The Influence of Prior Knee Conditions on the Survival of Total Knee Arthroplasties

A PhD Study based on the Danish Knee Arthroplasty Registry

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BY
ANDERS EL-GALALY

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AALBORG UNIVERSITY
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PREFACE

This thesis is submitted as a series of papers relying on the 4 peer-reviewed studies included in the appendix. The introductory chapters cover the studies' background, summarize their results in the context of the current literature and critical review the methodologies behind them. Finally, the introductory chapters discuss the studies' clinical interpretation and limitations, while providing future perspectives for arthroplasty registries.

Study I:

El-Galaly A, Haldrup S, Pedersen AB, Kappel A, Jensen MU, Nielsen PT (2017). Increased risk of early and medium-term revision after post-fracture total knee arthroplasty: Results from the Danish Knee Arthroplasty Register, Acta Orthopaedica, 88:3, 263-268.

Study II:

El-Galaly A, Nielsen PT, Jensen SL, Kappel A. Prior High Tibial Osteotomy Does Not Affect the Survival of Total Knee Arthroplasties: Results From the Danish Knee Arthroplasty Registry. J Arthroplasty. 2018;33(7):2131-2135.

Study III:

El-Galaly A, Kappel A, Nielsen PT, Jensen SL. Revision Risk for Total Knee Arthroplasty Converted from Medial Unicompartmental Knee Arthroplasty. J Bone Joint Surg Am. 2019;101(November):1999-2006

Study IV:

El-Galaly A., Nielsen P.T., Kappel A., & Jensen S.L. (2020) Reduced survival of total knee arthroplasty after previous unicompartmental knee arthroplasty compared with previous high tibial osteotomy: a propensity-score weighted mid-term cohort study based on 2,133 observations from the Danish Knee Arthroplasty Registry, Acta Orthopaedica. Published online 13. Jan 2020

ENGLISH SUMMARY

Total knee arthroplasty (TKA) is one of the most common orthopedic procedures and the future demand is expected to rise steadily. Failure of a TKA can be devasting for the patient as TKA-revision is associated with inferior clinical outcome and implant-survival compared with primary TKA. To hinder a future rise, studies evaluating factors associated with TKA-revision are needed. Based on the Danish Knee Arthroplasty Registry, this thesis investigated the influence of three knee conditions on the risk of TKA-revision.

Fractures of the distal femur or proximal tibia are associated with both chronic pain and a more rapid development of osteoarthritis. Study I investigated how these prior fractures affect the survival of TKAs. The study revealed that the risk of early revision was increased in patients treated with TKA due to post-fracture osteoarthritis compared with patients treated with TKA due to primary osteoarthritis.

High Tibial Osteotomy (HTO) is a joint preserving treatment of patients with osteoarthritis of the medial knee compartment and study II investigated the survival of TKAs converted from HTOs. In unadjusted analyses, the risk for revision was increased by prior HTO. However, following adjustment for a higher proportion of males and lower age in patients with TKA converted from HTO, the risk for revision associated with HTO became insignificant.

In the recent decade, medial unicompartmental knee arthroplasty (UKA) has gained popularity in the treatment of isolated osteoarthritis in the medial knee compartment. If UKA fails, conversion to TKA is a reliable and frequent solution. Study III investigated the risk for revision in these conversion TKAs and compared them with both primary TKAs and TKAs revised from TKAs. The study concluded that TKA converted from UKA shared revision risk with TKA revised from TKA and thus, the risk was 3-folded that of primary TKA.

As UKA has become more popular, the use of HTO has been declining. Study IV utilized propensity-score based inverse probability of treatment weighting to compare the survival of TKA converted from UKA with TKA converted from HTO. The study found a more than 2-fold increased risk for revision associated with UKA and thus highlighted that UKA should not be used as an intermediate treatment in order to postpone TKA.

In short, this thesis presents survival-estimates and relative risk of TKA-revision in patients treated with TKAs complicated by prior knee fracture, prior HTO or prior UKA. Thus, the thesis offers valuable insight when planning TKA-surgery in these patients.

DANSK RESUME

En total knæprotese (TKA) er den hyppigste kirurgiske behandling for svær slidgigt i knæet og indgrebet forventes at blive gradvist hyppigere i fremtiden. Hvis en TKA fejler, kan re-operationen have store konsekvenser for patienten, som ofte vil have forsatte smerter og nedsat funktion af knæet. Dansk Knæalloplastik Register har samlet klinisk information om knæproteser udført i Danmark siden 1997. Med udgangspunkt i registeret, har vi undersøgt tre forskellige knætilstandes betydning for re-operationsrisikoen af en TKA. Sammen med et metode-studie er disse tre undersøgelser samlet i denne Ph.d.-afhandling.

Knoglebrud i knæet øger risikoen for en senere TKA og derfor undersøgte studie I, hvordan tidligere knoglebrud påvirker risikoen for re-operation af en TKA. Studiet konkluderede, at risikoen for re-operation inden for de første 5 år er signifikant højere hos patienter, som tidligere har haft et knoglebrud i knæet.

Slidgigt i knæet starter ofte på indersiden, og her kan det behandles med en aksekorrigerende knæoperation. Patientens knæ lades urørt, mens knæets mekaniske akse forskydes mod den raske del af knæet. Senere kan patienten dog få behov for en TKA, hvorfor studie II undersøgte betydningen af en aksekorrigerende operation for overlevelsen af en efterfølgende TKA. Efter at have taget højde for forskelle i alder og køn, viste studiet at en tidligere aksekorrigerende operation ikke øgede risikoen for re-operation af en TKA.

En anden behandlingsmulighed ved isoleret slidgigt på indersiden af knæet er en halv knæprotese (UKA), hvor man kun indsætter protese i den syge del af knæet. Denne behandling er blevet mere populær igennem de senere år bl.a. grundet forkortet genoptræning og bedre knæfunktion. Hvis det resterende knæ rammes af slidgigt eller UKA'en fejler af anden grund, bliver den ofte udskiftet med en TKA. Studie III har undersøgt, hvordan en tidligere UKA påvirker overlevelsen af en TKA og fandt at TKA konverteret fra UKA havde samme risiko for re-operation som en re-opereret TKA og dermed en tredobbelt risiko for re-operation sammenlignet med TKA.

I takt med, at flere behandles med UKA, bliver færre behandlet med en aksekorrigerende knæoperation. Studie IV udnyttede en nyere statistik metode til at belyse, hvilken betydning en tidligere UKA har for overlevelsen af en TKA sammenlignet med en tidligere aksekorrigerende knæoperation. Studiet fandt, at en UKA mere end fordoblede risikoen for re-operation sammenlignet med en aksekorrigerende knæoperation.

Som konklusion, har studierne bag denne afhandling bidraget med estimater for re-operationsrisikoen af TKA'er hos bestemte patientgrupper. Denne viden er værdifuld i planlægningen af en TKA-operation hos disse patienter.

ACKNOWLEDGEMENTS

This thesis captivates the work I conducted at the Department of Orthopaedic Surgery, Aalborg University Hospital from 2016 to 2019. In many ways it depicts my journey from ignorant to scratching the surface of epidemiological research. A journey, I hope has just begun.

Yet, the thesis was not my first encounter with research. As a medical student, I completed a research year at the Department of Ophthalmology under the supervision of Professor Toke Bek. Tokes work ethic and passion for research inspired me greatly and I am thankful for his patient guidance during the painstakingly process of writing my first manuscript. The skills I acquired from my research year has been invaluable.

In 2015, Consultant Poul Torben Nielsen approached me with a small project aiming to evaluate the outcome of TKAs following tibia fractures. The study seemed manageable and I planned to conduct it before proceeding in field of Ophthalmology. During the project I was introduced to Consultant Andreas Kappel, who contributed with his profound clinical knowledge. Their guidance with the project and beyond, led me onto the path of Orthopaedic Surgery and for this, I am grateful.

When I first met ass. Professor Steen Lund Jensen at the hotel bar during the Danish Orthopaedic Society's annual meeting in 2016, I didn't know he'll be my main supervisor shortly after. Nevertheless, I highly appreciate his acceptance of being my main supervisor. His experience with the national arthroplasty registries and critical revision of my work have substantially increased the value of this thesis.

Furthermore, I am grateful for the financial support from the Orthopaedic Research Unit at Aalborg University Hospital and the year of absence granted by the Departments of Orthopaedic Surgery at Aalborg and Aarhus University hospitals. A special thanks must be address to Professor Søren Kold for his confidence in my capability of conducting this thesis my way and his support of my ongoing research.

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- Anders El-Galaly, March 2020

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LIST OF ABBREVATIONS

ATE: Average Treatment Effect

ATT: Average Treatment effect on the Treated

BMI: Body Mass Index

DAG: Directed Acyclic Graph

DHR: Danish Hip Arthroplasty Registry

DKR: Danish Knee Arthroplasty Registry

DKRR: Danish Knee Reconstructive Registry

HR: Hazard Ratio

HTO: High Tibial Osteotomy

IPTW: Inverse Probability of Treatment Weighting

OR: Odds Ratio

PJI: Periprosthetic Joint Infection

PPV: Positive Predicting Value

RCT: Randomized Controlled Trial

ROM: Range of Motion

RR: Relative Risk

TKA: Total Knee Arthroplasty

UKA: Unicompartmental Knee Arthroplasty

95% CI or **CI:** 95% Confidence Interval

CHAPTER 1. BACKGROUND

1.1. KNEE OSTEOARTHRITIS

1.1.1. DEFINITION

Osteoarthritis is a degenerative disease of synovial joints and one of the world's leading cause of disability (1). However, the disease is a continuum ranging from pain associated with weightbearing activities in an otherwise normal joint to invalidating pain in a joint with no range of motion (2). As a consequence, knee osteoarthritis is diagnosed by a combination of patient's history, clinical examination and radiographic findings with knee pain, bony tenderness, muscle atrophy and periarticular osteophytes as cornerstones (3).

1.1.2. PATHOLOGY

The pathology behind osteoarthritis is complicated and still not completely clarified (2). Therefore, the description within this thesis will be limited to a brief overview. Osteoarthritis is mainly a disease of the joint cartilage where biomechanical and biochemical changes result in failure of the repair process. As a result the cartilage get thinner and the stress on the subchondral bone increases (2). Over time the thinning of the cartilage and stress on the subchondral bone result in the classical x-ray findings, such as subchondral sclerosis, osteophytes, cysts and narrowing of the joint space (4).

1.1.3. CLINICAL FEATURES AND DIAGNOSIS

The clinical picture of osteoarthritis is diverse, and radiographic changes might not correspond with the symptoms reported by the patient. Therefore, osteoarthritis is a clinical diagnosis supported by radiographic findings (5). The cardinal symptoms of osteoarthritis are progressive pain from one or few synovial joints, joint stiffness that resolve with movement and muscle atrophy (5). The clinical diagnosis is supported by a x-ray with periarticular osteophytes, subchondral sclerosis, subchondral cysts and joint narrowing (6). As the knee is a multicompartmental joint, osteoarthritis might be isolated in one compartment or present in multiple compartments at once. Typically, symptomatic knee osteoarthritis evolves in two different patient phenotypes. The first phenotype is a middle-aged individual with osteoarthritis in the medial knee compartment due to prior injury or varus deformity. The second phenotype is older, often overweight and suffer from generalized osteoarthritis of the knee and other joints such as the opposite knee, hips or thumbs (5).

1.1.4. RISK FACTORS

The etiology behind osteoarthritis is a combination of systemic factors, such as genetic heritage, and mechanical factors, such as joint trauma (7). The importance of these factors seems to differ between joints with weightbearing joints being especially vulnerable to mechanical factors (8). This far, obesity and previous knee injury (e.g. meniscus/ligament injuries or fractures) are considered the most important mechanical factors leading to knee osteoarthritis (9).

The connection between obesity and knee osteoarthritis is not fully understood and both mechanical, humoral and genetic factors is being investigated (10). Nevertheless, the linkage between increasing body mass index (BMI) and knee osteoarthritis is reported strong in several studies (11). For instance, Grotle et al. reported that a BMI above 30 results in a 2.5-fold increased risk of developing knee osteoarthritis within 10 years when compared with a normal-range BMI (12). Obesity is not only associated with increased risk of developing knee osteoarthritis but also with the risk of receiving knee arthroplasty and affects the arthroplasty's outcome (10,13). Thus, weight loss is beneficial through all stages of knee osteoarthritis.

In knees with previous injury, the development of osteoarthritis is considered as a specific subtype, often referred to as post-traumatic osteoarthritis. Post-traumatic osteoarthritis is more prevalent among younger patients but is nevertheless estimated to account for 12% of the all patients diagnosed with osteoarthritis (14). Multiple prior injuries have been associated with the development of post-traumatic knee osteoarthritis including, but not limited to, meniscus tear, cruciate ligament rupture, and knee fractures (15). Whereas all severe intraarticular knee injuries are associated with initial cartilage damage, ligamentous injury might also result in knee instability leading to progressive cartilage damage (16). The progressive development of osteoarthritis might be accelerated further by knee fractures, due to intraarticular malunion and/or altered mechanical knee axis (17). Especially fractures of the proximal tibia and distal femur have been associated with the development of early post-traumatic osteoarthritis (18,19). Yet, knee fractures are not only associated with rapid development of osteoarthritis. They also increase the risk of subsequent total knee arthroplasty (TKA) while complicating the surgical procedure due to pathological knee anatomy, altered knee mechanics, scar tissue or retained surgical hardware (20,21).

1.1.5. PREVALENCE

In 1948, 5,209 adults between 28 and 61 years living around Framingham, MA, USA, were enrolled in the Framingham Heart Study to record risk factors for cardiac disease. Since then, this cohort have been used to investigate the epidemiology of other common diseases, including knee osteoarthritis (22). The Framingham Osteoarthritis Study evaluated the prevalence of knee osteoarthritis in 1,424 subjects

above 63 years. The study was among the first to highlight an age-related increased prevalence of knee osteoarthritis in elderly above 65 years and a 2:1 prevalence of symptomatic knee osteoarthritis in females (23). Likewise, the Framingham cohort highlighted obesity and knee injuries as major risk factors for knee osteoarthritis (chapter 1.1.4)

In the Framingham cohort, the prevalence of radiographic osteoarthritis was 33% with around 1/3 being reported as symptomatic (24). Since then, the estimates from the Framingham cohort have been confirmed in several contemporary cross-sectional studies with a recent Swedish study reporting symptomatic knee osteoarthritis to be present in 15% of middle-aged and elderly people (25). Together with hip osteoarthritis, knee osteoarthritis is deemed as the 11th highest contributor to global disability affecting around 4% of the world's population (26).

