: The majority of knee arthroplasties (KAs) are performed in patients with osteoarthritis (OA). Although bone mass may be increased in these patients, subjects with knee OA may have an increased risk of hip fracture, possibly due to an increased severity of falls. However, in patients with KAs, risk of hip fracture has not been studied extensively. The objective was to evaluate the association between KAs and hip fracture risk.

METHODS: A population-based case-control study was conducted using the Dutch PHARMO Record Linkage System (1991-2002, n=33,104). Cases were patients with a first admission for hip fracture; controls were matched by age, gender and geographical location. Neither group had a previous history of fracture. Time since first KA was calculated. Analyses were adjusted for disease and drug history.

RESULTS: A 54% increased hip fracture risk was found in patients who underwent KA (adjusted [adj.] OR 1.54; 95% CI 1.19-2.00). We found a strong effect modification by age in these patients: the youngest patients (aged 18-70 years) were at more increased risk for hip fracture (adj. OR 2.76; 95% CI 1.16-6.59), while we could not detect a statistical increase in patients aged >80 years. Furthermore, the association tended to be greater during the first few years after surgery, although it did not reach statistical significance.

CONCLUSIONS: We found that KAs are associated with a 54% increased risk of hip fracture, in particular among adult patients aged <71 years old. Fracture risk assessment could be considered in patients who are about to undergo a KA.

INTRODUCTION

Knee arthroplasties (KAs) are effective interventions, with low mortality rates and few severe adverse outcomes.[1] The surgery is primarily performed in patients with primary osteoarthritis (OA) and rheumatoid arthritis. In Finland, 81% of patients who underwent KA were diagnosed with OA (48,607 surgeries between 1980 and 2003).[2] In Sweden, 87% of the interventions were in patients with OA and 10% in patients with rheumatoid arthritis.[3]

Risk of hip fracture may either be decreased or increased in patients with KA or OA. In frail elderly patients, knee arthroplasty may protect against hip fracture by reducing the occurrence of falls. On the other hand, within the first month after KA, muscle strength is often decreased,[4] which can elevate fracture risk.

There is more evidence about the association of knee OA and fracture. Observational studies have provided conflicting results regarding the risk of hip fracture in patients with OA. A

decreased risk of fractures, compared to control patients, has been reported by several epidemiological studies.[5-7] This may be due to an increased bone mineral density (BMD), even at sites distant to the OA site.[8] Review of histomorphometric and densitometric studies at OA sites of the hip and knee revealed that cartilage fibrillation could not be differentiated from bony changes, even in the earliest stages of OA. Moreover, microfractures of subchondral trabecular bone were less frequently observed in patients with OA compared to controls.[5] Epidemiological studies have revealed that in cases of generalized OA, there are qualitative and quantitative differences, including hyper-mineralization and increased content of growth factors, suggesting a more generalized bone alteration.[5] In contrast, a UK study showed an increased risk of fracture in patients with knee OA,[9] which may have been the result of an increased severity of falls in these patients. The aim of this study was to evaluate the association between KA and the risk of hip fracture.

METHODS

SETTINGS AND STUDY DESIGN

A case-control study was performed using the Dutch PHARMO Record Linkage System (RLS) database (www.pharmo.nl).[10] The database contains pharmacy dispensing data (including dispensed drug, type of prescriber, dispensing date, amount dispensed and written dosage instructions) of about one million Dutch residents, linked to a nationwide hospital discharge register. Diagnoses are coded according to the International Classification of Diseases, 9th revision, (ICD-9). Patients are included irrespective of health insurance or socioeconomic status, and represent about 7% of the general population. The PHARMO RLS database has a high level of completeness, as shown in several independent validation studies.[11]

CASES AND CONTROL SUBJECTS

Cases were defined as patients who had sustained their first hip fracture during the 10-year study period (1 January 1991 to 31 December 2002; at least 18 years of age). Up to four controls were selected for each case, matched by year of birth, gender and geographical location. Control patients were registered on the database and had no record for a hip fracture hospitalization. Cases were assigned the date of hip fracture hospitalization as their index date. Controls were assigned the same index date as their case. In a sensitivity analysis, we restricted the study population to subjects who were at least 50 years of age at the index date.

KA DEFINITION

History of primary KA before index date was determined using ICD-9 surgical procedure codes 81.54. The time since onset ("recency") of the KA was determined by calculating the time between the index date and the earliest hospital admission for the KA. We created a proxy for unilateral / bilateral KA, by stratifying KA patients into (1) subjects with one primary KA record before the index date, and (2) those with multiple primary KA records before the index date. In a sensitivity analysis, we stratified patients who had undergone a KA, to the

region of the body in which osteoarthritis was recorded. We used ICD-9 codes 715.6 (OA of lower leg), and 715.0-715.5 and 715.7-715.9 (OA of other or unspecified regions) to identify a history of OA. In addition, time since onset of OA was calculated similarly to that of the time since KA.

STATISTICAL ANALYSIS

Odds ratios (ORs) for fracture risk were estimated using conditional logistic regression (SAS version 9.1.3, PHREG procedure). The following risk factors were considered as potential confounders: use of benzodiazepines in the three months before the index date;10 use of bronchodilators, inhaled corticosteroids, oral corticosteroids,[12,13] statins,[14] antipsychotics,[15] lithium,[16] antidepressants,[17] beta-blockers,[18] opioids (tramadol and stronger), anti-epileptics, thiazide diuretics,[19] renin-angiotensin-aldosterone system (RAAS) inhibitors, acid suppressants,[20] two or more dispensings of a non-steroidal anti-inflammatory drug, disease modifying anti-rheumatic drugs, organic nitrates,[21] anti-diabetic drugs, bisphosphonates, hormone replacement therapy, calcium / vitamin D supplements, digoxin, and other anti-arrhythmics, within the 6 months before the index date. In addition, a diagnosis of anaemia, mental disorders, impaired renal functioning, skin or subcutaneous disease, any serious injury within the year before the index date, or a history of malignant neoplasm, endocrine disorder, cardiovascular disease, obstructive airways disease, inflammatory bowel disease, musculoskeletal diseases (excluding OA), and connective tissue diseases or rheumatoid arthritis ever before index date were considered as potential confounders. Parameters were included in the final regression model if they independently changed the beta coefficient for arthroplasty with >5% in the logistic regression model. In a sensitivity analysis, we included use of bisphosphonates and hormone replacement therapy within 6 months before index date in the final regression model, regardless of the change in beta coefficient for arthroplasty caused by these treatments. The longitudinal relationship between the risk of hip fracture and time since KA was visualized using a smoothing spline regression plot (SAS version 9.1.3, GPLOT procedure). Spline regression has been advocated as an alternative to categorical analysis.[22]

RESULTS

Table 3.3.1 shows baseline characteristics of the fracture cases and controls. As expected (due to matching), cases and controls had a similar age and gender distribution. Fracture cases had recently used more medication that has been associated with fracture, such as oral glucocorticoids and strong opioid analgesic. Compared to controls, they had more often a history of comorbid conditions.

Table 3.3.2 shows the relationship between time since KA and the risk of hip fracture. In the adjusted analysis, we found a 54%-increased risk of hip fracture among patients with KA (adjusted [adj.] OR 1.54; 95% confidence interval [CI] 1.16-1.99). In the sensitivity analysis, use of bisphosphonates and hormone replacement therapy within 6 months before index date

did not substantially change the increased risk (adj. OR 1.54; 95% CI 1.19-2.00). Similarly, the increased risk was not changed when looking at subjects aged ≥ 50 years only (93.2% of the study population; adj. OR 1.55; 95% CI 1.19-2.01). There was a suggestion that the increased risk of hip fracture was greatest in the first few years after the first KA (Figure 3.3.1), although there were no statistically significant differences with time. No substantial differences were found with regards to the proxy for unilateral (adj. OR 1.40; 95% CI 1.01-1.95) and bilateral (adj. OR 1.81; 95% CI 1.20-2.74) KA (p=0.34). Furthermore, timing of increased hip fracture risk following the most recent KA was comparable between the two groups (data not shown).

TABLE 3.3.1 | Characteristics of hip fracture cases and controls.

Characteristic	Cases (%) n = 6,763		Controls (%) n = 26,341	
Gender				
Female	4,929	(72.9)	19,138	(72.7)
Age				
18-70 years	1,641	(24.3)	6,554	(24.9)
71-80 years	2,144	(31.7)	8,496	(32.3)
>80 years	2,978	(44.0)	11,291	(42.9)
Use 6 months prior to index date				
Oral glucocorticoids	366	(5.4)	918	(3.5)
Paracetamol	882	(13.0)	2,247	(8.5)
>1 NSAIDs	929	(13.7)	2,584	(9.8)
Opioids	253	(3.7)	455	(1.7)
DMARDs	115	(1.7)	202	(0.8)
Antipsychotics	412	(6.1)	921	(3.5)
Calcium / vitamin D supplements	362	(5.4)	894	(3.4)
Hospitalization ever prior to index date				
Osteoarthritis	220	(3.3)	773	(2.9)
Rheumatoid arthritis	245	(3.6)	731	(2.8)
Musculoskeletal / connective tissue disease (excluding osteoarthritis)	469	(6.9)	1,328	(5.0)
Endocrine disorders	199	(2.9)	381	(1.4)
Obstructive airway disease	266	(3.9)	643	(2.4)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs

TABLE 3.3.2 | Risk of hip fracture with knee arthroplasty.

	Cases (%) n = 6,763		Controls (%) n = 26,341		Crude OR (95% CI)	Adj. OR (95% CI) †
Never knee arthroplasty	6,674	(98.7)	26,133	(99.2)	1.00	1.00
Ever knee arthroplasty	89	(1.3)	208	(0.8)	1.69 (1.32-2.18)*	1.54 (1.19-2.00)*
<2 years before index	28	(0.4)	69	(0.3)	1.60 (1.03-2.49)*	1.43 (0.89-2.29)
2-5 years before index	40	(0.6)	79	(0.3)	2.01 (1.37-2.96)*	1.96 (1.31-2.92)*
>5 years before index	21	(0.3)	60	(0.2)	1.37 (0.83-2.26)	1.08 (0.63-1.85)
By number of primary KAs						
One KA record	53	(0.8)	135	(0.5)	1.54 (1.11-2.12)*	1.40 (1.01-1.95)*
Multiple KA records	36	(0.5)	73	(0.3)	1.98 (1.33-2.96)*	1.81 (1.20-2.74)*

Abbreviations: OR, odds ratio; adj, adjusted; CI, confidence interval.
* Statistically significant differences compared to referent.
† Adjusted for use of benzodiazepines within 3 months prior, use of bronchodilators, antipsychotics, antidepressants, opioids, antiepileptics, DMARDs, calcium / vitamin D supplements, a history of anemia, skin or subcutaneous disease, or serious injuries one year prior, malignant neoplasms, endocrine disorders, cardiovascular disease, obstructive airway disease, inflammatory bowel disease, musculoskeletal/connective tissue disease (excluding osteoarthritis), or rheumatoid arthritis ever before index date.

FIGURE 3.3.1 | Smoothed spline visualization of the relationship between time since first knee arthroplasty and adjusted risk of hip fracture. Dashed lines represent 95% confidence interval bands. Adjusted for confounders as shown in Table 2.

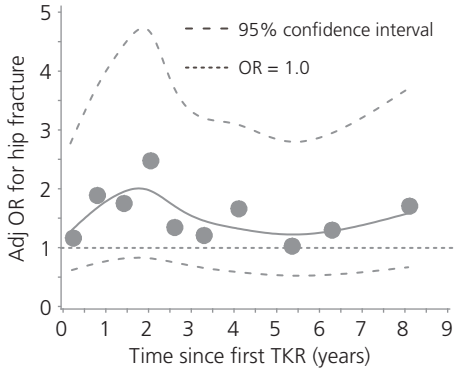

FIGURE 3.3.2 | Smoothed spline visualization of the association between first KA and adjusted risk of hip fracture, by age at the index date. Dashed lines represent 95% confidence interval bands. Adjusted for confounders as shown in Table 2.

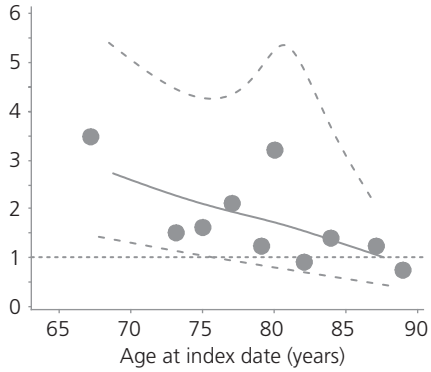

TABLE 3.3.3 | Risk of hip fracture with knee arthroplasty stratified by gender, age and medication use.

	Cases (%) n = 6,763		Controls (%) n = 26,341		Crude OR (95% CI)	Adj. OR (95% CI) †
Never knee arthroplasty	6,674	(98.7)	26,133	(99.2)	1.00	1.00
Ever knee arthroplasty	89	(1.3)	208	(0.8)	1.69 (1.32-2.18)*	1.54 (1.19-2.00)*
By gender						
Males	7	(0.1)	24	(0.1)	1.17 (0.50-2.74)	0.82 (0.33-2.03)
Females	82	(1.2)	184	(0.7)	1.76 (1.35-2.29)*	1.62 (1.22-2.15)*
By age						
18-70 years	13	(0.2)	13	(0.0)	4.18 (1.90-9.19)*	2.76 (1.16-6.59)*
71-80 years	43	(0.6)	95	(0.4)	1.82 (1.26-2.63)*	1.72 (1.15-2.57)*
>80 years	33	(0.5)	100	(0.4)	1.27 (0.85-1.89)	1.16 (0.77-1.75)
By use of pain relievers 6 months before ‡						
Yes	43	(0.6)	75	(0.3)	2.25 (1.55-3.28)*	1.93 (1.28-2.91)*
No	46	(0.7)	133	(0.5)	1.37 (0.97-1.92)	1.33 (0.93-1.89)
By use of oral corticosteroids 6 months before						
Yes	6	(0.1)	12	(0.0)	1.94 (0.73-5.18)	1.41 (0.47-4.21)
No	83	(1.2)	196	(0.7)	1.68 (1.29-2.17)*	1.56 (1.18-2.05)*
By use of calcium / vitamin D supplements 6 months before						
Yes	7	(0.1)	18	(0.1)	1.77 (0.73-4.30)	1.40 (0.55-3.58)
No	82	(1.2)	190	(0.7)	1.64 (1.25-2.15)*	1.56 (1.18-2.06)*

Abbreviations: OR, odds ratio; adj, adjusted; CI, confidence interval.
* Statistically significant differences.
† Adjusted confounders as shown in Table 3.3.2 compared to referent, except for the stratified covariate of interest.
‡ Opioids (tramadol or stronger), paracetamol, or >1 NSAID prescription.

Table 3.3.3 shows that the increase in risk of hip fracture in patients with KA was highest in patients aged 18-70 years (adj. OR 2.76; 95% CI 1.16-6.59). The increase in hip fracture risk rapidly decreased towards baseline levels with increasing age (Figure 3.3.2): patients aged

71-80 years had an adj. OR of 1.72 (95% CI 1.15-2.57), while the risk was no longer elevated in patients who were older than 80 years (adj. OR of 1.16; 95% CI 0.77-1.75). The increase in risk of hip fracture tended to be higher in females (adj. OR 1.62; 95% CI 1.22-2.15), when compared to males (adj. OR 0.82; 95% CI 0.33-2.03), although this difference did not reach statistical significance.

KA patients who were dispensed pain relievers (opioids [tramadol or stronger], paracetamol, or >1 NSAID prescription) 6 months before the index date did not have a significantly higher risk of hip fracture (adj. OR 1.93; 95% CI 1.28-2.91) when compared to patients without a history of pain reliever use (adj. OR 1.33; 95% CI 0.93-1.89) 6 months before (p=0.17; Table 3.3.3). Similarly, patients who had used oral corticosteroids in the 6 months before (adj. OR 1.41; 95% CI 0.47-4.21) were at same risk of hip fracture when compared to patients without a use of oral corticosteroids in the same period (adj. OR 1.56; 95% CI 1.18-2.05).

Table 3.3.4 shows that the association between KA and hip fracture did not substantially change, when KAs were restricted to patients with a history of OA. The proportion of lower leg OA in patients who had undergone KA was 85%. KA patients with lower leg OA had the same risk of hip fracture (adj. OR 1.45; 95% CI 1.08-1.95) when compared to KA patients without correction of lower leg OA (adj. OR 1.54; 95% CI 1.19-2.00).

TABLE 3.3.4 | Risk of hip fracture with knee arthroplasty among osteoarthritis of lower leg.

	Cases (%) n = 6,763		Controls (%) n = 26,341		Crude OR (95% CI)	Adj. OR (95% CI) †
Never knee arthroplasty	6,674	(98.7)	26,133	(99.2)	1.00	1.00
Ever knee arthroplasty	89	(1.3)	208	(0.8)	1.69 (1.32-2.18)*	1.54 (1.19-2.00)*
By osteoarthritis at any site						
Never before index	12	(0.2)	21	(0.1)	2.23 (1.10-4.55)*	1.84 (0.88-3.85)
Ever before index	77	(1.1)	187	(0.7)	1.63 (1.24-2.13)*	1.48 (1.11-1.97)*
By site of osteoarthritis						
Lower Leg	73	(1.1)	179	(0.7)	1.61 (1.22-2.12)*	1.45 (1.08-1.95)*
<2 years before	24	(0.4)	61	(0.2)	1.56 (0.97-2.50)	1.39 (0.83-2.32)
2-5 years before	32	(0.5)	64	(0.2)	1.98 (1.29-3.03)*	2.00 (1.29-3.11)*
>5 years before	17	(0.3)	54	(0.2)	1.24 (0.72-2.15)	0.93 (0.51-1.69)
Other regions	4	(0.1)	8	(0.0)	2.00 (0.60-6.64)	2.17 (0.61-7.66)

Abbreviations: OR, odds ratio; adj, adjusted; CI, confidence interval.
* Statistically significant differences compared to referent.
† Adjusted for confounders as shown in Table 3.3.2.

DISCUSSION

This study showed a 1.5-fold increased hip fracture risk in patients who had undergone a KA. The risk of hip fracture was greatest in young patients (18-70 years old). With increasing age, we found a rapid decrease in strength of association, which was no longer elevated in patients aged 81 years and older. The association tended to be greater during the first few years after surgery, but it did not reach statistical significance. Recent use of pain relievers or glucocorticoids did not alter the overall risk of hip fracture.

This is the second study that has evaluated risk of hip fracture in patients with a history of KA and is in line with the first study, which has shown a 58% increased risk of hip fracture in British patients within the first year after their KA.[23] Studies that investigated the association between OA (the main indication for KA) and risk of hip fracture have yielded conflicting findings. Some authors suggested a decreased fracture rate among patients with OA,[5-7] possibly due to higher BMD levels.[8] Although data are controversial, patients with OA may have an increased osteoblastic activity at the OA site, resulting into higher BMD levels and therefore lower fracture rates.[5] On the other hand, others reported an increased hip fracture risk, which is in line with our study results. Bergink et al found an increased risk of both vertebral (2.0-fold) and nonvertebral (1.5-fold) fractures in patients with knee OA.[24] Similarly, Arden et al demonstrated that patients with knee pain or a clinician diagnosis of knee OA have an increased risk of hip and nonvertebral fractures.[9] This is probably explained by an increased severity of falls, since they could not detect an increased number of falls. It should be noted however, that data collection on falls is often incomplete. This could explain the results of a different study that found an increased occurrence of falls among patients with lower limb OA.[25] Furthermore, looking at differences in fracture types, the studies by Arden et al and Vestergaard et al found a substantially higher increase in risk of hip fracture, as compared to other fractures (such as distal forearm fractures).[6,9] This may suggest an important role for the nature of falls in patients with knee OA, as explained by Arden et al. A US case-control study has shown that hip fractures tend to result from falling sideways or straight down (low walking speed), whereas forearm fractures may be more likely to be the result of falling backwards.[26] However, Bergink et al could not demonstrate a difference between hip and wrist fractures.[24] Overall, our findings support the studies that found an increased hip fracture risk, indicating that the increased number and severity of falls may attenuate any potentially beneficial effects of higher BMD levels on fracture risk in these patients.

Given this proposed mechanism, we would have expected hip fracture rates to decrease after the KA procedure, as the surgery relieves pain and partially restores biomechanical properties of the knee. However, evidence regarding this hypothesis is conflicting. One study reported less falls within one year after the KA,[27] while a recent Danish study could not detect any decreases in hip fracture rates during that period.[6] In line with the Danish study and the British study mentioned earlier,[23] we found no obvious decrease in hip fracture risk shortly after the surgery. A possible explanation for our findings is that patients become rapidly more active after their KA, due to effective knee pain relief.[28] An overestimation of their physical stability may therefore possibly increase the risk of falls. This could also explain our observed effect modification by age: the youngest patients were at highest hip fracture risk. As compared with elderly patients, these patients may be more likely to increase their physical activity quickly after their surgery had taken place. In addition, residual knee pain and stiffness in the first months after surgery may be present in some KA patients, and could further explain our observed increased hip fracture risk.

Strengths of our study include its population-based setting and that it had a reasonable sample

size and longitudinal data collection.[10,12-14] Linkage with the Dutch National Hospitalization Registry assured routinely collected KA surgeries, and hip fractures. Limitations include the lack of data on physical activity, which could be an alternative explanation for our observed association between KA and hip fracture. Physical activity is significantly increased in KA patients within 9 months postoperatively,[28] while a rapid increase could potentially initiate falls. In addition, we did not have data on body mass index (BMI), which could have underestimated our observed association between KA and hip fracture. An increased BMI is a well-known risk factor for knee OA,[29] while it is inversely associated with risk of hip fracture.[30] Nevertheless, our findings are similar to the BMI adjusted results from the GPRD study.[23] Similar to the British study,[23] we could not differentiate between the sides of KA or sides of hip fracture. This information could be helpful in understanding the mechanism of the observed increased risk of hip fracture following KA. Local bone loss may be induced on the side of the replaced knee, possibly resulting into an increased fracture risk of the hip on the same side.[31] The only feasible way to investigate this is to link a dedicated joint registry to a hospital / general practitioners database, which has been planned for the UK National Joint Registry (NJR) and the GPRD. Furthermore, we did not have data on BMD or falling, which could have been useful for the assessment of causality and the underlying mechanism. In addition, OA could only be identified in hospitalized patients. Frail unexposed subjects bias may have occurred if KA patients had lower mortality rates as compared to subjects who had not undergone KA (due to clinical assessment of operative risk).[32] This was probably not the case: within our control subjects (those without a hip fracture), proportions of cardiovascular hospitalisations were not lower in KA patients (6.7%) compared to patient without a history of KA (4.9%). Unfortunately, we did not have data on other fracture types (such as distal forearm fractures). As our data source only keeps track of hospitalisations, fractures other than those of the hip would suffer from under recording. Although OA diagnosis and KA surgery have not been validated in this data source, we expect high completeness for KA registration. Our hospitalisation source was primarily designed to keep track of economic parameters (e.g. health care cost). Given the high cost for a KA surgery, we would expect adequate recording of this procedure.

In conclusion, we showed that KA was associated with a 54% increased risk of hip fracture, which was not influenced by recent use of pain relievers or corticosteroids. The increase in risk was highest among younger patients (<71 years), which may reflect a rapid increase in physical activity immediately after surgery. Risk assessment of hip fracture could therefore be considered in patients who are about to undergo a KA. It is worthwhile to evaluate its health economic impact.

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CHAPTER 3.4

Risk of fracture after bariatric surgery in the United Kingdom: population based, retrospective cohort study

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ABSTRACT

BACKGROUND: Bariatric surgery can be considered among patients with morbid obesity. Such procedures have been associated with a post-operative reduction in bone mineral density, but it is not known whether this translates into an increased risk of fracture. The objective of this study was to estimate fracture risk in bariatric surgery patients versus matched controls.

METHODS: A retrospective cohort study was conducted within the UK General Practice Research Database (1987-2010). Patients had a record of bariatric surgery (n=2,079), and were matched to up to 6 controls without bariatric surgery by age, sex, practice, and body mass index. They were followed from the date of bariatric surgery for the occurrence of any fracture. Disease and medication adjusted relative rates were calculated using time dependent Cox regression.

RESULTS: Although there was a trend towards increased fracture risk in the first 3 months after surgery and then after 3 to 5 years, overall there was no statistically significant increased risk of fracture in patients who underwent bariatric surgery, compared to matched controls [adjusted relative rate 0.89 (95% confidence interval 0.60 to 1.33)]. There was a trend towards increasing fracture risk with greater post-operative decrease in body mass index, but again this was not statistically significant.

CONCLUSIONS: This is the first study that estimates risk of fracture after bariatric surgery compared to controls. Overall, for the first few post-operative years, these results are reassuring for patients undergoing bariatric surgery, but do not exclude a more protracted adverse influence on skeletal health.

INTRODUCTION

Obesity is an increasing public health problem worldwide. The prevalence of obesity, which is defined as a body mass index above 30 kg/m^2, amongst middle-aged Europeans has been estimated as 15-20%.[1] Data on the prevalence of morbid obesity (body mass index of greater than 40 kg/m^2) are lacking in Europe. In the United States, at least 5% of the population is morbidly obese.[2] It is now recognised that surgical treatment is the most effective route to weight loss for those with morbid obesity, accompanied by reduction of mortality and improvement of comorbid conditions.[3-5]

Bariatric surgical procedures (conventionally grouped as restrictive or malabsorptive) negatively affect bone remodeling, as suggested by studies on bone resorption markers, and bone mineral density. Restrictive procedures, such as vertical banded gastroplasty and laparoscopic adjustable banding, have been consistently reported to increase bone resorption,[6-11] an increase which is similar in magnitude to that observed in other forms of

weight reduction.[8] The mechanisms behind the increase in bone resorption after weight loss are not fully understood, but two factors appear to be involved. First, reduced fat volume may lead to a reduction in circulating estrogens, which are partly synthesised in adipose tissue.[10] A second consequence of reduced fat mass is a fall in leptin which could result in an increase in osteoclast recruitment and bone turnover.[12,13] Malabsorptive procedures such as jejuno-ileal bypass and bilio-pancreatic diversion have also been associated with an increase of bone resorption and a decrease in bone mineral density;[14-19] contributory factors clearly include calcium and vitamin D malabsorption, and secondary hyperparathyroidism.[20] The Roux-en-Y gastric bypass surgery (a combined restrictive and malabsorptive operation) is also associated with increased bone resorption and decreased bone mineral density.[14,21-27]

Although there is evidence that patients may have decreased bone mineral density after bariatric surgery, the impact of the procedure on fracture risk has not been determined. Furthermore, the link between body mass index change and fracture risk is unknown. The aims of this study were thus: (1) to estimate the risk of fracture in patients with bariatric surgery compared to morbidly obese patients who did not undergo surgery, and (2) to quantify the influence on fracture risk of the magnitude of body mass index decrease following surgery.

METHODS

STUDY POPULATION

A retrospective cohort study was conducted within the General Practice Research Database, now known as the Clinical Practice Research Datalink (www.cprd.com). The General Practice Research Database contains computerized medical records of 625 primary care practices in the United Kingdom, representing 8% of the British population. The database provides detailed information on demographics, drug prescriptions, clinical events, specialist referrals, and hospital admissions. Previous studies of General Practice Research Database data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed),[28] and high degrees of validity and completeness of other diagnoses / smoking status has been reported in several systematic reviews.[29-31]

The study population consisted of all patients with a General Practice Research Database Read code for bariatric surgery during the period of valid General Practice Research Database data collection (from 1987 through December 2010). Bariatric surgery for cancer was excluded in this study, as cancer itself may influence bone metabolism. The index date was defined as the first record for bariatric surgery. Bariatric surgery patients were only included if they had a body mass index record with a value of at least 30 kg/m^2 at some point before surgery. Bariatric surgery patients were stratified by surgical technique, including adjustable gastric banding, Roux-en-Y gastric bypass, and other techniques (e.g. gastrectomy, and malabsorptive procedures). Selection of control subjects Each patient was matched by age, gender, body mass index (within 10% difference), calendar time, and practice to up to 6 patients without a history of bariatric surgery (at any time during the study period). Body mass index entries were

selected as the latest record prior to surgery (measured at any time before the index date).

