Complications following Total Joint Arthroplasty in Patients with Rheumatoid Arthritis

by

Dr. Bheeshma Ravi, MD

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Health Policy, Management and Evaluation
University of Toronto

© Copyright by Bheeshma Ravi 2013
Complications following Total Joint Arthroplasty
in Patients with Rheumatoid Arthritis

Dr. Bheeshma Ravi, MD
Doctor of Philosophy
Institute of Health Policy, Management and Evaluation
University of Toronto
2013

**Background:** Total joint arthroplasty (TJA) is indicated in persons with end-stage arthritis of the hip and knee (THA and TKA, respectively). While most TJAs are performed for osteoarthritis (OA), 3%-13% are performed in patients with rheumatoid arthritis (RA). Most of the evidence regarding complications following TJA is based on studies of patients with OA. Comparatively little is known about outcomes of TJA in patients with RA. The purpose of this thesis was to summarize current evidence on the rates of complications following TJA in patients with RA, to quantify the risk of complications using validated methods, and to determine the impact of surgeon experience performing TJA in persons with RA on this risk.

**Methods:** For reports published between 1990 and 2011, we evaluated the evidence regarding the risk of complications following TJA in persons with RA using qualitative and, when feasible, quantitative methods. In a cohort of recipients of primary elective THA or TKA between 2002 and 2009, in Ontario, Canada, we identified patients with RA using a validated administrative data algorithm. Multivariable Cox proportional hazards regression was used to evaluate the relationship between arthritis type (RA, OA, other) and the occurrence of pre-specified surgical complications, and to evaluate the impact of surgeon experience (defined as the number of TJAs performed in patients with RA in the preceding year) on the risk of a complication.
**Results:** Forty published studies were reviewed. Relative to TJA recipients with OA, those with RA were found to be at increased risk of dislocation following THA, and increased risk for joint infection following TKA. These findings were confirmed in our cohort study: adjusted hazard ratio (HR) for dislocation 1.91, p=0.001; adjusted HR for infection 1.47, p=0.03. In TJA recipients with RA, greater surgeon RA volume, but not overall TJA volume, was associated with a reduced risk for surgical complications (adjusted HR per 10 additional cases: RA volume 0.81, p=0.002; overall volume: 0.98, p=0.09).

**Conclusions:** In a population-based cohort of primary elective TJA recipients, patients with RA were at significantly increased risk for dislocation following THA and joint infection following TKA. Increased surgeon experience performing TJA in patients with RA attenuated the risk for surgical complications among TJA recipients with RA, a potentially modifiable risk factor. Further research is required to identify the mediators of the increased complication risk in patients with RA, and to delineate strategies to optimize outcomes in these patients.
Acknowledgments

There are many people I would like to thank for their help in completing this dissertation.

Foremost, I would like to thank my supervisor, Gillian Hawker. I am very fortunate to have you as a mentor. You have taught me that the most important attribute for research is to find a question worth answering. I sincerely appreciate your patience, guidance and encouragement, and I hope that I am fortunate enough to continue to work with you in the future.

I would also like to thank my thesis committee: Hans Kreder, Michael Paterson, Earl Bogoch and Peter Austin, for all the effort expended in guiding and reviewing the many aspects of this study and ensuring that the finished product was worthwhile. I would also like to thank my examiners for their participation in the review of my thesis: Dr. Peter Cram and Dr. Dafna Gladman.

I am extremely grateful to Ruth Croxford for her invaluable guidance, particularly around data management and various statistical queries. Thank you so much for not only answering the questions I did have, but also directing me to the questions I had not thought of! I attribute much of my progress and success to your mentorship.

I would like to acknowledge Georgina Bisbikos whose unhesitating response to my administrative issues allowed me to focus on the research at hand.

I would also like to thank Raj Rampersaud for his continued guidance and mentorship.

Finally, and most importantly, I would like to express my gratitude for my parents. For my Mother, whose tireless example inspired me to pursue a career in medicine, and my Father, a true believer in hard work and life-long education. Any success I have had, and hope to achieve in the future, is due entirely to you both.
# Table of Contents

List of Tables vi
List of Figures vii
List of Appendices viii

Chapter 1 – Introduction 1

Chapter 2 – A Systematic Review and Meta-analysis Comparing Complications following Total Joint Arthroplasty for Rheumatoid Arthritis versus Osteoarthritis 19

Chapter 3 – Patients with rheumatoid arthritis are at increased risk for complications following total joint arthroplasty 49

Chapter 4 – Increased surgeon experience with rheumatoid arthritis reduces the risk of complications following total joint arthroplasty 69

Chapter 5 – Discussion 89

References 102

Appendices 130

Copyright Acknowledgements 156
List of Tables

Table 2.1 – Grading the strength of the evidence 36
Table 2.2 – Characteristics of included studies 37
Table 3.1 – Characteristics of Eligible THA Recipients by Arthritis Type 63
Table 3.2 – Characteristics of Eligible TKA Recipients by Arthritis Type 64
Table 3.3 – Age-sex standardized rates of complications (per 100 arthroplasty recipients) 65
Table 3.4 – Results for Cox Proportional Hazards - Fully Adjusted Models 66
Table 4.1 – Characteristics of Eligible TJA Recipients with RA 83
Table 4.2 – Standardized rates of complications (per 100 cases) within each surgeon volume category 84
Table 4.3 – Univariate and multivariate determinants of occurrence of a surgical complication 85
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Conceptual framework relating arthritis type to the occurrence of a complication following primary elective TJA</td>
<td>18</td>
</tr>
<tr>
<td>2.1</td>
<td>Search results and study selection</td>
<td>45</td>
</tr>
<tr>
<td>2.2</td>
<td>Dislocation of index hip arthroplasty within 5y</td>
<td>46</td>
</tr>
<tr>
<td>2.3</td>
<td>Revision of index arthroplasty following total hip replacement</td>
<td>47</td>
</tr>
<tr>
<td>2.4</td>
<td>Revision of index arthroplasty following total knee replacement</td>
<td>48</td>
</tr>
<tr>
<td>3.1</td>
<td>Selection of patients for inclusion</td>
<td>67</td>
</tr>
<tr>
<td>3.2</td>
<td>Cumulative survival curves for the occurrence of a dislocation following THA and infection following TKA, both within two years</td>
<td>68</td>
</tr>
<tr>
<td>4.1</td>
<td>Selection of patients for inclusion</td>
<td>86</td>
</tr>
<tr>
<td>4.2</td>
<td>Surgeon ‘all TJA’ versus ‘RA TJA’ volume</td>
<td>87</td>
</tr>
<tr>
<td>4.3</td>
<td>Log-hazards for occurrence of a surgical complication versus surgeon ‘RA TJA’ volume</td>
<td>88</td>
</tr>
</tbody>
</table>
### List of Appendices

| Appendix 2.1 – | Eligibility criteria for selected studies | 131 |
| Appendix 2.2 – | MeSH keywords and search strategies utilized | 132 |
| Appendix 2.3 – | Assessment of risk of bias | 134 |
| Appendix 2.4 – | Summary of comparative studies reporting hip dislocation following THA | 135 |
| Appendix 2.5 – | Summary of studies reporting hip revision | 136 |
| Appendix 2.6 – | Summary of studies reporting knee revision | 137 |
| Appendix 3.1 – | Diagnostic and procedural codes used to establish the TJA cohorts described in Chapters 3 & 4 | 138 |
I. CHAPTER 1 – INTRODUCTION