Due to the relationship with both age and BMI, the prevalence might rise as the population in the western world is expected to get older and more obese (27). A recent study supported this concern and estimated a 12% relative increase in the incidence of symptomatic knee osteoarthritis by 2032 (28).

1.2. BASELINE TREATMENT OF KNEE OSTEOARTHRITIS

First choice of treatment in osteoarthritis consist of patient education, physical training and weight loss, which is advantageous in all phases of knee osteoarthritis. In Denmark the treatment is largely standardized through the nationwide "Good Life with Osteoarthritis" program (GLA:D). In short, GLA:D consists of physiotherapist-delivered patient education, session with an "experienced" osteoarthritis-patient and supervised physical training for 3 month (29). If needed, GLA:D can be supplemented by oral or topical drugs with analgesics and non-steroid anti-inflammatory drugs (NSAID) as cornerstones (2). Yet, a recent study reported that the use of painkillers was reduced following the implementation of GLA:D, emphasizing the benefits of training and patient education (30).

If physical training and pharmacological treatment result in inadequate pain relief, minimal invasive procedures ranging from intraarticular injections (e.g. corticosteroid) to arthroscopy might be indicated, but the evidence supporting these procedures varies (31).

1.3. SURGICAL TREATMENT OF KNEE OSTEOARTHRITIS

In severe knee osteoarthritis more extensive surgical treatments are often indicated. Knee osteotomies (e.g. high tibial osteotomy) or unicompartmental knee arthroplasties might be suitable in the treatment of isolated unicompartmental knee osteoarthritis whereas more widespread osteoarthritis is often treated with total knee arthroplasties (31). In accordance with the studies included in this thesis, the in-depth

presentation of surgical treatments will be limited to High Tibial Osteotomy (HTO), Unicompartmental Knee Arthroplasty (UKA) and Total Knee Arthroplasty (TKA).

1.3.1. HIGH TIBIAL OSTEOTOMY

In unicompartmental knee osteoarthritis, the aim of an osteotomy is to alter the mechanical axis of the knee to unload the diseased compartment. The procedure can be conducted on either distal femur or proximal tibia. Of these, the most common procedure is proximal tibia osteotomy (i.e. HTO) treating osteoarthritis in the medial knee compartment (32).

HTO can be conducted as either a medial open wedge or lateral closed wedge osteotomy. Historically the lateral closed wedge osteotomy has been the most popular technique, even though it has an inherited risk of injuring the common peroneal nerve (33). In the recent decades, the medial open wedge osteotomy has gained popularity. While the risk of nerve injury is limited, this procedure carries a larger risk of leg lengthening and non-union (33). Both procedures adjust the mechanical axis of the knee to shift the load from the medial to the lateral compartment. Therefore, a healthy lateral compartment is an essential prerequisite for treating patients with HTO.

Appropriate patient selection is essential to achieve a desirable outcome from HTO. The traditional indication for HTO is lower age (<60-65 years), normal weight, localized pain from moderate osteoarthritis of the medial knee compartment in a stable knee with good range of motion and varus deformity (34). Poor prognostic factors include limited range of motion, severe joint destruction, advance patellofemoral osteoarthritis, obesity and high age (33,34).

The advantage of HTO is pain relief while preserving the knee function leading to a high rate of patients capable of resuming their sports activities (35). The limitations of HTO include prolonged recovery and time-limited pain-relief due to potential progression of osteoarthritis (33). Regarding the survival of HTO, Niinimäki et al. estimated that 27% of HTOs were converted to TKAs within 10 years based on the Finish Arthroplasty Registry and reported an higher conversion rate among females (36). However, in a recent study, van Wulfften et al. questioned the survival of HTOs beyond 10 years as they reported a TKA-conversion rate of 45% at 15 years and 60% at 20 years (37).

Within the Nordic countries there have been a declining incidence of HTO over the last decades (38,39). From Finland, Niinimäki et al. reported an annual decrease from 1987 to 2008 of 6% resulting in an incidence of 4/100,000 in 2008. In contrast, the corresponding incidence of TKA was above 200/100,000. However, Niinimäki et al. reported a small increase in patients younger than 50 years indicating that the use of osteotomies has not been abandoned (38).

In summary, the advancement and success of arthroplasty surgery (particularly unicompartmental knee arthroplasty) has reduced the use of osteotomies in the current orthopedic practice. However, HTO may still play a role when treating young, active patients with symptomatic osteoarthritis of the medial compartment as it relieves pain without compromising the knee joint (33).

1.3.2. UNICOMPARTMENTAL KNEE ARTHROPLASTY

Treatment with unicompartmental knee arthroplasty (UKA) is traditionally indicated by osteoarthritis isolated in either the medial, lateral or patella-femoral knee compartment, with medial UKAs being by far the most common procedure. UKA is not a novel treatment with the first UKA implanted by dr. MacIntosh in 1954 (40). Since then, its design, indication and outcome have substantially improved and consequently the use of UKA is rising (41,42).

In the recent decades, the indications of UKA have evolved. Traditional indications were isolated medial knee osteoarthritis, lower age (<60 years), low level of physical activity, normal weight and a ligamentous stable knee without severe contraction (42). As seen, there was a significant overlap with the indication of HTO. However, as opposed to HTO, the indications of UKA has since broadening and obesity, high level of physical activity and high age are no longer seen as contraindication of UKA (42).

The main advantages of UKA are optimized functional outcome, reduced postoperative length of stay, and fewer medical complications compared with TKA (43). The advantages of UKA and the broadening of their indication has led to a significant increase in the use of UKA in the last decades. In Denmark, this resulted in the annual number of UKAs increasing from less than 50 in 1997 to above 1.300 in 2017 and thus, UKA currently accounts for 20% of the knee arthroplasty cases (41).

The major disadvantage of UKA is the increased risk for revision compared with TKA, highlighted by a recent meta-analysis reporting a 15-year UKA survival rate of 76% (44). The low survival rate has been contributed to limited experience with UKA-surgery among the surgeons conducting these (45). This explanation is supported by a recent multi-center randomized controlled trial (RCT) reporting similar 5-year survival of TKA and UKA (46), by several retrospective studies from centers experienced in UKA surgery (47) and by a registry study reporting increase risk for revision of UKAs performed at low-volume centers (48). Consequently, surgeons are advised to use UKAs in 20% of their primary arthroplasties to maintain their expertise (45).

Yet, the inferior survival of UKA might also be explained by an inferior threshold for revision compared with TKA. Based on the New Zealand Joint Registry, Goodfellow et al., depicted a 6-fold increased rate of revision for UKA compared with TKA for patients with low Oxford Knee Score (49). The lower threshold might be caused by

an anticipated ease of converting UKA to TKA when compared with revising TKA (45).Often a UKA can be converted to a TKA using a standard primary implant and thus, the conversion has been reported to be as reliable as a primary TKA (50).

1.3.3. TOTAL KNEE ARTHROPLASTY

Total Knee Arthroplasty (TKA) is considered the classical treatment for end-stage osteoarthritis. The modern era of TKAs started with hinged-implants in the 1950's and from there, the designs has gradually improved into the modern prothesis designs used today (51).

Traditionally, TKA was offered to older patients with intolerable knee pain from severe osteoarthritis, but in recent decades the indication for TKA has gradually broadening (43). Surgeons were previously reluctant to operate on younger patients due to the risk of several reoperations during their lifetime, but as implant-survival improved also younger patients are offered TKAs (52). Similarly, TKA might be used in both multimorbid and obese patients, despite their risk of complications (43). The broadening of TKA indications is depicted by both demographical and radiological differences between patients treated with TKA in USA, Scandinavia and South Korea (53). Despite these differences, the predominant indications for TKA remains "bone-on-bone" osteoarthritis in one or more knee compartments affecting the quality of life in elderly patients.

Beside implant-related improvements and broadened indications, several other factors surrounding TKA-surgery have been optimized to improve the outcome for the patients. For instance, the use of standardized anesthetic protocols seeking to avoid general anesthesia has been shown to reduce perioperative mortality and shorten length of stay, while enhancing early recovery (54). These protocols are included in the so called "Fast-track surgery"-program which have shorten the length of stay following arthroplasty surgery without increasing the rate of complications by optimizing pre-, intra- and post-operative factors (55,56).

The advancements in TKA surgery have made it a reliable and successful procedure, improving both knee function and quality of life for patients with end-stage osteoarthritis (57). The success of TKA and the rising prevalence of knee osteoarthritis makes TKA one of the most frequent joint-replacement procedures with annual incidence ranging between 100 and 200 TKAs per 100,000 inhabitants in the Nordic countries (58), corresponding to around 7,000 TKAs inserted in Denmark per year. Yet, the future demand is still expected to rise and a recent study estimated that 1.5 million TKAs will be inserted in the USA in 2050 (59).

1.3.4. COMPLICATIONS TO SURGICAL TREATMENT

Complications following surgery are relatively rare but given the high incidence of knee arthroplasties they affect a considerable number of patients.

A pseudo-variable for the general rate of complications is readmission following discharge from knee surgery. Readmission not only implies some sort of complication but is also a significant healthcare expense and thus, used in the evaluation of treatments' cost-effectiveness. For instance, readmission within 30-days is used as treatment quality measure between geographical regions and individual hospitals within Denmark. The rate is published in the annual report from the Danish Knee Arthroplasty Registry and in 2018, 3% of the patients treated with knee arthroplasty due to primary osteoarthritis were readmitted within 30-days (60).

Within 90-days, studies have reported the rate of readmission following primary TKA-surgery to be ranging from 4 to 8%, with readmission equally caused by medical and surgical complications (56,61). The risk for readmission seems lower for patients treated with UKA when compared with TKA, with Liddle et al., reporting a risk ratio for readmission of 0.65 (95% CI: 0.58-0.72) in 101,330 matched patients from England and Wales (62). The inferior rate of general complications contributes to the increased interest and use of UKA in the current practice (45).

The most frequent medical complications following surgical treatment of knee osteoarthritis are symptomatic venous thromboses (deep venous thrombosis or pulmonary embolism) and wound complications (including superficial infections). At 90-days follow-up in 5,389 patients treated with TKA, 61 (1.14%) had venous thromboses and 58 had wound complications (1.08%) (61). The risk of venous thromboses seems reduced in UKA with a recent meta-analysis from pooled health-care databases estimating a hazard ratio (HR) of 0.62 (95% CI: 0.36-0.95) when compared with TKA. In contrast, the risk of superficial infections did not differ between the groups in the pooled analysis (HR=0.85, 95% CI: 0.51-1.37) (63). In general, however, there is compelling evidence that the risk of medical complications is lower for patients undergoing UKA when compared with patients undergoing both TKA and HTO (34,62,63).

Although rare, wound complications and superficial infections might lead to periprosthetic joint infection (PJI) which is considered the most devasting surgical complication to arthroplasty surgery. While superficial infection is often treatable with oral antibiotics, PJIs need surgical debridement and sometimes repetitive surgical procedures. PJI occurs in 1-2% of primary arthroplasties and is often identified by the clinical picture followed by synovial aspiration to confirm the diagnosis. Initial treatment consists of surgical debridement and antibiotic treatment after obtaining tissue samples for agent determination. Implant retention might be possible in acute infection whereas subacute and chronic infections might need implant removal in a

two-stage procedure. In both situations, prolonged antibiotic treatment is necessary and the outcome following PJI is inferior to TKAs revised by other indications (64,65).

Other complications include joint stiffness and persisting unexplained joint pain. Although they might be disabling to the patient, there is not always indication for revision surgery and thus, these complications go unnoticed in large arthroplasty registries. However, given that around 15% of the patients are dissatisfied 1 year after TKA-surgery, these "minor" complications play an important role when evaluating the outcome of knee surgeries (66). A recent RCT (TOPKAT) concluded that at 5-years follow-up UKA had less joint-stiffness and unexplained pain when compared to TKA (46). When comparing UKA and HTO, UKA might be associated with reduced post-operative pain, but HTO seems to have superior range of motion (34).

1.4. REVISION SURGERY

Revision surgery is often used as benchmark when comparing different surgical treatments of knee osteoarthritis. However, this comparison is not necessarily fair as both the indication and threshold for revision might differ.

HTO can be used to postpone arthroplasty surgery and thus, conversion to TKA might be expected and not considered an adverse event at all (33). If HTO provides limited pain-relief or the osteoarthritis progresses, conversion to TKA is a reliable and often used solution. The conversion can often be conducted with primary implants and is, in general, thought to provide favorable results (67,68).

Similarly, progression of osteoarthritis might occur in UKA causing pain from the lateral or patellofemoral compartment. Under these circumstances, the UKA can either be converted to a TKA or augmented by a lateral or patellofemoral UKA (bicompartmental knee arthroplasty) (50). The most frequent indications for UKA revision are progression of arthritis, aseptic loosening and unexplained pain, even though revising an arthroplasty due to pain without mechanical failure is questionable (47,50).

In contrast, revision of a TKA is almost always an unexpected and serious adverse event given their estimated 25-years survival of 82% (69). Early revisions are predominantly due to infection or instability whereas late revision is often due to aseptic loosening (70,71). TKA are also revised due to unexplained pain, although to a lesser extent than UKA (72). This difference emphasizes that the current threshold for revision might differ between implants.

Revising an implant is often complicated and thus, requires thorough examination, clinical imaging and pre-operative planning. While the conversion of HTO or UKA might be achieved with primary implants, the revision of TKA can be more

complicated (73). Compromised bone stock or inferior bone quality often call for the use of bone graft and augmented or stemmed implants. Similarly, soft tissue conditions, such as insufficient ligaments, might result in the need for constraint implants to achieve stability. Consequently, the outcome of revision TKA is significantly inferior to primary TKA both in terms of the patients' quality of life and implant-survival (60,74).

In conclusion, revision surgery is diverse but often complicated and might have devastating consequences for the patients. Thus, the decision of converting or revising an implant should be preceded by thorough considerations in alliance with the patient.

CHAPTER 2. STUDY AIMS, RESUME AND LITTERATURE OVERVIEW

2.1. STUDY I

Due to the association between previous knee fractures and long-time risk of TKA-surgery, study I aimed to evaluate the influence of fractures in the proximal tibia or distal femur on the survival of subsequent TKA.