OUTCOMES

Patients were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, the patient's death, or fracture (General Practice Research Database read codes), whichever came first. Fracture type was stratified according to WHO definitions into osteoporotic (spine, hip, forearm or humerus fracture), and non-osteoporotic fracture.[32] For the analyses looking at these two different fracture groups, all patients were followed up for the occurrence of a fracture in the specific group, regardless of whether a fracture already occurred in the other group (i.e. patients could have sustained both an osteoporotic and non-osteoporotic fracture).

POTENTIAL CONFOUNDERS

General risk factors considered in this study included age, gender, smoking status (a record of currently smoking, ex-smoker, or never smoked before; missing data were treated as a separate category in the analyses), a record of falls in the previous 6 - 12 months (any fall recorded by the general practitioner; falls in the prior 6 months were excluded), history of fracture, history of a chronic disease (cerebrovascular disease, heart failure, inflammatory bowel disease, asthma/chronic obstructive pulmonary disease, anaemia and dementia), and a prescription for glucocorticosteroids, antiobesity drugs, calcium / vitamin D supplements, antihypertensive drugs, loop diuretics, hypnotic/anxiolytic, antipsychotic, antidepressant, proton pump inhibitor, or antiepileptic agents, as well as drugs for the treatment of Parkinson's disease, in the previous 6 months.[34-37] Age and most recent body mass index record before the index date were handled as continuous variables in the analyses.

STATISTICAL ANALYSIS

Two main analyses were conducted using stratified Cox proportional hazards models (SAS 9.2, PHREG procedure; stratified matched cohort analysis). The first analysis compared the fracture rate in patients with bariatric surgery with that in control patients (with the same body mass index), to yield an estimate of the relative risk of fracture in bariatric surgery patients (stratified by type of fracture, and type of bariatric surgical technique). The total follow-up period was divided into 30-day intervals. The presence of risk factors was assessed by reviewing the computerized medical records of risk factors prior to the start of an interval. Potential confounders were included in the final model if they independently changed the beta-coefficient for bariatric surgery by at least 10%.

The second analysis studied the impact of excess (defining the limit of normality as 25 kg/m²) body mass index loss following surgery on fracture risk. For that purpose, we divided all bariatric surgery patients into four different groups: (1) patients with no excess body mass index loss after surgery, (2) patients with 0-50% excess body mass index loss after surgery, (3) patients with ≥50% excess body mass index loss after surgery, and (4) patients where the amount of excess body mass index loss was unknown. Excess body mass index loss was

calculated as follows: 100 * (preoperative body mass index – present body mass index) / (preoperative body mass index – 25). Based on this excess body mass index loss, person time was allocated to one of the four previously defined categories. In the event of no body mass index assessments in that given period, the person time was allocated to the unknown category (category 4).

Timing of fracture occurrence following bariatric surgery was examined by including time interaction terms (time period * bariatric surgery) into the model for the following time intervals: < 3 months, 3 – 12 months, 1 – 2 years, 2 – 5 years, and ≥ 5 years. Using smoothing spline regression,[38] we visualized the time trend for risk of fracture for these given time intervals.

In a sensitivity analysis, we restricted bariatric surgery patients to those with a body mass index record within 2 months before bariatric surgery, and reset the index date for controls as the date of most recent body mass index recording. These analyses were further adjusted for calendar year and age at the newly defined index date (along with all other confounders). Our power analysis demonstrated a power of 88%, assuming a relative risk of 1.6, a type I probability of 0.05, and based on our cohort sizes (2,079 bariatric surgery patients, on average 5.02 matched controls per patient, and a fracture probability in the control group of 2.0%).

TABLE 3.4.1 | Baseline characteristics of bariatric surgery patients and matched controls.

	Bariatric surgery patients		Matched controls	
Characteristic	n = 2,079	(%)	n = 10,442	(%)
Mean follow-up time (years)	2.2	(2.1)	2.3	(2.2)
Females	1,744	(83.9)	8,904	(85.3)
Mean age at index date (years)	44.6	(11.1)	45.0	(11.2)
Mean BMI at index date (kg/m^2)	43.2	(7.2)	40.8	(6.4)
Smoking status				
Never	1,092	(52.5)	5,957	(57.0)
Current	377	(18.1)	2,293	(22.0)
Ex	591	(28.4)	2,1	(20.1)
Unknown	19	(0.9)	92	(0.9)
Falls (6 - 12 months before)	22	(1.1)	58	(0.6)
History of disease ever before				
Fracture	407	(19.6)	1,876	(18.0)
Rheumatoid arthritis	30	(1.4)	120	(1.1)
Drug use within 6 months				
Glucocorticoids	89	(4.3)	370	(3.5)
Calcium / vitamin D supplements	104	(5.0)	174	(1.7)
Antiobesity drugs	248	(11.9)	576	(5.5)
Antidiabetics	401	(19.3)	1,102	(10.6)
Antidepressants	697	(33.5)	2,05	(19.6)
Anxyolytics / hypnotics	203	(9.8)	574	(5.5)
Bisphosphonates	8	(0.4)	68	(0.7)
Hormone replacement therapy	90	(4.3)	271	(2.6)
Proton pump inhibitors	503	(24.2)	1,315	(12.6)

Abbreviations: SD, standard deviation; BMI, body mass index.

RESULTS

Baseline characteristics of bariatric surgery patients and matched controls are shown in Table 3.4.1. We identified 2,079 patients who underwent bariatric surgery (mean age 44.6 years, 83.9% female, mean body mass index 43.2 kg/m^2), and a total of 10,442 matched controls (mean age 44.9 years, 85.3% female, mean body mass index 40.8 kg/m^2). Adjustable gastric banding was the most frequent surgical technique for bariatric surgery (60%), followed by Roux-en-Y gastric bypass (29%, Figure 3.4.1). The median difference between the index date and most recent body mass index record was 109 days (interquartile range 241 days) for bariatric surgery patients, and 321 days (interquartile range 680 days) for matched controls. Bariatric surgery patients were more likely to have used antidiabetics, antidepressants, anxiolytics / hypnotics, opioids, and proton pump inhibitors in the previous 6 months. Total duration of follow up was 28,899 person-years with a mean of 2.2 years for bariatric surgery patients and 2.3 years for matched controls.

FIGURE 3.4.1 | Number of bariatric surgeries, by year and type of bariatric surgery.

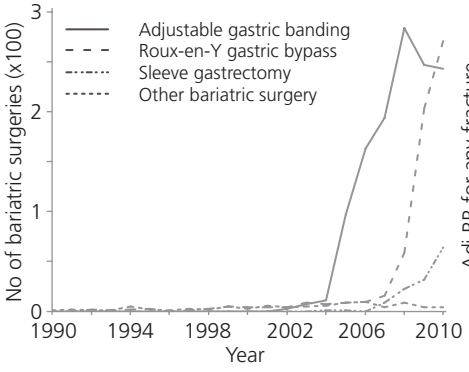

FIGURE 3.4.2 | Risk of any fracture in bariatric surgery patients versus controls.

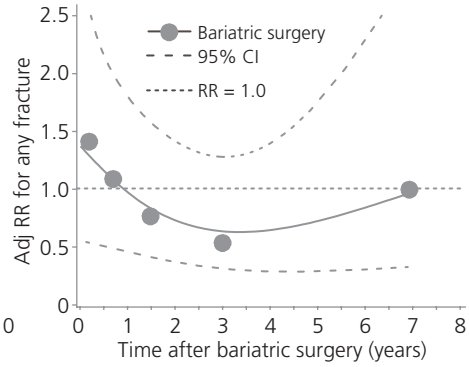

Table 3.4.2 shows the overall risk of fracture in bariatric surgery patients compared to matched controls, stratified by fracture type. We did not observe an increase in overall fracture risk: any fracture adjusted relative risk 0.89 (95% confidence interval 0.60 to 1.33), osteoporotic fracture adjusted relative risk 0.67 (0.34 to 1.32), or non-osteoporotic fracture adjusted relative risk 0.90 (0.56 to 1.45). Similar rates for any fracture were observed throughout the different surgical techniques. Figure 3.4.2 demonstrates the change in adjusted relative risk with time post-surgery, showing a modestly increased risk over the first three months, followed by a reduction and then a trend towards increasing fracture risk after 3 to 5 years. However, none of these trends achieved statistical significance, and overall there was no statistically significant interaction between bariatric surgery and time. Our sensitivity analysis showed similar findings when we restricted the sets to bariatric surgery with only recent body mass index records. Confounders that were included in the final adjusted models are listed in the footnote of Table 3.4.2.

TABLE 3.4.2 | Risk of fracture in bariatric surgery patients compared with age-, sex- and body mass index-matched controls, by type of fracture.

	Fracture			
	N =	(%)	Crude RR (95% CI) *	Adjusted RR (95% CI) †
No bariatric surgery	207	(2.0)	1.00	1.00
Bariatric surgery				
Any fracture	38	(1.8)	1.07 (0.74-1.54)	0.89 (0.60-1.33)
By type of bariatric surgery				
Gastric banding	21	(1.0)	0.85 (0.53-1.36)	0.82 (0.50-1.36)
RYGB	9	(0.4)	2.11 (0.98-4.56)	0.77 (0.27-2.16)
Other	8	(0.4)	1.24 (0.51-3.01)	1.28 (0.42-3.92)
Non-osteoporotic	26	(1.3)	1.01 (0.65-1.57)	0.90 (0.56-1.45)
Osteoporotic	13	(0.6)	0.88 (0.47-1.64)	0.67 (0.34-1.32)

Abbreviations: RR, relative risk; CI, confidence interval; RYGB, Roux-en-Y gastric bypass.
* Adjusted for age, sex, and most recent BMI record before the index date.
† Adjusted for age, sex, and most recent BMI record before the index date, a history of fracture, inflammatory bowel disease, and cerebrovascular disease ever before, a history of falls in the 6 - 12 months before, and use of glucocorticoids, calcium / vitamin D supplements, antiobesity drugs, antihypertensive drugs, loop diuretics, organic nitrates, antidepressants, anxiolytics / hypnotics, bisphosphonates, opioids (tramadol or stronger), and proton pump inhibitors in the previous 6 months.

Within bariatric surgery patients, use of anxiolytics in the previous 6 months (adjusted relative risk 1.82 (1.06 to 3.15)), and a history of cerebrovascular disease (adjusted relative risk 8.26 (4.40 to 15.52)), or previous fracture (adjusted relative risk 2.44 (1.59 to 3.76)) elevated the risk of fracture. Use of antidepressants, antidiabetics, proton pump inhibitors, or statins within 6 months did not significantly alter fracture risk within bariatric surgery patients (data not shown).

TABLE 3.4.3 | Risk of any fracture within bariatric surgery patients, by excess body mass index change during follow-up.

	Any fracture			
	N =	(%)	Crude RR (95% CI) *	Adj. RR (95% CI) †
Bariatric surgery				
Any fracture	38	(1.8)		
By excess BMI loss				
< 0% excess BMI loss	1	(0.0)	0.31 (0.04-2.49)	0.32 (0.04-2.57)
0 - 50% excess BMI loss	9	(0.4)	referent	referent
≥ 50% excess BMI loss	8	(0.4)	1.58 (0.61-4.11)	1.46 (0.55-3.85)
Unknown	20	(1.0)	0.56 (0.25-1.25)	0.51 (0.23-1.15)

Abbreviations: RR, relative risk; CI, confidence interval; BMI, body mass index.
* Adjusted for age, sex, and most recent BMI record before the index date.
† Adjusted for confounders as shown in Table 3.4.2.

Although there was a trend towards an increased risk of fracture with greater loss of post-operative excess body mass index, this was not statistically significant (Table 3.4.3). It should be noted, however, that this analysis had limited statistical power. Thus compared to subjects with medium excess body mass index loss (1% – 50%), the adjusted relative risk was 0.32 (0.04 to 2.57) in those with no excess body mass index loss, and 1.46 (0.55 to 3.85) in individuals who lost over 50% of their excess body mass index. The relationship between body mass index loss and fracture risk was similar when only including patients with a body mass index recording in the 2 months before bariatric surgery.

DISCUSSION

To our knowledge, this is the first study to investigate fracture risk in patients who underwent bariatric surgery versus matched controls. Although we observed a possible rise in fracture risk at five years post-surgery, overall, we were not able to demonstrate a statistically significantly increased risk of fracture (any, non-osteoporotic or osteoporotic) with bariatric surgery. There was a trend towards increasing fracture risk with greater magnitude of excess body mass index loss following bariatric surgery, but again this was not statistically significant.

Although there are no fracture studies in bariatric surgery patients versus matched controls up to date, our findings are indirectly supported by a meta-analysis conducted by De Laet and colleagues.[39] They showed that a decrease in body mass index was less predictive for fracture in obese patients (>30 kg/m^2), as compared to in those with a body mass index of less than 30 kg/m^2. For example, when comparing subjects with a body mass index of 15 kg/m^2 and 20 kg/m^2, they found a 3.7-fold elevated risk of hip fracture in the leaner subjects. When comparing subjects with a body mass index of 30 kg/m^2 and 35 kg/m^2 on the other hand, the relative risk was much lower (non-significant 1.1-fold increase in leaner patients). The authors suggested that leanness is a much more important risk factor for fracture, rather than considering obesity as a protective factor. A study by Nakamura et al estimated fracture rates in bariatric surgery patients, but could not compare this with body mass index matched control subjects.[40] Although they do suggest an increased risk based on expected age and gender specific incidence rates, this may well be the effect of obesity related comorbidities (as we have shown in our baseline characteristics).

Up to now, studies on bariatric surgery and bone effects have been limited to a number of reports on bone resorption markers and bone mineral density.[10,14-19,21-27] Although the effect appeared to be small and varied between studies, the results suggested that bariatric surgery might negatively affect bone. For example, Giusti and colleagues reported a slight decrease in bone mineral density at the femoral neck (-5.8%), trochanter (-6.5%), but not at the lumbar spine (+8.0%), 2 years after gastric banding procedures.[6] Similarly, Guney et al showed a 9.9% drop in bone mineral density at the femoral neck, one year following vertical banded gastroplasty.[6,10] The detrimental effect on bone seemed to be less apparent with malabsorptive procedures. Ten years following biliopancreatic diversion, a 4.2% decrease in spinal bone mineral density was found, but no significant change in hip bone mineral density.[16] For Roux-en-Y gastric bypass, a combined restrictive and malabsorptive procedure, decreases in femoral bone mineral density were found to be as low as 3.5% after 2 years,[23] and as high as 10% after 1 year.[27]

The reduction in bone mineral density following bariatric surgery may have several biological mechanisms. Firstly, a fall in bone active adipocyte hormones (estrogen and leptin) following bariatric surgery may initiate bone loss. Estrogen depletion has been associated with vertical banded gastroplasty (22% reduction after one year),[10] and is strongly linked to bone loss in

perimenopausal women.[41] Decreased leptin levels as a result of weight loss may enhance osteoclast activity and therefore initiate bone loss,[12,13] and alter the balance between osteoblast and adipocyte formation. Second, lowered insulin and amylin levels may follow weight loss, resulting in enhanced osteoclast recruitment and inhibition of osteoblast activity.[12] Finally, although evidence is conflicting, malabsorptive procedures may be associated with calcium and vitamin D deficiency (both are associated with a decrease in bone mineral density and increased fracture risk).[42] As malabsorptive procedures (including combined restrictive / malabsorptive, such as Roux-en-Y gastric bypass) are more likely to lead to malnutrition (hypocalcaemia) and vitamin deficiencies as compared with restrictive procedures (e.g. gastric banding),[43] risk of fracture may be different between these surgical techniques. Albeit limited in statistical power, we did not observe such a difference in fracture risk between gastric banding and Roux-en-Y gastric bypass. Finally, the effect of bariatric surgery on bone may also dependent not only on the type of surgical procedure itself but also on the degree of sarcopenia caused or accelerated by marked weight loss.

Alternatively, the observed decrease in bone mineral density may be explained by measurement errors of bone mineral density in morbidly obese patients.[6] Variability of bone mineral density substantially rises when soft tissue depths exceed 25 cm.[44] Moreover, Madsen and colleagues showed that fat around bone may falsely elevate measured bone mineral density levels.[45] As a consequence, reported falls in bone mineral density at femoral and trochanter sites following bariatric surgery may have been overestimated.

Our study has several strengths. To the best of our knowledge, this is the first cohort of bariatric surgery patients in which the risk of fracture has been investigated. We had a statistical power of 88% to detect a relative risk of at least 1.6. Our data sources had detailed longitudinal information on drug prescribing and other risk factors for fracture, such as smoking status. Furthermore, since 2004, body mass index is very well registered within the General Practice Research Database (>85%), which is a result of the introduction of the Quality Outcomes Framework in 2004. This allowed us to match controls by body mass index accurately, which is important given the relationship between body weight and bone mineral density.[12]

A major limitation of this study is that body mass index is not routinely collected over short time intervals. We have therefore selected the most recent recording of body mass index, assuming this has not substantially changed over time (prior to surgery). This also limited our statistical power in the analysis evaluating the influence of excess body mass index loss. It was therefore not possible to draw definite conclusions about the role of the magnitude of body mass index loss following bariatric surgery. Although obese patients are likely to change weight continuously, and we did not have information on body mass index at the exact day of bariatric surgery, restricting the study population to those with a body mass index recording in the previous 2 months did not substantially change the results. Furthermore, the General Practice Research Database describes events that occurred or were recorded in general practice. Events occurring in secondary / intermediary services may therefore be incompletely ascertained. In addition, we did not have information on bone mineral density, which may

have been useful for determining the underlying biological mechanism in the relationship between bariatric surgery and fracture. We cannot exclude the possibility of confounding by (contra)indication in this study. The NICE guidelines recommend bariatric surgery in morbidly obese patients, preferably with coexisting diseases (for example type II diabetes and hypertension) that could be improved by weight loss.[5] We do not have information on whether subjects were considered for bariatric surgery and then did not undergo an operation because of lack of associated comorbidities. However, as these comorbidities are very unlikely to be associated with reduced fracture rate, it is unlikely that this consideration would reduce our ability to detect a difference in fracture rate between bariatric surgery and control patients. Although there is still a possibility of residual confounding due to unmeasured unbalances between cases and controls, control subjects seem to be healthier (less obesity related comorbidities), and could therefore not have masked a true relationship between bariatric surgery and fracture. Additionally, poor general fitness (associated with a loss in bone mineral density) may be a reason to not undergo bariatric surgery. Indeed, Sjöström and colleagues showed that bariatric surgery patients are more physical active as compared to obese controls.[6] Although we have adjusted for factors such as hypertension and glucose lowering drug use, we could not adjust for physical activity. However, this "healthy user bias" would likely result into a decreased fracture risk shortly after surgery, whereas we found a trend towards the opposite. It is usual for patients to modify their diet preoperatively in order to reduce the fat and glycogen content of the liver. This diet may be based on solid or liquid foods. We did not have information on perioperative diet so were not able to adjust for this potential confounder, but feel that such dietary change over the period of a few weeks would be unlikely to significantly alter fracture risk, particularly as it is aimed at preservation of muscle tissue. We used a widely accepted definition of osteoporotic and non-osteoporotic fracture types, but it is difficult to be sure about fracture aetiology based simply on fracture site, with no information on level of trauma. Finally, we had a relatively short follow-up time (median time 2.3 years for bariatric surgery patients). This yielded reduced power to exclude an increase in fracture risk beyond 5 years.

In conclusion, this is the first study that has estimated risk of fracture after bariatric surgery compared to body mass index matched controls. Although, overall, we did not observe a statistically significant difference in fracture risk between bariatric surgery patients and controls, there was a trend towards an upturn in risk between three and five years post-surgery. Additionally there was a trend towards increasing postsurgical fracture risk with greater loss of excess body mass index, although again, this did not achieve statistical significance. Overall, for the first few post-operative years, these results are reassuring for patients undergoing bariatric surgery, but do not exclude a more protracted adverse influence on skeletal health.

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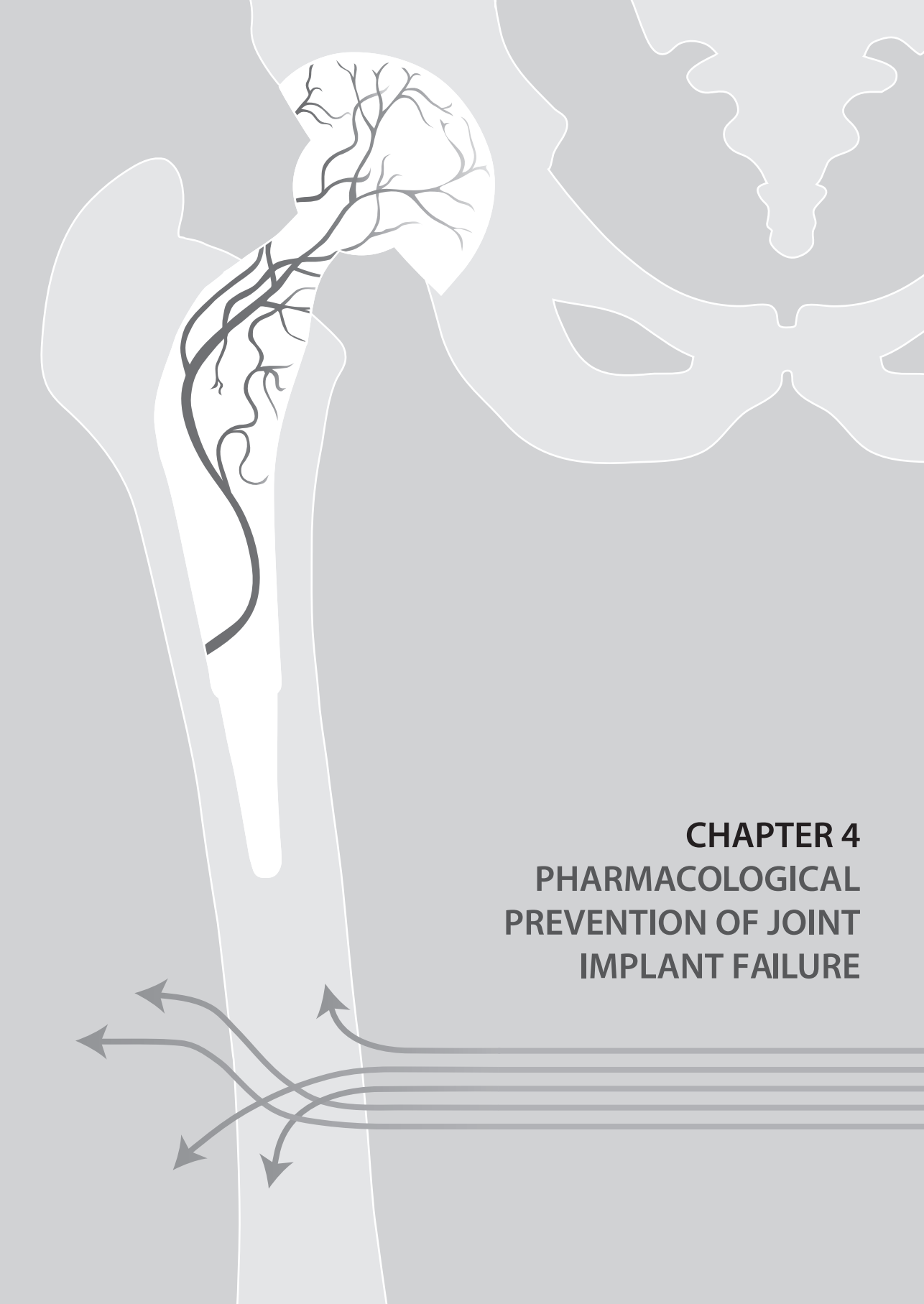

CHAPTER 4
PHARMACOLOGICAL PREVENTION OF JOINT IMPLANT FAILURE

CHAPTER 4.1

Statins and risk of lower limb revision surgery: the impact of differences in study design using electronic health care records from United Kingdom and Denmark

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Submitted.

ABSTRACT

BACKGROUND: Previous observational studies have shown conflicting results on beneficial effects of statins (e.g. reducing the risk of fracture and cancer), depending on the utilized methodology. Our objective was to study the association between statins and implant failure, and to explore the influence of methodological differences in study design.

METHODS: Our study base consisted of all patients with a primary TJR in Denmark and UK (N = 189,286). Within this base, we used four study designs: (1) case-control (patients with revision surgery matched to four controls without revision surgery), (2) time-dependent cohort (postoperative statin use as a time-varying exposure variable), (3) immortal time cohort (misclassifying the time postoperatively before statin use), and (4) time-exclusion cohort (excluding the time postoperatively before statin use). Cox-proportional hazards models (cohort) and logistic regression (case-control) were used to estimate relative risks (RRs) of revision surgery between statin use and non-use.

RESULTS: In the time-dependent cohort design, statin use was associated with a decreased risk of revision surgery (adj. RR 0.90, 95% CI 0.85-0.96), but the risk did not decrease with prolonged statin use. The case-control design (RR 0.87) performed equally well as compared to the time-dependent cohort design (RR 0.90). In contrast, both (methodologically incorrect) time-fixed cohort designs led to a substantially lowered risk (misclassification RR 0.36, exclusion RR 0.65), which further decreased with a prolonged duration of use.

CONCLUSIONS: Statin use was associated with a lowered risk of implant failure in patients with primary TJR, but our duration of use analysis did not suggest causality. The simple choice of how to classify exposure can substantially change results from biologically plausible to implausible results. The robustness of design choices in epidemiological studies needs to be checked.

INTRODUCTION

Primary total replacements of hip and knee (TJR) substantially alleviate pain, and increase physical function and quality of life in patients with moderate to severe osteoarthritis.[1] Each year, approximately 1.8 million of these procedures are performed worldwide.[2,3] Up to 8.3% needs their joint implant revised in the first 10 years,[4] which is associated with poorer clinical outcome compared to primary TJR.[5,6] Consequently, there is an urgent need for drug therapies that may reduce implant failure rates, but no drugs have been assessed in clinical trials up to date.

Observational studies have suggested many beneficial pleiotropic effects of statins, including a reduced risk of fracture and cancer.[7,8] Similarly, statins have been proposed to prevent implant revision failure.[9] One Danish case-control study demonstrated a 66% reduction in implant revision with statin use, although they could not find a dose relationship.[9]

On one hand, these potential beneficial effects could be explained on a biological etiologic basis. By reducing mevalonic acid formation in the bone, statins are thought to inhibit osteoclast-mediated bone resorption.[10] As osteolysis is the most important reason for joint implant failure, this mechanism could explain the observed inverse relationship between statins and implant failure.[9] This is supported by in vivo studies demonstrating the protective effects of statins on osteolysis.[11,12]

On the other hand, the seemingly beneficial effects from observational studies could be explained by study design and analytical choices. Previous studies on statins have shown discrepant results when the data were analysed for a second time in the exact same database. For example, the first British observational study on the risk of fracture with statin use yielded an odds ratio of 0.55 (95% CI 0.44-0.69, General Practice Research Databse, GPRD).[7] In contrast, the second study in the GPRD could not find such a protective effect (OR: 1.01, 95% CI 0.88-1.16).[13] In a third GPRD study, examining the reasons for the discrepant results, it was found that the age-band for matching cases and controls, the selection of potential confounders, the exclusion of high-risk patients and different definitions for exposure time-windows may explain these different results between the first two GPRD studies.[14] Similarly, a British cohort study on bisphosphonates showed a 46% reduction in joint implant failure,[15] whereas a 34% (non-significant) detrimental effect was found in a Danish case-control study.[16]

These reanalyses have taught us that arbitrary decisions in observational studies may have a large impact of the study results and need to be explored in great detail. Some of these micro-decisions that have been hypothesized to influence study results include: (1) case-control versus cohort designs, (2) time-dependent cohort versus time-fixed cohort designs, (3) selection of confounders, (4) techniques to deal with confounding (including propensity score analyses), and (5) selection of data source (e.g. nationwide hospitalization / pharmacy registries or general practice based electronic health care records).

The objectives of this study were therefore (1) to evaluate the association between statins and implant failure in patients with primary TJR surgery, (2) to study the impact of differences in study design, and (3) to assess the influence of using two different data sources.