Arthroplasty refers to ‘the surgical repair of joints,’ specifically a procedure that remolds or realigns a joint in an effort to preserve or provide a pain-free and functional articulation. In total joint arthroplasty (TJA), the entire joint is replaced with an artificial articulating weight-bearing surface. In addition to providing pain-relief(1-3), TJA also provides a functional range of motion(4, 5), with the aim of improving a patient’s joint-related and overall quality of life(4-6). TJA is the cornerstone of treatment for end-stage arthritis, a stage defined by unacceptable levels of pain and physical dysfunction despite adequate medical management(4, 5). End-stage arthritis may be caused by a number of conditions, including osteoarthritis (OA) and rheumatoid arthritis (RA). TJA is possible for several joints, including the hip, knee, elbow, and shoulder. However, the most commonly replaced joints are the hip (total hip arthroplasty, THA) and the knee (total knee arthroplasty, TKA). Compared with TKA recipients, THA recipients tend to be older, more often male, and less likely to be obese(7, 8). As a result, patient outcomes following TKA and THA, and their predictors differ(9-11).

Regardless, both hip and knee TJA have consistently been demonstrated to provide long-lasting pain relief and substantial and sustained improvement in joint functioning and health-related quality of life(6, 12-17), resulting in reduced arthritis-related health care costs(18). Thus, THA and TKA are considered to be amongst the most successful health care interventions. This success is reflected in the ever-increasing numbers of these procedures being performed worldwide(19). The utilization of primary hip and knee arthroplasty has increased substantially in both the US and Ontario. From 2001 to 2007, an increase in the age & sex standardized rates of both TKA (US – 59%; Ontario – 73%) and THA (25% and 29%, respectively) was documented(20). The median age at which a person has their first TJA is decreasing as well. The largest proportional increase in TJA rates for this same time period was in persons <60 years
of age(20). It is likely that the rates of TJA, both in younger age groups and overall, will continue to increase in tandem with increases in the burden of musculoskeletal disease and the aging population in the developed world(19, 21).

Epidemiology, pathophysiology and treatment of osteoarthritis

Current estimates of the prevalence of arthritis amongst the population >60 years of age in North America vary from 12-15%(22, 23). In Canada, it is estimated that the prevalence of arthritis amongst those >45 years of age will increase to ~16% over the next two decades, representing an additional 6.5 million Canadians with arthritis(21, 24-26). The most common type of arthritis, and the most common indication for TJA, is osteoarthritis (OA). The traditional view of OA was that it was a ‘degenerative condition’ that was a natural consequence of aging. The current understanding of the pathogenesis of OA is that it is a progressive disease of synovial joints that represents failed repair of joint damage resulting from stresses that may be initiated by an abnormality in ANY of the joint tissues (articular cartilage, subchondral bone, ligments, menisci, periarticular muscles, peripheral nerves, synovium), ultimately resulting in the breakdown of cartilage and bone(27, 28). Thus, OA is not so much a single entity but rather the final common pathway of a variety of conditions with distinct causes (genetic, developmental, metabolic, traumatic), but with similar biologic, morphologic and clinical outcomes. Two predominant pathogenetic pathways are exist: biomechanical imbalance between the mechanical forces within a joint and the ability of the joint tissues to withstand these forces(29, 30); and relatively normal loads on a joint characterized by abnormal joint tissues. The former may result a number of factors that negatively impact joint load, including meniscal injury and obesity, while the latter may result from articular cartilage that is biomechanically defective and insufficient to withstand normal load bearing(30-34). The cellular response to these ‘abnormal joint stresses’ results in the pathologic features of OA, which include fibrillation and erosion of
hyaline articular cartilage(35), formation of subchondral cysts, subchondral bone sclerosis, synovial hyperplasia, formation of peri-articular osteophytes, stretching of the articular capsule, a mild synovitis, and weakness of peri-articular muscles(27, 36).

According to guidelines promulgated by the Osteoarthritis Research Society International (OARSI), the treatment of OA spans both non-surgical and surgical modalities, and is directed towards: 1) educating patients about the nature of the disorder and its management, 2) reducing joint pain and stiffness, 3) maintaining and improving joint mobility, 4) reducing physical disability and handicap, 5) improving health-related quality of life, 6) limiting the progression of joint damage(37-41). Non-surgical management of OA can be broadly divided into two categories of roughly equal effect size(40): pharmacological and non-pharmacological. Non-pharmacologic therapies include: aerobic and strengthening exercise(42), muscle strengthening, braces(43, 44), walking aids, physiotherapy(45, 46), heat or cryotherapy, transcutaneous electrical nerve stimulators(47), and acupuncture(40, 48). Manual therapy may improve function (measured as timed walk-tests or stair climbing) in persons with OA, although the results are heterogeneous, with a high rate of attrition(49, 50). Pharmacologic therapies include prescription and non-prescription medications (e.g.: NSAIDs, acetaminophen), and intra-articular injections of either corticosteroids (with or without local anesthetic) or hyaluronic acid(38, 41, 51-59).

Complications following total joint arthroplasty

Total joint arthroplasty (TJA) is the surgical treatment of choice for end-stage OA of the hip or knee, a stage defined by unacceptable levels of pain and physical dysfunction despite appropriate medical management. Primary arthroplasty of the hip (THA) and knee (TKA) are, on average, effective in providing pain relief and improvement in joint functioning and health-
related quality of life(6, 12-17). While the risks of complications following TJA are relatively low (<5%), they are a considerable source of morbidity for the patient, with potentially devastating consequences. Furthermore, these complications are also associated with suboptimal patient-reported outcomes following TJA, which include worsening of pain and/or function(13, 14, 60-65). These surgical complications include:

- Deep vein thrombosis (DVT) or pulmonary embolism (PE): TJA is associated with venous stasis, trauma of the deep veins, liberation of procoagulation factors, and a short period of post-operative immobility (or limited mobility) all of which increase the risk for DVT or PE post-operatively(66, 67). In addition to leading to worse patient-reported outcomes(68, 69), this complication is associated with significant morbidity, and increased risk for death(70, 71). Furthermore, patients who have a DVT or PE post-operatively typically have longer lengths of stay (or may require re-admission) and are more likely to be admitted to the intensive care unit (ICU)(67). The associated medical costs are extensive(72); it is estimated that they raise the cost of the initial admission almost two-fold(67, 73, 74). The average cost of a DVT that occurs after discharge is over $5,000(CDN)(73).