From 1997 to 2013, 1,421 TKAs inserted in knees with prior proximal tibia or distal femur fractures (post-fracture TKA) were identified in the Danish Knee Arthroplasty Registry (DKR) and compared with 51,097 primary TKAs inserted due to osteoarthritis. The study concluded that post-fracture TKA was associated with a more than 1.5-fold increased risk for revision within the first 5 years after index surgery. Beyond the 5th year of index surgery, the study was unable to detect a significant increased risk for revision associated with prior femur or tibia fractures. Revision due to instability and infection was more prevalent in post-fracture TKA compared with primary TKA (75).

Like study I, other studies have investigated the influence of prior femur or tibia fractures on the survival of TKAs (Table 2.1). Most of the studies focused on specific challenges regarding TKA indicated by post-fracture osteoarthritis as well as their functional and radiographic outcome. Yet, Houdek et al. published a large cohort study based on the Mayo Clinic's arthroplasty registry in 2016 (76). In accordance with study I, they reported a significant increased risk for revision when TKA was indicated by post-fracture osteoarthritis. Other studies based on both multicenter cohorts and nationwide registries also reported inferior survival of TKA indicated by secondary osteoarthritis, however, these studies did not specify the etiology behind the secondary osteoarthritis (77–79). Thus, Study I contributed with the largest and most generalizable cohort in the evaluation of the survival of TKAs following fractures in the distal femur or proximal tibia and supported the results from most of the current literature (Table 2.1).

However, larger is not always better. While Study I provided externally valid survival estimates from a nationwide cohort, the study was not able to answer simple clinical questions such as "which challenges are encountered during TKA-surgery following fractures?". To answer questions like this, Saleh et al. reviewed several of the studies in Table 2.1 (80). The review highlighted an increased rate of complications in post-fracture TKAs, which might be a result of joint deformity, arthrofibrosis, compromised soft tissue or subclinical infections of the osteosynthesis hardware. Despite these challenges, Saleh et al. concluded that TKA significantly improved knee

function, limit pain and increased range of motion in patients with post-fracture osteoarthritis.

Table 2.1

Study	Design	Fractures (% of case-group)	Control group	Primary Outcome	Follow-up (years)	Revisions	Indication of revisions
Lonner 1999 (81)	Single center retrospective cohort	Femur: 11 (35%) Tibia 20 (65%)	-	Postoperative results	4	11 (35%)	Infection, aseptic loosening
Papadopoulos 2002 (82)	Single center retrospective cohort	Femur: 48 (100%)	-	Functional and radiological outcome	6	2 (4%)	Aseptic loosening, instability
Weiss 2003 (83)	Single center retrospective cohort	Femur: 48 (44%) Tibia: 62 56%	-	Complications and technical difficulties	5.5	6 (5%)	Aseptic loosening, instability
Deschamps 2010 (84)	Multi center retrospective cohort	Femur: 38 (49%) Tibia: 36 (46%) Combined: 4 (5%)	-	Complication	4	4 (5%)	Infection, aseptic loosening
Massin 2011 (85)	Single center retrospective cohort	Femur: 19 (48%) Tibia: 20 (50%)	-	Clinical outcome	5	3 (8%)	Infection, aseptic loosening
Shearer 2013 (86)	Single center retrospective cohort	Femur: 12 (26%) Tibia: 27 (57%) Combined: 8 (17%)	-	Postoperative pain and function	4.5	7 (15%)	Infection, instability, aseptic loosening
Benazzo 2014 (87)	Single center retrospective cohort	Femur: 7 (16%) Tibia: 27 (61%) Combined: 7 (16%)	-	Clinical outcome	6	3 (7%)	Infection, pain, aseptic loosening
Bala 2015 (77)	Retrospective multicenter registry cohort	-/3509 (fractures not reported)	257,611 primary osteoarthritis	Postoperative complications	5.5	171 (5%) OR: 1.23 (CI: 1.05-1.44)	-
Abdel 2015 (88)	Single center retrospective cohort	Tibia: 62 (100%)	-	15-year survival	16	11 (18%), 15-year survival: 82% (CI: 71-93)	Wear, aseptic loosening, instability

Study	Design	Fractures (% of case-group)	Control group	Primary Outcome	Follow-up (years)	Revisions	Indication of revisions
Lunebourg 2015 (20)	Single center retrospective cohort	Femur: 6 (18%) Tibia: 23 (70%) Combined: 4 (12%)	407 primary osteoarthritis	Implant survival rate	11	3 (9%), 10-year survival: 94% (CI:89-99)	Infection, aseptic loosing
Scott 2015 (89)	Single center matched retrospective cohort	Tibia 31 (100%)	93 primary osteoarthritis	PROM and survival	6.5	2 (6%), 5-year survival: 96% (CI: 88-100)	Infection, aseptic loosening
Lizaur-Utrilla 2015 (90)	Single center matched prospective cohort	Tibia 29 (100%)	58 primary osteoarthritis	Function and complication	6.5	1 (3%), 7-year survival: 90% (CI: 77-100)	Aseptic loosening
Houdek 2016 (76)	Single center retrospective registry cohort	Femur: 190 (36%) Tibia: 341 (64%)	19,641 primary osteoarthritis	Complication and implant survival	6	56 (11%) HR: 2.23 (p<0.0001)	Infection, instability, aseptic loosening
El-Galaly 2017 (75)	*Nationwide retrospective registry study*	*Femur: 300 (21%) Tibia: 1,121 (79%)*	*51,097 primary osteoarthritis*	*Survival and indication for revision, separated age-categories*	*6*	*159 (11%), HR ranging from 1.5 to 1.9 (p<0.01)*	*Aseptic loosening, infection, instability*
Putman 2018 (91)	Multi center retrospective cohort	Femur: 24 (9%) Tibia: 42 (16%) Total cohort: 263	-	Survival and functional outcome	9	16 (6%), 10-year survival: 89% (CI: 82-94)	Infection, aseptic loosening
Khoshbin 2019 (92)	Single center matched retrospective cohort	Femur: 35 (47%) Tibia: 40 (53%)	375 primary osteoarthritis	PROM and survival	7.5	3 (4%),4-year survival: 96% (CI: unknown)	Infection, instability

Table 2.1: Overview of studies evaluating the survival of TKA indicated by post-fracture osteoarthritis. OR: odds ratio, HR: hazard ratio. CI: 95% confidence interval.

2.2. STUDY II

The potential limited duration of pain-relief from HTO is of concern and often the progression of pain results in conversion to TKA. Therefore, study II aimed to evaluate the influence of prior HTO on the survival of conversion-TKA.

Using data retrieved from the Danish Knee Arthroplasty Registry (DKR), the study analyzed 1,044 TKAs converted from HTOs between 1997 and 2015 and compared them with 63,763 primary TKAs inserted due to osteoarthritis in the same period. The study reported a crude inferior survival of TKA following HTO compared with primary TKA. However, after adjustment for the higher percentage of men and the lower age in TKA following HTO, the study was unable to detect a significantly increased risk for revision associated with prior HTO. Additionally, the study compared the survival of TKA converted from HTO based on the level of implant-constraint and reported an increased risk for revision associated with posterior-stabilized TKAs. The study concluded that HTO did not increase the revision-risk in subsequent TKA however if posterior stabilized implants were used, the risk increased (93).

The study complemented other studies comparing the survival of TKAs following HTOs with primary TKAs. As depicted in Table 2.2, the studies ranges from small cohorts with either inter-patient (94–99) or intra-patient matching (patient with bilateral TKA) (100–102) to large registry cohorts (103–106). In a recent meta-analysis, Seo et al. collected the survival estimates from these studies and reported that HTOs negatively affected the long-term survival of TKAs and that neither age or sex impacted this survival (107). The neglectable impact of age and sex in the meta-analysis might have been expected as 12 out of 15 of the described studies analyzed cohorts matched on these variables, including the 1,036 TKAs Niinimäki et al. investigated from the Finnish Knee Arthroplasty Registry (104). One of the limitations of a matched study design is the inability to evaluate the risk associated with the matched covariates. Thus, study II contributed with an estimate of the influence of age and sex on the survival of TKA following HTO and suggested that these factors might be more important than the HTO.

A major limitation of study II is the lack of information regarding type of HTO (i.e. closed or open wedge), and if this affect the survival of a subsequent TKA. In 2013 Bastos et al. reported similar patient reported outcomes and risk of early complications between 24 TKAs converted from open wedge HTOs and 117 TKAs converted from closed wedge HTOs (108). In 2017, Ehlinger et al. conducted a similar comparison of 58 open wedge HTOs and 77 closed wedge HTOs and did not find any statistical difference in the survival of subsequent TKA (109). However, both studies were limited in both size and follow-up which might explain why Robertsson et al. found an increased risk for revision in TKA following closed wedge HTO and not in TKA following open wedge (105). Another explanation for this finding might be that closed wedge HTO is the "older" approach resulting in a longer follow up of TKAs converted

from these osteotomies. To summarize, it seems that the influence of the type of HTO on the survival of TKA is not fully elucidated and thus, more studies are needed.

Table 2.2

Study	Design	HTO	Primary Osteoarthritis	Type of osteotomy	Follow up (years)	Revision	Indication of revisions
Haddad 2000 (94)	Multicenter prospective matched cohort	50	50	Closed wedge: 42 Dome: 8	6	6 (12%) vs 7 (14%)	Patella resurfacing, aseptic loosening
Meding 2000/2011 (100,101)	Single center retrospective matched cohort	39	39	Closed wedge: 34 Dome: 5	7.5/14	2001: 4 (10%) vs 1 (3%) 2011: 0	Aseptic loosening
Karabatsos 2002 (98)	Single center retrospective matched cohort	20	20	Closed wedge: 20	5	None	-
Parvizi 2004 (102)	Single center retrospective matched cohort	34	34	-	15	2 (6%) vs 0	Aseptic loosening, infection, instability
Van Raaij 2007 (95)	Single center retrospective matched cohort	14	14	Closed wedge: 14	4	None	-
Haslam 2007 (110)	Single center retrospective matched cohort	51	51	Closed wedge: 51	13	11 (22%) vs 4 (8%)	Aseptic loosening, fracture, infection
Kazakos 2008 (99)	Single center retrospective matched cohort	38	38	Closed wedge: 38	5	None	-
Amendola 2010 (96)	Single center retrospective matched cohort	29	29	Closed/open wedge: 19/10	8	4 (14%) vs 0 (0%)	Patella resurfacing, aseptic loosening

Study	Design	HTO	Primary Osteoarthritis	Type of osteotomy	Follow up (years)	Revision	Indication of revisions
Efe 2010 (97)	Single center retrospective matched cohort	41	41	Closed wedge: 41	7	None	-
Erak 2011	Single center retrospective cohort	34	1315	Open wedge: 34	3	None	-
Pearse 2012 (103)	Nationwide retrospective registry cohort	711	34,369	-	-	45 (6%) vs. 650 (2%) RR: 3.3 (CI: 2.5-4.5)	Infection, pain, instability
Niinimäki 2014 (104)	Nationwide retrospective registry cohort	1,036	4143	-	7	93 (9%) vs. 258 (6%) HR: 1.4 (CI: 1.1-1.8)	Malalignment, infection, aseptic loosening
Robertsson 2015 (105)	Nationwide matched registry cohort	838	118,229	Closed/open wedge: 356/482	4.5	44 (5%) vs 3,167 (3%) HR: 1.4 (CI: 1.0-1.9)	-
Badawy 2015 (106)	Nationwide retrospective registry cohort	1,399	31,077	-	-	83 (6%) vs. 1,387 (4%) RR: 1.0 (CI: 0.8-1.2)	Aseptic loosening, dislocation, other
Bae 2017 (111)	Single center retrospective matched cohort	32	32	Closed wedge: 32	6	None	-
El-Galaly 2018 (93)	*Nationwide retrospective registry cohort*	*1,044*	*63,763*	-	*8.5*	*98 (10%) vs 2,933 (5%) HR: 1.2 (CI: 0.9-1.5)*	*Aseptic loosening, instability, infection*

Table 2.2: Overview of studies evaluating the survival of TKA following high tibial osteotomies (HTO). RR: relative risk, HR: hazard ratio. CI: 95% confidence interval.

2.3. STUDY III

Conversion to TKA is the most common solution for failed UKA. Yet, the influence of prior UKA on the survival of TKA is still debated. Therefore, Study III aimed to investigate whether the survival of TKAs converted from medial UKAs resembled the survival of primary TKAs or TKAs revised from TKAs.

1,012 TKAs converted from medial UKAs between 1997 and 2017 were retrieved from the Danish Knee Arthroplasty Registry (DKR). From the same period, 73,819 primary TKAs indicated by osteoarthritis, and their subsequent 2,572 revisions, were retrieved for comparison. The study reported comparable survival of TKA converted from UKA and TKA revised from TKA and consequently, that the survival of TKA converted from UKA was significantly inferior to that of primary TKA. The study estimated a 3-fold increased risk for revision associated with TKA converted from UKA compared with primary TKA. The inferior survival was unaffected by implant constraint, experience in revision surgery and type of UKA bearing (i.e. fixed or mobile). Like study I and II, revision due to instability was more pronounced in TKA following UKA compared with primary TKA and, surprisingly, also compared to TKA revised from TKA. The increase prevalence of instability in TKA converted from UKA indicated that conversion of a UKA is not always as straightforward as it might be expected (112).

In the recent literature, studies have reported conflicting results regarding the survival of TKAs converted from UKAs as depicted in Table 2.3. Some smaller single center studies reported similar survival of TKA following UKA and primary TKA (113–115) which was supported by a recent meta-analysis reporting no significant difference in the revision rate of these groups (116). However, several large registry studies, including study III, have reported that the survival of TKA following UKA is inferior to primary TKA. From the Swedish Knee Arthroplasty Registry, Robertsson et al., reported a relative risk of TKA-revision of 2.8 associated with TKA converted from UKA when compared with primary TKA and from the Norwegian Knee Arthroplasty Registry, Leta et al., found a similar revision rate when comparing TKA converted from UKA with TKA revised from TKA (105,117). Both studies omitted UKA-conversion due to infection to enhance the homogeneity of the studies, at the potential cost of inducing selection bias and limiting the external validity.

The inferior survival of TKA converted from UKA from nationwide registries compared with single center studies have been claimed to be due to surgical experience at high volume centers (118). To elucidate this relationship, study IV compared the risk for revision of TKA converted from UKA at centers with high and low volume of TKA-revisions. The study was unable to detect a significant difference and thus, cannot conclude whether the volume of TKA-revision affect the survival of TKA converted from UKA.