METHODS

SOURCE POPULATION

We conducted a retrospective multi-country study using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD), and the

Danish National Health System (DNHS). CPRD collates the computerised medical records of general practitioners (GPs). The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987 [www.CPRD.com]. DNHS keeps computerized medical records on all contacts to hospitals and general practitioners, on the use of drugs, income, degree of education, working status, civil status, migrations, and on causes of death for the entire Danish population (5.5 million inhabitants).

STUDY BASE

The study base consisted of all patients with a primary TJR in the study period (CPRD: 1 January 1987 – 31 August 2012; DNHS: 1 January 1998 – 31 December 2007 [i.e. the latest available collected data]) and within the patient's period of data collection. We restricted TJR surgeries to procedures that were likely to be elective: all subjects were at least 40 years of age, and did not have a record for hip / knee fracture in the previous three months and had no history of rheumatoid arthritis. Patients were followed up from the date of primary TJR surgery to the end of data collection, the date of transfer of the patient out of the practice area (CPRD) / migration, the patient's death, or a revision TJR, whichever came first.

OUTCOMES OF INTEREST

The outcome of interest concerned implant revision surgery. In CPRD, we identified revision surgery using CPRD READ codes. ICD10 procedure codes NFC and NGC were used in DNHS to detect revision surgery.

STUDY DESIGNS

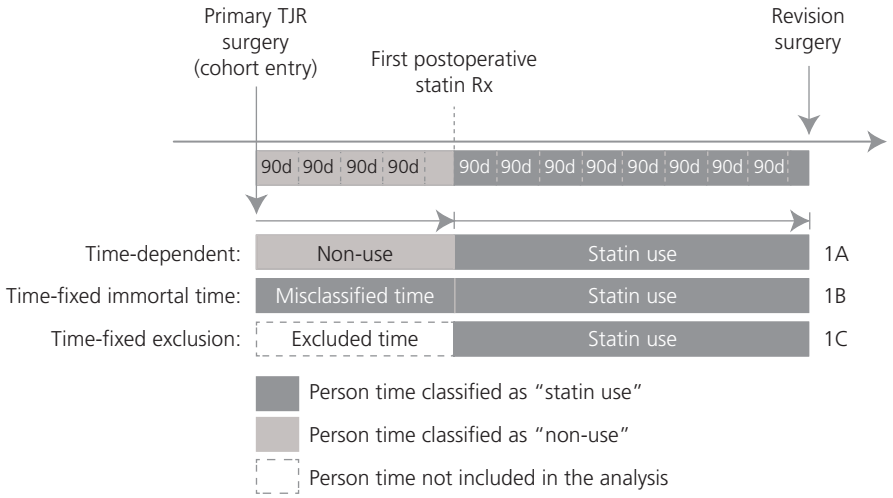
1) Time-dependent cohort study: In this study design, statin exposure was defined in a time-dependent manner (see Figure 4.1.1A). For statin users, total follow-up time was divided into two time periods: (1) the first period started at the time of primary TJR surgery and ended one day before the first postoperative statin prescription (this time period was defined as "non-use"), and (2) the second period started at the date of first postoperative statin and ended at the end of follow-up. Individuals who were exposed to statins only before primary TJR surgery were classified as non-users. For non-statin users, the total follow-up period was considered non-use.

2) Time-fixed immortal time cohort: For this design, the patient was defined as either a non-user or a statin user and, consequently, could not move between these exposure statuses. Statin users were those with at least 1 statin prescription between primary TJR surgery and end of follow-up. All other patients were considered non-users. Start of follow-up was defined as the date of primary TJR surgery, regardless of exposure status.

3) Time-fixed exclusion cohort: This cohort design was similar to the time-fixed immortal time cohort, with the exception of the start of follow-up. For statin users, the start of follow-up was defined as the date of the first postoperative statin prescription (i.e. the immortal time was excluded). For non-users, the date of primary TJR surgery remained the start of follow-up.

4) Case-control design: Nested within our study base, we selected all cases with a revision surgery (see 'cohort: outcomes'), which was considered the index date. For each case, up to four control individuals without revision surgery were selected using incidence density sampling. The index dates for controls were imputed from the corresponding case. Statin exposure was defined as having at least 1 statin prescription between date of primary TJR and the index date.

FIGURE 4.1.1 | Study overview of the three different cohort approaches. 1A: Time dependent exposure status in which each patient may contribute to both "non-use" and "statin use". 1B: Time fixed approach (time-fixed immortal time), (incorrectly) allocating 'immortal' time before the first statin prescription to the 'statin use' group (misclassification bias). 1C: Time fixed approach (time-fixed exclusion), excluding 'immortal' time before the first statin prescription (selection bias)



POTENTIAL CONFOUNDERS

The presence of risk factors was assessed at baseline, i.e. at the date of primary TJR surgery. Risk factors for implant failure were selected based on their association with bone remodelling. These included age, sex, type of joint replaced (hip or knee), year of primary TJR, and prior fractures. Further, we evaluated a history of comorbid diseases (osteoarthritis, inflammatory bowel disease, heart failure, ischaemic heart disease, cerebrovascular disease, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD)), and use of drugs that might affect bone modelling in the previous 6 months (bisphosphonates, calcium / vitamin D supplements, hormone replacement therapy (HRT), selective estrogen receptor modulating (SERM) drugs, glucose lowering agents, proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-parkinson drugs, thiazide diuretics, and anxiolytics). For the CPRD population, we made additional adjustments for body mass index, smoking status, and alcohol use. All covariates (including age and body mass index) were treated as categorical variables, and missing information were treated as a separate category.

As an additional step in the cohort studies, we further adjusted the analyses in a time-dependent manner: total follow-up was divided into 90-day periods (Figure 1) and the

confounder status was assessed at the start of each time interval.

In a separate analysis, we stratified statin users according to their preoperative statin use in the year before primary TJR surgery (which may be a proxy of good / poor prognosis).

STATISTICAL ANALYSIS

For the cohort designs, rate ratios (RRs) were calculated using Cox proportional hazards models (PHREG procedure of SAS 9.2, SAS Institute Inc, Cary, USA), comparing revision rates in statin users versus non-users. For the case-control design, we used logistic regression (LOGISTIC procedure of SAS 9.2). Conditional logistic regression was used for the propensity-matched case-control design. The hazard ratios from the cohort studies and the odds ratios from the case-control study are both estimates for the RR, hence we expressed the risk estimates for all analyses as the RR. We determined the influence of different confounder adjustment models:

1) no adjustments (crude),
2) adjusted for age and sex,
3) additionally adjusted for comorbid diseases and drug use,
4) additionally adjusted for lifestyle parameters,
5) additionally adjusted for calendar time,
6) additionally adjusted for all potential confounders in a time-dependent fashion (this was considered the "fully adjusted model"),
7) adjusted for all covariates that change the beta coefficient of statin use by at least 1%, 5%, and 10% (i.e. the change-in-estimate method),
8) propensity-adjusted model (including all potential confounders in the propensity model),
9) propensity-matched model: Cohort design: current statin users were matched to one non-user by propensity score, modelled for statin use, maximum caliper width of 0.02 SD, all potential confounders (assessed at time of primary TJR surgery) were included in the propensity model. Case-control design: up to four controls were matched to each case using the same propensity score technique.

To illustrate the dose/time-response relationship, we visualized (smoothing spline regression) the RR of revision surgery in relation with the cumulative number of statin DDDs after the primary TJR surgery.[17-19]

MULTI-COUNTRY: In order to evaluate regional differences, all of the above mentioned analyses were conducted in the CPRD and DNHS database separately, and accordingly, were compared against each other. Further, to aggregate the British and Danish results, we performed (1) an individual patient level meta-analysis (lumping all individuals into a 'mega-analysis'), and (2) a classical meta-analysis, i.e. combining the RR estimates of the two separate data sources.

TABLE 4.1.1 | Baseline characteristics of statin users and non-users. Values are percentages unless stated otherwise.

	United Kingdom (CPRD)		Denmark (DNHS)	
	Statin use	Non-use	Statin use	Non-use
Characteristic	N = 49,265 (%)	N = 69,917 (%)	N = 17,168 (%)	N = 52,936 (%)
Mean follow-up (years, SD)	6.1 (4.1)	5.2 (4.0)	4.4 (2.7)	3.9 (2.7)
Mean age at index date (years, SD)	70.2 (8.5)	69.5 (10.9)	68.2 (8.5)	68.3 (10.6)
Females	53.8	63.4	55.8	59.4
BMI (kg/m^2, mean, SD) *	29.2 (5.1)	27.9 (5.3)	-	-
Smoking status *				
Never	54.3	61.7	-	-
Current	11.9	11.7	-	-
Former	33.7	24.2	-	-
Alcohol use *				
No	21.4	19.2	-	-
Yes	74.9	70.3	-	-
Drug use within 6 months before the index date				
Calcium / Vitamin D	6.4	6.6	1.2	1.3
Oral corticosteroids	4.9	5.0	8.4	8.1
Non-insulin antidiabetics	12.0	2.1	14.1	2.9
Thiazide diuretics	28.3	18.8	22.9	17.5
Paracetamol / acetaminophen	62.5	56.4	33.8	30.4
NSAIDs	52.0	52.6	62.0	61.6
Opioids (tramadol or stronger)	37.1	34.8	29.4	28.4
Bisphosphonates	4.7	4.7	2.3	2.7
Beta blockers	25.4	10.7	23.8	11.1
Antiplatelet drugs	37.7	11.2	35.4	13.3
Anxiolytics / hypnotics	10.2	10.1	24.3	22.6
Proton pump inhibitors	27.5	20.8	13.6	10.4
Disease history ever before index date				
Fracture	20.7	20.5	21.6	24.0
Osteoarthritis	76.4	72.0	97.8	97.4
Rheumatoid arthritis	4.0	5.1	3.0	4.0
Chronic kidney disease	8.9	4.5	1.0	0.7
Heart failure	4.1	2.7	7.2	4.0
Ischaemic heart disease	24.9	5.7	23.8	6.3
Cerebrovascular disease	9.9	3.6	7.2	2.9
Hyperlipidaemia	24.0	4.5	11.6	0.8
Atrial fibrillation	5.1	3.3	6.6	4.2
Hypertension	57.7	34.6	21.6	9.8
Diabetes Mellitus type II	15.5	2.5	10.6	2.2
COPD	4.6	3.8	4.9	4.4
Asthma	12.4	11.4	2.6	2.4

Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, CPRD = Clinical Practice Research Datalink, DNHS = Danish National Health System, NSAIDs = non-steroidal anti-inflammatory drugs, SD = standard deviation.
* Missing proportions CPRD: statin users (BMI, 2.7%; smoking status, 0.1%; alcohol use, 3.6%), non-users (BMI, 10.5%; smoking status, 2.4%; alcohol use, 10.5%).

When adjusting for potential confounders in the aggregation part, we only considered confounder data which were available in both databases. In the mega-analysis, we tested for interaction between the two databases. For the classical meta-analysis, we used an inverse-variance fixed effect design (SAS 9.2 / Review Manager (RevMan) 5.2, Copenhagen, Denmark).

RESULTS

A total of 119,182 British and 70,104 Danish patients who underwent primary TJR surgery were identified (Table 4.1.1). Among these patients, 41.3% (49,265) were classified as postoperative statin users in the British cohort, and 24.5% (17,168) in the Danish cohort. Baseline characteristics were very similar between the two data sources. Overall, statin users and non-users had the same mean age (69 years), and a higher proportion of statin users were males. We had a longer follow-up in the British cohort (6.1 years for statin users, 5.2 years for non-users) than in the Danish cohort (4.4 years for statin users, 3.9 years for non-users). In both cohorts, statin users were more likely to have used glucose lowering drugs, thiazide diuretics, and more often had a history of ischaemic heart disease, cerebrovascular disease, and hyperlipidaemia. Among those included in the cohorts, 3,517 British and 3,747 Danish underwent revision surgery. They were included in the case-control design, and matched to 14,068 British and 14,988 Danish control subjects without revision surgery.

TABLE 4.1.2 | Statin use and implant revision surgery, stratified by study design.

	Fully adjusted relative rate (95% confidence interval) *			
	Cohort design			Case-control design **
	Time fixed		Time dependent	
	Method 1 †	Method 2 ‡		
United Kingdom (CPRD)				
No use	referent	referent	referent	referent
[events / PYs]	[2,471/359,856]	[2,471/359,856]	[2,471/449,101]	[2,471/11,903]
[rate per 10,000 PYs]	[68.7]	[68.7]	[55.0]	
Statin use	0.36 (0.33-0.39)	0.64 (0.58-0.71)	0.92 (0.84-1.01)	0.87 (0.79-0.95)
[events / PYs]	[1,046/299,640]	[1,046/210,395]	[1,046/210,395]	[1,046/5,682]
[rate per 10,000 PYs]	[34.9]	[49.7]	[49.7]	
Denmark (DNHS)				
No use	referent	referent	referent	referent
[events / PYs]	[3,220/207,154]	[3,220/207,154]	[3,220/239,298]	[3,220/15,896]
[rate per 10,000 PYs]	[155.4]	[155.4]	[134.6]	
Statin use	0.36 (0.33-0.40)	0.65 (0.59-0.72)	0.90 (0.81-0.99)	0.85 (0.76-0.95)
[events / PYs]	[527/74,655]	[527/42,510]	[527/42,510]	[527/2,839]
[rate per 10,000 PYs]	[70.6]	[124.0]	[124.0]	

Abbreviations: CPRD = Clinical Practice Research Datalink, DNHS = Danish National Health System, PY = person year.
* Adjusted for age, sex, type of replaced joint, year of primary surgery, a history of fracture, diseases (osteoarthritis, inflammatory bowel disease, heart failure, ischaemic heart disease, cerebrovascular disease, rheumatoid arthritis, COPD), and drug use (bisphosphonates, calcium / vitamin D supplements, HRT, SERM drugs, glucose lowering agents, proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-parkinson drugs, thiazide diuretics, and anxiolytics). In CPRD, additionally adjusted for body mass index, smoking status, and alcohol use.
† Misclassification of immortal time (see Figure 4.1.1B).
‡ Exclusion of immortal time (see Figure 4.1.1C).
** Numbers in parentheses represent the number of cases, divided by the total number of patients in each stratum.

Table 4.1.2 shows that there were no substantial differences between the results of the time dependent cohort and the case control study. The time dependent cohort study yielded an adj. RR of 0.92 (95% CI 0.84-1.01), closely resembling the risk estimate of the case control study (adj. RR 0.87, 95% CI 0.79-0.95). In contrast, both time fixed cohort studies resulted into substantially different results as compared to the time dependent cohort and the case-control study (Table 4.1.2). In the British population, misclassification of immortal time resulted in an

adj. RR of 0.36 (95% CI 0.33-0.39). The association weakened, but remained substantially lowered, when the period of time prior to starting a statin was excluded (adj. RR 0.64, 95% CI 0.58-0.71). Both time fixed approaches showed a significant relationship between the cumulative duration of statin use and the risk of revision surgery (Figure 4.1.2). This sharply contrasted with the time dependent cohort and case-control study, which both could not show such a relationship. The same findings were observed in the Danish population.

FIGURE 4.1.2 | Spline regression plot of statin use and risk of implant revision surgery, in relation with the cumulative statin DDD exposure, stratified by type of data collection / analysis design (CPRD data are shown). Results display fully adjusted models. Abbreviations: CPRD = Clinical Practice Research Datalink, DDD = daily-defined dosage, RR = rate ratio.

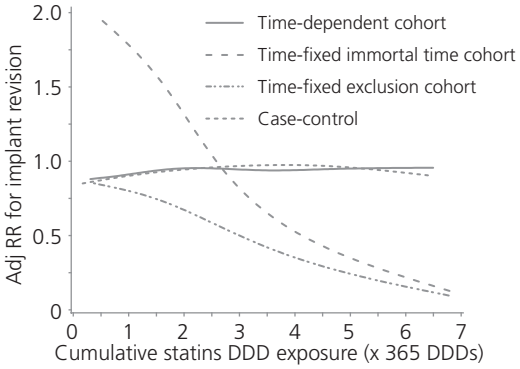


Table 4.1.3 shows that there were no substantial differences between the various techniques to deal with confounding. For example, in the British cohort using a time dependent approach, the fully adj. RR was 0.92 (95% CI 0.84-1.01), versus 0.92 (95% CI 0.84-1.01) with the change-in-estimate method (1% change), 0.96 (95% CI 0.88-1.04) using propensity adjusted models, and 0.96 (95% CI 0.87-1.05) with the propensity matched models. The same trend was present in the Danish analyses (data not shown).

Table 4.1.4 demonstrates the results of aggregating the British and Danish findings. Using the time-dependent approach, the individual patient level mega-analysis revealed an adj. RR of 0.90 (95% CI 0.85-0.96), which was comparable to the result of the classical meta-analysis (adj. RR 0.91, 95% CI 0.86-0.98). No heterogeneity was present in the classical meta-analysis ($p = 0.78$, $I2 = 0\%$), and there was no statistical interaction with the data source in the individual patient level mega-analysis ($p = 0.46$).

DISCUSSION

This study shows that there is probably no causal relationship between statins and implant failure in patients with a replaced hip or knee. Both the case control (RR 0.87) and time dependent cohort design (RR 0.90) revealed a slight reduction in implant failure rates. However, the risk did not decrease with a longer duration of statin use. The time-fixed cohorts

TABLE 4.1.3 | Statin use and implant revision surgery, stratified by methods to deal with confounding (UK CPRD).

	Rate ratio (95% confidence interval)			
	Cohort design			Case-control design
	Time fixed		Time-dependent	
	Method 1 *	Method 2 †		
No statin use	referent	referent	referent	referent
Statin use				
By confounder handling technique				
Unadjusted ‡	0.51 (0.47-0.55)	0.72 (0.67-0.78)	0.90 (0.84-0.97)	0.89 (0.82-0.95)
Confounder handing:				
Cox proportional hazards regression				
Adjusted for:				
Age and sex	0.50 (0.46-0.54)	0.73 (0.67-0.78)	0.93 (0.86-1.00)	0.89 (0.83-0.96)
+ Diseases / drugs **	0.42 (0.39-0.46)	0.67 (0.61-0.73)	0.90 (0.83-0.98)	0.88 (0.81-0.97)
+ Lifestyle ††	0.42 (0.38-0.45)	0.65 (0.60-0.71)	0.90 (0.82-0.97)	0.88 (0.80-0.96)
+ Calendar time	0.42 (0.38-0.45)	0.66 (0.61-0.72)	0.91 (0.84-0.99)	0.87 (0.79-0.95)
+ Time dep. adj.	0.36 (0.33-0.39)	0.64 (0.58-0.71)	0.92 (0.84-1.01)	-
Change-in-estimate method				
> 1% change ‡‡	0.43 (0.40-0.47)	0.67 (0.62-0.73)	0.92 (0.84-1.01)	0.86 (0.79-0.95)
> 5% change ***	0.45 (0.41-0.48)	0.67 (0.62-0.73)	0.92 (0.84-1.01)	0.86 (0.78-0.95)
> 10% change †††	0.51 (0.47-0.55)	0.72 (0.67-0.78)	0.96 (0.88-1.04)	0.89 (0.83-0.96)
Propensity score ‡‡‡	0.44 (0.40-0.47)	0.67 (0.61-0.73)	0.96 (0.88-1.04)	0.85 (0.78-0.94)
Propensity matched ‡‡‡	0.41 (0.37-0.45)	0.65 (0.59-0.71)	0.96 (0.87-1.05)	0.85 (0.77-0.95)

Abbreviations: CPRD = Clinical Practice Research Datalink.
* Misclassification of immortal time.
† Exclusion of immortal time.
‡ Not adjusted for any of the potential confounders, including age and sex.
* Adjusted for age, sex, type of replaced joint, year of primary surgery, a history of fracture, diseases (osteoarthritis, inflammatory bowel disease, heart failure, ischaemic heart disease, cerebrovascular disease, rheumatoid arthritis, COPD), and drug use (bisphosphonates, calcium / vitamin D supplements, HRT, SERM drugs, glucose lowering agents, proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-parkinson drugs, thiazide diuretics, and anxiolytics).
†† Adjusted for * and lifestyle (body mass index, smoking status, alcohol use, GP deprivation score).
‡‡ Cohort design: Adjusted for age, sex, type of replaced joint, year of primary surgery, use of thiazide diuretics, and a history of cerebrovascular disease, body mass index, and smoking status; Case-control design: Adjusted for age, sex, use of proton pump inhibitors, a history of cerebrovascular disease, body mass index, and smoking.
*** Cohort design: Adjusted for ‡‡ and use of glucose lowering drugs, proton pump inhibitors, and antidepressants; Case-control design: Adjusted for (e) and alcohol use, use of glucose lowering drugs, anticonvulsants, antidepressants, a history of heart failure, and ischaemic heart disease.
††† Cohort design: Adjusted for *** and use of HRT, anti-parkinson drugs, a history of heart failure, ischaemic heart disease, and COPD; Case-control design: Adjusted for (f) and alcohol use, use of glucose lowering drugs, antiarrhythmics, thiazide diuretics, anxiolytics, a history of fracture, and COPD.
‡‡‡ Propensity model (outcome = statin use) included all potential confounders and yielded a C-statistic score of 0.80 for all 3 cohort designs and 0.89 for the case-control design.

led to substantially lower risk estimates. This observation was present in both time-fixed cohort designs, but was greater when immortal time was misclassified (RR 0.36) compared to when it was excluded (RR 0.65). Differences in confounder handling techniques or data sources did not substantially alter the study findings.

In line with our findings, a Danish case control study found an overall protective effect of statins on implant failure, with the absence of a clear dose relationship.[9] However, the magnitude of their observed effect (RR of 0.34) was substantially

higher than any of the RRs we found in our Danish case control designs (lowest RR: 0.85). Compared to the first Danish study, we did not use dedicated joint replacement registries to identify revision surgery. Theoretically, this may have led to under recording of the outcome in our study. The revision rate observed in our study, however, was not lower than that in the first Danish study. Moreover, this under recording is likely to be non-differential and should therefore not influence the RR.

TABLE 4.1.4 | Statin use and risk of implant revision surgery, comparison and aggregation of British and Danish electronic health records.

	Rate ratio (95% confidence interval)			
	Cohort design			Case-control design
	Time fixed		Time-dependent	
	Method 1 *	Method 2 †		
No statin use	referent	referent	referent	referent
Statin use				
Unadjusted ‡				
United Kingdom (CPRD)	0.51 (0.47-0.55)	0.72 (0.67-0.78)	0.90 (0.84-0.97)	0.89 (0.82-0.95)
Denmark (DNHS)	0.45 (0.41-0.50)	0.80 (0.73-0.88)	0.92 (0.84-1.01)	0.92 (0.83-1.00)
Meta-analysis	0.49 (0.46-0.52)	0.75 (0.71-0.80)	0.91 (0.86-0.96)	0.90 (0.85-0.95)
Mega-analysis	0.49 (0.46-0.52)	0.75 (0.71-0.80)	0.91 (0.86-0.96)	0.90 (0.85-0.95)
Age- / sex-adjusted				
United Kingdom (CPRD)	0.50 (0.46-0.54)	0.73 (0.67-0.78)	0.93 (0.86-1.00)	0.89 (0.83-0.96)
Denmark (DNHS)	0.45 (0.41-0.49)	0.80 (0.73-0.87)	0.93 (0.85-1.02)	0.92 (0.84-1.01)
Meta-analysis	0.48 (0.45-0.51)	0.75 (0.71-0.80)	0.93 (0.88-0.99)	0.90 (0.85-0.96)
Mega-analysis	0.48 (0.45-0.51)	0.75 (0.71-0.80)	0.93 (0.88-0.99)	0.91 (0.86-0.96)
Fully adjusted **				
United Kingdom (CPRD)	0.36 (0.33-0.39)	0.64 (0.58-0.71)	0.92 (0.84-1.01)	0.87 (0.79-0.95)
Denmark (DNHS)	0.36 (0.33-0.40)	0.65 (0.59-0.72)	0.90 (0.81-0.99)	0.85 (0.76-0.95)
Meta-analysis	0.36 (0.34-0.38)	0.65 (0.63-0.68)	0.91 (0.86-0.98)	0.86 (0.80-0.92)
Mega-analysis ††	0.36 (0.34-0.38)	0.65 (0.63-0.68)	0.90 (0.85-0.96)	0.87 (0.81-0.93)

Abbreviations: CPRD = Clinical Practice Research Datalink, DNHS = Danish National Health System.
* Misclassification of immortal time.
† Exclusion of immortal time.
‡ Not adjusted for any of the potential confounders, including age and sex.
** Adjusted for confounders shown in Table 4.1.2.
†† Adjusted for confounders shown in Table 4.1.2, excluding body mass index, smoking status and alcohol use.

There is conflicting evidence on the beneficial effects of statins on bone metabolism. In vitro and in vivo, statins inhibit osteoclast-mediated bone resorption, by reducing mevalonic acid formation.[12] However, randomized controlled trials could not confirm this potential benefit on fracture risk.[14] While some observational studies suggested a protective effect on statins on preventing fracture,[7] others could not find such an effect.[13] Based on biological etiology, we expected statins to exert their effect on bone / joint implants only after 6 months of use, similar to what is observed for bisphosphonates and fractures.

The difference between the time fixed and time dependent cohort designs emphasizes the importance of immortal time bias. In time fixed cohorts, the immortal time can either be misclassified (Figure 4.1.1B) or excluded (Figure 4.1.1C). Both may lead to substantial bias, as was shown in our study. Time dependent cohort (Figure 4.1.1A) or nested case control designs are appropriate methods to prevent immortal time bias.[20] Our example showed that

these two designs were comparable in terms of the overall association, as well as in the duration of use analysis.

The various methods to deal with confounding did not result into differences in the rate ratios. This is in line with a simulation study comparing various propensity score methods to conventional regression adjustment.[21] In this simulation study, propensity adjustment, propensity matching, and conventional regression adjustment were comparable in terms of bias reduction and precision. However, propensity scores perform better when (1) a large number of prognostic factors are included in the regression model, (2) the treatment effect becomes larger, and (3) the incidence of the outcome increases.[22] It seems that these differences are based on artefacts in the conventional regression model under these circumstances, rather than a better handling of confounding by indication or residual confounding.

The use of different data sources was not a discriminating factor in this example of statins and implant revision. Although the British and Danish electronic health records differ in some important aspects, the results in any of the RR analyses were comparable. Absolute revision rates were substantially higher in the Danish population than in British individuals. This is likely the result of under recording using general practice electronic health records. However, as the under recording appeared to be non-differential, this did not influence the rate ratio.

The strengths of this study include a large sample size, longitudinal follow-up, the use of data sources from multiple countries, the routinely collected data on exposure, outcome and potential confounders, and the ability to compare different study designs. The routine data collection allowed us to analyze very fine timing patterns with a precision of a single day. A major limitation is that we used a proxy for implant failure, i.e. revision surgery. Revision surgery after implant failure may be conditional on surgical fitness, and this may have distorted our study findings. Furthermore, statin use - in particular adherence to statin use - may be associated with healthy user bias. There is a chance of under recording of revision surgery, but this is likely to be non-differential.

In conclusion, statins probably do not prevent implant failure in individuals with a TJR surgery. Despite a small inverse association, the duration of use analysis did not support a causal relationship. The time fixed cohorts resulted into a substantially biased risk estimate, regardless of the type of time fixed design. Confounder handling techniques (including propensity score analyses) and type of electronic health records only seemed to play a minor role in differences in study findings. When the association between statin use and revisions after TJR is evaluated, conventional study designs such as case-control studies or cohort studies that take into account time varying aspects of exposure are better than time-fixed cohort study designs. From a clinical point of perspective, this study does not support the use of statins to prevent joint implant failure in patients who underwent primary total hip or knee replacement surgery.

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CHAPTER 4.2

Bisphosphonate use and revisions of lower limb joint (hip / knee) arthroplasty: validation of results in an external population-based cohort

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Submitted.

ABSTRACT

BACKGROUND: Osteolysis and aseptic loosening are the most common causes of revision arthroplasty worldwide. Bisphosphonates could potentially improve implant survival through their anti-osteoclast effects. We aimed to study the association between bisphosphonate use and implant survival.