- Superficial or deep infections: Superficial infections occur within 30 days of procedure and involve only the skin or subcutaneous tissue around the incision. If discovered early enough, superficial infections are typically managed with a course of antibiotics (oral or intravenous) and watchful waiting(75, 76). In addition to the risks associated with antibiotic usage (e.g.: hypersensitivity reactions, diarrhea, seizures)(77), the implantation of a peripheral intravenous central catheter (PICC) line to deliver antibiotics, and associated maintenance of the PICC line, is a significant burden for the patient, and is resource-intensive for the system at large(78, 79). These patients also need more frequent follow-up, which adds to the cost(75, 76). Deep surgical infections generally
occur within one year of the procedure, and involve deep soft tissues, such as the fascia and muscles around the replaced joint (80). These can be managed with a lengthy course of intravenous antibiotics (6 weeks to 3 months) and either irrigation and debridement, or staged revision arthroplasty. In the latter, the implanted TJA is removed and is initially replaced with an antibiotic spacer. Then, once the infection has settled, the spacer is replaced with a revision prosthesis (78, 81, 82). Both of these strategies are resource-intensive and a significant source of morbidity for patients (83-85).

- **Prosthesis dislocation**: Dislocation following THA refers to the separation of the femoral component from the acetabular component of the prosthesis (86). In addition to being very painful, and necessitating revision arthroplasty and/or aggressive rehabilitation following closed reduction (87), it is estimated that dislocations increase the hospital costs of a primary THA by over 300% (88). Risk factors for dislocation that have been identified to date include the use of a smaller femoral head component (89, 90), protrusio acetabuli (91, 92), and suboptimal hip abductor strength post-operatively (93), which may result from a posterior surgical approach (94).

- **Peri-prosthetic fractures**: These can occur intra-operatively secondary to implantation of the prosthesis, or post-operatively secondary to a fall or other traumatic event (95, 96).

- **Revision arthroplasty**: Infection, dislocation and peri-prosthetic fracture can all result in the need for revision arthroplasty, wherein the original prosthesis is removed and replaced with what is typically a larger prosthesis (97, 98). Revision arthroplasty can also result from wear on the prosthesis, which typically occurs after 15-20 years. Compared with primary TJA, revision arthroplasty is associated with higher rates of both early and late post-operative complications and thus greater overall costs to the health-care system (99, 100). It is estimated that the mean operative time is ~40% longer for revisions, with
a higher mean estimated blood loss (~150% higher), and a higher mean complication rate (~30% higher) compared with primary TJA procedures(101). In Canada, the average hospital costs (not including physician fees) are $9,000(CDN) and $8,000(CDN) for primary hip and knee replacements, respectively(102). In contrast the average hospital costs for revision hip and knee arthroplasty are ~$11,000(CDN) without infection, and ~$18,000(CDN) if performed secondary to infection(103). The average cost for revision arthroplasty secondary to dislocation is ~$13,000(US), with an additional ~$2,500(US) for each closed reduction(88, 104). Additionally, patients undergoing revision arthroplasty in Canada typically have longer acute care (101, 105-107) and rehabilitation stays(107-109) compared to recipients of primary TJA.

**Risk factors for complications following total joint arthroplasty**

One or more early surgical complications are estimated to occur in approximately 5% of TJA recipients (2-3% are estimated to require early revision surgery)(110). A number of risk factors for early post-operative complications following primary TJA have been identified. These factors can be broadly divided into socio-demographics, co-morbidities, and provider characteristics.

**Socio-demographic factors**

- Age: younger age at the index procedure (defined as <70y of age)(8, 111) has been shown to increase risk for early revision following THA and TKA, after adjusting for potential confounders. The most common hypothesized explanation is that younger patients have increased levels of activity post-operatively, which leads to more rapid wear of the prosthesis(8). Older age is a risk factor for deep vein thrombosis, pulmonary embolism(112, 113), and peri-operative mortality following either THA or TKA(114,
Sex: male sex(8, 116-118) has been shown to be associated with higher rates of revision following TJA, after adjusting for potential confounders, with a proposed explanation that systematically higher levels of post-surgical physical activity in men versus women leads to earlier mechanical failure of the prosthesis(8, 111). Males have previously been found to be at increased risk for infection following trauma(119), elective spine surgery(120), and elective TJA procedures(121). One proposed mechanism is immunosuppression secondary to elevated testosterone and diminished estradiol levels in males following surgery(119).

Lower income has been variably shown to predict increased peri-operative morbidity(122, 123), possibly due to differential access to services and/or knowledge surrounding the signs and symptoms of complications for those with higher versus lower income.

Intra-articular injections with corticosteroids or hyaluronic acid (HA) are used in the non-operative management of hip and knee arthritis(51, 54-59). However, some reports have suggested that intra-articular injection of corticosteroids, particularly in the hip joint, in the year prior to TJA, increases the risk for revision secondary to infection (124, 125).

**Co-morbid conditions**

- Increased co-morbidity has been linked with increased rates of mortality, infection, and revision following TJA, after adjusting for additional potential confounders(8, 117).
- Frailty encompasses a progressive physiologic decline in multiple body systems. Most definitions describe a freestanding syndrome marked by loss of function, strength,
endurance, nutrition and physical activity(126). This decline in physical activity, muscle strength, and immune function, all contribute to an increased risk for fracture or dislocation and infection following TJA(127-130).

Provider characteristics

In the US, lower surgeon and/or hospital volume of arthroplasty cases performed have been linked with worse TJA outcomes (specifically early revision and mortality)(131-133), after adjusting for potential confounders. This relationship has not been demonstrated in Canada(8, 134).

Overall, early surgical complications place an enormous burden on both patients and on health care systems. Thus, the focus of this research was on early surgical complications following TJA. The ‘early’ period has been variably defined in previous studies, ranging from the index admission to 5 years following the surgery(8, 135-139). For this thesis, the ‘early’ period was defined a priori as within 90 days for ‘medical’ complications (death, deep vein thrombosis or pulmonary embolism), and within 2 years for ‘surgical’ complications (superficial or deep infection, joint dislocation, peri-prosthetic fracture, or revision arthroplasty). Furthermore, perceptions around the rates of early post-operative complications, and their associated morbidity play a major role in determining a patient’s willingness to undergo TJA, which in turn is the most important predictor of ultimately having the procedure(140, 141). Therefore, identification and clarification of predictors and mitigating factors for early surgical complications will aid in the decision-making around TJA, specifically helping select patients who are likely to experience significant improvements in pain, function and quality of life, with minimal risk for complications, including revision. This work also informs the patient-physician
conversation around TJA, allowing physicians to educate patients about the risks associated with arthroplasty, and come to a shared decision on proceeding with surgery(141, 142).