It has been claimed that when conversion from UKA to TKA is achieved with primary implants, the outcome is comparable with that of primary TKAs (50). Yet, this claim is disputed by a recent study from the Australian Arthroplasty Registry reported improved survival when stemmed implants were use in the conversion from UKA (119). Study III questioned this relationship further by reporting that the survival of TKA converted from UKA was unaffected by implant constraint or implant supplementation.

In summary, the survival of TKA following UKA is still debated. However, it is questionable that conversion from UKA to TKA is uncomplicated and that the outcome mimics that of primary TKA.

Table 2.3

Study	Design	TKA from medial UKA (% of cases)	Indication for conversion (top 3)	Control group	Follow up (year)	Revision	Indication of revisions (top 3)
Järvenpää 2010 (113)	Single center retrospective matched cohort	21 (100%)	Poly failure, aseptic loosening, progression of arthritis	28 primary TKA	11	2 (10%) vs. 1 (4%)	Infection, instability
Pearse 2010 (120)	Nationwide retrospective registry cohort	205 (100%)	Pain, aseptic loosening, progression of arthritis	Primary TKA from the same period	3	Rate: 1.97 per 100 component years vs 0.48 for primary TKA	Aseptic loosening, infection, pain
Sierra 2013 (121)	Multi center retrospective cohort	175 (100%)	Aseptic loosening, progression of arthritis, poly failure	-	6	9 (4.5%)	Aseptic loosening, infection, arthrofibrosis
Jonas 2014 (122)	Single center retrospective matched cohort	23 (100%)	Progression of arthritis, aseptic loosening, pain	42 Primary TKA	5	2 (9%) vs 0(0%)	Instability
Robertsson 2015 (105)	Nationwide retrospective matched registry cohort	920 (100%)	Aseptic loosening, progression of arthritis, pain	118,229 Primary TKA	4.5	81 (9%) vs. 3,167 (3%), RR: 2.8 (CI: 2.2-3.5)	-
Lunebourg 2015(123)	Single center retrospective matched cohort	43 (90%)	Progression of osteoarthritis, aseptic loosening	48/48 primary/ revision TKA	7	4 (8%) vs. 2 (4%)/5 (10%)	Aseptic loosening, instability, infection
Leta 2016 (117)	Nationwide retrospective registry cohort	578 (100%)	Aseptic loosening, pain, progression of arthritis	768 Revision TKA	4	67 (12%) vs 96 (13%), RR: 1.2 (CI: 0.9-1.7)	Aseptic loosening, pain, instability

Study	**Design**	**TKA from medial UKA (% of cases)**	**Indication for conversion (top 3)**	**Control group**	**Follow up (year)**	**Revision**	**Indication of revisions (top 3)**
Scott 2018 (124)	Single center retrospective cohort	60 (100%)	Progression of osteoarthritis, pain, aseptic loosening	-	7	7 (12%) 5-year survival: 91% (CI: 82-99)	Aseptic loosening, pain, fracture
Lombardi 2018 (115)	Single center retrospective cohort	175 (91%)	Aseptic loosening, progression of arthritis, tibial collapse	177/257 primary/ revision TKA	6	8 (4%) vs. 6 (3%)/35 (13%)	Aseptic loosening, instability, arthrofibrosis
Lim 2019 (114)	Single center retrospective matched cohort	70 (100%)	Progression of arthritis, aseptic loosening, fracture	140 primary TKA	6	0 (0%) vs. 2 (1%)	-
El-Galaly 2019 (112)	*Nationwide retrospective registry cohort*	*1,012 (100%)*	*Aseptic loosening, progression of arthritis, pain*	*73,819/2,572 primary/ Revision TKA*	*4*	*105 (10%) vs. 2,572 (3%)/244 (9%)* *HR: 3 (CI: 2.5-3.7)/ HR: 0.9 (CI: 0.7-1.2)*	*Aseptic loosening, instability, pain*

Table 2.3: Overview of studies evaluating the survival of TKA following medial unicompartmental knee arthroplasties. RR: relative risk, HR: hazard ratio. CI: 95% Confidence interval.

2.4. STUDY IV

In the recent decades, the use of HTO has declined parallel to a rise in UKA surgeries. Some patients fulfill the indications of both UKA and HTO and with the recent development there seems to be a tendency to treat these patients with UKA. Yet, regardless of the treatment, the patients are at risk of subsequent conversion to TKA.

Study IV compared the survival of TKA converted from medial UKA and TKA converted from HTO, and thus merge the results from study II and III. A direct comparison of the risk for revision presented in study II and III is vulnerable to residual confounding and selection bias due to the non-random assignment of prior UKA or HTO. To cope with these limitations, study IV utilized a more advanced statistical method, called propensity-score based inverse probability of treatment weighting. In short, we statistically weighted the two groups to create acceptable balance in a wide range of baseline covariates. 978 TKAs converted from UKAs inserted due to primary osteoarthritis in knee without prior surgeries were compared with 1,155 TKAs converted from HTOs due to primary osteoarthritis. In the unadjusted comparison, prior UKA was associated with a hazard ratio (HR) for revision of 2.3 (95% CI: 2.1-2.6) compared with prior HTO. In the statically balanced groups, the HR rose to 2.7 (95% CI: 2.4-3.1). Thus, the study indicated that UKA should be considered a definitive treatment in line with TKA whereas HTO might be used as an intermediate treatment with the aim of postponing a TKA (125).

A recent review was unable to claim superiority of either UKA and HTO in the treatment of medial knee osteoarthritis but reported that HTO might be advantageous in younger patient whereas UKA provided a faster recovery (126). Nevertheless, we have seen a shift from HTO to UKA in the current orthopedic practice (52). Few studies have directly compared the outcome of TKA following UKA and TKA following HTO while many studies have evaluated the survival of TKA following either UKA or HTO (Table 2.2 and Table 2.3). Recently, Lee et al. collected the results of studies comparing TKA following UKA or HTO with primary TKA in a meta-analysis (127). They concluded a comparable clinical outcome of TKA following UKA and TKA following HTO but were unable to present a forest-plot of the risk for revision. In a single center retrospective study, Cross et al. compared 49 TKAs following UKAs with 43 TKAs following HTOs with a respective mean follow-up of 4.5 and 8.5 years. They reported a higher rate of revision in TKAs following HTOs with 3 recorded revisions (7%) compared with 1 recorded revision (1%) in TKAs following UKAs (73). Similarly, Lee et al. published a single-center retrospective comparison of 75 TKAs from UKAs with 217 TKAs from HTOs (99% closed wedge). At a mean follow-up of 5 and 7 years, respectively, the rate of revision was low in both groups with 3 (1%) re-revisions in TKAs following HTOs and none in TKAs following UKAs (128).

Study IV complements the current literature with the first propensity-score weighted direct comparison of TKA following UKA and TKA following HTO. The more than 2-fold increased risk for revision in TKA following UKA compared with TKA following HTO disputed the results of both Cross et al. and Lee et al. However, in both studies the number of TKAs from UKAs were low questioning the studies' power to estimate their true revision rates.

CHAPTER 3. METHODOLOGICAL CONSIDERATIONS

3.1. THE DANISH KNEE ARTHROPLASTY REGISTRY

3.1.1. INTRODUCTION

In 1997, the Danish Orthopaedic Society and the Danish Society for Hip and Knee Arthroplasty Surgery initiated the Danish Knee Arthroplasty Registry (DKR). Years earlier, the other Scandinavian countries had started monitoring their knee arthroplasties, with the Swedish Knee Arthroplasty Registry being the first in 1975.

The importance of monitoring arthroplasties through large nationwide registries became evident with the Boneloc disaster in the mid-90's. In short, a new type of cement was introduced following promising results from animal studies. Without additional clinical trials, Boneloc was used in cemented hip arthroplasties throughout Scandinavia (129). Following the introduction of Boneloc, surgeons were worried by a rise in early implant failure due to aseptic loosening (130). This concern was reinforced when data from the Norwegian Hip Arthroplasty Registry were published in 1995. Havelin et al. compared the short-term risk for revision in hip arthroplasties cemented with either Boneloc or conventional bone cements and reported a 8-fold increased risk of failure associated with Boneloc (131). The combination of the surgeons' experiences and the results from both clinical studies and a nationwide arthroplasty registry lead to abandoning the use of Boneloc.

The advantage of nationwide arthroplasty registries was obvious and several registries was initiated parallel with the DKR (132). As a new registry, a major challenge for the DKR was to get the surgeons to record their surgeries and within the registry's first decade the completeness of the registered primary arthroplasties was below 90% (60). A turning-point for the DKR was the inclusion in the Danish Clinical Quality Program – National Clinical Registries (RKKP) in 2006 (133). As a part of RKKP, reporting to the DKR became mandatory and in the following decade, the registry completeness rose to above 95% (60).

3.1.2. DATA COLLECTION

The Danish Knee Arthroplasty Registry (DKR) is led by a steering committee which mainly consist of experienced knee arthroplasty surgeons from the different geographical regions within Denmark. The steering committee decides which variables should be registered in the DKR and routinely update these to reflect the current clinical practice. The data are then reported prospectively by the Danish knee

arthroplasty surgeons through standardized forms (133). The prospective collection contributes to the reliability of the collected data and shields against information bias (134). The DKR collects a range of patient characteristics, surgical information and administrative registrations. The main variables included in this thesis are presented in table 3.1.2.

Table 3.1.2

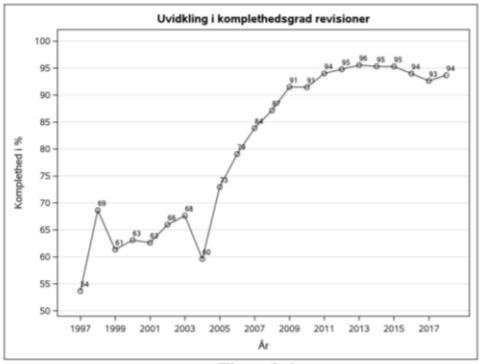
Variables	Definition
Patient ID	Numeric variable uniquely identifying each patient
Date of Birth	Date variable for the patient's birthday
Vital Status and date	The DKR is linked with the Danish Civil Registration System providing vital status for each observation
Date of Surgery	Date variable for the arthroplasty surgery
Side of Surgery	Binomial variable for the side of surgery
Revision Surgery	Binomial variable for primary or revision surgery
Sex	Binomial variable for the patient's sex
Age	Numeric variable for the patient's age at the time of surgery
Weight	Numeric variable for the patient's weight
Height	Numeric variable for the patient's height – registered from 2011
Charnley Class	Categorical variable for the patient's Charnley class
American Knee Society Score	Clinical and functional score of the knee (ranging from 0 to 100
Indication of arthroplasty surgery	Binomial variables for the indication of primary surgery/revision
Prior Surgeries	Binomial variables for prior knee surgeries, e.g. prior proximal tibia/distal femur fractures or HTO
Type of Arthroplasty	Categorical variable for the type of arthroplasty surgery e.g. total knee arthroplasty, medial unicompartmental knee arthroplasty etc.
Specific implants	Categorical variables for the specific implants, e.g. manufacturer and implant name
Fixation	Categorical variables for cementation of femur, tibia and patella
Patella resurfacing	Binomial variables indicating patella resurfacing
Use of implant-supplementation	Binomial variables for the use of additional stem, augments or cones
Duration of Surgery	Numeric variable for the duration of surgery
Perioperative complication	Categorical variable for perioperative complication e.g. iatrogenic fracture, tendon/ligament rupture.

Table 3.1.2: *Overview of the variables from the DKR used in this thesis*

3.1.3. DATA COMPLETENESS

Figure 3.1.3

Figur 9.3.



Figur 9.4.

Figure 3.1.3: *Data completeness since the initiation of the DKR. Source: DKR's annual report 2019* (60)*, with courtesy from Anders Odgaard, Chairman of the steering committee of DKR.*

Figure 3.1.3 depicts the completeness of primary (Figure 9.3) and revision (Figure 9.4) arthroplasties since 1997. After the registration became mandatory in 2006, the completeness of DKR rose rapidly with a completeness above 90% for both primary and revision arthroplasties since 2007. Before this, the completeness of the DKR was relative low and a recent study questioned whether registration from this period is influenced by selection bias (41).

How the low completeness might have biased the comparisons in this thesis can be approximated from study IV (125). Table 3.1.3a is a 2x2 table from study IV depicting TKAs following either UKAs or HTOs and their subsequent revisions.

Table 3.1.3a

	TKA following UKA	**TKA following HTO**
Unrevised TKA	857 (88%)	1,054 (91%)
Revised TKA	121 (12%)	101 (9%)

Table 3.1.3a: *2x2 table of the results presented in study IV.*

More TKAs were converted from HTOs before 2008 than converted from UKAs and thus, the overall completeness of TKAs following HTOs and their subsequent

revisions might be lower than the overall completeness of TKAs following UKAs and their revisions. Before 2008, the mean completeness was 84% for primary arthroplasties and 69% for revision arthroplasties. Following 2008, the completeness rose to 97% and 94%, respectively. We used these numbers to estimate how a 2x2 table from study IV might have looked like if the lifetime completeness of the DKR was 100% (Table 3.1.3b). In each cell of Table 3.1.3a the registered observations were split by period of surgery (i.e. before or after 2008), the subgroups were divided by their period's mean completeness and finally the sum of the subgroups were inserted in Table 3.1.3b.

Table 3.1.3b

	TKA following UKA	**TKA following HTO**
Unrevised TKA	1,003 (86%)	1,169 (89%)
Revised TKA	161 (14%)	121 (11%)

Table 3.1.3b: *An approximated 2x2 table of the results from study IV if the completeness of DKR was 100%.*
Estimates = Registered observations/completeness within the period x 100%.

As seen in Table 3.1.3b, the distribution of revised and unrevised TKAs remained stable between the groups after approximation of the actual number of surgeries in the study period. Similarly, the relative risk for revision (RR) was almost unchanged from 1.4 (95% CI: 1.1-1.8) in Table 3.1.3a to 1.5 (95% CI: 1.2-1.8) in Table 3.1.3b. Thus, the influence of the reduced completeness before 2008 seems small in comparative studies (e.g. study IV). However, RR is a simplified estimate of the risk of an outcome when dealing with time-to-event data. Consequently, it is not possible to reject the influence of selection bias completely from this simple approximation.

3.1.4. DATA QUALITY

Data completeness is important when evaluating the results from arthroplasty registries but at least as important is the correctness of each variable within the registry, often referred to as the data validity.