METHODS: A retrospective cohort study was conducted within the Danish nationwide registries (5.5 million residents). We identified patients aged >=40 years undergoing total joint replacement (TJR) during the study period (1998-2007) using ICD10 codes. Patients with rheumatoid arthritis, Paget bone disease, hip fracture, and use of DMARDs were excluded. Each participant was followed up until revision surgery, loss to follow-up or patient's death, whatever came first. Participants were classified as bisphosphonate users (BPU) if they had been on treatment for at least 6 months. A time-varying exposure was used to avoid immortal-time bias. Up to 6 BP non-users (BPNU) undergoing arthroplasty were matched to each BPU using propensity scores. Stratified Cox regression was used to model implant survival according to bisphosphonate use. Further, we studied the association between duration of use, adherence (medication possession ratio=MPR), and timing of therapy initiation (pre-op vs post-op) and implant survival.

RESULTS: 80,342/95,392 (84.2%) subjects were eligible. We identified 1,590 (2.0%) BPU, and 1,558 (98.0%) of them were matched to 8,966 BPNU. In total, 426/10,524 (4.05%) of the participants (27/1,558 BPU and 399/8,966 matched BPNU) underwent revision surgery during study follow-up (median 2.61 years, inter-quartile range 1.04-5.41). Cox regression models showed reduced revision risk in BPU (HR 0.41 [95% Confidence Interval 0.27-0.61]). This protective effect was highest in patients with longest duration of treatment and/or highest adherence.

CONCLUSIONS: BPU are at 59% reduced risk of revision compared to matched BPNU. These results are similar to previous findings using similar data from the UK. Confirmation of these effects in randomized controlled trials is urgently needed.

INTRODUCTION

As the prevalence of osteoarthritis (OA) raises worldwide, the numbers of patients undergoing total knee (TKA) and hip arthroplasty (THA) increase continuously.[1] Although total joint replacement surgery offers excellent results, still almost 10% of the total number of arthroplasties carried out in Danish hospitals in 2011 were revision surgeries, procedures that have been shown to be very costly and with a poorer outcome.[2-4] Aseptic loosening and related osteolysis are the most common indications for revision, accounting for about 55-

65% hip and 38-45% knee procedures according to different european joint registries.[5-10]

There is no approved pharmacological intervention to avoid these, but anti-resorptive drugs have putative preventive effects through inhibition of wear debris-related osteoclast activity and consequent minimisation of osteolysis.[11] Consistent with this hypothesis, observational data from the british population-based Clinical Practice Research Datalink (CPRD) (former General Practice Research Database) have suggested that bisphosphonate use might increase implant survival time by almost twofold.[12] However, these data need replication in external cohorts.

We therefore studied the association between bisphosphonate use and lower limb implant survival among patients undergoing primary TKA or THA in a separate nation-wide dataset: the Danish health registries.

METHODS

DATA SOURCE AND SETTINGS

A nationwide retrospective cohort study was conducted within the Danish nationwide registries (5.5 million residents). Detailed information was available for all Danish residents, including data on secondary care visits (hospitals, outpatient clinics, and emergency rooms; from 1977 onwards), drugs dispensed at community pharmacies (from 1996 onwards), citizen status (vital status, date of death, residence, migration, and socioeconomic status; from 1968 onwards), and date and cause of death. Previous reports have demonstrated high quality, completeness and validity of these data,[13,14] which has been used in numerous epidemiological studies.[15-17] This study was carried out under supervision of Statistics Denmark, and Danish Data Protection Agency.

STUDY POPULATION

We screened the Danish health registries to identify all patients aged 40 years or older undergoing either a total hip (ICD-10 procedure code NFB.XX) or total knee replacement (ICD-10 procedure code NGB.XX) during the study period (January 1, 1998 to December 31, 2007). The index date was defined as the date of hospitalization for surgery. Each participant was then followed up from the date of primary surgery until the end of study, the date of transfer out of the practice area (loss to follow-up), revision surgery, a new primary arthroplasty, or patient's death, whichever came first. Patients with a history of the following conditions / diseases / drug use were excluded: a hip/femur fracture, rheumatoid arthritis, Paget's disease, use of DMARDs (methotrexate, leflunomide, chloroquine, hydroxychloroquine, anakinra, auranofine), and use of bisphosphonates indicated for cancer / Paget disease of bone (i.e. clodronic acid and high-dose risedronate).

EXPOSURE ASSESSMENT: IDENTIFICATION OF BISPHOSPHONATE USERS

Bisphosphonate (BP) use was determined using dispensing data from the pharmacies of the

study population (ATC codes M05BA, M05BB). The exposure time window was defined as the time between primary hip / knee surgery and end of follow-up. Participants were defined as BP users if they had been dispensed at least 182 DDDs of BPs (worth 6 months of treatment) during this time window. Patients without any BP use or less than 182 DDDs in the exposure time window were classified as BP non-users. We matched up to 6 BP non-users to each BP user using propensity score matching (see Potential confounding). We used a caliper matching technique, with a maximum caliper width of 0.02 SDs, as recommended by Austin et al.[20] In short, this means that BP non-users were only eligible to be matched if their propensity score fell within a bandwidth of 0.02 SD of the BP-treated subject's propensity score.

BP use was defined in a time-dependent manner in order to prevent immortal time bias. For individuals who were classified as BP-users (i.e. at least 182 DDDs) after the primary surgery (i.e. after start of follow-up), person time until the 182nd DDD was allocated to BP non-use. Medication possession ratio (MPR) was calculated as the cumulative number of DDDs (during follow-up) filled by the patient divided by the expected duration of use (i.e. the time between first prescription and last prescription, extended by the duration of the last prescription).

ASCERTAINMENT OF OUTCOME: IMPLANT FAILURE

The main outcome of this study was the first revision surgery after primary hip / knee replacement surgery (identified using ICD10 procedure codes NFC for hip, and NGC for knee).

POTENTIAL CONFOUNDING

We minimized confounding by using propensity score matching techniques.[18] This is a standard method for minimizing confounding by indication, which provides participants with balanced baseline characteristics in both treatment arms, and has been shown to be useful to estimate drug effects comparable to those obtained in randomized controlled trials.[19] Propensity scores, defined here as the probability of BP use (at least 182 DDDs), were estimated for each individual participant using multivariable logistic regression (i.e. all potential confounders were modelled for having at least 182 DDDs of BPs as the outcome). Matching was then carried out using a maximum caliper width of 0.02 SDs, as recommended by Austin PC et al.[20] Variables entered in the propensity model were prognostic factors for arthroplasty revision surgery (main outcome) as based on biological plausibility and available literature. Potential confounders were assessed at baseline (i.e. the date of primary hip / knee replacement surgery), and these included the following: age, sex, joint replaced (hip / knee), year of primary hip / knee replacement surgery, marital status, working status, income, number of GP / specialist visits (in the previous year), a history of fracture (other than hip fracture), osteoarthritis, malignancy, heart failure, inflammatory bowel disease, renal disease, ischaemic heart disease, stroke (any type), and the use of estrogen containing drugs, systemic glucocorticoids, antidiabetics, asthma / COPD drugs, proton pump inhibitors, antiarrhythmics, statins, thiazide diuretics, beta blockers, RAAS inhibitors, calcium channel blockers, calcium / vitamin D supplements, strontium ranelate, parathyroid hormone, anticonvulsants, antidepressants, and benzodiazepines in the previous 6 months.

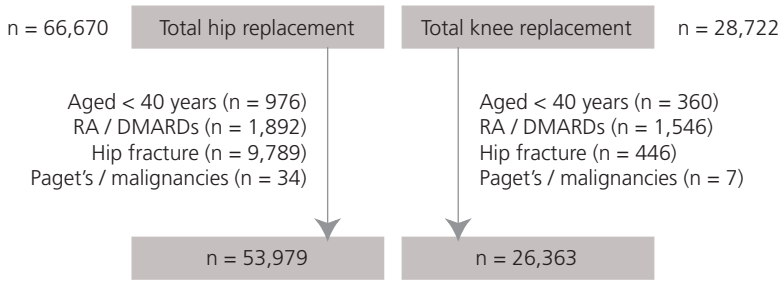
STATISTICAL ANALYSIS

Cox proportional hazards models stratified by matched sets were used to model revision surgery in BP users versus BP non-users (PHREG procedure, SAS 9.2). The model comprised a univariate model, i.e., only BP-use was included in the model.

Based on the survival function and the estimated Hazard Ratio (HR) obtained from Cox models, we estimated the number needed to treat (NNT) to avoid one revision in the first 2 years after primary total joint arthroplasty using the methods proposed by Barratt A et al.[21]

The final model was tested for a-priori defined interactions (between BP use and age, sex, joint replaced (hip/knee), and prior fracture on outcome) by introducing multiplicative terms in the equation. Stratified analyses were carried out only if the previously described interactions were significant. Further, we classified BP users according to duration of BP use, medication possession ratio (see 'Exposure assessment'), and timing of BP therapy initiation (before versus after surgery). Duration of BP use was defined in a time-dependent manner in order to prevent immortal time bias.

FIGURE 4.2.1 | Population flowchart. Figures outside of boxes represent exclusion numbers.



In a sensitivity analysis, and in order to rule out a potential association between BP use and health-seeking behaviors, we studied the effect of a completely unrelated drug (benzodiazepines) on implant survival using these same methods.

Secondly, we addressed the possibility that patients receiving BPs could differ from non-users in the accrual rate for chronic diseases, which could preclude surgery and drive an apparent reduction in revision rates. To do so, we assessed the rate of increase in Charlson Comorbidity Index (CCI) score among BP users versus BP non-users, and evaluated CCI as a time-varying predictor of surgical revision among BP non-users. Finally, we analyzed the association between BP use and implant survival adjusting for CCI changes over time as a time-dependent covariate.

Kaplan-Meier estimates were plotted to visualize the effect of BP use on implant survival over time. The HR for revision rates according to duration of BP use was illustrated using smoothing spline techniques.[22 23]

RESULTS

We identified a total of 95,392 patients with a primary total joint replacement (66,670 THA; 28,722 TKA), of which 80,342 (84.2%) subjects met our inclusion criteria (Figure 4.2.1). Among these, 1,590 (2.0%) participants were defined as BP-users, and 1,558 (98.0%) of them were calliper- matched to 8,966 BP non-users by propensity score, constituting the study population. The characteristics of matched BP-users and BP non-users are shown in Table 4.2.1: participants in both treatment arms were overall comparable, and the logistic propensity score equation predicted BP use accurately (area under the ROC curve 0.82). However, some clinical characteristics remained imbalanced between both arms: BP users had attended a higher number of GP/specialist visits in the year pre-surgery, and were more likely to be users of calcium/vitamin D supplements.

TABLE 4.2.1 | Baseline characteristics of bisphosphonate users and matched non-users.

	Bisphosphonate users		Matched non-users	
Characteristic	n = 1,558	(%)	n = 8,966	(%)
Age (years, mean, SD)	75.4	(8.7)	75.6	(8.9)
Gross income (DKK, mean, SD)	146,774	(119,596)	143,525	(97,518)
GP / specialist visits in previous year (mean, SD)	11.0	(10.2)	10.5	(9.8)*
Females	1,404	(73.5)	8,161	(75.9)
Hip replaced	1,21	(63.4)	6,908	(64.2)
History of:				
Osteoarthritis	1,012	(53.0)	5,962	(55.4)
Fracture (other than hip fracture)	644	(33.7)	3,605	(33.5)
Inflammatory bowel disease	15	(0.8)	70	(0.7)
Heart failure	108	(5.7)	621	(5.8)
Renal disease	14	(0.7)	84	(0.8)
Malignancy	205	(10.7)	1,176	(10.9)
Ischaemic heart disease	163	(8.5)	944	(8.8)
Stroke	91	(4.8)	522	(4.9)
Drug use in the 6 months before primary hip / knee replacement surgery				
Estrogen containing drugs	137	(7.2)	801	(7.4)
Systemic glucocorticoids	244	(12.8)	1,282	(11.9)
Antidiabetics	50	(2.6)	275	(2.6)
Asthma / COPD drugs	214	(11.2)	1,148	(10.7)
Proton pump inhibitors	244	(12.8)	1,442	(13.4)
Antiarrhythmics	17	(0.9)	99	(0.9)
Statins	157	(8.2)	939	(8.7)
Thiazides	320	(16.8)	1,846	(17.2)
Beta blockers	211	(11.0)	1,292	(12.0)
Calcium channel antagonists	307	(16.1)	1,759	(16.4)
RAAS inhibitors	260	(13.6)	1,488	(13.8)
Calcium / vitamin D supplements	138	(7.2)	468	(4.4) ‡
Anticonvulsants	55	(2.9)	327	(3.0)
Antidepressants	271	(14.2)	1,606	(14.9)
Benzodiazepines	499	(26.1)	2,968	(27.6)

* p<0.05; † p<0.01; ‡ p<0.001.
Abbreviations: COPD = chronic obstructive pulmonary disease, DKK = Danish Kroner, GP = general practitioner, RAAS = renin-angiotensin-aldosterone system, SD = standard deviation.

In total, 426/10,524 (4.05%) of the study participants (27/1,558 (1.73%) BP users and

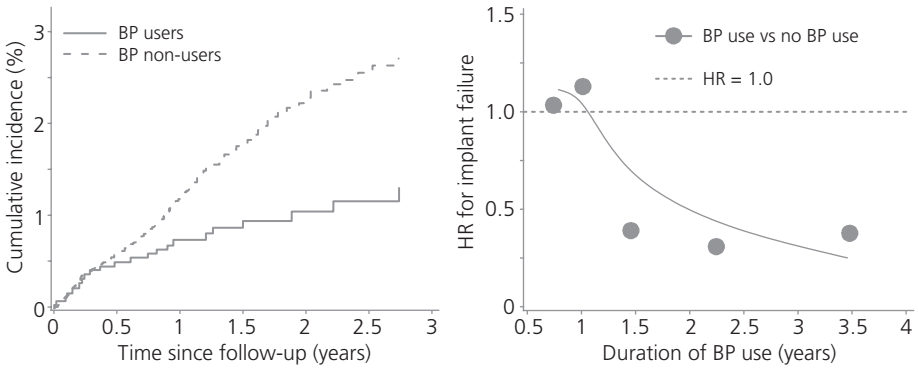
399/8,966 (4.45%) matched BP non-users) underwent revision surgery during study follow-up (median 2.61 years, inter-quartile range 1.04-5.41 years). Accordingly, cumulative incidence of revision was 0.75% and 1.05% at 1 and 2 years respectively among BP users, compared to 1.20% and 2.26% in BP non-users (Figure 4.2.2). Cox regression models showed reduced revision risk in BP users (HR 0.41 [0.27-0.61], p<0.0001).

TABLE 4.2.2 | Risk of implant failure among TJR patients with BP use versus no-BP use, stratified by age, sex, prior fracture, and type of TJR.

BP exposure	All patients n = 10,524	Implant failure n = 426	Hazard ratio (95% CI)
Total joint arthroplasty			
No BP use	8,966	399	referent
BP use	1,558	27	0.41 (0.27-0.61)
By age			
40-64 years	176	7	0.99 (0.30-2.39)
65-74 years	447	11	0.41 (0.15-1.10)
≥ 75 years	935	9	0.21 (0.10-0.44)
	p for interaction = 0.35 (65-74 vs 40-64) and 0.01 (≥ 75 vs 40-64)		
By sex			
Males	154	3	0.71 (0.14-3.61)
Females	1,404	24	0.39 (0.25-0.60)
		p for interaction = 0.35	
By prior fracture			
No	914	13	0.31 (0.16-0.58)
Yes	644	14	0.43 (0.22-0.83)
		p for interaction = 0.37	
By replaced joint			
Hip	1,21	19	0.30 (0.18-0.51)
Knee	348	8	0.53 (0.17-1.66)
		p for interaction = 0.97	
Abbreviations: BP, bisphosphonate; HR, hazard ratio; CI, confidence interval.			

FIGURE 4.2.2 | Kaplan-Meier estimates of implant revision surgery among BP-users and non-users.

FIGURE 4.2.3 | Spline visualisation of implant revision rates with BP use vs no BP use, by duration of BP use.



The observed association between BP use and implant survival was not modified by interactions with sex, prior fracture, or type of joint replaced (all p for interaction>0.2), but the association was the strongest in individuals of 75+ years of age (HR 0.21 [0.10-0.44]).

Results for the analyses of the association between BP use duration, cumulative use, timing of BP therapy initiation, and implant survival are shown in detail in Table 4.2.3. The protective effect observed only became apparent after one year of BP use (p = 0.02, Table 4.2.3): HR 1.12 (95% CI 0.70-2.01) for 6-12 months of BP use, HR 0.36 (0.17-0.72) for 1-2 years, 0.35 (0.09-1.25) for >2 years of use (Figure 4.2.3). This association was also only present for BP users who had good compliance (HR 0.38 (0.24-0.62) for patients with MPR>0.8), compared to no effect in those with poorest adherence to therapy (0.91 (0.31-2.45) for BP users with MPR<0.5). Finally, the protective effects of BP use on implant revision seemed to be only significant amongst BP users who started therapy after primary surgery (adjusted HR 0.31 (0.17-0.58)), and not for BP users who started treatment before primary arthroplasty (adjusted HR 0.72 (0.40-1.14)).

TABLE 4.2.3 | Risk of implant failure among TJR patients with BP use versus no-BP use, stratified by duration of use, medication possession ratio, and prior BP use.

BP exposure	All patients n = 10,524	Implant failure n = 426	Hazard ratio (95% CI)
Total joint arthroplasty			
No BP use	8,966	399	referent
BP use	1,558	27	0.41 (0.27-0.61)
By duration of use *			
6-12 months	251	12	1.12 (0.70-2.01)
1-2 years	920	12	0.36 (0.17-0.72)
>2 years	387	3	0.35 (0.09-1.25)
By medication possession ratio			
< 0.5	213	6	0.91 (0.31-2.45)
0.5 - 0.79	139	4	0.47 (0.14-1.57)
≥ 0.8	1,206	17	0.38 (0.24-0.62)
By BP use in the 12 months before surgery			
No	652	7	0.31 (0.17-0.58)
Yes	906	20	0.72 (0.40-1.14)

Abbreviations: BP, bisphosphonate; HR, hazard ratio; CI, confidence interval.
* Statistically significant difference between 6-12 months and >1 year (p = 0.02).

CLINICAL RELEVANCE

The estimated number of patients needed to treat (NNT) to prevent one of them undergoing revision in the first 2 years after primary arthroplasty overall was 127. In the best-case scenario, starting therapy post-op, the NNT would be of 72 participants.

TABLE 4.2.4 | Increase in CCI rates with BP use versus no BP use.

BP exposure	All patients n = 10,524	Increased CCI n = 1,296	Hazard ratio (95% CI)
Total joint arthroplasty			
No BP use	8,966	1,154	referent
BP use	1,558	142	0.68 (0.54-0.86)

Abbreviations: BP, bisphosphonate; HR, hazard ratio; CI, confidence interval.

SENSITIVITY ANALYSES

Our sensitivity analysis showed that the protective effect observed is not explained by BP users accruing more comorbidity: in our data, BP users were less likely to accrue more comorbidity

as compared to matched controls (Table 4.2.4). Moreover, time-dependent adjustments for CCI scores did not substantially change the main finding (CCI adjusted HR 0.44, 95% CI 0.30-0.65, data not shown).

In addition, replicating the Cox regression analyses for the association between benzodiazepine use and implant survival showed no effect for these drugs: after propensity score matching with a good model for prediction of benzodiazepine use (area under ROC curve 0.81) yielded a HR of 0.98 [0.82-1.17].

DISCUSSION

KEY RESULTS / OUTCOME DATA

We report that bisphosphonate use is associated with a significantly reduced revision rate by 59%. In our data, such protective effect was only apparent in patients with high adherence to bisphosphonate therapy, and who persisted on treatment for at least 1 year. According to our results, patients starting oral bisphosphonates in the post-operative period tended to benefit further when compared to those who started pre-operatively. The observed association was not modified by interactions with age, gender, previous history of (non-hip) fracture, or joint replaced (hip versus knee).

In our sensitivity analyses, we also demonstrate that these findings are unlikely to be confounded by residual (unobserved) variables such as patient co-morbidity (constant or time-variant) or health-seeking behavior. Finally, an additional analysis looking at the association between use of a "dummy" drug (benzodiazepines, with no known effects on our outcome of interest) showed a null effect on implant revision.

COMPARISON WITH PREVIOUS STUDIES

There is biological plausibility to support a beneficial effect of anti-resorptive drugs (bisphosphonates and potentially others) on preventing TKA/THA loosening by minimisation of osteoclast-mediated periprosthetic bone loss and osteolysis.[24] Consistent with this, a number of small and short-term studies including randomised controlled trials (RCTs) have tested the effects of bisphosphonates on surrogates for implant failure. There is moderate evidence (at least one meta-analysis including 14 randomised controlled trials and 671 patients with up to 7 years follow-up) suggesting that bisphosphonates are effective at minimising short and middle-term peri-prosthetic bone loss.[25] Similarly, a number of randomised controlled trials[26-28] but not all[29-32] have shown beneficial effects of both intravenous and oral bisphosphonates on minimising implant migration. However, the validity of these surrogate outcomes remains controversial,[33] with only a few reports demonstrating good ability of implant migration as measured using complex radiographic techniques (radioestereometric analysis) to predict long-term revision.[34 35]

In contrast, implant revision is a hard outcome with obvious implications to patients, clinicians

and health-care providers: revision surgery is very costly,[4] and is related to poorer patient-reported outcomes[36] and to higher complications and hospital readmission rates.[37] Along these lines, an observational study using data from the British population-based CPRD database suggested that bisphosphonate use was associated with an almost halved revision rate amongst patients undergoing total joint arthroplasty.[12] The data presented in this manuscript validates these findings in an external cohort: among patients undergoing TKA/THA in the Danish Health Registries, BP users had 59% lower risk of revision when compared to matched BP non-users.

Unsolved issues remaining are lack of individual validation of revision events, residual confounding due to unobserved variables (bone mineral density, implant design, cement use for fixation, etc), and the absence of a placebo arm for ideal comparison. However, the data used have been shown to be highly valid for surgical interventions,[38] the numbers of patients included in these two observational studies are high, the effect sizes observed are similar, and the methods used to adjust for confounding have been shown to robustly approximate RCT results.[19]

These data, which validate findings from a previously published external cohort, strengthen the case for a randomized controlled trial to test for causality in the association between bisphosphonate use and implant survival following TKA/THA.

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CHAPTER 4.3

Bisphosphonates and risk of lower limb revision surgery: the impact of differences in study design

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ABSTRACT

BACKGROUND: Various analytical designs are used to study drug effects on implant failure in observational studies. In our example of statin use studies, a case-control and a (methodologically incorrect) time-fixed cohort design was used, providing opposite results. In this study, we wished to explore the influence of these two analytical study designs in the example of bisphosphonate use and implant failure in patients with a total hip / knee surgery (TJR) within the same database.

METHODS: All Danish patients with a TJR between 1998 and 2007 were selected (n = 80,342). Four analytical study designs were used (based on previous studies): (1) case-control, (2) time-dependent cohort, (3) time-fixed cohort incorrectly allocating time before the first postoperative bisphosphonate dispensing (i.e., the immortal time) to exposed patients, and (4) time-fixed cohort excluding immortal time. Revision surgery was the defined outcome, and postoperative bisphosphonate use (at least 182 DDDs) was the exposure of interest. In all analyses, we used propensity scores to match patients based on drug use and comorbidities.

RESULTS: Bisphosphonate use was associated with a decreased risk of implant failure in all study designs, but with some substantial differences: the methodologically correct analytical designs produced very similar risk estimates (time-dependent cohort study: RR 0.41, 95% CI 0.27-0.61; case-control study: RR 0.46, 95% CI 0.22-0.78). Even the (conceptionally incorrect) time-fixed analysis that (falsely) excluded immortal time (RR 0.37, 95% CI 0.24-0.55) produced a somewhat similar result. In contrast, the time-fixed analysis that incorrectly misclassified immortal time produced a substantially lower risk estimate (RR 0.22, 95% CI 0.14-0.34).

CONCLUSIONS: We found substantial differences in key findings with the various analytical study designs in the example of bisphosphonate use and implant failure in patients with TJR surgery. From a methodological point of view, we do not promote the use of time-fixed cohort study designs in pharmacological etiologic studies.

INTRODUCTION

Total hip or knee replacement surgeries (TJR) are highly effective procedures and are performed in large numbers worldwide.[1] Each year, an estimated number of 1.8 million of these procedures are performed worldwide.[2,3] Unfortunately, up to 8.3% needs a revision surgery due to implant failure within 10 years,[4] which is associated with poorer clinical outcome than primary TJR surgery.[5,6]

Previous studies have suggested a potential benefit of bisphosphonates in the prevention of implant failure in patients with a TJR surgery. A British observational time-fixed cohort analysis yielded a rate ratio (RR) of 0.54 (95 CI 0.29-0.99),[7] very similar to findings of our Danish observational time dependent cohort analysis in Chapter 4.2 (RR 0.41, 95% CI 0.27-0.61).

However, as was observed in our example with statins and implant failure (Chapter 4.1), the analytical study design may drastically influence the study findings. In our statin study, time-fixed cohort analyses suffered from immortal time bias, and falsely showed an inverse relationship between statin use and implant failure. These analyses yielded a RR of 0.36, 95% CI 0.34-0.38 with misclassification of immortal time, and a RR of 0.65, 95% CI 0.63-0.68 with exclusion of immortal time. When correctly analysed by either a time-dependent cohort design (RR 0.90, 95% CI 0.85-0.96) or a case-control study (RR 0.87, 95% CI 0.81-0.93), the seemingly protective effect of statins disappeared.

Given the differences in analytical study design between the two previous studies on bisphosphonates and implant failure, we wished to explore the influence of these analytical study designs on the risk estimates. As these two previous bisphosphonate studies were carried out in two separate independent databases, it is difficult to determine the sole influence of the analytical study design. We therefore aimed to study the impact of these two analytical study designs using the example of bisphosphonates and implant failure in patients with TJR within the same data source.

METHODS

SOURCE POPULATION

A nationwide cohort study was conducted within the Danish registries (5.5 million inhabitants). These databases provide information on all contacts to hospitals, pharmacy dispensings, income, degree of education, working status, civil status, migrations, and on causes of death for the entire Danish population.

STUDY BASE

We selected all patients with a first TJR surgery between 1 January 1998 and 31 December 2007. As we wished to include elective procedures only, we selected all patients at least 40 years of age. Patients with a history of the following conditions / diseases / drug use were excluded: a hip/femur fracture, rheumatoid arthritis, Paget's disease, use of DMARDs (methotrexate, leflunomide, chloroquine, hydroxychloroquine, anakinra, auranofine), and use of bisphosphonates indicated for cancer / Paget disease of bone (i.e. clodronic acid and high-dose risedronate). All patients were followed up from the date of primary TJR surgery until the end of data collection, migration, the patient's death, or a new primary TJR, whichever came first.

STUDY OUTCOMES

The outcome of interest concerned implant revision surgery (ICD10 procedure codes NFC and NGC).

EXPOSURE DEFINITION

1) Time-dependent cohort study: Bisphosphonate (BP) use was determined using dispensing data from the pharmacies of the study population (ATC codes M05BA, M05BB). The exposure time window was defined as the time between primary hip / knee surgery and end of follow-up. Participants were defined as BP users if they had been dispensed at least 182 DDDs of BPs (worth 6 months of treatment) during this time window. We chose a period of 6 months of exposure, as this is the minimum duration of use previously shown to influence fracture risk for most bone remodelling drugs. Patients without any BP use or less than 182 DDDs in the exposure time window were classified as BP non-users. We matched up to 6 BP non-users to each BP user using propensity score matching (see Potential confounding). We used a caliper matching technique, with a maximum caliper width of 0.02 SDs, as recommended by Austin et al.11 In short, this means that BP non-users were only eligible to be matched if their propensity score fell within a bandwidth of 0.02 SD of the BP-treated subject's propensity score. In the time-dependent analysis, BP use was handled as a time-varying status. For bisphosphonate users, they were defined as "non-users" from the date of primary TJR until the day of the 182nd bisphosphonate DDD. Afterwards, they were classified as bisphosphonate users.