**Epidemiology, pathophysiology and treatment of rheumatoid arthritis**

The vast majority of the studies that have identified and delineated these risk factors were conducted in patients with OA. The generalizability of these findings to individuals who undergo TJA for other indications, such as rheumatoid arthritis (RA), is unknown. It is estimated that anywhere from 3% to 13% of TJAs in Ontario are performed in patients with RA(8, 143). Although RA also leads to end-stage arthritis, it is distinct from OA in terms of age at onset of symptoms, etiology, pathogenesis and the agents employed in medical management. RA is a chronic systemic autoimmune disease that affects synovial joints. It affects ~0.8% of the general population in North America (0.3–2.1%), with women affected three times more often than men(144). RA usually presents earlier in life than OA; 80% of RA patients develop the disease between the ages of 35 and 50(144). The articular disease is characterized by a profound synovitis in multiple joints, resulting in pain, swelling, tenderness, and limitation in range of motion – all of which result in physical impairments(145, 146). The characteristic pain of RA originate from stretching and distention of the joint capsule, which occurs secondary to accumulation of synovial fluid, hypertrophy of the synovium, and thickening of the joint capsule(27). To minimize distention, and the resulting pain, patients will maximize joint volume by holding the joint in flexion. Over time, however, this results in fibrous or bony ankylosis and/or soft tissue contractures, leading to fixed deformities. The characteristic long-term joint changes in RA are a result of recurrent bouts of inflammation and swelling. These include: laxity of supporting soft tissues; weakening of ligaments, tendons, and the joint capsule; cartilage destruction; muscle imbalance; and unopposed physical forces associated with the use of affected joints(27, 147). Reflecting the systemic nature of RA, 40% of patients have extra-
articular manifestations, such as vasculitis, pleuropulmonary disease and osteoporosis(148-150). Additionally, RA is an independent risk factor for coronary heart disease; patients with RA have a median life expectancy that is shortened by 3-7 years as a direct consequence of their RA diagnosis(27, 151, 152).

As for OA, the medical management of RA is comprised of pharmacologic and non-pharmacologic therapies. The latter are similar to those used in OA (previously described). The pharmacologic therapy of RA varies by disease severity (presence or absence of poor prognostic factors), and by the duration of the disease (early versus established – generally defined as greater than 6months of duration). Poor prognostic factors include: persistent synovitis, early erosive disease, subcutaneous rheumatoid nodules, positive serum rheumatoid factor and/or anti-CCP autoantibodies, HLA-DR4 carri

ership, family history of RA, poor functional status, elevated acute phase reactants, and increased clinical severity. The mainstay of pharmacologic therapy is the application of disease modifying anti-rheumatic drugs (DMARD)(153). These drugs include methotrexate, sulfasalazine, and hydroxychloroquine(27), and are typically used in combinations of two or three, have been shown to decrease elevated levels of acute-phase reactants, and mitigate the destructive capacity of the disease(149, 154). Treatment with a DMARD(s) should be started as soon as a diagnosis of RA is made. According to guidelines promulgated by the American College of Rheumatology (ACR), patients with early RA should be treated with DMARD monotherapy, specifically methotrexate, particularly if they have low disease activity, or moderate to high disease activity in the absence of poor prognostic features(155). In the presence of poor prognostic features, DMARD combination therapy (double or triple therapy) should be initiated. For patients who fail an adequate trial of methotrexate, the ACR panel recommends initiation of biologic DMARD therapy. These drugs include TNG-neutralizing agents (infliximab, etanercept, and adalimumab), IL-1-neutralizing
agents (anakinra)\(^{(156)}\), those that deplete B cells (rituximab)\(^{(157)}\), and those that interfere with T cell activation (abatacept)\(^{(27)}\). Biologic DMARDs (biologics) have a profound impact on the signs and symptoms of RA, and also help stem the tide of damage to articular surfaces, as assessed radiographically and clinically. In persons with established disease, the ACR recommendations again vary based on the presence or absence of poor prognostic features. All of these medications have potential serious side effects, including increased risk for serious infections and malignancies\(^{(148-150, 158)}\).

**Complication rates following TJA in rheumatoid arthritis versus osteoarthritis**

The fundamental differences between OA and RA in terms of the populations affected, etiopathogenesis and medical management suggest that the results of TJA in patients with OA may not be generalizable to those with RA \(^{(1)}\). However, few studies have examined TJA outcomes specifically in the setting of RA, or have directly compared outcomes of TJA among patients with RA versus those with OA. Higher rates of early revision and/or infection in TJA recipients with RA have been shown in some studies\(^{(159-162)}\), but not in others\(^{(163, 164)}\).

There are several reasons patients with RA may be at higher risk of early complications following TJA than recipients with OA. DMARDs, systemic corticosteroids and biologics all work by immunomodulation, and have been linked with poor wound healing and increased risk of infection post-operatively\(^{(165-168)}\). Additionally, the systemic nature of RA can result in multiple co-morbidities\(^{(169-172)}\), and may contribute to post-operative mortality. There are several surgical challenges in persons with RA relative to those with OA that may increase the risk for complications in these patients. In addition to severe synovitis\(^{(173, 174)}\), patients with RA have more delicate soft tissues\(^{(175-177)}\) relative to patients with OA, with weaker tendons\(^{(178)}\), ligaments\(^{(173, 174)}\), and bone-tendon attachments\(^{(179, 180)}\). Patients with RA are also more likely to have osteopenic bone\(^{(181-183)}\), and altered peri-articular bony
anatomy (91, 92, 184, 185). These anatomic differences have implications for soft tissue handling, joint alignment, implant fixation, and successful joint mechanics following TJA. Furthermore, the previously described predictors of early complications, and protective factors, may be different for recipients with RA than for those with OA. For example, as noted above, young age has been identified as a risk factor for revision arthroplasty secondary to increased activity relative to elderly recipients. While RA patients may be younger than those with OA by the time they reach end-stage arthritis, they may also be less active than the latter due to the polyarticular nature of the disease. As such, their young age may not lead to an increased risk of revision. Additionally, increased surgeon TJA volume may not have as strong a protective benefit in persons with RA. Rather, this benefit may be conferred by specific experience performing TJA in persons with RA. Thus, it is important to delineate if TJA recipients with RA are at increased risk for complications relative to those with OA, and if there are specific factors associated with an increased or decreased risk for complications in TJA recipients with RA.

**Data sources utilized to compare complication rates following TJA between RA and OA**

Studies that have attempted to determine if there is a differential risk for complications in TJA recipients with RA versus those for OA have used various data sources, including: 1) clinical cohorts, 2) arthroplasty registries, and 3) administrative databases. Although the information that is captured and the quality of the data vary significantly, there are a few generalizations that illustrate the advantages and disadvantages of each data source. Clinical cohorts usually carry in-depth information for each TJA recipient, including baseline function, health-related quality of life and the underlying arthritis diagnosis (typically provided by the referring physician). However, as the rate of complications following TJA is low (<2%), these cohorts are often inadequately powered to delineate the relationship between arthritis diagnosis and occurrence of complications. This is not an issue with arthroplasty registries, which typically collect
information from several centres in a large geographical area (e.g.: Swedish Hip Arthroplasty Register). However the information collected tends to be focused on technical aspects of the procedure (e.g.: implant type, use of bone cement, antibiotic prophylaxis, DVT prophylaxis, etc), as opposed to patient factors (demographics, or data on baseline pain, function, quality of life, or co-morbidity). The underlying diagnosis is typically recorded by the surgeon, but unfortunately this may not be accurate as the joint may have an appearance more consistent with OA, and be recorded as such(186).