In study I, the validity of the registrations "prior proximal tibia fracture" and "prior distal femur fracture" were not evaluated. This was a major limitation of study I, as extensive misclassifications within fracture-types are plausible (e.g. tibial fractures being registered as femur fractures). Similarly, "previous patella fracture" might be wrongly denoted as either femur or tibial fractures. To shield against these incorrect registrations, the survival analysis was conducted on post-fracture TKA as a group including both tibia and femur fracture. It could have been beneficial to include

patella-fractures in study I and thereby, enclosing all fractures around the knee in one group.

Based on the experience from study I, we reviewed the registration of "prior high tibial osteotomy (HTO)" in 134 patients operated within the North Denmark Region before conducting study II (93). Through the patient reports, 128 of the HTOs were confirmed corresponding to a positive predicting value (PPV) of 0.96 (95% CI: 0.91-0.98). The PPV of prior HTO is comparable with the PPV reported for validated variables in both the Danish Hip Arthroplasty Registry (DHR) and the Danish Knee Ligament Reconstruction Registry (DKRR), where the PPV of most variables ranged from 0.85 to 1.00 (135,136). This far, no other studies have evaluated the validity of the remaining variables in the DKR and thus, it is unknown if these are like that of prior HTO. We have obtained approval from both the steering committee of the DKR and from Danish Patient Safety Authority to conduct a systematic validation of the DKR from 1997 to 2018, which is planned to be finished within 2020 (60).

A major concern of studies conducted on clinical registries is the extent of misclassifications or "measurement errors" (134). As the extent of misclassifications in the DKR is unknown, we have illustrated how these might have affected the studies in Figure 3.1.4a-c.

Figure 3.1.4a shows the correct distribution of crosses, triangles, circles and squares, which is that crosses are the predominant shape in the box to the left and circles are the predominant shape in the box to the right. In Figure 3.1.4b, this distribution is influenced by non-differential misclassifications depicted by an increased number of triangles and squares on both sides. Consequently, the higher prevalence of either crosses or circles between the sides becomes less clear. In short, non-differential misclassifications bias the difference towards zero and thus tends to underestimate the true result. In contrast, differential misclassifications might lead to the acceptance of a false distribution as depicted in Figure 3.1.4c where the number of triangles is increased to the left and the number of squares is increased to the right. This alters the distribution between the sides, leading to the false conclusion that triangles are the predominant shape to the left and squares are the predominant to the right.

In summary, non-differential misclassifications will tend to underestimate the strength of the true relationship whereas differential misclassifications might lead to the acceptance of a false relationship. As data are collected prospectively in the DKR and unassociated with subsequent studies, the potential misclassifications are most likely non-differential.

Figure 3.1.4a

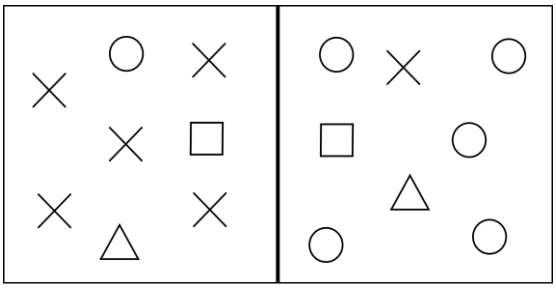


Figure 3.1.4a: *No misclassifications leading to the correct conclusion that crosses are predominant to the left and circles to the right*

Figure 3.1.4b

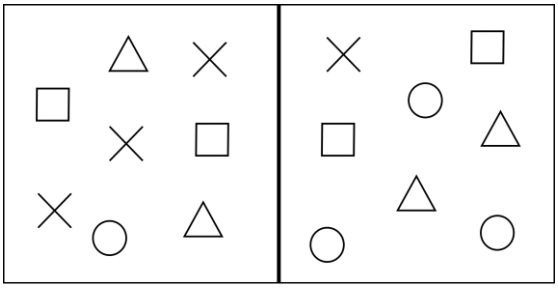


Figure 3.1.4b: *Non-differentiated misclassifications leading to a less significant, but correct conclusion that crosses are predominant to the left and circles to the right*

Figure 3.1.4c

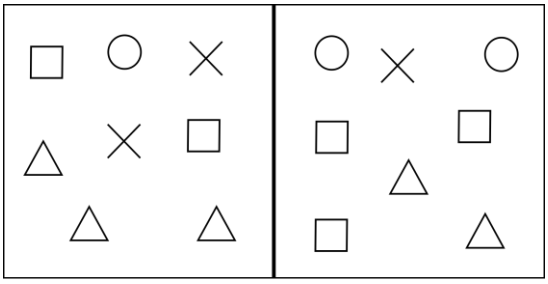


Figure 3.1.4c: *Differentiated misclassifications leading to a false conclusion that triangles are predominant to the left and squared to the right*

3.1.5. MISSING DATA

Like in most clinical studies, missing data are also unavoidable in arthroplasty registry studies. Thus, it is important to analyze which variables have missing data, the amount of missing data and in which pattern these data are missing. These factors determine how missing data should be handled and thus, play an important role when assessing the reliability of registry studies.

Of the 128,661 unique primary arthroplasties registered in the DKR from 1997 to 2018, less than 2% of the data points used in this thesis were missing. However, height was not included in the registry before 2011 and thus, 52% the data in this variable was absent. Consequently, height was omitted from the analyses in all four studies. Second to height, weight was the variable with the highest amount of missing data (3%) followed by American Knee Society Clinical- and Functional score (2% each) and implant fixation (1%). 5 of the remaining variables had less than 1% missing datapoints (including implant constraint) and the rest of the variables were complete.

Although the DKR is a rather complete database, missing data should still be analyzed. When deciding how to handle missing data, the pattern of the missing datapoints is important. In short, data can be missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR) (137). MCAR denotes that the missing datapoints are independent of both observed and unobserved data which would be the case if the datapoints was randomly deleted. If the data are MAR, they are dependent on the observed data but not the unobserved data. In the DKR, height is an example of MAR as it is, among other variables, depending on the date of surgery. In contrast, MNAR is when the missing datapoints are also depending on unobserved datapoints, either unrecorded variables or the missing datapoints themselves. Such a scenario would be if weight was missing in obese patients as they might be less likely to be weighted.

Often data are MAR, but it is not possible to prove this by a simple statistical test and thus, we must rely on assumptions. The pattern of missing datapoints can depicted graphically as showed in Figure 3.1.5. The figure tells us that weight was missing in more than 3,000 observations and in 2,426 of these, it was the only missing variable. Furthermore, 1,170 observations were missing data in both American Knee Society Clinical score and Functional score, whereas only 5 observations had missing data in all 5 most frequently missing variables. From Figure 3.1.5 we can conclude that when an observation has missing data it is most often in one or two variables and thus, it is reasonable to assumed that we can make reliable estimates of these missing datapoints.

Figure 3.1.5

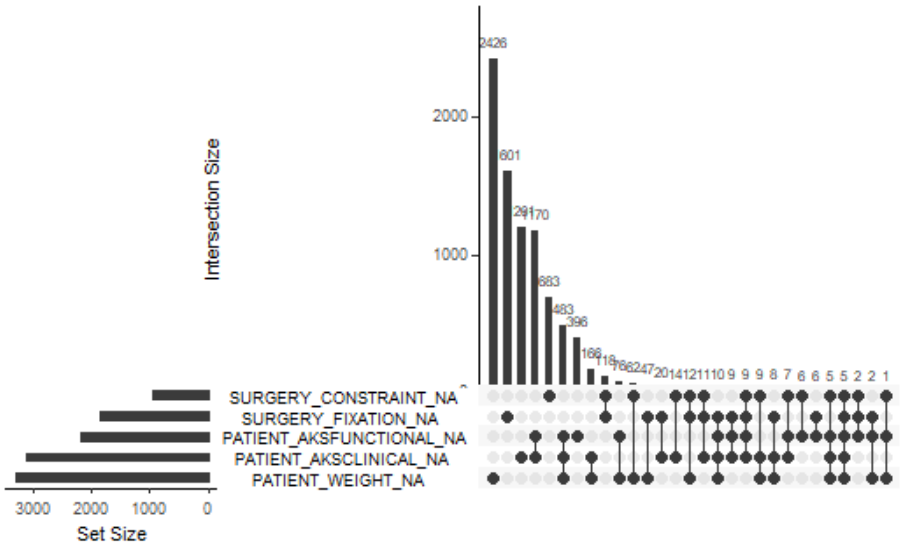


Figure 3.1.5: *Graphical presentation of the missing data for primary arthroplasties registered in the DKR from 1997 to 2018 (128,661 observations).*

Several methods can be utilized when dealing with missing data in registry studies. Study I utilized complete case analysis, which is the simplest and most frequent approach (93,137). In this approach, registrations with missing values are deleted and thus, the final dataset is restricted to complete observations. The price for simplicity is loss of sample size and potential introduction of selection bias if the data is not MCAR. A more advanced approach is multiple imputation, which was used in study II, III and IV (93,112,125,137). In this approach, a statistical method (e.g. logistic regression) is used to repeatedly impute the missing datapoint based the observed data resulting in multiple complete datasets. Finally, the study analysis is carried out on each of the imputed datasets and the estimates are combined to a single final estimate, incorporating the uncertainly related to each imputation (138). However, multiple imputation only handles MAR and is affected by the relationship between the variables (i.e. how well a logistic regression is fitted). Parallel to the evolution of Machine-Learning algorithms in clinical medicine, imputation by Random Forest algorithm has gain popularity. In short, Random Forest is a classifier algorithm build upon multiple classification trees used to estimate the missing datapoints based on all observed data. This approach is advantageous when dealing with different datatypes (e.g. categorical and continuous), non-linear relationships and might be able to handle datapoints MNAR (139). From a non-statistician point of view, another major

advantage of imputing by Random Forest is that only one complete dataset is generated and thus, it simplifies the subsequent analyses. Therefore, future studies might benefit from the use of Random Forest algorithms when dealing with missing data.

As seen in this section, dealing with missing data is not simple. Fortunately, missing datapoints in the DKR are limited and, as evaluated in Study II and III, a simple approach such as complete case analyses was comparable to more sophisticated methods such as multiple imputation (93,112). Yet, if a study is based on more incomplete data, the consideration regarding missing data becomes more influential.

3.1.6. BILATERAL OBSERVATIONS

As osteoarthritis often affects both knees, 21% of the patients in DKR have bilateral knee arthroplasties (Figure 3.1.6). If each knee is considered as one observation, 35% of the observations in the DKR arises from the 21% of patients with bilateral arthroplasties. The correlation between 35% of the arthroplasties represent both methodological and statistical challenges.

Figure 3.1.6

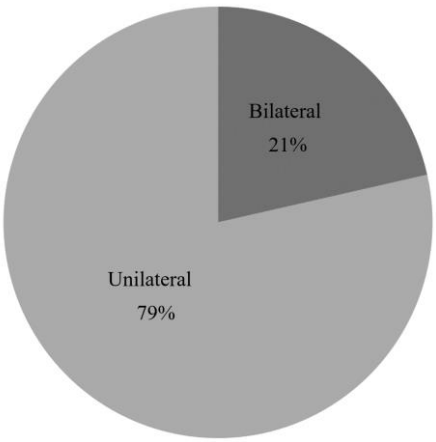


Figure 3.1.6: *Distribution of patient with unilateral and bilateral knee arthroplasties in DKR from 1997-2018*

Methodologically, patients getting their second knee replaced might differ from those getting their first. The functional outcome following arthroplasty surgery is equally depending on the operated knee and the contralateral knee. Thus, patients with bilateral knee replacement might have a systematically different post-operative knee function compared with patients who has unilateral knee replacement. Similarly, patient with bilateral knee replacement might be older or overweight which affects

their risk of TKA-revision (140). Na et al. analyzed the differences in patients undergoing bilateral and unilateral TKA in an Asian population (141). They found statistically significant differences in, among others, sex, age and BMI, but concluded that these differences only induced limited bias. A similar analysis has not been conducted in the DKR and thus, the distribution of baseline characteristics between bilateral and unilateral observations is currently unknown. A potential imbalance might induce significant bias if the distribution of bilateral observations is uneven between the study groups. Such a scenario was likely in study I as post-fracture osteoarthritis is more often a unilateral disease compared with primary osteoarthritis (75). To cope with this, we removed bilateral observations by including only the first knee to receive surgery in each patient. This approach reduced the potential bias from bilateral observation however also limited the statistical power of study I.

Statistically, bilateral observations are not independent of each other, which violates a critical assumption in most analyses (142). Robertsson and Ranstam investigated the influence of this violation when estimating the survival of knee arthroplasties (143). Based on the Swedish Knee Arthroplasty Registry, they compared the traditional proportional hazards model (i.e. Cox regression) assuming independence between each observation (i.e. each knee) with an extended proportional hazards model (shared frailty) allowing multiple events from each patient. In short, a shared frailty model includes a patient-related factor to the statistical analysis and thus, incorporate the “frailty” two knees shares by belonging to the same patient. A major downside of a shared-frailty model is the computer power required to run it, making it a time-consuming analysis in large registry studies. The two approaches provided clinical similar risks of revision and thus, Robertsson and Ranstam concluded that the revision risk of knee arthroplasties can be analyzed without consideration for bilateral observations (143). Consequently, we ignored bilateral observations in study II, III and IV (93,112,125). However, to depict the possible effect of uneven distribution of bilateral observations between the groups (as described for study I) we repeated the analyses of study II and III including only the first knee to receive surgery. These sensitivity analyses resulted in clinically similar survival estimates.

In summary, whether to include bilateral observations must be considered within the context of each study. Yet, when estimating implant survival from large arthroplasty registries it seems reasonable to neglect the potential bias induced by bilateral observations.

3.2. SURVIVAL ANALYSES

How to calculate time to arthroplasty revision (i.e. implant survival) is still debated within the orthopedic literature. The discussion is whether death during follow up should be considered a competing outcome or the observations should be censored at the time of death. Basically, the question is: "How should a patient's death be handled when evaluating the survival of her or his arthroplasty?" (144,145).

3.2.1. KAPLAN-MEIER METHOD VS. CUMMULATIVE INCIDENCE FUNCTION

In arthroplasty registries the observations have uneven follow-up, and not all observations will experience the outcome of interest (e.g. implant-revision) before they are lost to follow up or the study ends. This data pattern is called "right-censored" and the observations not experiencing the outcome are referred to as incomplete observations (Figure 3.2.1). In 1958, E.L. Kaplan and P. Meier published a nonparametric statistical method to incorporate the information of the incomplete observations, which is referred to as the Kaplan-Meier Method (KM) (146).