2) Immortal time-fixed cohort: This design was similar to the time-dependent cohort study, with the exception of the time-varying exposure status. In this analysis, BP users were classified as BP users from primary TJR surgery until the end of follow-up. Similarly, non-users were classified as such throughout the entire period from primary surgery until the end of follow-up.

3) Exclusion time-fixed cohort: Except for the start of follow-up for BP users, this design was similar to the immortal time-fixed cohort study. In the excludion cohort, start of follow-up for BP users began at the 182nd bisphosphonate DDD (i.e. the period of time before the 182nd bisphosphonate DDD was excluded from the analysis).

4) Case-control design: For our case-control study design, we selected all revision surgeries from our study base (see study outcomes). Four controls without revision surgery were selected using incidence density sampling. The index date for cases was defined as the date of revision surgery and was similar for the corresponding controls. Exposed patients were those with at least 182 bisphosphonate DDDs between primary TJR surgery and the index date.

POTENTIAL CONFOUNDERS

We minimized confounding by using propensity score matching techniques. Propensity scores, defined here as the probability of BP use (at least 182 DDDs), were estimated for each individual participant using multivariable logistic regression (i.e. all potential confounders were modelled for having at least 182 DDDs of BPs as the outcome). Matching was then

carried out using a maximum caliper width of 0.02 SDs, as recommended by Austin PC et al.[11] The presence of risk factors was assessed at baseline, i.e. at the date of primary TJR surgery. Risk factors for implant failure were selected based on their association with bone remodelling. These included age, sex, type of joint replaced (hip or knee), year of primary TJR, and prior fractures. Further, we evaluated a history of comorbid diseases (osteoarthritis, inflammatory bowel disease, heart failure, ischaemic heart disease, cerebrovascular disease, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD)), and use of drugs that might affect bone modelling in the previous 6 months (bisphosphonates, calcium / vitamin D supplements, hormone replacement therapy (HRT), selective estrogen receptor modulating (SERM) drugs, glucose lowering agents, proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-parkinson drugs, thiazide diuretics, and anxiolytics). All covariates (including age) were treated as categorical variables. Age was further included as a (continuous) time-dependent variable to further adjust for time-varying age differences.

STATISTICAL ANALYSIS

For the cohort designs, adjusted rate ratios (RRs) were calculated using Cox proportional hazards models (PHREG procedure of SAS 9.2, SAS Institute Inc, Cary, USA), comparing revision rates in bisphosphonate users versus non-users. For the case-control design, we used adjusted conditional logistic regression (LOGISTIC procedure of SAS 9.2).

RESULTS

We included 80,342 Danish patients who underwent primary TJR surgery (Table 4.3.1). A total of 2.0% (n = 1,590) had been dispensed 182 bisphosphonate DDDs between primary TJR and end of follow-up. Due to propensity matching, bisphosphonate users were of similar age as compared to non-users (75.4 years versus 75.6 years), and in both groups there was a similar proportion of females (73.5% versus 75.9%). Drug use was similar across the two groups, with the exception of calcium / vitamin D supplements.

Looking at the association between bisphosphonates and implant failure (Table 4.3.2), no substantial differences could be observed between the findings from the case-control (adj. RR 0.46, 95% CI 0.22-0.78) and the time-dependent cohort design (adj. RR 0.41, 95% CI 0.27-0.61). A very similar risk estimate was found for the (methodologically incorrect) time-fixed cohort study that excluded immortal time (adj. RR 0.37, 95% CI 0.24-0.55). In contrast, the (methodologically incorrect) time-fixed analysis that misclassified immortal time yielded a substantially lower RR (adj. RR 0.22, 95% CI 0.14-0.34).

DISCUSSION

This study shows that bisphosphonate use is associated with a lower rate of implant revision surgery in patients with a primary TJR surgery, regardless of the utilized methodology. The analytical study design, however, substantially influenced the relative risk estimates: The

TABLE 4.2.1 | Baseline characteristics of bisphosphonate users and matched non-users.

Characteristic	Bisphosphonate users n = 1,558	(%)	Matched non-users n = 8,966	(%)
Age (years, mean, SD)	75.4	(8.7)	75.6	(8.9)
Gross income (DKK, mean, SD)	146,774	(119,596)	143,525	(97,518)
GP / specialist visits in previous year (mean, SD)	11.0	(10.2)	10.5	(9.8)*
Females	1,404	(73.5)	8,161	(75.9)
Hip replaced	1,210	(63.4)	6,908	(64.2)
History of:				
Osteoarthritis	1,012	(53.0)	5,962	(55.4)
Fracture (other than hip fracture)	644	(33.7)	3,605	(33.5)
Inflammatory bowel disease	15	(0.8)	70	(0.7)
Heart failure	108	(5.7)	621	(5.8)
Renal disease	14	(0.7)	84	(0.8)
Malignancy	205	(10.7)	1,176	(10.9)
Ischaemic heart disease	163	(8.5)	944	(8.8)
Stroke	91	(4.8)	522	(4.9)
Drug use in the 6 months before primary hip / knee replacement surgery				
Estrogen containing drugs	137	(7.2)	801	(7.4)
Systemic glucocorticoids	244	(12.8)	1,282	(11.9)
Antidiabetics	50	(2.6)	275	(2.6)
Asthma / COPD drugs	214	(11.2)	1,148	(10.7)
Proton pump inhibitors	244	(12.8)	1,442	(13.4)
Antiarrhythmics	17	(0.9)	99	(0.9)
Statins	157	(8.2)	939	(8.7)
Thiazides	320	(16.8)	1,846	(17.2)
Beta blockers	211	(11.0)	1,292	(12.0)
Calcium channel antagonists	307	(16.1)	1,759	(16.4)
RAAS inhibitors	260	(13.6)	1,488	(13.8)
Calcium / vitamin D supplements	138	(7.2)	468	(4.4) ‡
Anticonvulsants	55	(2.9)	327	(3.0)
Antidepressants	271	(14.2)	1,606	(14.9)
Benzodiazepines	499	(26.1)	2,968	(27.6)

* p<0.05; † p<0.01; ‡ p<0.001.
Abbreviations: COPD = chronic obstructive pulmonary disease, DKK = Danish Kroner, GP = general practitioner, RAAS = renin-angiotensin-aldosterone system, SD = standard deviation.

TABLE 4.3.2 | Bisphosphonate use and implant revision surgery, stratified by study design.

	Cohort study design			Case-control study design *
	Time fixed, immortal time:		Time-dependent	
	Misclassified	Excluded		
No use	referent	referent	referent	referent
[events / PYs]	[399 / 15,576]	[399 / 15,576]	[399 / 18,249]	[399 / 1,945]
[rate per 10,000 PYs]	[256.2]	[256.2]	[218.6]	
Bisphosphonate use relative rate (95% CI)	0.22 (0.14-0.34)	0.37 (0.24-0.55)	0.41 (0.27-0.61)	0.46 (0.22-0.78)
[events / PYs]	[27 / 5,042]	[27 / 2,368]	[27 / 2368]	[27 / 185]
[rate per 10,000 PYs]	[53.6]	[114.0]	[114.0]	

Abbreviations: CI = confidence interval, PY = person year.
* Numbers in parentheses represent the number of cases, divided by the total number of patients in each stratum.

methodologically correct time-dependent cohort and case-control study design both provided similar results. Even the (methodologically incorrect) time-fixed cohort study that falsely excluded immortal time bias yielded a similar risk estimate. In contrast, the methodologically

incorrect time-fixed cohort study that falsely misclassified immortal time bias resulted into substantially lower relative risk estimates.

The clinical findings of this study are in line with the two previous observational studies on the association between bisphosphonates and implant failure (Chapter 4.2).[7] Consistent with this, a number of small and short-term studies including randomized clinical trials suggested that bisphosphonates are effective at minimising short and middle-term peri-prosthetic bone loss.[8] The proposed biological mechanism behind these findings is that bisphosphonates may prevent osteolysis by inhibiting osteoclastic activity in the bone surrounding the joint implant.[9] However, the relationship between these rather surrogate outcomes and long-term implant failure is controversial.[10] Hence, the influence of bisphosphonates on implant survival needs to be confirmed in randomized clinical trials.

The discrepant findings between the analytical study designs are largely in line with our previous example on statins and implant failure (Chapter 4.1). Time-fixed cohort studies tend to yield lower relative risk estimates as compared to time-dependent cohort studies or nested case-control studies. In this bisphosphonate example, however, the time-fixed cohort analysis that excluded immortal time did not substantially lower the relative risk. This may be explained by the relatively small proportion of bisphosphonate users in the study population. As the immortal time was only a small fraction of the person time that contributed to follow-up of the control patients, excluding this immortal time will not substantially influence the risk estimates. We did find such an effect in our statins example, as the proportion of exposed patients was much larger in that study. Hence, excluding this immortal time in the statin study significantly higher absolute risks of implant failure in unexposed patients.

The strengths of this study include a large sample size, longitudinal follow-up, the routinely collected data on exposure, outcome and potential confounders, and the ability to compare different study designs. A major limitation is that we cannot compare our results with the "absolute truth", as no randomized clinical trials are carried out on the association between bisphosphonate use and implant failure. We used a proxy for implant failure, i.e. revision surgery. Revision surgery after implant failure may be conditional on surgical fitness, and this may have distorted our study findings. Furthermore, bisphosphonate use, in particular adherence to bisphosphonate use, may be associated with healthy user bias. There is a chance of under recording of revision surgery, but this is likely to be non-differential.

In conclusion, from a clinical point of perspective, bisphosphonates were associated with a lowered rate of implant revision in individuals with a TJR surgery, regardless of the utilized methodology. This study confirms that the analytical study design can substantially alter key findings: on one hand, our findings from the case-control study design did not substantially differ from those of the time-dependent cohort study or the (methodologically incorrect) time-fixed cohort design that falsely excluded immortal time bias. On the other hand, the methodologically incorrect time-fixed cohort study that misclassified immortal time did result

into substantially lower relative risk estimates. From a methodological point of view, we do not promote the use of time-fixed cohort studies when studying associations between drug use and joint implant failure.

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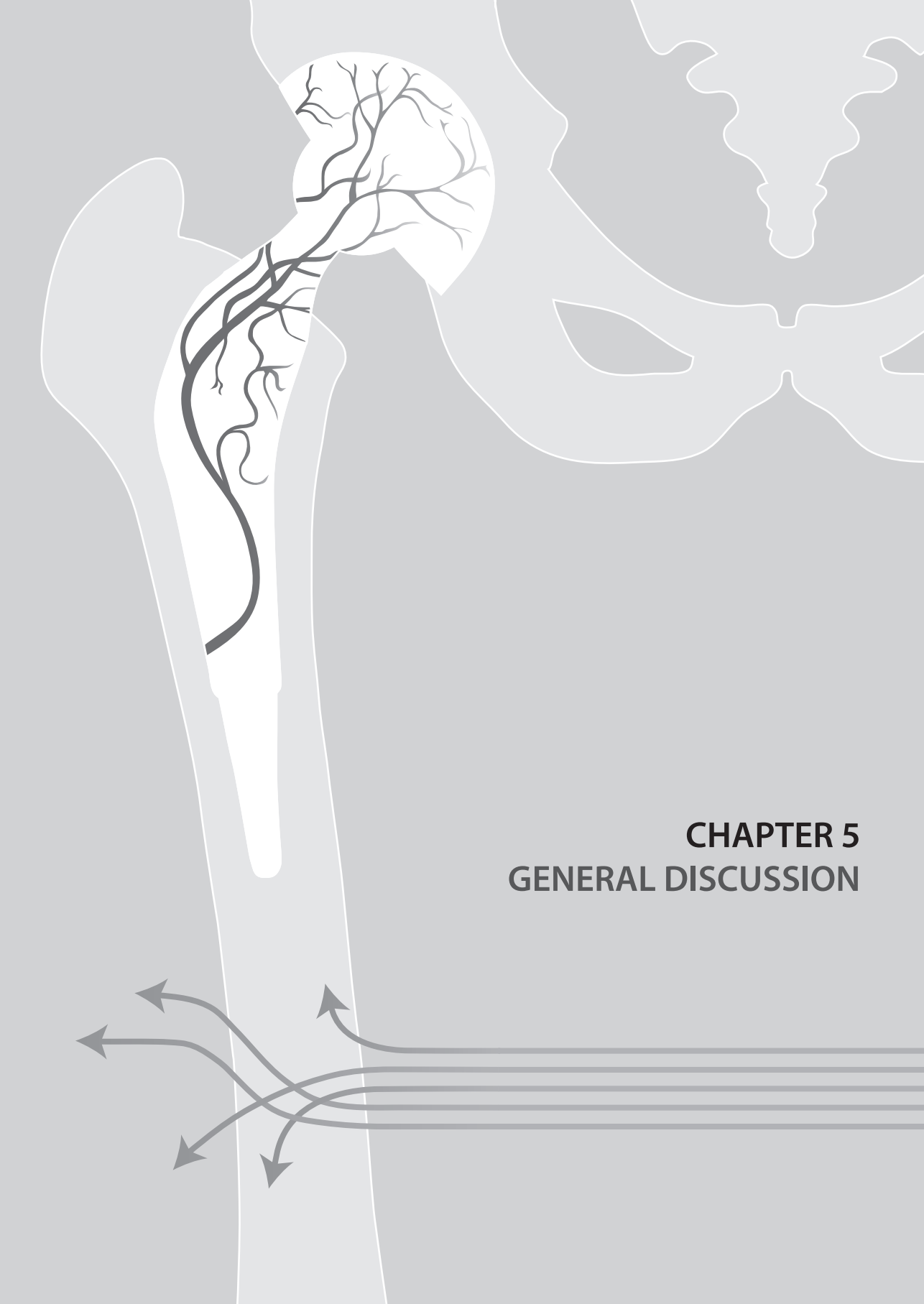


CHAPTER 5
GENERAL DISCUSSION

In this chapter, we will discuss several clinical and methodological aspects of this thesis. The first part of our overall thesis aim was to evaluate adverse outcomes following THR / TKR surgery, which will be discussed in the first section of this chapter. Where possible, the occurrence of these adverse outcomes will be discussed in terms of relative and absolute figures, secular time trends, mortality patterns, and how drug use might influence the risk of developing these negative outcomes. The second section of this chapter will focus on the methodological thesis aim, namely to explore the impact of various differences in methodological study design. We will discuss the methodological variations we have used throughout this thesis and how this might impact study results. Following from this discussion, we will conclude this chapter with some general recommendations concerning both the clinical as well as the methodological aspects described in this thesis.

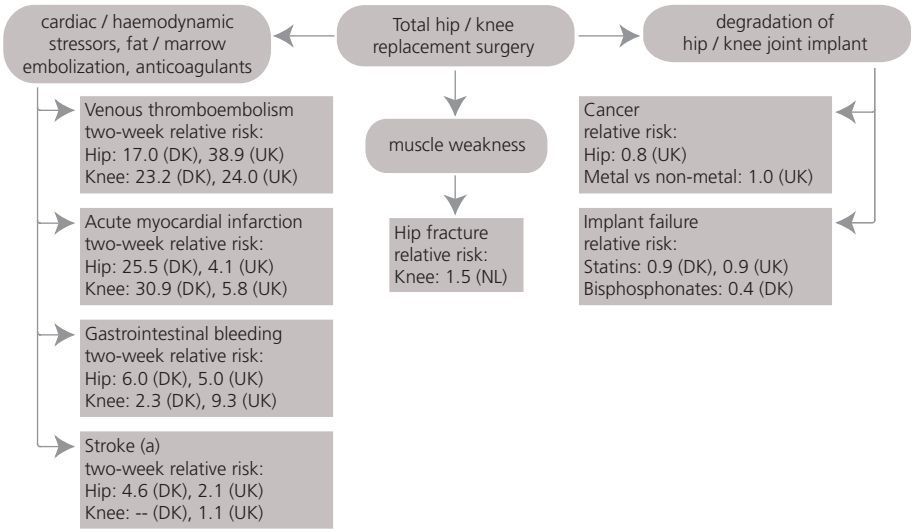
ADVERSE OUTCOMES FOLLOWING TOTAL HIP / KNEE REPLACEMENT

- VENOUS THROMBOEMBOLISM. In both Denmark (Chapter 2.1) and the United Kingdom (Chapter 2.5), we found a substantially increased excess risk of venous thromboembolism (VTE) in patients undergoing THR / TKR surgery, compared to matched controls who did not have this procedure. The risk was highest during the first 2 postoperative weeks (RR 17.0 - 38.9, Figure 5.1), but remained significantly elevated for at least four months in Denmark, and even beyond the first postoperative year in the United Kingdom. These findings are in line with a previous observational study in women who were primarily taking hormone replacement therapy and underwent THR / TKR surgery,[1] and suggest that a longer duration of thromboprophlaxis than currently recommended in international guidelines may be warranted.[2,3] These international guidelines typically recommend thromboprophylaxis during the first 10 to 35 postoperative days, which is much shorter than our observed prolonged period of excess VTE risk. These relatively short time windows are based on clinical trials with a relatively short duration of thromboprophylaxis (at most 39 days after discharge).[4,5] Although these trials demonstrated an added value of extended thromboprophylaxis (i.e. up to 39 days compared to shorter durations), no clinical trials have evaluated the benefits of prophylactic regimens beyond these initial 39 days. Indeed, our results suggested a beneficial role of outpatient vitamin K antagonist use for up to four months following THR / TKR surgery, but this has yet to be confirmed in randomized clinical trials.

  Despite this substantial increase in relative risk of VTE following THR / TKR, the absolute excess risk of VTE remains low (1.2% during the first 90 days), very much in line with findings from previous studies.[6-12] Moreover, VTE occurrence has tremendously declined over the past 25 years (Chapter 2.5), possibly related to the introduction of low-molecular weight-heparins (LMWHs) in the early 90s. Most recent figures from our research (calendar time 2008-2012) show that the 60-day excess risk of VTE following THR / TKR surgery has decreased to 0.9% (coming from 2.3% in 1987-1991). This

was confirmed in our Danish study (Chapter 3.1). In this study we found that less than 0.01% died from VTE following THR / TKR during the first 60 days in 2003-2007 (compared to 0.11% in 1989-1991).

FIGURE 5.1 | Adverse outcomes follow total hip / knee replacement surgery. (a) Stroke was not assessed in TKR patients because of an anticipated low number of events. Numbers represent hazard ratios.



- ACUTE MYOCARDIAL INFARCTION. We found an excess risk of acute myocardial infarction (AMI) shortly after THR / TKR surgery in both the Danish (Chapter 2.2) and British registries (Chapter 2.5). During the first 2 postoperative weeks, the risk of AMI was 4.1- to 30.9-fold increased as compared to individuals who did not undergo surgery (Figure 5.1) In contrast with the timing patterns of VTE risk, the risk of AMI following THR / TKR quickly diminished: for example, in the United Kingdom, the risk was only significantly elevated during the first 6 postoperative weeks following THR, and the first 2 weeks following TKR (very similar to the Danish results). These timing patterns are in line with the study by Gandhi et al, reporting that 91% of all in-hospital AMI events had occurred during the first 5 days.[13] Interestingly, the excess risk of AMI following THR / TKR was much higher in Denmark, as compared to United Kingdom. Methodological explanations for this discrepancy will be discussed in the methodological paragraph of this chapter. Clinical biological explanations may lie in the difference between Danish and British orthopaedic approaches for hip / knee replacement surgeries. For example, cemented procedures are more commonly performed in Scandinavian countries, as compared to the United Kingdom.[14,15] Bone cement has been hypothesized to induce hypoxia, hypotension, and arrhythmias, which may contribute to the excess risk of AMI.[16,17] We could not find any beneficial effects of antiplatelet use on the risk of AMI following THR / TKR, but this may have been complicated by confounding by indication. Although non-steroidal anti-inflammatory

drugs (NSAIDs) were associated with short-term AMI risk following THR surgery, we believe this to be non-causal. The association was not accompanied by a relationship with the cumulative dose, which strongly suggests that NSAIDs may be a proxy for (poor) health status (rather than a true causal effect). For similar reasons, cardiac drugs were associated with an excess risk of AMI following THR surgery.

In terms of absolute AMI risk, the 60-day risk is comparable with VTE rates found in Denmark, and roughly a quarter of VTE rates in United Kingdom. In line with previous findings, both figures seem to be low in absolute numbers (60-day risk 0.46% in Denmark, 0.23% in United Kingdom).[18-23,13] Moreover, our work showed that these rates have greatly improved compared to the late 80s / early 90s. In Denmark, between 2003 and 2007, approximately 0.03% died from AMI during the first 60 days after THR / TKR surgery, compared to 0.20% between 1989 and 1991 (Chapter 3.1). One possible explanation for this positive change of course is the introduction of LMWHs. These drugs, now standard of care for THR / TKR, have been shown to lower the risk of death and myocardial infarction during the first 6 days of therapy in patients with unstable coronary artery disease. Another explanation is the introduction of "fast-track" rehabilitation programs, which are focused at accelerated mobilisation of the patient after THR / TKR surgery.[24]

- GASTROINTESTINAL BLEEDING. Both our Danish (Chapter 2.3) and British studies (Chapter 2.5) showed an increased risk of gastrointestinal (GI) bleeding shortly following THR / TKR surgery. The risk of GI bleeding was increased by 2.3- to 9.3-fold during the first 2 postoperative weeks (Figure 5.1). This translated into an absolute risk of 0.52% for THR and 0.18% for TKR during the first 6 weeks, which is consistent with previous findings from clinical trials.[25,26,4] Anticoagulant prophylaxis – considered to be the reason behind the success in preventing VTE (and possibly AMI) following THR / TKR – may be seen as a double-edged sword that needs careful fine-tuning. Indeed, GI bleeding was the only haemostatic outcome that did not (tend to) improve over the past 25 years (Chapter 2.5), and may be because of the widespread use of anticoagulant prophylaxis. Nevertheless, our Danish mortality analyses did not show an obvious increase in GI bleeding related death over the past two decades, which is reassuring (Chapter 3.1). Moreover, GI bleeding related death rates remain low (< 0.01% during the first 60 postoperative days). This suggests an adequately balanced fine-tuning of the harms and benefits of anticoagulant use, although it might be interesting to study the risk / benefit balance when evaluating thromboprophylaxis for extended periods of use (i.e. > 39 days after surgery). Timing patterns were similar between the Danish and British cohorts: the risk of GI bleeding remained significantly elevated during the first 12 weeks following THR surgery, and the first 6 weeks after TKR surgery.

  Our Danish study suggested that proton pump inhibitors (PPIs) may be beneficial in

preventing GI bleeding following THR surgery (Chapter 2.3). The use of PPIs cut the 60-day GI bleeding risk following THR by 74%, which was statistically significant. Although the overall absolute risk of GI bleeding following THR might be too low to justify the widespread use of PPIs, it might be worth evaluating the use of PPIs in high-risk patients who are about to undergo THR surgery in randomized clinical trials.

- STROKE. THR surgery briefly boosted the risk of stroke during the first 2 weeks after the procedure in British patients (Chapter 2.5), and remained elevated during the first 6 weeks in Danish patients (Chapter 2.4). In Denmark, we were able to differentiate between ischaemic and haemorrhagic stroke, for which we found comparable excess risks and timing patterns. In patients undergoing THR surgery, the risk of any stroke was 2.1- to 4.6-fold increased during the first 2 weeks (Figure 5.1). This translated into an absolute risk of 0.7%, which is consistent with previous literature.[27-30,22] Remarkably, the excess risk was not found in patients undergoing TKR surgery (could only be assessed in UK). A possible explanation for this observation is the difference in marrow embolization following THR / TKR surgery. Marrow embolization – thought to be one of the causes of ischaemic stroke following THR surgery – is more likely to occur following THR than after TKR surgery: the marrow embolization is particularly triggered by surgical invasion of the medullary canal of the femur.[31,32,13] Another explanation may lie in the baseline cardiovascular disease burden of the study population. A proportion of the THR surgical patients may have required (non-elective) surgery for a hip fracture. These patients are known to have a greater disease burden (even before they sustain a hip fracture).[33] Following from our baseline tables, our included THR patients tended to suffer from heart failure more often, although cardiovascular drug use was similar between the two groups (suggesting no substantial difference in the baseline cardiovascular risk profile). Remaining biological mechanisms for ischaemic stroke are hypotension and the decreased blood flow during surgery. Intraoperative hypotension may result in cerebral hypoperfusion, and the decreased blood flow may slow down the washout of embolic material in the cerebral blood vessels.[34]

  Our Danish mortality analyses revealed that deaths from haemorrhagic or ischaemic stroke both sharply diminished over the past two decades (Chapter 3.1). In the years between 2003 and 2007, less than 0.01% of the Danish patients undergoing THR / TKR surgery died from either haemorrhagic or ischaemic stroke. This is an improvement of 87% (ischaemic stroke) and 93% (haemorrhagic stroke) as compared to death rates between 1989 and 1991. The most likely explanation is improved pharmacological / non-pharmacological interventions to prevent and treat stroke events. As seen with AMI and VTE, it is likely that the "fast-track" rehabilitation programs (as discussed earlier) played a role in this improved care.[24] It is remarkable that the greatest reduction in deaths from stroke was found in the early 90s, suggesting that LMWHs may have played a role in this. Although several authors proposed that LMWHs may lower risk of stroke,[35] this beneficial effect could not be confirmed in a large meta-analysis.[36]

The results from our Danish study (Chapter 2.4) suggested a potential beneficial effect of antiplatelet drugs in preventing ischaemic stroke following THR surgery (while not negatively affecting the risk of haemorrhagic stroke). During the first 6 postoperative weeks, risk of ischaemic stroke was 1.8-fold increased in antiplatelet users (adjusted HR 1.81, 95% confidence interval 1.24-2.66), compared to an increase by 3.7-fold in non-users (adjusted HR 3.73, 95% CI 2.65-5.24). It is questionable whether this should be further investigated in randomized clinical trials, as the absolute risk of sustaining ischaemic stroke following THR surgery is low (on average, 0.6% during the first 6 postoperative weeks). It could be studied in high-risk patients undergoing THR surgery, but on the other hand, the beneficial effects of low-dose aspirin (and statins) for (secondary) prevention have been demonstrated previously several times.[37,38] Hence, these drugs should perhaps already be considered in these patients, regardless of them undergoing THR surgery or not.

- CANCER. Similar to the two previous observational studies,[39,40] we could not identify an excess risk of cancer in patients who had received metal-on-metal hip implants versus patients with hip devices of non-metal material (adjusted RR 0.96, 95% confidence interval 0.64-1.43, Chapter 3.2). Substantial baseline differences between these two groups of patients warranted for careful interpretations: patients receiving metal-on-metal hip implant devices were generally much healthier than other THR patients, complicating a direct comparison. Even with the available information on confounders in the data source, residual confounding is of great concern in such analyses. As an example, and very similarly, implant failure rates among metal-on-metal hip devices gained much attention worldwide.[41] Authors from the study concluded from their results that metal-on-metal devices were more often revised as compared to non-metal hip devices. However, surgical fitness for THR revision – a very drastic procedure with poorer clinical outcome than with primary THR surgery – may vastly differ between generally healthier patients who received metal-on-metal hip implants and older and frail patients with non-metal hip devices. The latter group may be refrained from revision surgery (because of their poorer surgical fitness), thereby falsely creating a difference in implant failure rates (typically measured as revision surgery rates). This calls for more sophisticated analyses, such as careful treatment patterns and timing of risk, rather than just one overall direct comparison. In the case of cancer, a greater increase in excess cancer risk over time would be suggestive of some sort of causal association. No such trend could be observed in our analysis and is reassuring for patients who received metal-on-metal hip implant devices. Nevertheless, we cannot exclude the possibility of a causal relationship with cancer. Some types of cancer may have a latency of at least 10 years, which could not be captured in our study with a follow-up of 8 years for some patients at most (and a median follow-up of 4 years).