The use of administrative databases offers several advantages over clinical cohorts and arthroplasty registries. These databases are population-based, and therefore broadly representative, with less selection bias than a clinical cohort. They are more likely to have accurate demographic data, and they allow for long-term follow-up irrespective of further patient contact. The main concern with administrative databases is the accuracy of the data, particularly around co-morbid conditions. It has been demonstrated that there is a high false-negative rate for co-morbid conditions, and that the quality of coding is improved in teaching hospitals versus community hospitals(187). Furthermore, these databases were established to serve billing purposes, not to answer specific research questions; as such, they do not have the rich patient-level information available in clinical cohorts (such as body-mass index and smoking status), or the technical information available in arthroplasty registries. Studies utilizing administrative databases are more likely to be overpowered, which can promote statistical significance over clinical relevance. Finally these databases utilize diagnostic codes to identify persons with RA, but without appropriate re-abstraction and validation, the diagnosis may be inaccurate(188). The misclassification of diagnoses between RA and OA would reduce the ability to find differences between these groups(189, 190).
Overview of the thesis

The overall objective of this research was to determine if persons with RA are at greater risk for complications following TJA relative to recipients with OA. And, in cases where higher complication rates are found, to identify risk factors that may be modifiable through changes in care and care processes. This work will potentially provide information to enhance TJA outcomes in this population. An outline of the dissertation, including brief synopses of the problems and specific objectives of each of the three papers, is provided below.

Chapter 2.

PAPER 1: A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY FOR RHEUMATOID ARTHRITIS VERSUS OSTEOARTHRITIS

This paper quantitatively and qualitatively synthesizes the existing evidence on the relative risk for complications following TJA in persons with RA versus those with OA. It also systematically gauges the quality of this research, and identifies study limitations (such as misclassification bias or lack of adjustment for confounders) that may have affected the authors’ ability to characterize the difference in outcomes, if any, between these groups.

Description of the problem

Most of the evidence regarding complications following total hip arthroplasty (THA) and total knee arthroplasty (TKA) is based on studies of patients with osteoarthritis (OA), with little being known about outcomes in patients with rheumatoid arthritis (RA). This lack of clarity regarding outcomes following arthroplasty, and their determinants, in patients with RA impedes patient-physician decision-making regarding when, and in which RA patients, TJA should be considered.
Objective

The objectives of this study were (1) to compare the odds of complications following THA and TKA in patients with RA versus OA, using meta-analysis and systematic literature review; and (2) to identify specific actionable limitations in methodology that may have militated the ability of previous investigators to draw conclusions.

Chapter 3.

PAPER 2: PATIENTS WITH RHEUMATOID ARTHRITIS ARE AT INCREASED RISK FOR COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY

This paper reports the results of a large, population-based, retrospective cohort study that utilized administrative data to compare the complication rates following THA and TKA in patients with RA versus those with OA.

Description of the Problem

Most of the evidence regarding complications following joint replacement is based on studies of patients with osteoarthritis (OA). Previous studies have that examined the relative risk of complications in patients with rheumatoid arthritis (RA) versus OA have been limited methodologically. Specifically, the vast majority (>90%) of these studies used variable definitions for RA diagnosis, in most cases no definition at all, which raises concerns about misclassification bias. Some studies combined primary and revision procedures, which limited their generalizability. Finally, there was variable adjustment for confounders, with several studies not accounting for the systematic differences between RA and OA patients. The current study sought to overcome the limitations of prior studies by capitalizing on the availability of a
recently validated algorithm for RA using administrative data. No previous study of this size has utilized a validated definition for RA, with extensive control of potential confounders.

**Objective**

To compare the rates of surgical complications, following THA and TKA in recipients with RA versus OA, after controlling for potential confounders and for clustering by surgeons.

**Chapter 4.**

**PAPER 3: INCREASED SURGEON EXPERIENCE WITH RHEUMATOID ARTHRITIS REDUCES THE RISK OF COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY**

This paper reports the results of a retrospective cohort study, utilizing administrative data, comparing the impact of surgeon TJA volume versus TJA volume specifically in patients with RA, on the rates of complications following TJA in persons with RA.

**Description of the problem**

Volume-outcome relationships have been demonstrated for total joint arthroplasty (TJA), with the risk for surgical complications roughly inversely proportional to the annual surgeon volume (defined as the number of cases performed by the surgeon in the year prior to the surgery). However, most of this research focused on patients with osteoarthritis (OA), and may not apply to patients with rheumatoid arthritis (RA), who pose several unique surgical challenges. In addition to severe synovitis, patients with RA have more delicate tissue relative to patients with OA, with weaker tendons, ligaments, bone-tendon attachments, and osteopoenic bone. These anatomic differences have implications for soft tissue handling, joint alignment, and implant fixation. They all potentially contribute to an increased risk for surgical complications post-
operatively. The particular challenges in this subgroup of patients may require specific experience on the part of the surgeon to mitigate these risks – increased TJA volume overall may not suffice.

**Objective**

We set out to determine if specific experience on the part of the surgeon with respect to performance of TJA procedures in patients with RA has a protective benefit above that provided by high surgeon TJA volume overall (i.e. regardless of the patient’s underlying diagnosis).

**Chapter 5. DISCUSSION**

This chapter will provide an overview of the conclusions from the three papers that make up the body of this thesis, will discuss the implications of our research findings, and provide suggestions for future research. This chapter will be divided into three sections: 1) a description of the contributions to the literature of each of the three papers; 2) a summary of potential strategies to address the differential risk for complications following TJA based on arthritis type; 3) a summary of the results of the thesis.
**Figure 1.1:** Conceptual framework relating arthritis type to the occurrence of a complication following primary elective TJA

**Main exposure:** Arthritis type (e.g.: osteoarthritis, rheumatoid arthritis)

**Outcome:** occurrence of a complication (within 90d: DVT/PE, death; within 2y: infection, dislocation, periprosthetic fracture, revision)

- **Blue outline:** potential mediators of effect between arthritis type and occurrence of a complication
- **Red outline:** factors known to be associated with the outcome, but not known to be associated with the main effect
- **Green outline:** potential confounders that are related to the main effect and the outcome
II. CHAPTER 2 – A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY FOR RHEUMATOID ARTHRITIS VERSUS OSTEOARTHRITIS

Bheeshma Ravi¹
Benjamin Escott¹
Prakesh S Shah²
Richard Jenkinson¹
Jas Chahal¹
Earl Bogoch¹
Hans Kreder¹,²
Gillian Hawker²,³

From the ¹Department of Surgery, Division of Orthopaedic Surgery, and the ²Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada. As well as the ³Division of Rheumatology, Department of Medicine, Women's College Hospital, Toronto, Canada.