Figure 3.2.1

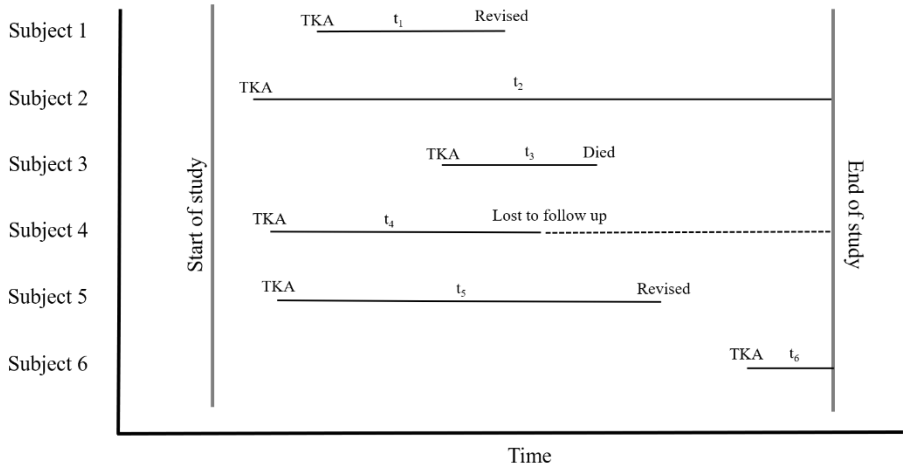


Figure 3.2.1: *An overview of time-to-revision data in the DKR.*

In short, KM differentiate between subjects with a known implant-survival (e.g. subject 1 and 5 in Figure 3.2.1) and subjects with terminated follow-up (e.g. subject 2,3,4 and 6 in Figure 3.2.1). The subjects with a known implant-survival contribute with time-to-outcome while the censored subjects contribute with their observed time-at-risk. Thus, the KM estimate the probability of a subject not experiencing the

outcome at a given time. KM is the most widely used methods to evaluate the implant-survival following arthroplasty surgery. A cruciate assumption in the KM is that censored subjects are still at risk of experiencing the outcome. This assumption is fulfilled when investigated subject-survival as subjects who are lost to follow up or survived the study period will die at some unknown later time-point. However, this assumption is violated when investigated implant-survival as subjects lost to follow up due to death (subject 3, Figure 3.2.1) are not at risk for revision anymore. In an older population (as those receiving arthroplasty surgery) this violation makes the KM underestimate the implant-survival and therefore, the use of KM is questioned (145,147). In opposition, Cumulative Incidence Function (CIF) incorporate the possibility of another event precluding the event of interest. Thus, in the presence of a competing event, CIF provide a more unbiased estimate of the probability of the event of interest (148). Yet, the difference between the estimates of KM and CIF relies on the frequency of the competing event and thus, in orthopedic studies the difference between the models will be more evident in studies with long-term follow up in an older population (145).

In summary, KM estimates the frequency of revisions in an immortal cohort of patients and thus tells which implant last the longest. In contrast, CIF provide the frequency of revision in a mortal cohort and thus provide an estimate of the number of revision likely to be seen in practice (144). In this thesis we presented the KM estimates as these are; the most widely used survival method and fits the objective of the studies which was to estimate the influence of prior conditions on the survival of TKAs and not on the survival of the patients.

3.2.2. COX REGRESSION VS. FINE AND GRAY'S REGRESSION

When estimating the relative risk for revision between two groups, Cox regression and Fine and Gray's proportional hazard regression is the equivalent to KM and CIF. Thus, the controversy of how to handle death during follow-up remains with the choice of censoring it (Cox regression) or handle it as a competing event (Fine and Gray's regression). Similar, to the discussion of KM vs. CIF, Cox regression answers which of the groups had the highest risk for revision if they lived long enough, while Fine and Gray answer which of the two groups will most likely experience a revision during their lifetime.

Besides providing the relative risk for revision, Cox regression is often used to adjust for potential confounders such as age or sex. Thus, the estimate of a multivariate Cox regression provides the relative risk for revision between two groups given there are no intergroup difference in the included covariates. In this regard, Fine and Gray's regression have a major limitation as covariates associated with the risk of the competing event (e.g. male sex and death) will appear to effect the event of interest (e.g. implant revision) as shown by Ranstam and Robertsson (149).

In this thesis, we used Cox regression to estimate the relative risk for revision and to adjust for confounders. However, to depict the potential influence of a higher mortality in the control group (TKA inserted due to primary osteoarthritis) we used univariate Fine and Gray's proportional hazard regression in the sensitivity analyses of study I-III (75,93,112).

3.2.3. THE PROPORTIONAL HAZARD ASSUMPTION

The assumption of proportional hazards is crucial for both Cox regression, Fine and Grays's regression and the log-rank test used to evaluate statistical significance between survival estimates (150). The assumption is that the difference in hazard is constant over time implying that the condition associated with the highest risk for revision remains so during the entire study period. The assumption can be evaluated graphically (e.g. Schoenfeld residuals plot) or by Schoenfeld residual test which might provide a more observer-independent result (151).

In study I, both prior fractures and age violated the assumption of proportional hazards when evaluated for the entire study period. To fulfill the assumption, we stratified the study cohort in age categories and conducted time axis division, as recommend in the statistical guidelines from the Nordic Arthroplasty Register Association (NARA) (151). While fulfilling the assumption, this approach limits the readability and interpretation of study I. In study II, and parts of study III, age also violated the assumption of proportional hazards and to enhance the readability we included age as a time-varying covariate in these studies (151).

The assumption of proportional hazards must be fulfilled for all covariates included in the Cox regression. As described, this sometimes requires extensive adjustments of the raw data. These adjustments might limit both the readability of the results and the number of covariates reasonable to include. Covariate adjustments (confounding) are addressed in chapter 3.3.3 with the introduction of pre-hoc propensity-score based adjustments. This approach incorporates multiple covariates in a single variable and thus eases the subsequent use and clinical interpretation of a proportional hazard regression (e.g. Cox regression). However, this approach also hinders the evaluation of the individual effect from the covariates included in the propensity-score. A feasible future approach could be to combine the approaches by including confounders of minor interest in the propensity-score calculations and subsequently, adjust for confounders of major interest in the Cox regression.

3.2.4. A STATISTICAL VIEW ON INDICATIONS FOR REVISION

In all four studies, the primary endpoint was revision defined in accordance with the Danish Knee Arthroplasty Registry (DKR) as removal, substitution or addition of an implant or part of an implant. When collecting data, the DKR allows several indications for a single revision (i.e. a single revision can be indicated by both instability and aseptic loosening). This possibility is evident from study I, where the number of indications exceeded the total number of revised TKAs (75).

In the studies, we utilized Chi-squared test/Fishers' exact test to analyze the statistical difference in the distribution of indications for revision between the groups. A key assumption in these tests is that each observation only contribute with data to one category and this assumption is violated when one revision have several indications (152). To cope with this violation, we introduced a clinical hierarchy of indications in study II (Table 3.2.4) (93). Due to the hierarchy, each revision only contributed with one indication and thus, fulfills the assumption of the Chi-square/Fischer's exact test.

Table 3.2.4

	Indication	Definition
1.	Infection	Confirmed or suspected infection
2.	Aseptic loosening	Aseptic implant loosening
3.	Wear	Polyethylene failure
4.	Instability	Reported knee instability
5.	Patella resurfacing	Secondary insertion of patella implant
6.	Pain	Patient reported pain
7.	Other	Indication reported as "other", including soft tissue injury, stiffness, fractures
8.	Undefined	Revision without registered indication

Table 3.2.4: *The clinical hierarchy used to sort the indications for revision in study II and III.*

Yet, it should be noted that chi-squared test is sensitive to large sample sizes, and thus a clinical irrelevant difference between to large groups might be statistically significant. Thus, as with all statistical tests, the results should be interpreted in their clinical context (153).

3.3. VALIDITY

The validity of a study can be divided in internal validity (i.e. is the study capable of fulfilling its aim) and external validity (i.e. is the study's conclusion valid in other set ups). The use of a nationwide registry ensures the external validity of the studies within this thesis. However, a high external validity does not necessarily transfer to a high internal validity, and especially in non-randomized studies the influence of potential bias must be evaluated. Systemic errors (i.e. bias) comes in a range of different forms, but the internal validity of this thesis is especially vulnerable to selection bias, information bias and confounding (154).

3.3.1. SELECTION BIAS

Selection bias occurs when the study population does not represent the target population. For example, if young healthy individuals are exposed to a new treatment which is intended to treat elderly, multimorbid patients. The Danish Knee Arthroplasty Registry (DKR) ensures a representative cohort with a complete follow-up and thus shields against selection bias in the traditional sense (155). However, the inclusion of all available observations from the DKR's lifespan might open another pathway for selection bias. The study cohorts of this thesis received TKA surgery over period of 20 years and thus, patients receiving surgery in the late 90's might not be representative of the patients receiving surgery today. Similarly, the used of implants have varied during the past two decades as depicted in Figure 3.3.1. In Denmark, PS-implants were more frequent during primary surgeries around 2010 compared with the recent years. Consequently, the inclusion of implants from this period could be a source of selection bias as they are not in line with the current distribution of implant. This concern of time-dependent selection bias was further encouraged by a recent study presenting higher 10-year revision-free survival in the recent decade compared with the previous decade (156). Limiting the inclusion criteria to the TKA-surgery within the last 5 or 10 years would effectively shield against time-dependent selection bias. However, this would significantly limit the power and clinical relevance of the studies, as a long follow-up is needed to investigate the risk of TKA-revision. Instead we divided the cohorts of study II and III in different time periods and found comparable implant-survival between these periods.

Figure 3.3.1

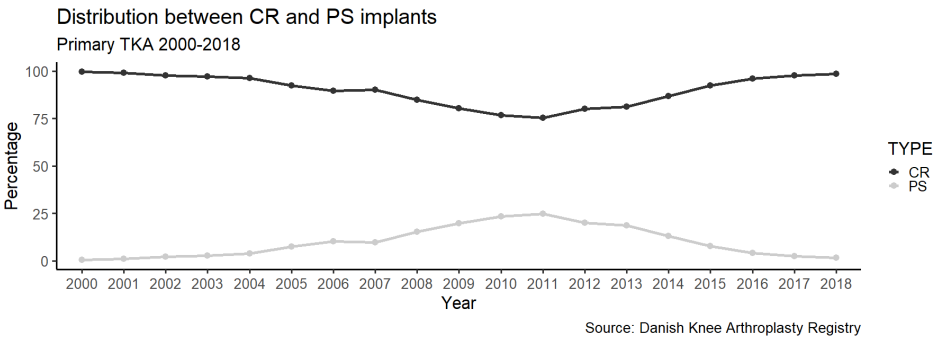


Figure 3.3.1: *The distribution between Cruciate-Retaining (CR) and Posterior-Stabilized (PS) implants in Denmark from 2000 to 2018.*

3.3.2. INFORMATION BIAS

Information bias occurs when the included variables are systematically incorrect or unprecise, such as the differential misclassifications described in chapter 3.1.4. All nationwide administrative databases are prone to information bias. However, the prospective data collection in the DKR and its independence from the study hypotheses limit the risk of reporting-, recall-, and observer bias. Yet, misclassification have the potential of disrupting the validity of studies based on the DKR. Even though misclassifications are likely non-differential, the need of investigating these is evident.

3.3.3. CONFOUNDING

Bias by confounding occurs when a condition is associated with both exposure and outcome without being caused by or causing them (Figure 3.3.3a). Such a condition is called a confounder and can be divided in known- and unknown confounders, with a subdivision of known confounders in measured- and unmeasured confounders. In observational studies, we can adjust for known, measured confounders and discuss the potential influence of known, unmeasured confounders. Known confounders can be evaluated through a causal graph (e.g. directed acyclic graph), which depicts the consideration of confounders in relation to the study hypothesis. Figure 3.3.3a depicts a simple directed acyclic graph (DAG) constructed like the DAG presented in the Supplementary data of study IV (125). In a DAG, the relationship between the conditions must be directed (i.e. causal) and thus, all arrows must be unidirectional. Furthermore, the graph should not lead you from a condition, through directed arrows and back to the same condition (i.e. acyclic), which would imply that a condition caused itself. A confounder is represented by a condition with arrows pointed towards

both the exposure and outcome and thus, have the possibility of disrupting the study conclusion. Noteworthy, a condition on the path from exposure to outcome is a mediator and not a confounder (e.g. longer duration of surgery in complicated TKAs). Adjusting for a mediator might falsely de- or inflate the calculated estimates (157).

Figure 3.3.3a

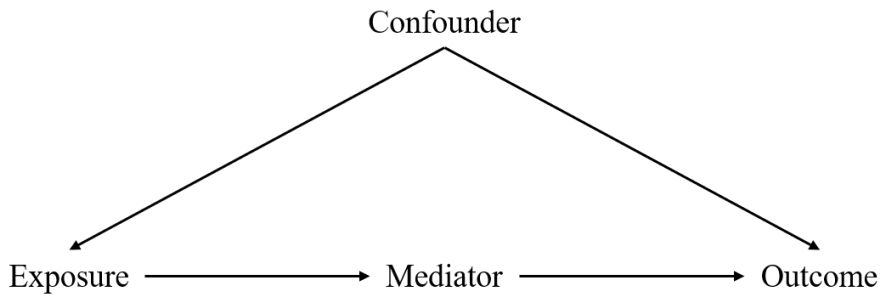


Figure 3.3.3a: *A simplified directed acyclic graph with exposure, outcome, mediator and confounder connected through unidirectional arrows and with no directed cyclic relationship.*

In the orthopedic literature, post-hoc multivariate analyses, such as logistic regression or Cox regression, are often used to adjust for known, measured confounders. In accordance, we used Cox regression to adjusted for potential confounders in study I, II and III (75,93,112). Cox regression relies on several assumptions with the assumption of proportional hazard and independent censoring being predominant (chapter 3.2). Even if these assumptions are fulfilled, the "post-hoc"-nature of Cox regression contains the possibility of introducing information bias (i.e. observer bias) as the researcher might, unintendedly, seek a result – especially if the analysis is not preceded by consideration for confounding (e.g. through a DAG).

To limit the influence of observer bias and to include a range of known measured confounder, study IV utilized a propensity-score based statistics resembling the set-up of a randomized controlled trial (RCT) (125,158). Propensity-score is often estimated through logistic regression and is interpreted as the probability of receiving treatment (e.g. prior UKA in study IV) conditioned on the included covariates (i.e. the measured confounders). Consequently, dependence on the propensity score balances the included covariates between treatment and control. For example, figure 3.3.3b depicts the distribution of age in TKA following UKA and TKA following HTO before and after dependence on the propensity score.