- FRACTURE. Our Dutch study demonstrated a 1.5 fold increased risk of hip fracture among patients who received TKR surgery (adjusted OR 1.54, 95% confidence interval

1.19-2.00, Chapter 3.3), which is in line with previous British findings.[42] The biological explanation of this finding is complex, and may be intertwined with the effects of osteoarthritis – the main indication for TKR surgery – on hip bone strength and falls. Some authors found a decreased fracture rate among patients with osteoarthritis, possibly due to higher bone mineral density levels.[43-45] On the other hand, others reported an increased fracture risk with osteoarthritis, which is more in line with our findings.[42,46] This latter observation is thought to be related to the nature of falls (increased severity of falls), rather than an actual increase in the number of falls.[47] We would have hypothesized that the risk of hip fracture should decrease shortly after surgery, as patients gradually regain their physical strength over time. Possible explanations for our contradicting observation could be patient's overestimation of their physical strength shortly after surgery, sarcopaenia, and residual knee pain and stiffness (in particular in the first few months following the procedure).[62]

- IMPLANT FAILURE. We found an inverse relationship in the Danish registries between bisphosphonate use and implant failure (Chapter 4.2), whereas we could not find such an association for statin use (Chapter 4.1). For bisphosphonates, the protective effect was only apparent after one year of use (HRs: 6-12 months HR 1.12 [95% confidence interval 0.70-2.01], 1-2 years HR 0.35 [95% confidence interval 0.17-0.72], >2 years HR 0.35 [95% confidence interval 0.09-1.25]), which is suggestive for a causal relationship. This is the second study demonstrating the potential of bisphosphonates to reduce implant failure (very similar to the first British CPRD study),[48] and may be explained by the reduction of joint loosening by strengthening the bone around the joint.[49] Interestingly, statins interfere in the very same osteoclast / melavonate pathway as bisphosphonates,[50] but do apparently not exert such an effect on implant failure. This is much in line with the discrepancy between the two drugs on hip fracture,[51,52] where statins do not seem to have the ability to strengthen femoral bone. A possible explanation for the absent effect on bone is that statins were designed to exert their effects on the liver, rather than on bone (in contrast to bisphosphonates, which explicitly distribute to the bone).

IMPACT OF DIFFERENCES IN STUDY DESIGN

- DATA SOURCE. We used two widely utilized pharmacoepidemiological data sources in this thesis: the Danish National Healthcare Service (DNHS) registries and the British Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD) (Figure 5.2). Both data sources have shown their clinical value many times, but differ in some crucial aspects. The major difference between these two data sources lies in the "data collector". In the CPRD, the computerized data is collected by the general practitioners (GPs). GPs play a key role in the United Kingdom healthcare system, as they are responsible for primary healthcare and specialist referrals (i.e., they are the "gatekeeper" of the British healthcare system).

FIGURE 5.2 | Methodological differences between the Danish and British source population.

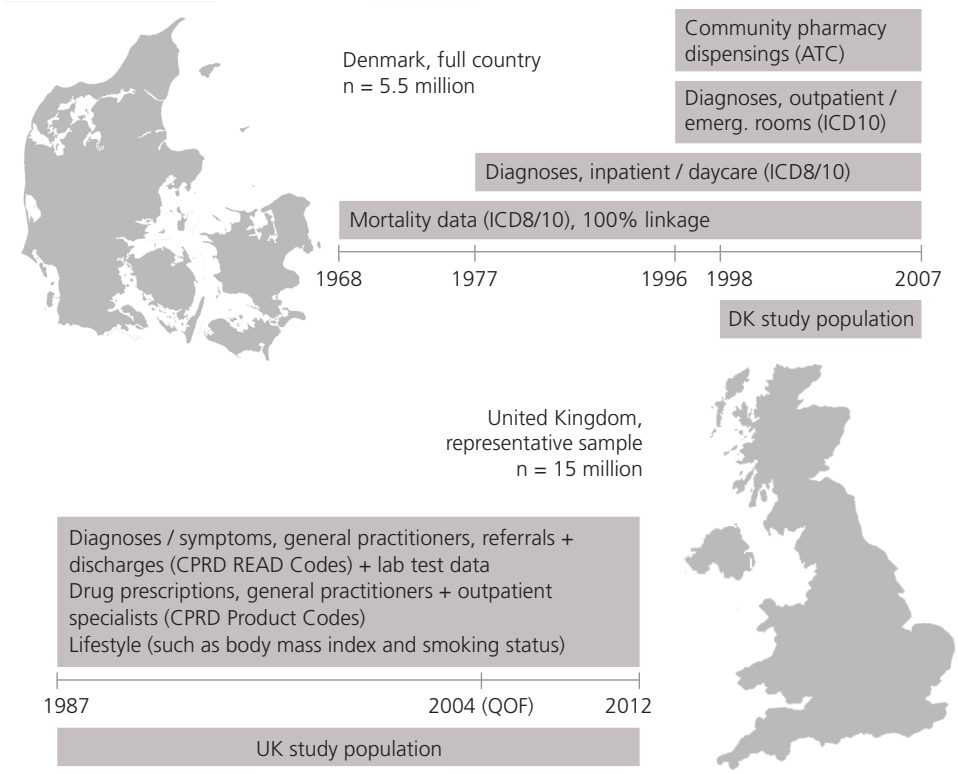


TABLE 5.1 | Clinical outcomes following THR / TKR surgery, stratified by source population.

	2-week risk of adverse outcome following THR / TKR					
	Denmark		United Kingdom		ratio DK / UK	
Outcome	RR (95% CI)	IR *	RR (95% CI)	IR *	RR	IR
Total hip replacement						
Venous thromboembolism	17.0 (14.5-21.0)	77.0	38.9 (17.2-88.0)	92.3	0.44	0.83
Acute myocardial infarction	25.5 (17.1-37.9)	97.5	4.11 (2.35-7.18)	24.4	6.20	4.00
Gastrointestinal bleeding	6.02 (4.06-8.92)	40.1	5.00 (2.34-10.7)	12.2	1.20	3.29
Stroke	4.62 (3.30-6.81)	74.3	2.11 (1.40-3.19)	23.7	2.19	3.14
Total knee replacement						
Venous thromboembolism	23.2 (16.7-31.0)	91.1	24.0 (11.1-52.1)	99.2	0.97	0.92
Acute myocardial infarction	30.9 (11.1-85.5)	45.5	5.78 (2.44-13.7)	26.2	5.35	1.74
Gastrointestinal bleeding	2.30 (1.17-4.54)	17.3	9.28 (2.82-30.5)	12.6	0.25	1.37
Stroke †	-	-	1.12 (0.63-1.97)	10.7	-	-

Abbreviations: adj = adjusted, IR = incidence rate, RR = relative risk.
* IR is calculated for THR or TKR patients as the number of events divided by follow-up time (expressed as per 1000 person years).
† Stroke was not assessed in TKR patients because of an anticipated low number of events.

The data recorded in the CPRD include demographic information, prescription details, clinical events, specialist referrals, hospital admissions, and major outcomes since 1987. In Denmark on the other hand, the DNHS is based on a linkage between non-GP registries. These include hospitalization registries (with information from outpatient

wards and emergency rooms), death certificate data, and community pharmacy dispensings.

OUTCOME RECORDING RATES. As a result of these differences in type of registry, some diagnoses are more easily caught in the CPRD (e.g. common cold), while others are more readily available in DNHS (e.g. colorectal cancer). The potential influence of this difference in "data collector" is displayed by our thesis findings in Table 5.1. In general, incidence rates for adverse outcomes following THR / TKR were higher in the DNHS, as compared to the CPRD. As most of these events are likely to occur while still hospitalized for the surgery, they are easier caught by hospitalization registries (as long as the recording of such events is mandatory / routine care). In addition, when a patient sustains an AMI after hospital discharge, it is likely that he will be admitted to the hospital (rather than visiting a GP first). The GP relies on hospital discharge letters that should be sent back to the GP (or a later patient visit at the GP). Although this should have improved for the CPRD with the introduction of electronic discharge letters, it could still explain the difference in incidence rates between DNHS and the CPRD. Interestingly, such a difference in incidence rates does not necessarily translate into a difference in relative risks (Table 5.1). For example, the 2-week incidence rate of GI bleed following THR was 3.3 times higher in DNHS as compared to the CPRD. The relative risks on the other hand were more or less comparable. This is the result of non-differential under recording of the outcome of interest in the CPRD. As long as the under recording rate is similar for exposed patients and control subjects, this will not result into a biased relative risk. Another good example of non-differential under recording of the outcome is our study on the relationship between metal-on-metal hip devices and cancer. Within the CPRD, we used several disease outcome registries: (1) GP-based recordings [diagnoses or referrals], (2) hospitalization registries, and (3) cause of death records. Although the cancer incidence rates differed vastly between the types of outcome registries, it did not affect the relative risks. We found a similar phenomenon in our study on statins and implant revision. Implant revision rates were more than doubled in Denmark as compared to in the United Kingdom, yet the relative risks were strikingly similar between the two countries.

On the other hand, under recording of the outcome may occur on a differential basis as well rather than non-differential (i.e. different for exposed and unexposed patients). As an example, the 2-week incidence rate of AMI following THR was 4.0 times higher in DNHS as compared to the CPRD, and the relative risk was 6.2 times higher. Assuming that this difference is not based on biological explanations (i.e. Danish patients being more susceptible to negative outcomes following THR surgery than British patients), this observation may point to non-differential under recording. This means that, in the CPRD, AMIs among THR surgical patients are more readily recorded by the GP, as compared to AMIs sustained by non-surgical controls. At least a few possible explanations exist: (1) Berksonian bias, i.e. AMIs among THR surgical patients are more

likely to be noted (because they reside in the hospital and are being monitored) than in non-surgical patients in the general population, (2) patients at home sustaining an AMI may die before getting hospitalized; this might be missed in the CPRD, but not in DNHS (which is linked to cause of death registries), and (3) THR surgical patients may have more GP visits as compared to non-surgical patients (including follow-up visits); AMIs among THR surgical patients may therefore be easier to catch by the GP.

Coding systems. Another important difference between the two data sources is the detail level of recorded diagnoses and symptoms. Hospitalization registries, including the one in DNHS, are typically coded using the International Classification of Diseases (ICD). While sufficient in most cases, the ICD system provides less detailed information as compared to GP codes (in case of the CPRD, the CPRD READ code system). For example, the CPRD READ code system is detailed enough to differentiate between several THR surgical techniques (e.g. Exeter or Charnley procedures), whereas the ICD system is not. Although this is, in theory, an advantage of the CPRD READ code system over the ICD system, more detailed CPRD READ codes are sparsely used in the CPRD. As an example, in CPRD, the most frequently used stroke code is "Stroke and cerebrovascular accident unspecified", while codes such as "Intracebral haemorrhage" and "Cerebral artery occlusion" are much less frequently utilized. Although the (potential) level of detail for stroke in DNHS is much lower, Danish hospital specialists specify the type of stroke (e.g. haemorrhagic versus ischaemic) more often (59%) than GPs in the CPRD (30%). This allowed us to differentiate between ischaemic and haemorrhagic stroke in DNHS, whereas such a discrimination was not possible in the CPRD. Although the CPRD can be linked to the hospitalization registry of England (the Hospital Episodes Statistics) and cause of death records, it is only available for a limited period of calendar time and a certain proportion of practices.

INFORMATION ON CONFOUNDING. Information on confounding was found to be more readily available in the CPRD as compared to DNHS. Because of the high level of detail of the CPRD READ code system, not only diagnoses are recorded, but also symptoms. This includes symptoms that generally do not require hospital admission (and as such, are not captured in hospitalization registries), but may provide important information on confounders. In addition, the CPRD has the possibility to record lifestyle parameters, such as body mass index, smoking status, and alcohol use. With the introduction of the Quality and Outcomes Framework (QOF) in 2004, the recording rates of these specific confounders have increased.[53] The QOF was introduced to improve the quality of general practice by financially rewarding "good practice" (including recording lab tests and lifestyle parameters for certain QOF diseases such as diabetes mellitus).

EXPOSURE STATUS. In our studies, we used two types of exposure statuses, namely (1) surgery status and (2) drug use. In this paragraph, we will only focus on the British and Danish studies. For surgery status, we defined our exposure on the basis of four different data sources: (1) DNHS hospitalization registries, (2) CPRD GP records, (3)

UK Hospital Episode Statistics (HES), and (4) the UK National Joint Registry (NJR), a prospective dedicated joint replacement registry. Taking into account the linkage proportion and the available calendar years for all data sources, the number of included THR / TKR patients were comparable across the data sources. In addition, the baseline characteristics between these four cohorts were very similar (Table 5.2). Hence, the risk of selection bias is not very likely, and should not have had a major impact on the key findings. The real difference between these data sources again lies in the richness of data. For example, the NJR has detailed information on the material of the hip implant device, which was not available in hospitalization registries such as the Danish DNHS or British HES. A powerful feature of the CPRD is the possibility to analyse "free-text" data entered by the GP. By using this anonymized non-computerized data, we were able to derive the materials of the hip implant device for some THR patients in the CPRD. Although this analysis showed similar trends as the NJR analysis, the statistical power using this "free text" technique was much lower than in the NJR analysis: we were only able to derive the type of hip implant device for 1.8% of all THR patients in the CPRD.

TABLE 5.2 | Baseline characteristics of THR patients across four different data sources.

	Total hip replacement			
	Denmark	United Kingdom		
Characteristic	DNHS	CPRD	HES	NJR
Mean follow-up time (years, SD)	3.9 (2.8)	5.2 (3.7)	5.2 (3.3)	3.2 (2.1)
Males	41.5%	38.5%	37.8%	40.5%
Mean age (years, SD)	68.3 (10.6)	68.5 (10.9)	69.1 (10.7)	67.9 (11.0)
Medication use 6 months before				
NSAIDs	61.7%	47.9%	46.9%	43.2%
Paracetamol	31.2%	58.9%	58.6%	58.4%
Antidiabetics	5.7%	5.0%	5.5%	5.5%
Systemic glucocorticoids	8.2%	4.9%	5.2%	4.8%
Statins	24.5%	21.0%	22.3%	27.2%
Calcium / vitamin D supplements	1.3%	7.1%	7.0%	8.4%

Data are presented as means (SD) or percentages (among THR patients), unless stated otherwise.
Abbreviations: CPRD = Clinical Practice Research Datalink, DNHS = Danish National Health Service, HES = Hospital Episodes Statistics, NJR = National Joint Registry, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation; THR = total hip replacement.

For drug use status, we used either community pharmacy dispensings (DNHS) or GP / outpatient specialist prescribings (CPRD). In Chapter 4.1, we observed that, although in general there were no major differences in drug use between the two data sources, some notable differences remained. For example, the use of calcium / vitamin D supplements, paracetamol, and proton pump inhibitors was much higher in the CPRD, whereas use of anxiolytics / hypnotics was more common in DNHS. It is difficult to conclude whether this is related to misclassification in the data source or to actual international differences in drug use between Denmark and the United Kingdom. In the case of misclassification, this could mean that patients were classified as "exposed" to drugs, whereas in reality they were not (and vice versa). This type of misclassification leads to "bias towards the null" (assuming the misclassification

is random, i.e. independent of future disease statuses). This type of bias nullifies any association (assuming there is an association in absence of the misclassification), and is in general considered as a less severe form of bias as it does not inflate study findings. In our statins and bisphosphonates examples in Chapter 4, we did not find any substantial differences in the study findings, suggesting that this does not have a major impact on the results.

COMPLETENESS OF FOLLOW-UP. One of the great advantages of a nationwide cohort study is the completeness of follow-up. This is in particular true for the Danish registries, as Danish residents tend to stay in the same place / country for generations. While this is unlikely to be a major contributor to differential study findings for short-term outcomes (such as our cardiovascular outcomes), it could be of importance when looking at outcomes with a long latency (such as cancer). Nevertheless, the CPRD has information on migration status and transfer out of the GP's practice, and such patients can be censored accordingly to deal with this problem in some degree.

- TYPE OF ANALYTICAL STUDY DESIGN. Following from Chapter 4, we found substantial differences in study findings when various analytical study designs were used. Time-fixed cohort analyses underestimated the relative risk, and was strongest with misclassification of immortal time (Chapter 4.1: 54% lower rate ratios as compared with time-dependent cohort analyses). This is in line with an example using statins and diabetes progression, previously reported by Levesque et al.[54] When the immortal time was excluded from the analysis, the underestimation diminished slightly, but remained present in the example of statins (Chapter 4.1). In contrast, our bisphosphonate analysis (Chapter 4.3) did not show a substantial difference between time-dependent cohort analyses and time-fixed analyses that excluded immortal time. This is explained by the relatively small proportion of bisphosphonate users in the study population. As the immortal time was only a small fraction of the person time that contributed to follow-up of the control patients, excluding this immortal time will not substantially influence the risk estimates. We did find such an effect in our statins example (Chapter 4.1), as the proportion of exposed patients was much larger in that study. Hence, excluding this immortal time in the statin study significantly overestimated the risk of implant failure in unexposed patients. This overestimation becomes even more troublesome when looking at dose response relationships, as time fixed cohort studies tend to show an inverse relationship between the cumulative dose and the risk of the outcome of interest (Chapter 4.1). As causality in observational studies is often indirectly tested on the basis of these dose response relationships, great care should be taken when interpreting findings from time fixed cohort studies. In contrast, time dependent analytical study designs, and case-control studies as well, did not show this artefact.

- TIMING OF FOLLOW-UP. Defining appropriate time windows for both exposure status and "at risk" status is crucial to derive undiluted risk estimates. For example, if we had chosen to estimate the overall risk of AMI at any time after THR surgery, we would have missed the excess risk in the first few weeks. This initially increased risk would have been diluted, and we would have yielded a relative risk of 1.0. Similarly, in the case of outcomes with a long latency period (such as some types of cancer), it makes less sense from a clinical point of perspective to include the first few months in the "at risk" time window. Doing so would dilute the effect of the exposure on cancer in the years thereafter. It is therefore crucial to define these time windows a prior (on the basis of biological mechanisms) and to analyse the data accordingly. An indirect way to do this is to divide total follow-up into smaller time intervals and to calculate the relative risks in each time interval (as we have done in our studies). The transparency of this method (i.e. it displays the relative risk for all time intervals, rather than one arbitrarily preselected time interval) is what appeals this strategy. The reader can then decide which time interval he thinks to be the most plausible from a biological point of perspective. In addition, it can filter out biased results, as we have shown in Chapter 3.2 with our cancer example: the risk of cancer should not be altered in the first 6 months of exposure. If any change in the risk is present during this period, it strongly suggests bias, and the results should be interpreted carefully.

  Another aspect of timing of follow-up is calendar time. Often, calendar time is considered as a confounder, and hence exposed and unexposed patients are matched on calendar time. In our studies, we have shown that calendar time can be an important effect modifier as well, on top of being a confounder. Relative risks of adverse outcomes following THR / TKR surgery differed between the various investigated calendar time periods. If the primary objective is to show health care outcomes of current practice, calendar time should be restricted to a relevant recent time period (or stratified into various calendar time periods). By neglecting this methodological aspect, the overall analysis may yield diluted or inflated results that may not be true for current health care practice.

- TECHNIQUES TO DEAL WITH CONFOUNDING. In none of the performed analyses in this thesis, adjustments for confounding made any substantial difference as compared to crude analyses. This could have several explanations: (1) confounding was not present in these studies, (2) residual confounding was of greater concern, (3) the information on confounders was of poor quality, and (4) the techniques to deal with confounding were inadequate. Defending the first explanation, osteoarthritic patients typically do not have a different cardiac baseline risk profile as compared to patients from the general population.[55] This would imply only minimal confounding. While it is true that THR / TKR surgical patients receive anaesthetics during surgery, which could well alter the cardiac risk profile, we consider this as "part of the surgery".[56] It is therefore in the causal pathway and not considered as a confounder. For most of the

adverse outcomes, the relative risk eventually reached a value of 1.0, which further supports the lack of major (residual) confounding.

On the other hand, some residual confounding was present in the statin study. The overall crude relative risk was 0.90 (95% confidence interval 0.84-0.97), which we did not believe to represent a causal effect. Even when fully adjusted for all potential confounders, the relative risk remained significantly lowered (adjusted relative risk of 0.91, 95% confidence interval 0.84-0.99). This strongly suggests residual confounding, either by the lack of certain confounders or the relatively low (non-informative) quality of available confounders. For example, suppose heart failure is a confounder and we adjust for a history of heart failure. There may still be a vast difference between two patients both suffering from heart failure, as the severity (or current activity) of heart failure is difficult to capture. More likely, this severity of heart failure is a determining factor for the outcome, rather than having a recorded diagnosis of heart failure. Functional scores would be more informative in this case, but are rarely recorded in these types of pharmacoepidemiological databases.

The specific methodology to deal with confounding did not make a substantial difference for the study findings. The classical "change-in-estimate" method (originally advocated by Greenland and colleagues)[57] was not worse than the relatively new propensity score techniques. Although propensity score matching results into (seemingly) balanced groups, this is only true for confounders that are entered into the propensity model. Hence, residual confounding may still exist, and to the same extent as with classical multivariate regression techniques. We advocate the use of full multivariate regression techniques, whenever the model can handle it. Change-in-estimate techniques may be helpful in eliminating less important confounders, but rely on univariate checks. For example, covariate C1 might not be a confounding factor when entered univariately into the model. However, on a higher level, covariate C1 might be a confounding factor when entered into a multivariate regression models with multiple other confounding covariates.[58] The change-in-estimate method does not take this difficulty into consideration. In many cases however, the number of confounders in a full regression model is more than what the model can handle. Entering too many confounders into a regression model may result into artefacts and may falsely increase the relative risk.[59] Therefore, in these cases, we advocate the use of propensity score adjustments. This technique has the advantage of being able to incorporate all potential confounders, but summarizes them into a single variable so that the regression model can handle such adjustments. Although conceptionally not wrong, we do not promote the use of propensity-matched models. Matching may result into "trimming off" the extreme sides of the propensity score, which could include a relevant proportion of the study population. Moreover, we could not find any substantial differences in relative risks between propensity adjustments and matching, which is consistent with previous findings.[60]

Instrumental variable (IV) adjusted analyses would be another good alternative to deal with confounding (not studied in this thesis).[61] A valid IV analysis results into pseudo randomization and therefore deals with unmeasured confounders as well (in contrast with, for example, a propensity score adjusted model). The drawback of an IV model is that it is challenging to find an IV that meets the key assumptions: (1) it must be strongly correlated with the exposure status, (2) it must be independent of other covariates, and (3) it must not have a direct effect on the outcome of interest. In essence, randomized clinical trials are perfect examples of "IV models", as the randomization procedure meets all of these three key assumptions of an IV. In pharmacoepidemiology, the physician's prescribing preference is often used as an IV, but this methodology is not always possible because of privacy reasons (as was the case with our studies).

CLINICAL RECOMMENDATIONS

Looking at the previously established benefits of THR / TKR surgery,[62] we feel that these advantageous effects outweigh the clinical harms that we found in our work. Although evidently elevated, the risk of clinical harms are generally limited to the first 2 to 6 weeks post-surgery. At the same time, not undergoing surgery may also pose a risk for several adverse outcomes, which may have a longer duration of increased risk. For example, albeit slowly, THR / TKR surgeries are effective in mobilizing osteoarthritic patients who were previously unable to walk by themselves. Such an improvement in physical activity may indeed reduce the risk of cardiovascular events in the long run. Taken all of this together, we promote THR / TKR surgery for patients who require them and we consider this as a relatively safe procedure with a high benefit-risk ratio.

Nevertheless, there is an excess risk of adverse outcomes following THR / TKR surgery. While this excess risk is low for the majority of the patients, careful risk assessments should be considered. A 20-fold increase for a low-risk patient may be acceptable, but for an individual with an already high baseline cardiovascular risk this may be a discussion worthy issue. One current limitation is that there are no validated risk prediction tools that classifies an individual patient (who is about to undergo THR / TKR surgery) as a low-, medium-, or high-risk patient. We therefore promote the development of such risk tools, which should enable physicians to easily classify each individual patient according to their risk profile.

Further, we promote the ongoing safety and efficacy studies for THR / TKR surgery. Besides longitudinal observational studies, we call for the conduct of randomized trials. Although observational studies clearly have its benefits, some findings can never be conclusive without the availability of results from randomized trials. Earlier in this chapter, we discussed the example of implant failure rates between metal-on-metal versus non-metal hip implant devices,[41] and how selection / confounding bias may substantially distort the study findings in observational studies. Valid conclusions on this topic would require randomized trials, in which confounding is dealt with by randomization and information bias by blinding.

Pragmatic randomized trials could be a suitable option to evaluate these types of research questions, assuming that both treatments (i.e. surgery type A and B) are already in use and there is no clear evidence to guide the decision for treatment type.[63] Rather than choosing a treatment based on arbitrary decisions, pragmatic randomization eliminates confounding and may provide the physician with new evidence. A major advantage of these pragmatic trials over explanatory (clinical) trials, is that pragmatic trials can evaluate the effectiveness of a treatment under real-life conditions (as opposed to ideal or selected conditions in explanatory / clinical trials). One example is the Randomised Evaluations of Accepted Choices in Treatment (REACT) trial, conducted within in the CPRD.[63] The REACT trial currently consists of several pilot trials, one, for example, comparing the effectiveness of simvastatin to atorvastatin in patients with primary hypercholesterolaemia and high cardiovascular disease risk.[64] These pilot trials should provide some answers on the feasibility of conducting pragmatic randomized trials using general practice electronic health care records.

With VTE still being one of the most important adverse outcomes following THR / TKR, we further call for randomized trials investigating extended duration of thromboprophylaxis, as we found some supportive indications for the prolonged use of vitamin K antagonists. Lastly, the consistent findings on the potential benefits of bisphosphonates in preventing implant failure should be confirmed in randomized clinical trials.

METHODOLOGICAL RECOMMENDATIONS

It is impossible to provide researchers with the "gold standard" on how to conduct observational studies, as this greatly depends on the available data sources and the specific purpose of the study. Therefore, by no means, we intend to provide such a gold standard, but we will share some methodological recommendations and points of interest to take into consideration when performing observational studies.

The choice of (retrospective) electronic health care records depends on the research question. Knowing its strengths and limitations in great detail will allow the researcher to make this choice much easier. In general, GP based registries will provide the researcher with richer information. For example, if body mass index is a major confounding factor, it may seem more logical to choose a GP based register as a data source. An important consideration is that GPs may miss some diagnoses that are made in the hospital, in particular if there is no electronic communication from the hospital back to the GP. General practices may therefore suffer from under recording of some diseases. If such a disease is the outcome of interest and the purpose of the study is to provide absolute risk estimates, the use of hospitalization registries may seem more appropriate. If, however, this under recording is non-differential and the estimate of interest is a relative risk (rather than an absolute risk estimate), a GP based register may be suitable as well.

We strongly promote the use of time-dependent cohort studies whenever possible. Although not in all cases, time fixed cohort studies may suffer from substantial person time

misclassification bias (immortal time bias) or selection bias. The use of (nested) case-control studies may be a reasonable and valid alternative when the use of time dependent cohort studies is not possible. Even when using a time dependent cohort methodology, the design, in particular the allocation of person time, should be carefully considered. Incorrect person time allocation (even with time dependent cohort designs) may in particular occur with cumulative dose and duration of hospitalization analyses. We promote the clear description of person time allocation (including start / end of follow-up) in the methods section of the research paper, and, if possible, a schematic illustration of these definitions.

We advocate hazard pattern analyses, in particular when the relative risk is not constant over time. Long latency periods or short time intervals of an excess risk are examples of non-constant relative risks over time. Not only does this violate assumptions of several regression models (including Cox proportional-hazards models), it may dilute associations leaving the researcher with invalid conclusions. These timing pattern analyses can, for example, be achieved by splitting total follow-up into smaller time intervals (and calculate the relative risk for each time interval in separate models) or by introducing interaction terms (time period x exposure status) into the regression model. An alternative is to restrict the "at risk" window to a predefined (biologically plausible) time window, but this is not transparent and may hide important information originating from the omitted time windows.

Dealing with confounding can be difficult and, in our examples, may be limited by the quality and quantity of available confounders. Residual confounding may therefore still be an issue, regardless of the techniques we have evaluated (fully adjusted multivariate model, "change-in-estimate" method, propensity adjusted models, propensity matched analyses). In our examples, the different confounder handling techniques performed equally well. From a conceptional point of perspective, we promote the use of fully adjusted multivariate regression, as long as the model can handle it. The only downside of this method is that, in the event of too many confounding variables in the model, this technique may introduce some artefacts, biasing the risk estimate. In these cases, we advocate the use of propensity adjustments, as this requires only one covariate to be entered into the full model, while still making use of all potential confounders.