Published in Arthritis & Rheumatism (2012 Dec;64(12):3839-49. doi: 10.1002/art.37690.)
ABSTRACT

Objective: Most of the evidence regarding complications following total hip arthroplasty (THA) and total knee arthroplasty (TKA) is based on studies of patients with osteoarthritis (OA), with little being known about outcomes in patients with rheumatoid arthritis (RA). The objective of the present study was to review the current evidence regarding rates of THA/TKA complications in RA versus OA.

Methods: Data sources used were Medline, EMBase, Cinahl, Web of Science, and reference lists of articles. We included reports published between 1990 and 2011 that described studies of primary total joint arthroplasty of the hip or knee and contained information on outcomes in ≥200 RA and OA joints. Outcomes of interest included revision, hip dislocation, infection, 90-day mortality, and venous thromboembolic events. Two reviewers independently assessed each study for quality and extracted data. Where appropriate, meta-analysis was performed; if this was not possible, the level of evidence was assessed qualitatively.

Results: Forty studies were included in this review. The results indicated that patients with RA are at increased risk of dislocation following THA (adjusted odds ratio 2.16 [95% confidence interval 1.52-3.07]). There was fair evidence to support the notion that risk of infection and risk of early revision following TKA are increased in RA versus OA. There was no evidence of any differences in rates of revision at later time points, 90-day mortality, or rates of venous thromboembolic events following THA or TKA in patients with RA versus OA. RA was explicitly defined in only 3 studies (7.5%), and only 11 studies (27.5%) included adjustment for covariates (e.g., age, sex, and comorbidity).

Conclusion: The findings of this literature review and meta-analysis indicate that, compared to patients with OA, patients with RA are at higher risk of dislocation following THA and higher risk of infection following TKA.
INTRODUCTION

Rationale

Total joint arthroplasty (TJA) is considered one of the most successful health care interventions for end-stage arthritis of the hip or knee (6, 9, 191). Estimates of cost-utility consistently rank TJA at or near the top among medical and surgical interventions for cost-effectiveness and patient satisfaction (4, 5, 192). This success is reflected in the increasing rates of total hip arthroplasty (THA) and total knee arthroplasty (TKA). Outcomes following THA and TKA are generally excellent, with low complication rates. However, some complications have significant consequences, including: early revision, infection or dislocation, venous thromboembolism (VTE) and death (8, 193-196).

The vast majority of THA and TKA procedures are performed for osteoarthritis (OA), which is the most common form of arthritis (197, 198). Thus, most of the literature regarding outcomes of TJA, and their predictors, is based on the experience of patients with OA. Among the inflammatory arthritides, rheumatoid arthritis (RA) is the most common. RA affects ~0.8% of the population of North America (0.3–2.1%); 80% develop RA between the ages of 35 and 50 (199, 200). As for OA, TJA is indicated for the management of end-stage hip and knee arthritis in RA. Estimates of the prevalence of RA amongst TJA recipients vary considerably, in part because of the difficulty in accurately establishing this diagnosis using arthroplasty registries. However, a recent study which evaluated the past medical history of TJA recipients in Ontario, Canada found that ~13% of these recipients had RA (8), translating to ~170,000 TJAs from 2002-2010.

As RA is a fundamentally different condition from OA in terms of etio-pathogenesis, prognosis and medical management, systematic differences in TJA outcomes would be expected (201).
However, few studies have examined the outcomes of TJA for patients with RA, or their predictors, including whether or not there are differences in outcomes for patients with RA versus OA. Those that have, have reported conflicting results. For example, Stea (2009) reported a higher risk for revision following THA for RA versus OA patients, whereas Rud-Sorensen (2010) and Furnes (2001) found no difference (163, 202, 203). This lack of clarity regarding TJA outcomes, and their determinants, in patients with RA impedes patient-physician decision-making regarding when, and in which RA patients, TJA should be considered.

**Objective**

Our primary objective was to compare odds of complications following THA and TKA for patients with RA versus OA using meta-analysis or systematic review of the literature.

**METHODS**

**Protocol**

This review was conducted using a pre-defined protocol and in accordance with guidelines suggested for Meta-analyses of Observational Studies in Epidemiology (204).

**Eligibility criteria**

The eligibility criteria for inclusion are shown in Appendix 2.1.

Participants: Ambulatory adult patients (18y or older) with RA or OA were included in this review. We included studies reporting data on RA patients in comparison with OA; the criteria used to establish the RA diagnosis were recorded, where available. For studies that utilized diagnostic codes for RA from administrative databases or arthroplasty registers, we recorded if
any information was provided on the validity of these diagnostic codes. We excluded TJA performed secondary to fracture, malignancy, “juvenile RA,” or post-traumatic arthritis.

Studies: We included peer-reviewed cohort, case-control or case series published from 1990 (to more closely reflect current clinical practice) through December 2011 that examined primary TJA of the hip or knee. We excluded studies on partial knee arthroplasty, hip hemiarthroplasty, and hip resurfacing. We limited our selection to studies that examined outcomes in both OA and RA patients, and described results in at least 200 joints. We chose this sample size to have sufficient statistical power to evaluate the effect of multiple factors on rare outcomes, such as death or revision. Studies examining revision rates and those examining peri-operative complications were required to have at least 1 year and 90d of follow-up, respectively. We did not include annual reports from arthroplasty registries unless they were published in a peer-reviewed journal. We did not include meeting abstracts, as they did not include enough information to assess for bias. We excluded editorials, commentaries, letter to editors and reviews but they were read to identify any potential articles. We e-mailed the corresponding authors of each paper selected for inclusion to clarify any details, and to request access to patient-level data.

Outcomes: Studies reporting on any of the following TJA complications in patients with RA in comparison with complication rates in patients with OA, were evaluated: 1) revision, defined as exchange of any or all of the components secondary to any cause; 2) Infection of the arthroplasty requiring therapy with antibiotics (any route) or surgery; 3) Dislocation following THA; 4) mortality within 90 days of operation, for any reason; and 5) Venous thromboembolism (VTE) within 90 days of the surgery.
Information sources and search strategy

With the aid of an experienced librarian, we searched 4 bibliographic databases (MEDLINE, EMBASE, CINAHL, Web of Science) without language restriction from January 1990 to December 2011. Medical Subject Headings (MeSH) and keywords used for the search are shown in Appendix 2.2. We also reviewed the bibliography of included studies.

Study selection

Two authors (BR, BE) reviewed the titles of all citations generated by the literature search, and removed any that did not discuss THA or TKA. We reviewed the abstracts of the remaining studies, and removed those that did not discuss RA, or inflammatory arthritis. Thirty-eight abstracts that were not available online or at the University of Toronto libraries; all were from non-English journals and were excluded from the review. Two additional researchers (RJ, JC) independently reviewed all excluded citations to determine appropriateness of exclusion. Three citations were found to be inappropriately excluded and were restored. The abstract of each remaining citation was assessed (BR, BE) for its primary outcome and sample size. We excluded articles that did not examine at least one of our outcomes of interest, or if they did not meet our sample size requirements.