Figure 3.3.3b

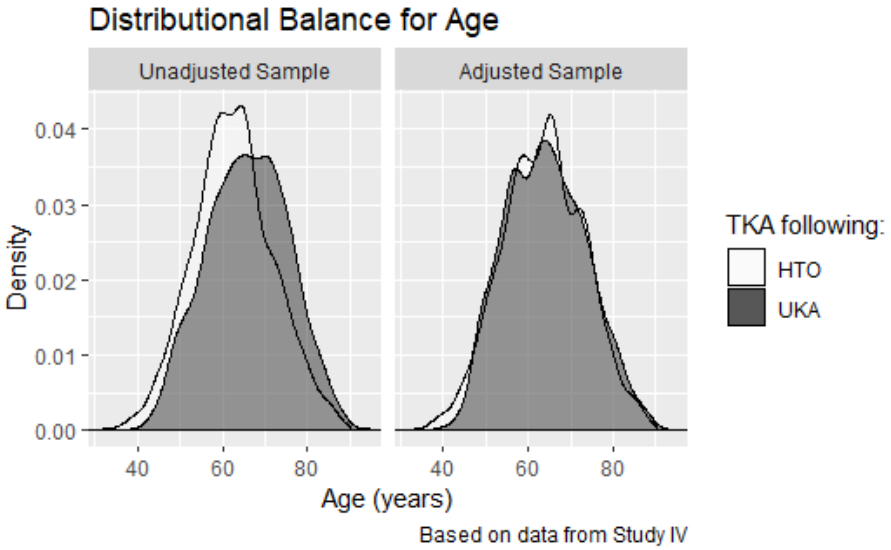


Figure 3.3.3b: *The distribution of age in TKA following UKA and TKA following HTO before and after depending on the calculated propensity score.*

Dependence on the propensity score can be achieve through different methodologies with matching or weighting being the most common (158). Several aspects should be considered when deciding how to depend on the propensity score. To be successful, matching requires either a large control group or limited differences between the groups. Otherwise, matching might introduce selection bias by reducing the study cohort. In opposition, weighting does not exclude observations but might achieve statistical balance in clinical incomparable groups. Another important consideration is to decide whether the study seeks to estimate the average treatment effect (ATE) or the average treatment effect on the treated (ATT). By selecting a cohort that resembles the treated patients, propensity-score matching estimates the ATT. ATT is interpreted as the impact of treatment (e.g. prior UKA) among those who received the treatment. In opposition, dependence on the propensity-score through inverse probability of treatment weighting (PS-IPTW) allows for the estimation of ATE because the whole cohort is included in the analysis. ATE is interpreted as the general effect of treatment if it was applied to the whole cohort (i.e. population) (159). Study IV compared two similar sized groups and aimed to estimate the average effect of UKA in a population treated with either UKA or HTO (i.e. ATE) and thus, utilized PS-IPTW (125).

Even if all known confounders were measured and included in a sophisticated statistical analysis, such as PS-IPTW, observational studies can never adjust for unknown confounders. In 2017, VanderWeele and Ding introduced the E-value to

estimate the potential influence of unknown or unmeasured confounders (160). The E-value is calculated as depicted in Figure 3.3.3c and is interpreted as the estimated magnitude of relationship non-included confounders must have with both exposure and outcome to remove the significance of the presented estimate (e.g. hazard ratio) (161). Similarly, the lower 95% confidence bound can be interpreted at the lowest plausible E-value to equalize the presented hazards and thus, a high lower 95% confidence bound indicates a hazard ratio (HR) robust to residual confounding.

Figure 3.3.3c

$$E\text{-}value = HR + \sqrt{(HR \times (HR - 1))}$$

Figure 3.3.3c: *E-value calculated for a hazard ratio (HR) > 1.*

In the PS-IPTW cohort of study IV the E-value was 4.9 with a lower 95% confidence bound of 3.5. Thus, unknown and/or unmeasured confounders must be associated with both prior UKA and TKA-revision with a HR of (at least) 3.5 to remove the significance of the HR presented in the study (125).

In summary, confounding is unavoidable in non-randomized studies, but thorough preparations will limit its influence. First, the pathways for all thinkable confounders should be evaluated before study start, preferable through a causal graph. Second, pre-hoc statistical adjustment for confounders (e.g. propensity-score based analyses) possess advantages over traditional post-hoc analyses (e.g. regression models). Finally, the study robustness for residual confounding (i.e. unmeasured or unknown confounders) can be estimated through the E-value, which might prevent false conclusions about causality.

CHAPTER 4. DISCUSSION AND LIMITATIONS

An in-depth discussion of the results and limitation of each study can be found in the four papers included in the appendix. The following chapter provide a general interpretation of the studies and reflects upon their own limitations and limitations inherited from the Danish Knee Arthroplasty Registry (DKR).

4.1. THE INFLUENCE OF PRIOR KNEE CONDITIONS

4.1.1. KNEE FRACTURES

Study I reported an increased risk for revision in TKAs preceded by fractures of the proximal tibia or distal femur. The study presented an inverse relationship between age at the time of post-fracture TKA and cumulative prevalence of TKA-revision, which is in accordance with several studies highlighting age at time of surgery as a major predictor of TKA-revision (140). Yet, it cannot be deducted that surgeon should refrain from treating young patients with post-facture TKA (or TKA in general), as the cumulative prevalence of TKA-revision depends on the patients' remaining lifetime. Thus, a higher cumulative prevalence is unavoidable in young patients compared with older patients.

Across all age-categories, study I found an increased risk of early revision (<1 year) in post-fracture TKAs. At mid-term follow-up (1-5 years), a previous fracture was associated with increased risk for revision only in the higher age-categories. Beyond the fifth year of follow-up, post-fracture TKA was not significantly associated with increased risk for revision in any age-category. Loss of power caused by small groups might be the main reason for the insignificance in later follow-ups. The relatively small groups were caused stratifying by age-category and dividing in time-series which were necessary to fulfill the assumption of proportional hazards (chapter 3.2.3). With a mean follow-up of 6.1 years in 227 post-fracture TKAs in patients < 50 years, the power to detect revision beyond short-term follow-up is questionable. The number of patients were higher in the other age-categories and thus, they retain power to detect a significant difference between 1 and 5 years of follow-up. Beyond the fifth year of follow-up none of the post-fractures TKA group had enough power to detect a statistically significant difference, depicted by their broad confidence intervals (75).

Despite the lack of power, study I was able to highlight an increased risk for revision in post-fracture TKA within the first 5 years of follow-up. Furthermore, the study showed an increased prevalence of revision due to infection in post-fracture TKAs beyond the first year of follow-up (table 4, study I) (75). Previous open reduction and

internal fixation of fractures carries a risk chronic low-virulence infections due to the non-biological surface of the fixation device (162). Based on study I, it might be hypothesized that post-fracture TKA carries an increased risk of low virulence periprosthetic joint infection (PJI). To answer this, a future study could obtain the type of bacteria found during revision for PJI in post-fracture TKAs and compare these with a matched cohort of primary TKAs. A higher prevalence of low-virulence bacteria might lead to the use of advanced imagining, such as PET-CT, before treatment with post-fracture TKA.

4.1.2. HIGH TIBIAL OSTEOTOMY

The incidence of high tibial osteotomy (HTO) in Denmark has not been reported. Yet, it is reasonable to assume an incidence comparable with the one Niinimäki reported for osteotomies Finland in 2008 (4/100,000) (38). Assuming a gradual decrease since then, around 100 osteotomies (predominantly HTOs) can be estimated to be conducted in Denmark annually. Study II concluded that, if converted, previous HTO did not alter the survival of TKA. Instead, the inferior survival of TKA converted from HTO were driven by patients characteristic enclosed by age and male sex (93).

Both male sex and lower age have been associated with increased risk of TKA revision in several previous studies (140) and this presumable strong relationship might have contained the influence of prior HTO. Thus, from the estimates reported by study II and by Badawy et al. from the Norwegian Knee Arthroplasty Registry, it is not possible to conclude that HTO does not affect the survival of TKA (106). However, together they support that the treatment with HTO does not change the baseline risk for revision in this group of patients.

In study II, posterior-stabilized (PS) implants accounted for around 15% of the implants in both groups. As depicted by figure 3.3.1 (chapter 3.3.1), there was a contemporary rise in the use of PS-implants in Denmark around 2010 with a high in 2011, where 1 PS-implant was used for every 3 cruciate-retaining (CR) implants. This contemporary rise in the use of PS-implants might also have affected higher proportion of PS-implants in TKA converted from UKA, as they were predominantly converted from 2008 to 2018 (study IV) (125). In study II, PS-implants were associated with increased risk for revision in both groups which support previous findings from the Australian National Joint Replacement Registry (163). The inferior survival of PS-implant, presented in other studies, might have attributed to the current, almost exclusive, use of CR-implants for primary TKA in Denmark (figure 3.3.1).

4.1.3. UNICOMPARTMENTAL KNEE ARTHROPLASTY

Within the last decade there have been a rise in the use of unicompartmental knee arthroplasty (UKA) which currently accounts for 20% of the primary arthroplasties in

Denmark (41). Mobile-bearing UKAs are predominantly used in Denmark and in a recent study, the 10-year survival of these implants (Oxford Phase 3 UKA) was estimated to 93% (47). Although superior to registry-reported UKA survival, the survival is still inferior to TKA (44).

Study III estimated the survival of TKA converted from UKA and found it comparable to TKA revised from TKA and thus significantly inferior to primary TKA (112). However, the study cannot be use as an argument against the use of UKA for several reasons.

First, the study did not evaluate the clinical outcome or survival of UKA, and thus conclusion about these cannot be drawn. The only UKA characteristics included in the study were conversion rate from UKA to TKA and indications for conversion. Time to TKA-conversion (i.e. UKA survival) would have been interesting to include in the study analysis. This information is valuable for the comparison between TKA converted from UKA and TKA revised from TKA and could have indicated if early UKA conversion were associated with inferior TKA survival. Other research groups are studying the survival of UKA, and since the steering committee of DKR does not allow reporting of the same data in different projects, we could not include UKA survival in study IV. Leta et al., included time from UKA to TKA and TKA to TKA in their propensity-score, but did report how it influenced the implant-survival (117).

Secondly, UKA may be converted to bicompartmental knee arthroplasty or to another UKA highlighting that conversion to TKA, as investigated in study IV, is not the only feasible solution for failed UKA (164).

Finally, the increased use of UKAs, the advancements in implant design and the evidence – like that of study III and IV – supporting that conversion of UKA is not like primary TKA might result in a lower revision rate of UKA in the future. Ideally, the rate of UKA conversion assembles the revision rate of TKA making the survival of TKA converted from UKA less concerning.

4.2. HIGH TIBIAL OSTEOTOMY VS. UNICOMPARTMENTAL KNEE ARTHROPLASTY

Often, high tibial osteotomy (HTO) and unicompartmental knee arthroplasty (UKA) is used in the treatment of different groups of patients. Yet, there is an overlap in the indications and young (<60 years), moderately active, non-obese patients with moderate medial knee osteoarthritis in a stable knee with good range of motion might be suitable for both HTO and UKA (126). In an overview of surgical treatments of young patients with osteoarthritis in Sweden, W-Dahl et al. reported an rise in UKA surgery and fall in HTO surgery among patients younger than 55 years (52). These results might indicate that patients fulfilling the indications of both HTO and UKA predominantly are treated with UKA.

Several studies have compared the outcome of UKA and HTO with conflicting results. These studies are summarized in two recent reviews concluding that both treatments have advantages with faster recovery being highlighted for UKA and superior range of motion for HTO (34,126). Thus, the choice of treatment in patients suitable for both procedures should be based on thorough pre-operative information leading to shared decision making.

Study IV does not analyze the outcome of either HTO or UKA but evaluate the survival of a subsequent TKA, if this is needed. Crucially, the study does not report the risk of TKA-conversion in neither of the groups. Thus, the study cannot be used as an argument for either HTO or UKA as primary treatment. However, the study highlighted that at the time of TKA-conversion, prior UKA was associated with an almost 3-fold increased risk for revision, even after adjustments for a range of potential confounders (125).

The application of confounding adjustment at the time of conversion to TKA was suboptimal and thereby reduced the internal validity of study IV. In Denmark, HTO-surgeries are not recorded in a nationwide registry like the UK Knee Osteotomy Registry (165). Ideally, study IV should have collected baseline patient characteristics at the time of UKA or HTO instead of at the time of TKA-conversion. By matching on the traditional indications for HTO-surgery, it would have been possible to estimate the average effect of receiving UKA for patient treatable with both UKA and HTO, in other words the average treatment effect on the treated (ATT, chapter 3.3.3).

Still, the imperfect comparison in study IV emphasized that when faced with a patient treatable with either HTO or UKA, UKA seems to be a more definitive treatment compared with HTO.

4.3. INDICATIONS FOR REVISION SURGERY

Time to TKA-revision was considered as the primary outcome measurement for all four studies in this thesis. Yet, from sub analyses on the indications for revision study I-III provided some additional insights.

4.3.1. TOP 3 INDICATIONS FOR REVISION

Across all observations, aseptic loosening, infection and instability were the main indications for TKA-revision accounting for almost 70% of the revisions.

Aseptic loosening is generally reported as the most frequent long-term indication for revision (71,156). Aseptic loosening is often surgery- and/or implant-related and thus, often used to compare different implants or surgical techniques (166). Not surprisingly, aseptic loosening was the most prevalent indication for revision across all subgroups analyze in this thesis and became more frequent in later follow-up (75,93,112). However, the proportion of aseptic loosening was significant higher in TKA converted from UKA (40%) (112). This relationship might be explained by bone loss during removal of UKA potentially leading to inadequate fixation of the TKA (121).

Deep infections, also known as periprosthetic joint infection (PJI), is a devastating adverse event as introduced in chapter 1.3.4. PJIs are often divided in acute, subacute and chronic, depending on the time between arthroplasty surgery and detection of infection (64). Often infections lead to early implant revision which is supported by the reduced prevalence of infections, in general, beyond the first year of follow-up as demonstrated in study I (75). However, retained surgical hardware from prior surgeries might increase the risk of chronic infections and thus, implant-revision due to infection in later follow-ups (chapter 4.4.1). The prevalence of PJI might also be affected by other factors such as tradition in the surgical management of these. Despite decades of improvements in arthroplasty surgery, Dyrhovden et al., reported a higher prevalence of early revisions due to PJI in the past decade, but attributed this to a more aggressive treatment of PJI (156). In the light of these considerations, it is surprising that the frequency of revision due to infection was lowest in TKA converted from UKA, given the retained surgical hardware and that the UKAs were predominantly converted within the most recent decade. However, the relative small number of revisions (n=105) calls for caution when interpreting the proportion of PJI as it may have been influenced by random sampling error (112).