CONCLUSIONS

Total hip / knee replacement surgery briefly boosts the risk of several potentially fatal complications, including acute myocardial infarction, venous thromboembolism, stroke, and gastrointestinal bleeding. For most of these outcomes, the excess risk is limited to the first 2 to 6 postoperative weeks. For venous thromboembolism, however, the risk remains elevated for at least four months after surgery. This calls for the conduct of clinical trials evaluating the benefit / risk balance of commencing extended thromboprophylaxis (beyond the currently recommended duration of 10 to 35 days). Indeed, our results suggested a protective effect of this extended thromboprophylaxis, but this needs to be confirmed in randomized clinical trials.

In addition, we found some indications that proton pump inhibitors might lower the risk of gastrointestinal bleeding, and that antiplatelets might reduce the chance of ischaemic stroke (while not negatively affecting the risk of haemorrhagic stroke or gastrointestinal bleeding). On an overall level, the absolute risk of these outcomes remained low, but the excess might be substantial in high-risk patients. This is of particular interest, given the trend to perform surgery in individuals with more comorbidities, and we therefore promote (cardiovascular) risk assessment in these patients. Finally, our results pointed towards a substantial benefit of bisphosphonates in lowering implant failure rates. As there currently are no pharmacological interventions to prevent implant failure, this needs to be further explored in randomized clinical trials. No such effect could be observed for statin use on the other hand, which is consistent with findings on the association between statin use and the risk of fracture.

From a methodological point of view, we found that different confounder handling techniques did not make a substantial difference in our examples. Regardless of the technique, residual confounding probably remained present, emphasizing the need for careful interpretation when looking at overall risk estimates. Given this finding, we would suggest to perform timing / pattern and bias analyses to accompany the overall risk estimates (which should provide some insight on bias and causal probability). The analytical study design was the most important determinant of differential key findings in our examples: time-dependent cohort studies performed equally well as case-control studies, whereas it appeared that time-fixed cohort studies substantially underestimated relative risk estimates. In most of the associations, the type of data source did not substantially alter relative risk estimates (suggesting non-differential under recording, if present at all), but care should be taken when interpreting absolute risk estimates. The type of data source should be chosen on the basis of the desired risk estimate type and the validity / recording quality of the covariate in the data source of interest.

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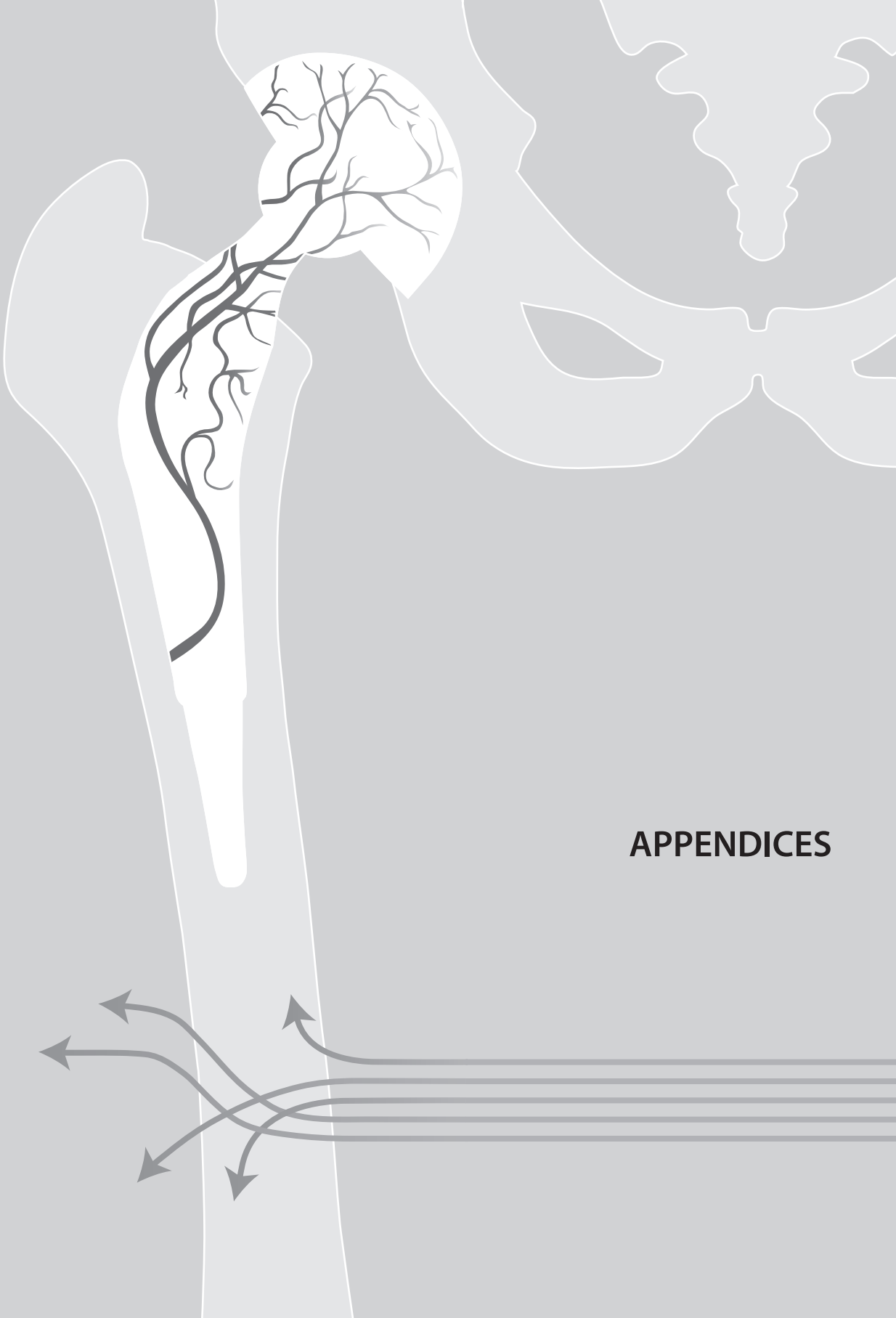

APPENDICES

APPENDIX A

Summary

1. INTRODUCTION

Osteoarthritis is the most common form of joint disorders, and is the leading cause of pain and physical disability in older individuals. It affects one fifth of all individuals aged 65 years and older, and severely limits day-to-day activities such as walking, climbing stairs, and sleeping. Total hip (THR) or knee replacement (TKR) surgery substantially improves quality of life in patients with moderate to severe osteoarthritis. However, potentially fatal adverse outcomes, such as venous thromboembolism (VTE) and acute myocardial infarction (AMI), may occur shortly after the surgery.

In light of these adverse outcomes following THR and TKR surgery, there is a need to overcome the following knowledge gaps: (1) when do these adverse outcomes occur (e.g. only during the first 2 weeks or perhaps even for months after surgery), (2) what is the size of excess risk (compared to patients who did not undergo THR or TKR surgery), and (3) what is the influence of patient characteristics, in particular drug use. Providing insight on these knowledge gaps should be beneficial in optimizing postoperative care with regards to THR and TKR surgery.

Studying these knowledge gaps requires the use of millions of sophisticated computerized electronic health care records. Previous examples showed us that simple decisions in such epidemiological studies can substantially alter key findings, even when studied within the same database. As studies are rarely repeated within the same database, little is known about the robustness of study designs. Hence, it is essential to check the robustness and to identify which parts of the methodology may explain discrepancies between epidemiological studies.

Therefore, the aims of this thesis were (1) to evaluate unintended outcomes following THR and TKR surgery, and (2) to expore the impact of various differences in the methodological design.

2. THROMBOTIC AND HAEMOSTATIC ADVERSE OUTCOMES

In the first study (Chapter 2.1), the risk of VTE was compared with matched controls, and the influence of prolonged vitamin K antagonist (VKA) use was determined. Using Danish nationwide registries, we found a 13-fold increased risk of VTE during the first 6 weeks following THR (adj. HR 12.9, 95% CI 11.2-14.7) and a 14-fold increase for TKR (adj. HR 13.6, 95% CI 11.0-16.7). The risk remained substantially increased for at least 4 months following THR and TKR surgery. This is far more than what was previously thought and the recommended duration of thromboprophylaxis (10 to 35 days following surgery). Within these 4 postoperative months, prolonged outpatient VKA use reduced the increase in VTE risk by 69% for THR and by 54% for TKR.

Next, we studied the risk of AMI following THR and TKR surgery in Denmark (Chapter 2.2). During the first 2 postoperative weeks, the risk of AMI was substantially increased in

THR patients compared with matched controls (adj. HR 25.5, 95% CI 17.1-37.9). The risk remained elevated for 2 to 6 weeks after surgery (adj. HR 5.05, 95% CI 3.58-7.13) and then decreased to baseline levels. For TKR patients, AMI risk was also increased during the first 2 weeks (adj. HR 30.9, 95% CI 11.1-85.5), but did not differ from controls after the first 2 weeks. The association was strongest in patients who were 80 years or older, whereas we could not detect a significantly increased risk in patients younger than 60 years. Furthermore, a previous AMI in the 6 months before surgery increased the risk of new AMI during the first 6 weeks after THR and TKR surgery (4-fold increase), while this relationship diminished with a longer time since most recent previous AMI.

In Chapter 2.3, the risk of gastrointestinal (GI) bleeding was evaluated following THR and TKR surgery. Danish THR patients were at 6-fold increased of GI bleeding during the first 2 weeks (adj. HR 6.02, 95% CI 4.06-8.92), and for TKR patients the risk of GI bleeding was boosted by 2.3-fold (adj. HR 2.30, 95% CI 1.17-4.54), both compared with matched control patients. The elevated risk was more prolonged in THR patients (12 weeks), as compared with TKR patients (6 weeks). The use of proton pump inhibitors lowered the excess risk of GI bleeding by 74% during the first 6 weeks following THR surgery, while it did not affect the relationship between TKR surgery and GI bleeding. A higher age, male sex, a history of GI bleeding, non-bleeding GI ulcers, and the use of COX-2 selective NSAIDs, loop diuretics, RAAS inhibitors, and outpatient use of thromboprophylaxis (regardless of the class) were associated with a higher risk of GI bleeding during the first 6 weeks after THR. For TKR, we could only identify previous GI bleeding, non-bleeding ulcers, RAAS inhibitors, and antiplatelet drugs as significant determinants for GI bleeding within the same time interval.

The risk of stroke following THR and TKR surgery was evaluated using Danish patient registry files (Chapter 2.4). A 4.7-fold increased risk of ischaemic stroke (adj. HR 4.69, 95% CI 3.12-7.06), and a 4.4-fold increased risk of haemorrhagic stroke (adj. HR 4.40, 95% CI 2.01-9.62) were found within 2 weeks following THR, compared with matched controls. The risk remained elevated during the first 6 postoperative weeks for ischaemic stroke, and the first 12 weeks for haemorrhagic stroke. Outpatient antiplatelet drug use lowered the 6-week HR for ischaemic stroke by 70%, while not affecting the risk of haemorrhagic stroke.

In Chapter 2.5, we assessed timing patterns of cardiovascular events following THR and TKR surgery and secular trends of these events over the past 25 years. During the first 2 weeks following THR surgery, risk of VTE (adj. HR 38.9, 95% CI 17.2-88.0), AMI (adj. HR 4.11, 95% CI 2.35-7.18), stroke (adj. HR 2.11, 95% CI 1.40-3.19), and GI bleeding (adj. HR 5.00, 95% CI 2.34-10.7) were substantially elevated in British patients compared to matched controls. Most of these excess risks diminished within a few weeks, with the exception of VTE (which persisted even beyond the first postoperative year). These trends were similar for TKR surgery, although we could not find an elevated risk of stroke. Sixty-day rates of VTE had declined by 64% in 2008-2012 compared to 1987-1991, but still remained significantly elevated as to patients who did not undergo THR or TKR surgery (excess risk of 0.9% during the first 60 days

between 2008 and 2012).

3. MISCELLANEOUS ADVERSE OUTCOMES

Mortality patterns between 1989 and 2007 in Danish patients undergoing THR and TKR surgery was evaluated in Chapter 3.1. In this chapter, we found that, since the early 90s, short-term survival following THR and TKR surgery has greatly improved. As compared to 1989-1991, 60-day mortality rates were substantially lower between 2004 and 2007 for THR (RR 0.40, 95% CI 0.28-0.58) and TKR patients (RR 0.37, 95% CI 0.21-0.67). This trend was far more superior to what was seen in the general population. The decrease in mortality was greatest for deaths from AMI, VTE, pneumonia, and stroke. Patients tended to have more co-morbidity over time, and the length of hospital stay roughly halved.

In Chapter 3.2, the risk of cancer in patients with metal-on-metal THR was studied. Using a linkage between British electronic health care registries, we found that the risk of cancer was comparable in patients with hip resurfacing (adj. RR 0.69, 95% CI 0.39-1.22) or non-metal bearing surfaces (adj. RR 0.96, 95% CI 0.64-1.43), compared to individuals with stemmed metal-on-metal THR. The pattern of cancer risk over time did not support a detrimental effect of metal hip implants. There was a potential for substantial confounding, complicating a direct comparison between hip implant bearing surface types: patients with metal-on-metal THRs used fewer drugs and had less co-morbidity.

Finally, we evaluated the risk of hip fracture in Dutch patients who underwent TKR surgery (Chapter 3.3). A 54% increased hip fracture risk was found in TKR surgical patients (adj. OR 1.54, 95% CI 1.19-2.00). We found a strong effect modification by age in these patients: the youngest patients (aged 18-70 years old) were at more increased risk for hip fracture (adj. OR 2.76, 95% CI 1.16-6.59), while we could not detect a statistical increase in patients aged >80 years. Furthermore, the association tended to be greater during the first few years after surgery, although this trend did not reach statistical significance.

4. PHARMACOLOGICAL PREVENTION OF JOINT IMPLANT FAILURE

In the first study pharmacological prevention of joint implant failure, we studied the association between statins and implant failure (Chapter 4.1). In addition, this multi-country study explored the influence of methodological differences with various study designs. In our time-dependent cohort design (which we considered a valid study design), statin use was associated with a lowered risk of revision surgery (adj. RR 0.90, 95% CI 0.85-0.96). However, the risk did not further decrease with prolonged statin use, suggesting that the inverse association is not likely to be causal. Another study design that we considered to be valid, the case-control study design, performed equally well as compared to the time-dependent cohort design (adj. OR 0.87, 95% CI 0.81-0.93). In contrast, both (methodologically incorrect) time-fixed

cohort designs led to a substantially lowered risk (time-fixed misclassification cohort: adj. RR 0.36, 95% CI 0.34-0.38; time-fixed exclusion cohort: adj. RR 0.65, 95% CI 0.63-0.68), which further decreased with a prolonged duration of statin use. Source of data (i.e. Denmark or United Kingdom), or confounder handling techniques (including crude analyses, multivariate Cox regression adjusted analyses, the selection of confounders in the multivariate analyses [i.e. considering the availability of confounders, and the method to select the number of confounders], propensity score adjusted regression models, and propensity matched analyses) did not substantially alter the study findings.

In Chapter 4.2, the potential benefit of bisphosphonates on preventing implant failure was evaluated in Danish patients undergoing elective THR or TKR surgery. In our Cox regression model, a reduced revision risk was found in bisphosphonate users compared to propensity matched THR individuals who were not classified as bisphosphonate users (HR 0.41, 95% CI 0.27-0.61). This protective effect was highest in patients with the longest duration of treatment and / or highest adherence. Both of these findings are supportive for a potential causal inverse relationship between bisphosphonate use and implant failure.

We checked the robustness of the study design / findings from Chapter 4.2 in the final chapter (Chapter 4.3). In all of the investigated analytical study designs, bisphosphonate use was associated with a decreased risk of implant failure, but with some substantial differences: the methodologically correct analytical designs produced very similar risk estimates (time-dependent cohort study: HR 0.41, 95% CI 0.27-0.61; case-control study: OR 0.46, 95% CI 0.22-0.78). Even the (conceptionally incorrect) time-fixed analysis that (falsely) excluded immortal time (HR 0.37, 95% CI 0.24-0.55) produced a somewhat similar result. In contrast, the time-fixed analysis that incorrectly misclassified immortal time produced a substantially lower risk estimate (RR 0.22, 95% CI 0.14-0.34).

5. DISCUSSION

In the general discussion, several clinical and methodological aspects of this thesis were discussed. We compared the observed study findings between the two data sources (i.e. Denmark or United Kingdom), and described explanations for the (dis)concordances. The discussion was concluded with some clinical and methodological recommendations.

Our studies show that THR and TKR surgery briefly are accompanied with an increased risk of several potentially fatal complications, including VTE, AMI, stroke, and GI bleeding. Although evidently elevated, the risk of clinical harms are generally limited to the first 2 to 6 weeks (with the exception of VTE). Given the well-established benefits of THR and TKR surgery, we still promote the surgery in patients who require them, and we consider this as a relatively safe procedure with a high benefit-risk ratio. Although the average excess risk of adverse outcomes following THR and TKR surgery was low in absolute figures, we call for careful risk assessment in patients undergoing this surgery. A 20-fold increase for a low-risk patient may

be acceptable, but for an individual with an already high baseline cardiovascular risk, this may be a discussion worthy issue. Risk prediction tools could be helpful for such risk assessments, and we therefore promote the development of these tools. The consistent findings on the potential benefits of bisphosphonates in preventing implant failure are promising, and this should be further investigated in randomized clinical trials.

In the second part of our discussion, we share some methodological recommendations and points of interest to take into consideration when performing observational studies. In particular, we strongly promote the use of time-dependent cohort studies (or even case-control studies) whenever possible. Our examples showed strong deviations in study results when the data were analyzed using a time-fixed cohort design. It is crucial to feel comfortable with the strengths and limitations of the available databases. Aspects such as under recording (differential or non-differential), availability of covariates, and calendar time span should be put against the type of research question and point estimate (i.e. relative or absolute risk estimate). Dealing with confounding can be difficult and, in our examples, may be limited by the quality and quantity of available confounders. Residual confounding may therefore still be an issue, regardless of the utilized technique to deal with confounding. We feel it is therefore important to focus on causality / timing pattern analyses, rather than to look at overall risk estimates solely.

In conclusion, from a clinical point of perspective, THR and TKR surgery briefly boosts the risk of several potentially fatal complications. Although the excess risk is generally limited to 2 to 6 weeks following surgery, we promote careful risk assessments, as such relative increases may be substantial in patients already at elevated risk of developing one or more of these negative outcomes. The use of prophylactic drug regimens (e.g. prolonged thromboprophylaxis, proton pump inhibitors to prevent GI bleeding, antiplatelets to lower stroke rates, and bisphosphonate use to lengthen implant survival) should be further explored in randomized clinical trials. From a methodological point of view, we found that simple choices in study design (e.g. time-dependent versus time-fixed cohort) may vastly influence study findings. We could not find a major impact of other methodological differences (e.g. confounder handling techniques and data source), but we cannot exclude this possibility in other research settings in observational studies. Hence, the robustness of design choices in epidemiological studies need to be further explored.

APPENDIX B

Samenvatting

1. INTRODUCTIE

Artrose is de meest voorkomende vorm van gewrichtsaandoeningen en is de hoofdoorzaak van pijn en invaliditeit bij ouderen. Ongeveer een vijfde van alle mensen van 65 jaar of ouder lijdt aan artrose en het kan het uitvoeren van dagelijkse activiteiten (zoals lopen, traplopen en slapen) ernstig beperken. Totale heup (THR) en knie-vervangingen (TKR) bevorderen de kwaliteit van het leven substantieel in patiënten met matig tot ernstig artrose. Aan de andere kant kunnen deze operaties ook leiden tot mogelijk fatale uitkomsten, zoals een veneuze trombo-embolie (VTE) en een acuut myocardinfarct (AMI).

Met het oog op deze negatieve uitkomsten na een THR of TKR, is er een grote behoefte om de volgende kenniskloven te beantwoorden: (1) wanneer treden deze complicaties exact op (bijvoorbeeld alleen tijdens de eerste 2 postoperatieve weken of juist gedurende enkele maanden na de operatie), (2) hoe groot is het risico (in vergelijking met patiënten die zo een operatie niet ondergaan) en (3) wat is de invloed van patiëntkarakteristieken op het ontwikkelen van zo een complicatie (in het bijzonder het gebruik van bepaalde geneesmiddelen). De beantwoording van deze kenniskloven zouden de optimalisatie van postoperatieve zorg en het verder beperken van deze complicaties moeten vergemakkelijken.

Om deze onderzoeksvragen te kunnen beantwoorden is het gebruik van complexe gecomputeriseerde gezondheidszorgregisters noodzakelijk, ofwel het gebruik van epidemiologische studies. Eerdere voorbeelden hebben ons echter laten zien dat ogenschijnlijk simpele beslissingen in dergelijke epidemiologische studies een grote invloed kunnen hebben op de studieresultaten, zelfs als de twee studies zijn uitgevoerd in dezelfde database. Gezien het feit dat epidemiologische studies zelden worden herhaald in dezelfde database, is er beperkte kennis over de robuustheid van de studie-opzet. Het is daarom van groot belang om deze robuustheid te verkennen en te identificeren welke onderdelen van de studie-opzet minder robuust zijn en verschillen in studieresultaten kunnen verklaren.

Hieruit voortvloeiende zijn de onderzoeksdoelen van dit proefschrift (1) om complicaties na een THR- of TKR-operatie te bestuderen en (2) om de invloed van verschillen in studie-opzet op studieresultaten te onderzoeken.

2. TROMBOTISCHE EN HEMOSTATISCHE COMPLICATIES

In de eerste studie (hoofdstuk 2.1) werd het risico op VTE na een THR of TKR bestudeerd, inclusief de invloed van verlengde antistolling met vitamine K antagonisten (VKA's) op dit risico. In vergelijking met gematchte controle-patiënten werd een 13-voudig verhoogd risico op VTE gevonden in de eerste 6 weken na een THR (adj. HR 12,9, 95% CI 11,2-14,7) en een 14-voudige verhoging voor TKR (adj. HR 13,6, 95% CI 11,0-16,7). Het risico bleef substantieel verhoogd voor ten minste 4 maanden na de THR en TKR. Dit is veel sterker

verlengd dan wat voorheen werd gedacht en wat internationale richtlijnen adviseren over de duur van profylaxe (gemiddeld 10 tot 35 dagen na een THR- of TKR-operatie). Gedurende deze eerste 4 maanden werd in deze studie verlengd VKA-gebruik in verband gebracht met een VTE-risicoreductie van 69% bij THR en 54% bij TKR.

In de volgende studie werd het risico op een AMI na een THR- of TKR-operatie in Denemarken onderzocht (hoofdstuk 2.2). Gedurende de eerste 2 postoperatieve weken was het risico op een AMI substantieel verhoogd bij THR-patiënten versus gematchte controles (adj. HR 25,5, 95% CI 17,1-37,9). Ook in de 4 daaropvolgende weken bleef het risico op een AMI verhoogd (adj. HR 5,05, 95% CI 3,58-7,13), waarna de kans terugviel naar die van gematchte controles. Bij TKR-patiënten was het risico tevens in de eerste 2 weken verhoogd (adj. HR 30,9, 95% CI 11,1-85,5), maar in de daaropvolgende weken kon geen statistisch significant hoger risico worden gevonden. De associatie was het sterkst bij patiënten van 80 jaar en ouder, terwijl geen significant verhoogd risico werd gezien bij patiënten jonger dan 60 jaar. Verder zorgde een eerder doorgemaakte AMI in de 6 maanden voorafgaande de operatie voor een sterk verhoogd risico op een nieuwe AMI in de 6 weken na een THR of TKR (4-voudige verhoging), terwijl dat effect sterk afnam bij een langere tijdsperiode sinds het meest recente pre-operatieve AMI.

In hoofdstuk 2.3 werd de kans op een gastro-intestinale (GI) bloeding na een THR of TKR bestudeerd. Deense THR-patiënten liepen een 6-voudig verhoogd risico op een GI bloeding gedurende de eerste 2 postoperatieve weken (adj. HR 6,02, 95% CI 4,06-8,92) in vergelijking met controle-patiënten. Bij TKR-patiënten was dit weliswaar lager, maar nog steeds significant verhoogd (adj. HR 2,30, 95% CI 1,17-4,54). Het effect zette langer door bij THR- (12 weken) dan bij TKR-patiënten (6 weken). Protonpompremmers bleken het risico met 74% te verlagen gedurende de eerste 6 weken na een THR-operatie, terwijl ze geen invloed hadden op het risico op een GI bloeding na een TKR-operatie. Een hogere leeftijd, het mannelijk geslacht, een historie van GI bloedingen of GI zweren zonder bloedingen en het gebruik van COX-2-selectieve NSAID's, loopdiuretica, RAAS-remmers en het gebruik van antitrombotica (onafhankelijk van het soort) zorgden allen voor meer GI bloedingen gedurende de eerste 6 weken na een THR. In diezelfde periode na een TKR werd alleen een associatie gevonden met een historie van GI bloedingen of GI zweren zonder bloedingen, RAAS-remmers en plaatjesremmers.

Het risico op een beroerte na een THR-operatie werd in hoofdstuk 2.4 onderzocht gebruikmakend van Deense gezondheidsregisters. Een 4,7-voudig verhoogd risico op een herseninfarct (adj. HR 4,69, 95% CI 3,12-7,06) en een 4,4-voudige verhoging op het risico van een hersenbloeding (adj. HR 4,40, 95% CI 2,01-9,62) werden waargenomen in de eerste 2 weken na een THR, in vergelijking met controle-patiënten. Tot 6 weken na de operatie bleef het risico op een herseninfarct verhoogd, terwijl dat bij een hersenbloeding tot 12 weken duurde. Plaatjesremmers verlaagden het 6-weken-risico op een herseninfarct met 70%, terwijl ze geen invloed hadden op het ontwikkelen van een hersenbloeding.

In hoofdstuk 2.5 werden tijdspatronen van cardiovasculaire complicaties na een THR en TKR bestudeerd, inclusief de seculaire trends over de afgelopen 25 jaar. Gedurende de eerste 2 weken na een THR-operatie was het risico op een VTE (adj. HR 38,9, 95% CI 17,2-88,0), AMI (adj. HR 4,11, 95% CI 2,35-7,18), beroerte (adj. HR 2,11, 95% CI 1,40-3,19) en een GI bloeding (adj. HR 5,00, 95% CI 2,34-10,7) substantieel verhoogd in Britse patiënten in vergelijking met gematchte controles. Bij de meeste van deze complicaties was het risico vooral alleen de eerste 2 postoperatieve weken verhoogd, met uitzondering van het risico op een VTE (dat zelfs voortging na het eerste postoperatieve jaar). Deze trends waren vergelijkbaar bij een TKR-operatie, hoewel geen verhoogd risico kon worden gevonden bij het optreden van postoperatieve beroertes. Het risico op een VTE in de eerste 60 dagen na een THR of TKR is sinds 1987 sterk afgenomen (een afname van 64% in 2008-2012 versus 1987-1991). Desalniettemin bleef de kans op een VTE in 2008-2012 nog steeds sterk verhoogd ten opzichte gematchte controles die geen operatie ondergingen (een absoluut risico van 0,9% versus 0,0%).

3. OVERIGE COMPLICATIES

Trends in sterfte na een THR- of TKR-operatie in Deense patiënten voor de periode 1989-2007 werden in hoofdstuk 3.1 bestudeerd. In dit hoofdstuk werd gezien dat, sinds de begin jaren '90, de mortaliteit na een THR- en TKR-operatie sterk is afgenomen. Vergeleken met de 60-dagen mortaliteit in 1989-1991 is de sterfte in 2004-2007 met 60% afgenomen bij een THR (RR 0,40, 95% CI 0,28-0,58) en met 63% bij een TKR (RR 0,37, 95% CI 0,21-0,67). Deze dalende trend was substantieel sterker dan de algemeen dalende trend in sterfte in de algehele Deense populatie. De daling in sterfte was vooral waargenomen voor sterfgevallen ten gevolge van een AMI, VTE, pneumonie en beroertes. Andere opvallende trends waren gevonden in het aantal comorbiditeiten (over de jaren werden steeds meer mensen met meerdere comorbiditeiten geopereerd) en de duur van ziekenhuisopname (die grofweg is gehalveerd in de beschreven periode).