Data collection process and data items

The complete manuscripts of the 217 eligible citations were assessed by three authors (BR, BE, RJ) for data abstraction. At least two reviewers, who were not blinded to citation identifiers, independently abstracted data from each article. In brief, for each study, we determined: number of replaced joints (RA and OA), number of centers, outcome measure, mean follow-up, criteria used to establish arthritis diagnosis, and the type of implant(s) used. Discrepancies were resolved by consensus. Table 2.2 summarizes the data from each manuscript. We excluded 173
studies that did not stratify their outcome measure by arthritis diagnosis. For all selected studies, we attempted to contact the corresponding author for additional study details.

**Assessment of risk of bias**

For each included study, risk of bias was evaluated using published validity criteria (205). The domains included: case definition (i.e.: RA/OA classification), patient selection, follow-up, outcome assessment, and analyses. An additional criterion assessed data validation for database studies (Appendix 2.3)(9). Articles with scores of ≥10 were classified as having a ‘low’ risk of bias, scores of 7 to 9 indicated ‘moderate’ risk, and scores of ≤6 indicated ‘high’ risk of bias.

**Summary measures**

Studies were stratified by the joint replaced (hip vs. knee), outcome of interest, and by duration of follow-up. For revision, we stratified follow-up into three periods: early (≤5 years), middle (6-10 years), and late (>10 years). Where possible, studies were also stratified by the type of prosthesis and the use of bone cement. Studies were evaluated within each group to determine if meta-analysis was feasible and appropriate. If appropriate, meta-analyses were performed using random effects models using the Review Manager software (version 5.1). Meta-analytic estimates of proportion, unadjusted odds ratio [UAOR], adjusted odds ratio [AOR], adjusted relative risk [ARR], unadjusted relative risk [UARR]) were reported with 95% confidence intervals (CIs). For studies that provided adjusted estimates, but also provided information on the number of patients with OA and RA for both the treatment and outcome, unadjusted estimates were calculated for pooling with other unadjusted estimates. The relative weight of each individual study in the meta-analysis was calculated based on the inverse of variance. Clinical heterogeneity among studies was assessed based on clinical criteria described above. Statistical heterogeneity was assessed using I-squared statistics. Where meta-analysis was not
appropriate, a systematic review of relevant studies was conducted with the overall direction of evidence summarized qualitatively.

**Synthesis of results**

Evidence based on meta-analysis was assumed to be ‘good’ if there was adjustment for potential confounders, and ‘fair’ if adjustment was not performed. For outcomes where meta-analysis was not possible, two reviewers independently graded the overall strength of the evidence as good, fair, inconsistent or insufficient (Table 2.1). A third reviewer resolved any differences. Grades were assigned using three criteria: quality, quantity and consistency of findings. Quality was assessed based on the study’s risk of bias, as defined above. Quantity was assessed based on the number of studies that evaluated each risk factor. Consistency was assessed based on similarity of findings reported across a range of study populations and study designs. The findings are reported using the PRISMA guidelines(206).

**Risk of bias across studies**

We set out *a priori* to assess publication bias via funnel plot asymmetry only for meta-analyses with 10 or more studies(186).

**RESULTS**

*Study selection & quality of included studies*

The results of the search, the study selection log, and the number of studies are shown in Figure 2.1. Forty studies were included in this review. The results of the assessment of the overall risk of bias for included studies are reported in Table 2.2. Seventeen studies had low risk of bias, 17 had moderate risk, and 6 had a high risk of bias. We were unable to obtain patient-level data for
any of the studies selected for inclusion. Funnel plots were not assessed for asymmetry as none of our meta-analyses included ten or more studies.

**Hip Dislocation**

Five studies compared the rates of hip dislocation in patients with RA versus OA within 5 years of THA (risk for bias: 4 moderate, 1 high) (Appendix 2.4). Meta-analysis of five studies that reported unadjusted comparative data revealed an increased risk of hip dislocation within 5 years of THA in patients with RA relative to those with OA [UAOR 2.74; 95CI 1.73, 4.34; 2,842 RA, 61,861 OA patients; $I^2 = 27\%$] (Figure 2.2a). This increased risk was also found after meta-analysis of four studies that reported comparative data, adjusted for several variables (including age, sex, surgical approach, and surgeon-volume) [adjusted OR 2.16; 95CI 1.52, 3.07; 1,637 RA, 61,810 OA patients; $I^2 = 0\%$] (Figure 2.2b).

**Hip Revision**

Fifteen studies reported on THA revision (risk for bias: 9 low, 5 moderate, 1 high) (Appendix 2.5).

**Hip revision ≤ 5 y**

Meta-analysis of four studies that reported unadjusted comparative data revealed increased odds of early revision for RA versus OA patients [UAOR 1.33; 95CI 1.03, 1.71; 3913 RA, 76,098 OA patients; $I^2 = 6\%$] (Figure 2.3a). However, a study that adjusted for age, sex, and comorbidity did not find increased odds of revision within 1 year of THA in patients with RA [adjusted OR 1.11; 95CI 0.82, 1.51; 3,805 RA, 23,412 OA patients](8).

**Hip revision at 6-10 y**
Meta-analysis of seven studies revealed no difference in the unadjusted odds of revision at 6-10 years for RA versus OA overall [UAOR 1.16; 95CI 0.94, 1.43; 9,118 RA, 210,674 OA patients; $I^2 = 46\%$] (Figure 2.3b). Allami (2006) also found no difference in the unadjusted risk of revision at 10y [unadjusted HR RA versus OA 3.33; 95CI 0.45, 24.5](207). Similarly, meta-analysis of two studies that adjusted for age and gender (among other covariates) found no difference in the risk of revision following THA between RA and OA [adjusted RR 0.91; 95CI 0.74, 1.11; 2,110 RA, 88,103 OA patients; $I^2 = 86\%$]. Similarly, Furnes (2001) found no difference in the odds of revision after adjusting for age, sex, and type of prosthesis [adjusted OR 1.10; 95CI 0.90, 1.35](202).

**Hip revision at >10y**

Meta-analysis of two studies revealed lower unadjusted odds of late revision in RA vs. OA patients for cemented implants [UAOR 0.28, 95%CI 0.17-0.47; 229 RA, 1,710 OA patients; $I^2 = 0\%$](Figure 2.3c).

**Knee Revision**

Eleven studies reported on knee revision (risk for bias: 4 low, 4 moderate, 3 high) (Appendix 2.6).

**Knee revision ≤5y**

Meta-analysis of three studies indicated slightly increased odds for early revision in patients with RA versus OA [UAOR 1.24; 95CI 1.10, 1.40; 8,974 RA, 35,274 OA patients; $I^2 = 0\%$] (Figure 2.4a). Himanen (2005) found no difference in revision at 4y [UARR 1.25, 95CI 0.87, 1.8](208). Paterson (2010) controlled for potential confounders (age, sex, co-morbidity, provider volume) and found no significant difference in revision rates at 1y [adjusted OR 1.08, 95 CI
Knee revision at 6-10y

Meta-analysis of six studies revealed no difference in the odds of revision at 6-10 years between RA and OA [UAOR 2.02; 95CI 0.96, 4.28; 3,116 RA, 29,670 OA patients; $I^2 = 69\%$] (Figure 2.4b). This was not affected by stratification by prosthesis type: cruciate-retaining [UAOR 3.90; 95CI 0.46, 33.17; 235 RA, 1,171 OA patients] or posterior-stabilized prostheses [UAOR 1.11; 95CI 0.56, 2.18; 298 RA, 6,743 OA patients]. Schrama (2010) looked specifically at revision due to infection after 6y of follow-up, and found an unadjusted RR of 1.6 [95CI 1.06, 2.38](164).