Although frequent in all groups, revision due to instability was significantly more frequent in post-fracture TKA and TKA converted from either HTO or UKA (75,93,112). Ideally, instability should be addressed intra-operatively and thus, meticulous planning and adequate surgical technique should minimize the risk of revision due to instability (167). The increased proportion of instability in TKA

preceded by fracture, HTO or UKA when compared with primary TKA supports the numerous clinical studies emphasizing that these conversions can be complicated (80,127). However, the finding that the proportion of instability was also higher than in TKA revised from TKA imply that difficulty of these conversions might have been undervalued.

4.3.2. UNEXPLAINED PAIN AS INDICATION FOR REVISION

Revision due to unexplained pain is questionable, but a relatively frequent indication for revision. In Norway around 13% of the revision is indicated by pain whereas the number seemed lower in England and Wales (9%) (72,156). Study I give the impression that 13% of the revision of primary TKAs in Denmark are indicated by pain (75). However, following the implementation of the clinical hierarchy, presented in study II, the proportion of revision due to pain decreased to 7% (chapter 3.2.4). In general, pain without an identified and surgical resolvable problem is not an indication for extensive surgical procedures like revising a TKA. In this perspective, 7% still seems like a high percentage of revision due to unexplained pain and might imply that the actual indication for revision was not possible to report because an appropriate field was lacking. An audit of the patient records from the TKAs revised due to unexplained pain might elucidate if an unreported surgical problem was addressed, and the proportion of unexplained pain thus can be attributed to limitations within the Danish Knee Arthroplasty Registry (DKR).

The comparison of revision due to pain between study I and II highlights the influence of data-collection and analyzation on the results from the DKR. Other registries might face similar challenges with several indications for a single revision or limited options in the reporting of indications. Consequently, caution is advisable when comparing indications for revision between registries and between studies based on the same registry.

Nevertheless, the proportion UKA-conversions due to unexplained pain was high in study III and more frequent that progression of osteoarthritis (25% vs 18%) (112). This supports the findings from Goodfellow et al., reporting that surgeons were more willing to revise dissatisfied patients initially treated with UKA than with TKA (49). Perhaps due to the belief that an outcome comparable with primary TKA is achievable (50). At least in terms of implant-survival, this was disputed by study IV.

4.3.3. IMPLANT-REVISION AS OUTCOME

Across the nationwide joint registries implant-revision is used as the predominant outcome when evaluating the result of arthroplasty surgery. In the Danish Knee Arthroplasty Registry (DKR), implant-revision is the only included outcome-measure and defined as removal, insertion or substitution of an implant or part of an implant

(60). Yet, the use of implant-revision as outcome is problematic for research seeking to compare the outcome of arthroplasty in different groups of patients.

First, not all reoperations involve implant changes. Arthrofibrosis is a recognized complication from joint surgery and sometimes requires joint manipulation under anesthesia or even soft tissue surgery to regain range of motion (168). This far, soft tissue surgery due to arthrofibrosis is not registered in most arthroplasty registries leading to the lack of population-based information about this complication (169). However, for the patient and surgeon, reoperation due to arthrofibrosis can be as problematic as some implant-revisions, like secondary patella resurfacing.

Secondly, although not an implant-failure, periprosthetic fractures are implant-related through stress shielding and bone decalcification. Periprosthetic knee fractures occur in around 2% of all primary TKAs with highest prevalence in the geriatric population. However, the fractures are not commonly reported in arthroplasty registries as they often can be treated with open reduction and internal fixation without implant-revision (170). Although periprosthetic fractures are relatively rare, the outcome can be devastating depicted by a 30-days mortality of 10% following periprosthetic distal femur fractures (171).

Thirdly, implant-revision might not be an adequate measure of the success of an arthroplasty. 15-20% of the patients treated with TKA report that they are dissatisfied following surgery (43). Yet, only a percentage of these undergo revision-surgery. For some the dissatisfaction arise from problems without a surgical solution and thus, the lack of revision is justified. Yet, for others, the level of constrain or additional components in their current implant might refrain the surgeons from offering a revision – or the patients from accepting one.

An example of how the level of constraint or use of additional component might "improve" the survival, and thus perceived outcome, of TKA can be found in Lewis et al. evaluation of survival of TKA converted from UKA with the usage of stems or augments (119). The authors reported superior survival if stem was utilized during the conversion of UKA. The results support that, if needed, additional components are important for the outcome of TKA converted from UKA as stated in case-series (121). However, the possible reluctance to revision might have biased the survival in this group.

As depicted, the use of implant-revision as isolated measure for arthroplasty surgery only reflects part of the outcome. A more thorough assessment is obtainable by including more outcome-measures in the arthroplasty registries such as reoperations other than revision and/or patient reported outcomes (chapter 4.4).

4.4. CLINICAL LIMITATIONS IN THE DANISH KNEE ARTHROPLASTY REGISTRY

4.4.1. PATIENT REPORTED OUTCOME MEASURE (PROM)

As mentioned above, a revision-free TKA is not necessarily the same as a successful TKA. This limitation is well-known throughout the nationwide registries. To provide a more complete clinical picture, several registries have already included patient reported outcome measures (PROMs). In Denmark, this is true for, among others, the Danish Shoulder Arthroplasty Registry and Danish Knee Reconstructive Registry. Similarly have PROMs been a part of the New Zealand Joint Registry for years (49). This far, PROMs are not included in the Danish Knee Arthroplasty Registry despite good intentions (60).

The lack of PROM in study I-III limit their clinical application by providing an incomplete picture of the outcome for TKA preceded by knee fractures, HTO or UKA. Furthermore, the incorporation of pre-operative PROMs might elucidate different thresholds for revision of HTO, UKA and TKA.

The use of relevant PROM-data would also make it possible to calculate Quality-Adjusted Life Years (QALYs) and patient reported improvement following arthroplasty surgery (172). These measurements might provide a more refined view on the treatment of young patients with arthroplasty, than the current inverse relationship between age and cumulative risk for revision. Through the collection PROMs we might be able to identify patients for which the improvement in quality of life is worth the risk of experiencing one or more revisions.

Finally, the incorporation of PROMs in the DKR might enable future research to shed light on the 15-20% patients who are dissatisfied with their TKA without undergoing revision (43).

4.4.2. LACK OF INFORMATION

The Danish Knee Arthroplasty Registry (DKR) collects extensive clinical and surgical information regarding arthroplasty surgery (133). However, the registry also lacks important patients' characteristics such as degree of osteoarthritis or comorbidity, preferable through a comorbidity index (e.g. Charlson Comorbidity Index).

Although obtainable, not all the variables were included in the studies of this thesis. For instance, knee range of motion (ROM) can be retrieved from the DKR but the registrations are too divergent to conduct meaningful analyses. The divergence can be illustrated from the disagreement if a 10˚ extension lag should be denoted as 10, -10 or 170. These inconsistencies highlight the difficulties arising with numerous reporters. The inclusion of knee ROM would have been a valuable pseudo-

measurement of knee function in the propensity-score of study IV, although it is incorporated as part of the American Knee Society Score (125).

The DKR lacks information on degree of osteoarthritis (e.g. Kellgren-Lawrence classification) which would have been beneficial in comparing the baseline characteritics. Whether to adjust for the degree of osteoarthritis must depend on the research questions. For instance, the degree of osteoarhtritis might be more severe in the post-fracture TKAs of study I. However, this is potentially mediated by the prior knee fracture and thus, adjusting for degree of osteoarthritis would falsely reduce the effect of prior knee fractures (chapter 3.3.3).

Patient comorbidity is not accessible through the DKR, but retrieable from several other Danish clinical registries such as the Danish National Patient Registry (DNPR). The DNPR is the Danish healthcare administrative registry and contain individual-level information on disease and treatment of Danish citizens since 1977 (173). From there, information about comorbidities (e.g. diabetes) affecting the risk for revision in arthroplasty surgery could have been retrieved (140). Similiarly, pre-operative use of analgesics could have been retrieved from the Danish National Prescription Registry containing individual-level information on prescription medications (174). Including information from these sources would undoubtable have increased the internal validity of this thesis.

In conclusion, “the more, the merrier”-concept also applies for covariates in arthroplasty registry research and the studies of this thesis would have benefitted from information retrievable from other Danish registries. However, caution should also be taken when determining which and how many variables to include. True causality is unobtainable in non-randomized studies but adjusting for non-confounding variables might disguise causality further.

CHAPTER 5. CONCLUSION

The thesis at hand presents four studies analyzing the influence of three prior knee conditions on the survival of total knee arthroplasties (TKAs) inserted in Denmark over the last two decades. The studies concluded that both prior knee fracture and prior unicompartmental knee arthroplasty (UKA) negatively affected the survival of subsequent TKA. Whereas the apparent negative effect from high tibial osteotomy (HTO) was explainable by patient characteristics. The findings are valuable when consulting patients with these conditions prior to TKA-surgery.

Patients undergoing post-fracture TKA or TKA converted from either UKA or HTO are not common in the everyday orthopedic practice. Yet, by comparing these relatively rare cases with TKAs inserted due to primary osteoarthritis, the thesis also provided general information on patient characteristics, implant-survival and indications for revision of TKAs inserted in Denmark. The studies concluded that aseptic loosening, infection and instability accounted for almost 70% of TKA-revisions.

The distribution of indications for revision is also public available through the Danish Knee Arthroplasty Registry's annual report. However, the possibility of several indications for a single revision causes both clinical and statistical challenges as highlighted in chapter 3 and 4. Consequently, the thesis presented a clinical hierarchy usable in future research seeking to analyze indications for revision on the Danish Knee Arthroplasty Registry.

Finally, study IV utilized propensity-score based inverse probability of treatment weighting (PS-IPTW) to compare the risk for revision between TKA converted from UKA and TKA converted from HTO. The use of propensity-score based statistics is rather novel in orthopedic research but possess advantages when approximating causality in retrospective studies and eases the readability of such studies. Using this method, the study presented rather robust estimates of increased risk for revision associated with TKA converted from UKA compared with TKA converted from HTO.

CHAPTER 6. FUTURE PERSPECTIVES FOR ARTHROPLASTY REGISTRIES

Recent publications have discussed the future of arthroplasty registries with a major focus on their role in the post-marketing surveillance of implants (132,175,176). Underlining this interest is the assumption that data collected in the registries are comprehensive and of good quality, which is often investigated by validation studies. However, validation studies are limited by being retrospective of nature and the amount of registrations and variables validated. To enhance validity, arthroplasty registries would benefit from automated registrations. For instance, scanning implant barcodes would eliminate potential errors from manual implant registrations. Such scanning is already performed for implant-tracking purposes in the newly established Danish Implant Registry. Data from this registry will hopefully be available for arthroplasty registries in the future. Automated registration ensures both more reliable and detailed implant registration and enables surveillance of implants by the batch. However, the automatization of registration should not be limited to implants. The advancement of electronic health records gives the possibility of real-time, automated, registration of patient information, such as height and weight and thus, increasing the validity of the collected variables and avoiding double registration.

Yet, with their long-term follow up in large cohorts the registries should still play an important role in orthopedic research. As discussed in this thesis, it is time to expand the measurements of arthroplasty outcome. First, the need for patient-reported outcome measures (PROMs) is evident and should ideally be included as both pre- and post-operative variables with long-term follow up (e.g. 5 or 10 years). Given that they are patient reported, these variables may easily be collected through secured online services available to the patient before and after surgery. Such data collections may also benefit the individual patient by personalized follow-up based on the reported PROMs.

Another advantage of incorporation direct reporting from patients and automated registration from the electronic health record could be to illuminate the prevalence of degenerative joint disease within a nationwide population. By combining the surgeon's clinical diagnosis and interpretation of the x-ray with the patient-reported symptoms from all patients referred to orthopedic care, the joint registries could provide valuable insight to both the prevalence and surgical treatment of degenerative joint diseases. And maybe even more important, provide information about the clinical outcome for patients not receiving surgical treatment.

The list of possible comparisons within the registries is already endless and thus, it is important to ensure a strong clinical perspective in each comparative study. In January 2020, more than 20.000 studies investigating knee replacements were available

through PubMed with 1000 of these published in 2019. It is impossible for the average surgeon to keep track of all the newest research and even the most informed surgeon will have difficulties merging hers or his knowledge to estimate the prognosis for the individual patient. When considering implant failure in arthroplasty research, the information overload might already be a reality. As a result, a recent review highlighted that Machine Learning might be able to assist surgeons with personalized risk of implant failure and that these algorithms could be based on the arthroplasty registries (176).

Predictive algorithms, though, are vulnerable to both differential and non-differential misclassifications presented in chapter 3.1.4. Differential misclassifications might highlight a false relationship between the misclassified variable and the outcome of interest, especially if the misclassification is frequent in patients experiencing the outcome. However, non-differential misclassifications are often just as devastating for predictive algorithms. These misclassifications are more common and occur across all variables, especially in large nationwide registries with numerous reporters. Non-differential misclassifications can be viewed as a fog encircling the predictive variables making them difficult to find. The advancement of more reliable, automated, variable-registration is therefore crucial for the development of usable predictive models from arthroplasty registries.

Another limitation for the success of predictive models, is the rarity of TKA-revision which is currently the only registered failure-outcome in the DKR. The problem with rare outcomes is often referred to as class-imbalance, because of the imbalance between observations experiencing the outcome and those not experiencing the outcome. In brief, if an algorithm predicts that none of the primary TKAs in the DKR will be revised within 2 years it will be correct in 97% of the cases, given that only 3% are revised within 2 years (60). Thus, the incorporation of PROMs and other types of outcome measures is also beneficial for the success and clinical utilization of future predictive models.

Providing individualized reliable predictions of time to implant-failure or functional improvement from arthroplasty surgery should be one of the goals for future research. As a spinoff, we will hopefully see studies estimating the outcome of arthroplasty in the obese, diabetic patient who smokes and not, as now, studies estimating the individual effect of smoking, obesity or diabetes on the outcome of arthroplasties.

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APPENDIX

Study I:

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Study IV:

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