In hoofdstuk 3.2 werd het risico op kanker bestudeerd in patiënten met een metaal-op-metaal heupimplantaat. Gebruikmakende van een koppeling tussen diverse Britse gezondheidsregisters werd gevonden dat het risico op kanker bij patiënten met een sportheup (adj. RR 0,69, 95% CI 0,39-1,22) of niet-metalen heupimplantaten (adj. RR 0,96, 95% CI 0,64-1,43) vergelijkbaar was met het risico bij patiënten met een metaal-op-metaal heupimplantaat. De tijdspatronen voor kanker waren niet ondersteunend voor een carcinogeen effect van metalen heupimplantaten. Er was een groot potentieel aanwezig voor confounding, waardoor een directe vergelijking tussen typen heupimplantaten complex is: patiënten met een metaal-op-metaal heupimplantaat gebruikten over het algemeen veel minder geneesmiddelen en hadden minder comorbiditeiten.

Tot slot werd het risico op heupfracturen na een TKR onderzocht in Nederlandse patiënten (hoofdstuk 3.3). Een 54% verhoogd risico op heupfracturen werd gevonden bij patiënten

die een TKR ondergingen (adj. OR 1,54, 95% CI 1,19-2,00). Dat effect werd zwakker bij een hogere leeftijd: bij de jongste patiënten (18-70 jaar oud) werd een groter effect gevonden (adj. OR 2.76, 95% CI 1,16-6,59) dan bij patiënten ouder dan 80 jaar, waar geen significant verhoogd risico kon worden gedetecteerd.

4. FARMACOLOGISCHE PREVENTIE VAN IMPLANTAATFALEN

In de eerste studie van deze reeks werd de associatie tussen statines en implantaatfalen onderzocht (hoofdstuk 4.1). Daarnaast werd in dat hoofdstuk gekeken naar de invloed van methodologische verschillen in de studie-opzet. In onze "time-dependent" cohort-analyse (wat als een valide design werd beschouwd) was statine-gebruik geassocieerd met een verlaagd risico op een implantaat-revisie-operatie (adj. RR 0.90, 95% CI 0,85-0,96). Het risico daalde echter niet verder bij langer gebruik van statines, wat aangeeft dat de inverse associatie waarschijnlijk niet causaal van aard is. Een andere studie-opzet die als valide werd beschouwd, de "case-control" analyse, liet een vergelijkbaar effect zien (adj. OR 0,87, 95% CI 0,81-0,93). In tegenstelling tot deze valide studie-opzetten lieten de (methdologisch onjuiste) "time-fixed" analyses beiden een substantieel groter effect zien ("time-fixed misclassification" cohort-analyse: adj. RR 0,36, 95% CI 0,34-0,38; "time-fixed exclusion" cohort-analyse: adj. RR 0,65, 95% CI 0,63-0,68). Bovendien werd bij deze "time-fixed" analyses wel een significante relatie gevonden met de gebruiksduur (wat onjuist een causale relatie kan suggereren). Overige variaties in de studie-opzet, zoals de bron van de data (Denemarken of Verenigd Koninkrijk), de methodologie omtrent confounding (inclusief de confounderselectie en de specifieke manier om te adjusteren voor confounding [zoals multivariate regressie en propensity scores]) hadden allen geen differentieel effect op de studieresultaten.

In hoofdstuk 4.2 werd de potentie van bisfosfonaten om implantaatfalen in Deense THR- en TKR-patiënten te voorkomen geëvalueerd. In het Cox-regressie-model werd een 59% gereduceerd risico op implantaatfalen gevonden bij bisfosfonaat-gebruikers versus propensity gematchte patiënten die geen bisfosfonaten hadden gebruikt (HR 0,41, 95% CI 0,27-0,61). Dit beschermend effect was vooral aanwezig bij patiënten die bisfosfonaten langdurig hadden gebruikt en die een hogere therapietrouw hadden. Beide bevindingen zijn ondersteunend voor een causale relatie tussen het gebruik van bisfosfonaten en het voorkomen van implantaatfalen.

De robuustheid van de bevindingen uit hoofdstuk 4.2 werden bestudeerd in het daaropvolgende hoofdstuk (hoofdstuk 4.3). In alle onderzochte analytische studie-opzetten was het gebruik van bisfosfonaten geassocieerd met een verlaagd risico op implantaatfalen, echter wel met substantiële verschillen: de methodologisch juiste analytische studie-opzetten resulteerden in vergelijkbare resultaten ("time-dependent" cohort-analyse: HR 0,41, 95% CI 0,27-0,61; "case-control" analyse: OR 0,46, 95% CI 0,22-0,78). Zelfs de (conceptioneel onjuiste) "time-fixed" analyse die "immortal time" onjuist excludeerde gaf een niet sterk afwijkend resultaat (HR 0,37, 95% CI 0,24-0,55). In tegenstelling leidde de "time-fixed"

analyse die "immortal time" onjuist misclassificeerde tot een substantieel sterker effect (HR 0,22, 95% CI 0,14-0,34).

5. DISCUSSIE

In de discussie van dit proefschrift zijn enkele klinische en methodologische aspecten besproken. De onderzoeksresultaten van de Deense en Britse studies werden met elkaar vergeleken, waarbij de overeenkomsten en verschillen wat betreft de studie-opzet in detail werden besproken. De discussie werd afgesloten met een aantal klinische en methodologische aanbevelingen.

Dit proefschrift laat zien dat THR- en TKR-operaties gepaard gaan met een (voornamelijk kortdurend) verhoogd risico op een aantal potentieel fatale complicaties (zoals VTE, AMI, beroertes en GI bloedingen). Hoewel deze verhoging evident aanwezig is, zijn de complicaties veelal beperkt tot de eerste 2 tot 6 weken (met uitzondering van VTE). Gezien de veelvuldig aangetoonde sterke voordelen van een THR en TKR kunnen deze operaties nog steeds sterk worden aanbevolen in patiënten die een dergelijke ingreep nodig hebben. We beschouwen deze operatie dan ook nog steeds als een relatief veilige procedure met de balans sterk richting de baten ten opzichte van de risico's. Hoewel op populatieniveau het absoluut risico op complicaties na een THR- en TKR-operatie laag was, vragen de resultaten uit dit proefschrift wel sterk om een risico-analyse in de individuele patiënt die overweegt om zo een operatie te ondergaan. Een (kortdurende) 20-voudige verhoging van het risico op complicaties kan voor een kerngezonde patiënt acceptabel zijn, terwijl een dergelijke relatieve verhoging substantieel kan zijn voor iemand met diverse cardiovasculaire risicofactoren. Risicomodellen die de kans op complicaties in individuele patiënten kunnen voorspellen kunnen behulpzaam zijn bij een dergelijke risico-analyse en we stimuleren daarom ook de ontwikkeling van zulke tools. Verder zijn de consistente bevindingen over het mogelijk beschermende effect van bisfosfonaten op implantaatfalen veelbelovend en dienen deze bevindingen te worden onderzocht in gerandomiseerde placebogecontroleerde studies.

In het tweede deel van de discussie worden een aantal methodologische aanbevelingen op het gebied van observationele studies gedeeld. Hoofdzakelijk wordt het gebruik van "time-dependent" analyses (of zelfs "case-control" analyses) gestimuleerd. De voorbeelden uit dit proefschrift laten zien dat (methodologisch onjuiste) "time-fixed" analyses kunnen leiden tot substantieel andere studieresultaten. Daarnaast is het essentieel om bekend te zijn met de sterktes en zwaktes van de beschikbare patiëntenregisters. Aspecten zoals onderregistratie (zowel differentieel als non-differentieel), de beschikbaarheid van covariaten en beschikbare kalenderjaren zijn onderdelen die hevig kunnen verschillen tussen diverse datasets en dienen derhalve te worden getoetst aan de hand van de onderzoeksvraag en de effectschattingsmaat (dat wil zeggen, gaat het bijvoorbeeld om een absoluut of een relatief risico). Corrigeren voor confounding kan een hele uitdaging zijn en, in ons geval, kan het vaak gelimiteerd zijn door de beschikbaarheid van de confounders (zowel in aantal als in kwaliteit). Niet gemeten

confounding kan daarom nog steeds aanwezig zijn, ongeacht de methodologie waarmee wordt gecorrigeerd voor confounding (met uitzondering van technieken zoals randomisatie en instrumentele variabelen). Met het oog hierop is het van groot belang om in observationele studies tevens te richten op causaliteits- en patroonanalyses in plaats van een conclusie te baseren op slechts een overall schatting.

Als conclusie kan vanuit het klinisch perspectief worden gesteld dat een THR- en TKR-operatie gepaard gaat met een kortdurend verhoogd risico op mogelijk fatale complicaties. Hoewel dit risico veelal is beperkt tot de eerste 2 tot 6 weken (met uitzondering van VTE), stimuleren deze bevindingen het uitvoeren van individuele risico-analyses. Dergelijke relatieve verhogingen in het risico op complicaties kunnen immers substantieel zijn bij patiënten die reeds een verhoogd risico hebben op het ontwikkelen van zulke negatieve uitkomsten. Het profylactisch regime met diverse geneesmiddelen (zoals een verlengde tromboprofylaxe [langer dan 10 tot 35 dagen], het gebruik van protonpompremmers om GI bloedingen te voorkomen, plaatjesremmers ter preventie van beroertes en bisfosfonaten om implantaatfalen te voorkomen) zou op basis van de bevindingen in dit proefschrift verder moeten worden onderzocht in gerandomiseerde gecontroleerde onderzoeken. Vanuit het methodologisch oogpunt laat dit proefschrift zien dat ogenschijnlijk eenvoudige methodologische beslissingen (zoals "time-dependent" versus "time-fixed") kunnen leiden tot aanzienlijke verschillen in studieresultaten. Hoewel we geen differentiële invloed hebben kunnen aantonen van diverse andere verschillen in studie-opzet (zoals het omgaan met confounding en de bron van de dataset), kan niet worden uitgesloten dat een dergelijke impact weldegelijk bestaat in andere settings bij observationeel onderzoek. De robuustheid van keuzes in de studie-opzet in observationeel onderzoek zou daarom verder moeten worden onderzocht.

APPENDIX C

Dankwoord

DANKWOORD

Het proefschrift is af, wat een heerlijk gevoel! Al snel werd echter duidelijk dat niet het boekje het belangrijkst was, maar vooral de weg er naar toe: de leerprocessen, het zien en ontdekken van de te bewandelen wegen en vooral het leren kennen van de vele bijzondere mensen die mij hebben geholpen om aan dit proefschrift te kunnen werken. Een ieder ontzettend bedankt voor de hulp en het tonen van de interesse in mijn onderzoek! Een aantal personen zou ik graag in dit hoofdstuk apart willen bedanken.

Mijn promotieteam, prof.dr. Anthonius de Boer, prof.dr. Hubert Leufkens, prof.dr. Tjeerd-Pieter van Staa en dr. Frank de Vries, wil ik als eerste en in het bijzonder bedanken voor hun vertrouwen in mij en het enthousiasme waar ze mij mee hebben begeleid. Ik had me geen beter promotieteam kunnen wensen!

Beste Frank, ik kan me nog goed herinneren dat we tijdens mijn onderzoeksstage in 2008 met elkaar kennismaakten. Je enthousiasme voor botten en farmaco-epidemiologie en je gedrevenheid waren aanstekelijk. Vrijwel direct raakte ik hierdoor ook 'verslaafd' aan het vak! Het was daarom voor mij ook niet meer dan logisch dat ik na farmacie wilde gaan promoveren op het gebied van farmaco-epidemiologie en dan het liefst onder jouw hoede. Dankzij jouw hulp hebben we dat gelukkig ook voor elkaar gekregen. De toekenning van de NWO-Mozaïek-promotiebeurs, het meedingen voor prijzen op internationale congressen: het was allemaal niet mogelijk geweest zonder jouw sublieme begeleiding. Ik heb in de afgelopen jaren ontzettend veel van je geleerd over het doen van farmaco-epidemiologisch onderzoek, het programmeren in SAS (tot op het punt dat je zelfs 'proc's' en 'punt-komma's' in je dromen tegenkomt!), het schrijven / publiceren van wetenschappelijke artikelen en alle andere processen die bij de 'publication game' komen kijken. Over welk aspect van het proces het ook gaat, je had altijd wel een gouden tip die je van niemand anders kon leren. Beste Frank, ontzettend bedankt voor al deze zaken, je betrokkenheid, het vertrouwen in mij en al je begeleiding!

Beste Ton, ik ben ontzettend blij om jou sinds 2005 altijd al om me heen gehad te hebben. Eerst als mentor bij het Honours Programme, kort daarop als directe begeleider bij mijn bachelorscriptie, later als begeleider bij het keuzevak farmaco-epidemiologie (waar je me enthousiasmeerde voor het vak), als supervisor bij mijn onderzoeksstage en uiteindelijk ook als promotor bij mijn promotietraject. Ik beschrijf je altijd als iemand met een zeer groot hart voor het vak. Je passie en opgewektheid zijn zo aanstekelijk en werken uitermate motiverend. Je begeleiding is onnavolgbaar. Zelfs als ik je om 1 uur 's nachts nog een mailtje toestuurde, dan had ik om 1:05 al een reactie van je terug! Je bent zeer vriendelijk en laagdrempelig: ik kon altijd wel even bij je langslopen om iets te bespreken. Daarnaast ben je een zeer ervaren epidemioloog met veel klinische kennis, waar ik veel van heb geleerd. Het was altijd erg leuk om regels-lange formules voor logistische regressie met je te bespreken (het liefst met een aantal dubbele interactietermen er in)! Ik wil je in dit hoofdstuk niet alleen bedanken voor

het zijn van een uitstekende promotor, maar ook voor al die jaren daarvóór waarin je constant volledig vertrouwen en geloof in mij hebt gehad. Beste Ton, dank voor alles!

Beste Bert, zonder jouw helikopter-view was het niet gelukt om de puzzelstukjes op de juiste plaats te leggen. Je hebt mij ontzettend geholpen om de bevindingen van de studies in het juiste perspectief te plaatsen. Met jouw zeer breed georienteerde kennis was het altijd een genot om de studieresultaten te bespreken. Bedankt voor je vertrouwen in mij en je goede begeleiding.

Beste Tjeerd, wat was het toch elke keer weer ontzettend fijn om met veel enthousiasme over epidemiologische probleemstukken te praten. We konden zo uren vullen over confounding (en de zin / onzin van diverse corrigeertechnieken), competing risks, pragmatisch gerandomiseerd onderzoek, enzovoorts. Als ik er methodologisch niet uitkwam, dan had jij altijd wel weer een oplossing. Je stond ook altijd voor me klaar als ik met een vraag zat. Eerst vooral telefonisch en via de mail, later ook in Londen toen we aan ons CPRD-NJR-project werkten. Jouw epidemiologische kennis en ervaring heeft ook vooral de methodologische discussie van dit proefschrift naar een hoger niveau getild. Daarnaast was het ook een zeer gezellige tijd met je. Ik weet nog heel goed dat je me een rondleiding door Londen hebt gegeven tijdens mijn eerste bezoek aan de CPRD om vervolgens de dag af te sluiten met een etentje in een Indiaas restaurant (waar jij nog veel beter alle Indiase gerechten kende dan ik als Indiër, wat een schande :-)). Beste Tjeerd, dank voor het delen van je kennis, ervaring en enthousiasme en het vertrouwen dat je in mij hebt gehad.

I am grateful to prof.dr. Peter Vestergaard. Dear Peter, your contribution has been incredible throughout my entire PhD project. Your vast knowledge on endocrinology and bone metabolism and your lightning fast and very helpful replies to my questions have been extremely helpful. You were always the first person to send feedback on my manuscripts and it really helped improving the quality of our work. Besides your professional expertise, you are truly one of the kindest persons I have ever met. I remember my first (short) visit to Aarhus, and for some reason the software was not working on my laptop (blame Apple!). The very next day early in the morning, you personally brought me your working laptop from home to the hospital. Afterwards, I stayed for several months in Aarhus, and you helped me with making the reservations for a student room. You were always there to help me, whether it was related to arthroplasty or to the daily living in Aarhus (before you told me the Danish word for 'salmon', the people at the grocery store showed me a cucumber when I asked for salmon in English!). Dear Peter, many thanks for all your help, expertise and your kindness the past few years.

I would like to thank prof.dr. Cyrus Cooper, prof.dr. Nigel Arden, dr. Nicholas Harvey, dr. Daniel Prieto-Alhambra, and dr. Kassim Javaid for the pleasant collaboration with the MRC Lifecourse Epidemiology Unit in Southampton during my PhD project. Dear Cyrus, I feel priviliged to have collaborated with you. I very much appreciated the discussions of our study

results in Southampton / Oxford. Many thanks for all your help throughout the project and for all the helpful feedback on our manuscripts. Dear Nigel, thank you very much for sharing your knowledge, in particular on arthroplasties. Your feedback has been invaluable ever since we started drafting the PhD grant proposal. Dear Nick, many thanks for all your help with the osteoporosis related studies. It was a pleasure to collaborate with you on the bariatric surgery study back in Southampton. I very much appreciate your expertise and hospitality. Dear Daniel, we share the same field of interest and it was therefore a delight to collaborate with you. Thank you for your fast replies, enthusiasm, and sharing your knowledge. It was great to work on the Danish bisphosphonate project together and I'm looking forward to your future publications. Dear Kassim, many thanks for all your feedback on our arthroplasty manuscripts. It has really helped improving the quality of our work.

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I am grateful to dr. Erik Grove for sharing his expertise in cardiology. Dear Erik, it was fantastic to work together on the Danish cardiovascular papers! We managed to publish our very first Danish study in the Archives of Internal Medicine, which could never have been possible without your help. Thank you very much!

Ik wil graag dr. Pieter Emans van het Maastricht Universitair Medisch Centrum bedanken voor het delen van zijn orthopedische kennis. Beste Pieter, jouw kennis over knie- en heupoperaties was onmisbaar voor dit proefschrift. Ontzettend bedankt voor je feedback en dat ik af en toe met je kon sparren over hoe de operatie in de praktijk verloopt.

I would like to thank prof.dr. Bo Abrahamsen for sharing his expertise in musculoskeletal disorders. Dear Bo, many thanks for your very helpful feedback, and it was a pleasure to collaborate with you on the Danish bisphosphonate project.

Mijn dank gaat uit naar de mensen van de afdeling Geriatrie van het Universitair Medisch Centrum Utrecht, met name dr. Paul Jansen en de andere klinisch farmacologen. Beste Paul, wat heb ik ontzettend veel van je geleerd tijdens de opleiding tot klinisch farmacoloog! Inspirerend, de wijze waarop je je klinische kennis hebt gedeeld, wat tevens ideeën heeft opgeleverd voor potentieel onderzoek. Je kennis was ook onmisbaar bij ons project over trombo-embolische complicaties bij knie- en heupoperaties. Beste Astrid, Karen, Erna en Clara, het was erg fijn om samen met jullie de opleiding tot klinisch farmacoloog te volgen. Iedereen bedankt voor de hulp!

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onze samenwerking in de toekomst kunnen voortzetten!

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Graag bedank ik de leden van de beoordelingscommissie (prof.dr. Hans Bijlsma, prof.dr. Hugo ten Cate, prof.dr. Toine Egberts, prof.dr. Cumhur Öner en prof.dr. Koos Zwinderman) voor het doornemen van mijn manuscript.

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lopen om te sparren over methodologische vraagstukken. Beste Willem, dank voor al je ICT-gerelateerde hulp. Ik zou waarschijnlijk gek geworden zijn van al mijn vragen / wensen op het gebied van ICT, maar jij bleef er erg kalm onder en je kreeg het altijd weer voor elkaar. Beste Ineke, Suzanne en Anja, dank jullie wel voor al jullie hulp de afgelopen jaren en de ondersteuning bij de praktische zaken van deze promotie.

Lieve familie en vrienden, ontzettend fijn dat jullie zo geïnteresseerd waren, dat jullie me altijd hebben gesteund en heel erg bedankt voor jullie gezelligheid. In het bijzonder wil ik mijn beste vrienden - Bisnoe Adhien, Hassan Boulkhrif en Simeen Akhtar - bedanken voor hun steun en gezelligheid, al sinds de start van onze farmacie-opleiding!

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APPENDIX D

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APPENDIX E

List of publications

LIST OF PUBLICATIONS

asterisks represent publications related to thesis

RISK OF FRACTURE AFTER BARIATRIC SURGERY IN THE UNITED KINGDOM: POPULATION BASED, RETROSPECTIVE COHORT STUDY. (*)

- Lalmohamed A, de Vries F, Bazelier MT, et al.
- BMJ 2012;345:e5085 (impact factor 17.2)

TIMING OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS UNDERGOING TOTAL HIP OR KNEE REPLACEMENT: A NATIONWIDE COHORT STUDY. (*)

- Lalmohamed A, Vestergaard P, Klop C, et al.
- Arch Intern Med. 2012;172:1229-35 (impact factor 11.5)

HARMFUL EFFECTS OF PROTON PUMP INHIBITORS: DISCREPANCIES BETWEEN OBSERVATIONAL STUDIES AND RANDOMIZED CLINICAL TRIALS.

- Lalmohamed A, Vermeer N, de Vries F.
- JAMA Intern Med. 2013 Sep 9;173(16):1559 (impact factor 11.5)

RISK OF GASTROINTESTINAL BLEEDING IN PATIENTS UNDERGOING TOTAL HIP OR KNEE REPLACEMENT COMPARED WITH MATCHED CONTROLS: A NATIONWIDE COHORT STUDY. (*)

- Lalmohamed A, Vestergaard P, Javaid MK, et al.
- Am J Gastroenterol. 2013;108:1277-1285 (impact factor 7.6)

CHANGES IN MORTALITY PATTERNS FOLLOWING TOTAL HIP OR KNEE REPLACEMENT OVER THE PAST TWO DECADES: A NATIONWIDE COHORT STUDY. (*)

- Lalmohamed A, Vestergaard P, de Boer A, et al.
- Arthritis Rheum 2013; in press (impact factor 7.5)

USE OF ORGANIC NITRATES AND RISK OF HIP FRACTURE: A POPULATION-BASED CASE-CONTROL STUDY.

- Pouwels S, Lalmohamed A, van Staa T, et al.
- J Clin Endocrinol Metab 2010;95:1924-1931 (impact factor 6.4)

TIMING OF STROKE IN PATIENTS UNDERGOING TOTAL HIP REPLACEMENT AND MATCHED CONTROLS: A NATIONWIDE COHORT STUDY. (*)

- Lalmohamed A, Vestergaard P, Cooper C, et al.
- Stroke. 2012;43:3225-9 (impact factor 6.2)

RISK OF HIP FRACTURE AFTER STROKE: A POPULATION-BASED CASE-CONTROL STUDY.

- Pouwels S, Lalmohamed A, Leufkens B, et al.
- Stroke 2009;40:3281-3285 (impact factor 6.2)

RESPONSE TO LETTER BY TSUDA.

- Pouwels S, Lalmohamed A, Leufkens HGM, et al.
- Stroke 2010;41:e60 (impact factor 6.2)

PROLONGED OUTPATIENT VITAMING K ANTAGONIST USE AND RISK OF VENOUS THROMBOEMBOLISM IN PATIENTS UNDERGOING TOTAL HIP OR KNEE REPLACEMENT. (*)

- Lalmohamed A, Vestergaard P, Jansen PAF, et al.
- J Thromb Haemost. 2013;11:642-650 (impact factor 6.1)

THE ASSOCIATION BETWEEN HIV INFECTION AND CLINICAL FRACTURE RISK: A NATION-WIDE CASE-CONTROL STUDY.

- Prieto-Alhambra D, Güerri-Fernandez R, de Vries F, Lalmohamed A, et al.
- JAIDS 2013;accepted for publication (impact factor 4.7)

CAUSES OF DEATH IN PATIENTS WITH MULITPLE SCLEROSIS AND MATCHED REFERENT SUBJECTS: A POPULATION-BASED COHORT STUDY.

- Lalmohamed A, Bazelier MT, van Staa TP, et al.
- Eur J Neurol 2012;19:1007-1014 (impact factor 4.2)

PATTERNS OF RISK OF CANCER IN PATIENTS WITH METAL-ON-METAL HIP REPLACEMENTS VERSUS OTHER BEARING SURFACE TYPES: A RECORD LINKAGE STUDY BETWEEN A PROSPECTIVE JOINT REGISTRY AND GENERAL PRACTICE ELECTRONIC HEALTH RECORDS IN ENGLAND. (*)

- Lalmohamed A, MacGregor A, de Vries F, et al.
- PLoS ONE 2013;8:e65891 (impact factor 4.1)

CALIBRATION OF FRAX ® 3.1 TO THE DUTCH POPULATION WITH DATA ON THE EPIDEMIOLOGY OF HIP FRACTURES.

- Lalmohamed A, Welsing PM, Lems WF, et al.
- Osteoporos Int 2012;23:861-869 (impact factor 4.1)

USE OF PROTON PUMP INHIBITORS AND RISK OF HIP/FEMUR FRACTURE: A POPULATION-BASED CASE-CONTROL STUDY.

- Pouwels S, Lalmohamed A, Souverein P, et al.
- Osteoporos Int 2011;22:903-910 (impact factor 4.1)

ELEVATED RISK OF CLINICAL FRACTURES AND ASSOCIATED RISK FACTORS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS VERSUS MATCHED CONTROLS: A POPULATION-BASED STUDY IN THE UNITED KINGDOM.

- Bultink IEM, Lalmohamed A, Lems WF, et al.
- Osteoporos Int 2013; in press (impact factor 4.1)

COX-2-SELECTIVE NSAIDS AND RISK OF HIP OR KNEE REPLACEMENTS: A POPULATION-BASED CASE-CONTROL STUDY. (*)

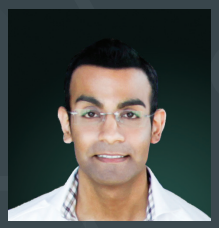
- Klop C, de Vries F, Lalmohamed A, et al.
- Calcif Tissue Int. 2012;91:387-94 (impact factor 2.5)

KNEE ARTHROPLASTY AND RISK OF HIP FRACTURE: A POPULATION-BASED, CASE-CONTROL STUDY. (*)

- Lalmohamed A, Opdam F, Arden NK, et al.
- Calcif Tissue Int 2012;90:144-150 (impact factor 2.5)

EXPERIENCE WITH EUTHANASIA SINCE 2007.

- Lalmohamed A, Horikx A.
- Ned Tijdschr Geneeskd 2010;154:A1882



ARIEF LALMOHAMED was born in the Hague, the Netherlands, on October 12, 1986. He completed Atheneum in 2004 and subsequently started studying Pharmacy at Utrecht University. He obtained his Master of Science in Pharmacy with the distinction cum laude in 2010 and completed the Honours Programme in Pharmacy. For his extracurricular teaching and research activities, he received the KNMP award upon completing the Pharmacy programme.

In 2010, Arief was awarded a personal NWO Mosaic grant (a subsidy worth € 200,000 for young and talented scientists). With this grant, he started his PhD at the Division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University. He performed several studies in Denmark (Aarhus University Hospital) and the United Kingdom (Medicines and Healthcare Products Regulatory Agency and Southampton General Hospital). Arief presented his work at several international conferences, and was given a total of 8 awards for his oral presentations.

During his PhD, Arief was trained as a clinical pharmacologist (Department of Geriatric Medicine, University Medical Center Utrecht) and an epidemiologist (Julius Center, University Medical Center Utrecht). For his specialisation in pharmacoepidemiology, he completed several training activities at McGill University in Montreal (Canada).

In January 2013, Arief started his training as a hospital pharmacist at the Department of Clinical Pharmacy, University Medical Center Utrecht. At this department, he continues his research activities and also holds a researcher position at the Division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University.

VE•NOUS THROM•BO•EM•BO•LISM
Obstruction of blood vessel by an embolus from site of clot formation
1 θρόμβος *(thrombos)*
blood clot
2 έμβολος *(embolos)*
plug