Knee revision at >10y

Meta-analysis of two studies that reported unadjusted comparative data for cemented implants revealed no difference in late revision between RA and OA [UAOR 2.46; 95CI 0.71, 8.92; 297 RA, 256 OA patients; $I^2 = 50\%$] (Figure 2.4c). No studies were identified that provided adjusted estimates.

Infection

Five studies compared the rates of index joint infection in patients with RA versus OA following TJA (risk for bias: 2 low, 2 moderate, 1 high) (Table 2.2). Meta-analysis was not possible due to variable definitions of infection and pre-operative antibiotic protocols (with some centers forgoing antibiotics altogether), and pooling of primary and revision arthroplasty cases. Controlling for age, sex, prosthesis type, and antibiotic cement, Jamsen (2009) reported that patients with RA had an adjusted HR of 1.86 [95CI 1.31, 2.63] for infection following TKA relative to OA(209). Uncontrolled for other factors, Wymenga (1992) found that RA increased
the risk of infection following TKA compared to recipients with OA [UARR 4.8, 95%CI 1.2-19](210). Bongartz (2008) matched 402 RA patients (primary and revision THA/TKA) to patients with OA by age, time of surgery, sex, and site of surgery(159). Compared with matched OA controls, RA patients had higher odds of infection in the first year [OR 10.30; 95CI 1.31, 80.26]. Among those with RA, increased infection risk was associated with: prior infection in the replaced joint, prior infection in any joint, and longer duration of operating time [HR 1.36 per 60-minute increase; 95CI 1.02, 1.81]. No association was found with peri-operative systemic corticosteroid use [HR 1.28; 95CI 0.46, 3.60], or withdrawing biologics prior to surgery [HR 0.65, 95CI 0.09, 4.95].

**Mortality within 90 days of TJA**

Four studies reported on mortality following TJA (risk of bias: 1 low, 3 moderate) (Table 2.2). Meta-analysis of two studies revealed no difference in the odds of mortality within 90d of THA [adjusted OR 1.40; 95CI 0.82, 2.39; I² = 68%]. Similarly, meta-analysis of two studies examining rates of death within 90d of TKA found no difference between RA and OA [adjusted OR 0.86; 95CI 0.66, 1.12; I² = 0%]. Gill (2003) reported 14 deaths within 90d of surgery among 2994 TKAs (2871 OA + 177 RA); with all the deaths occurred in patients with OA(195).

**Venous thrombo-embolism within 90 days of TJA**

Five studies reported on VTE following TJA (risk of bias: 3 low, 2 moderate) (Table 2.2). Meta-analysis of two studies revealed no difference in the odds of VTE within 90d of THA in patients with RA versus those with OA [adjusted OR 0.84; 95CI 0.28, 2.54; I² = 85%]. Similarly, White (1990) found that the unadjusted rates of in-hospital VTE, was similar for RA and OA (p=0.07)(211). Niki (2010) found no difference in the rates of proximal DVTs on routine
ultrasound performed 7 days after TKA in patients with RA versus OA [UAOR 0.81; 95CI 0.26, 2.52].

DISCUSSION
To our knowledge, this is the first systematic review to assess rates of complications following THA and TKA in patients with RA versus OA. In this review of 40 studies, we found strong evidence for increased risk for hip dislocation following THA, and fair evidence for an increased risk of infection following TKA, in patients with RA versus OA. We also found fair evidence for an increased early revision risk following TKA, but no evidence to support any differences in later revision rates, 90d mortality, or rates of VTE following THA or TKA in patients with RA versus OA.

The increased risk of dislocation following THA in patients with RA versus OA was an unexpected finding, which, to our knowledge, has not been well appreciated previously, possibly due to the lack of meta-analysis. Susceptibility to dislocation could be the result of poorer soft tissue quality in RA relative to OA, resulting in suboptimal hip abductor strength post-operatively. Other potential explanations include systematic differences in surgical approach, head size, or use of bone cement between groups. However, Khatod (2006) adjusted for surgical approach as well as head size, and still noted an increased risk for dislocation for RA patients(212). Further research is warranted to confirm this finding and elucidate potential modifiable risk factors such as head size, surgical approach, or use of cement.

It makes intuitive sense that risk of infection following TJA would be increased in patients with RA versus OA due to differences in the pathogenesis and medical management of these conditions. As a systemic autoimmune disease, RA is typically managed with
immunosuppressive agents, including systemic corticosteroids, methotrexate, anti-malarials, and more recently biologics, e.g. adalimumab and etanercept (213-215). Evidence around the impact of these medications on the rate of infection post-operatively is inconsistent (214, 216). Our review found fair evidence to support an increased risk of infection following TKA in patients with RA versus OA. Three of four studies showed an increased risk for infection following TKA in patients with RA, and two of these studies had a low risk of bias. This is consistent with our finding that RA patients had higher odds of revision within 5 years of TKA (although this did not adjust for confounders). Only one study found an increased risk of infection following THA in patients with RA, and this study had a low risk of bias (159). Bongartz (2008) also found that peri-operative systemic corticosteroid use and withdrawing biologics prior to surgery did not have any impact on the rate of infection following THA or TKA in patients with RA (159). However, most of the studies did not comment on the role of drug use on the rate of infection following arthroplasty. Our review has identified the need for larger studies to confirm these findings, and if confirmed, to determine the impact of specific medical therapies and other factors on risk of infection in RA.

Although dislocation rates were higher following THA in RA than OA, this was not reflected in an increased rate of early revision following THA. Potential explanations for this observed disparity include: 1) systemic differences in the management of dislocations between RA and OA, with the former being preferentially managed with closed reduction and activity modification due to either surgeon or patient preference (217); or 2) an increased early revision rate in RA does exist, but does was not observed in our study due to lack of power.

We also did not find a difference between RA and OA in terms of 90d mortality or VTE following THA or TKA. However, as the reported risk for these complications is low, the
studies reviewed may have been inadequately powered to detect significant differences in rates for patients with RA versus OA.

RA can be a challenging diagnosis to establish clinically, particularly early on in the disease(218). Only 3 of 40 (7.5%) studies discussed the process by which the diagnosis of RA was established. One of these used the American College of Rheumatology (ACR) criteria, and the other two used a referral diagnosis from an internist or rheumatologist. There were 16 (40%) studies that utilized administrative databases or arthroplasty registries to establish the diagnosis of RA. Only one of these provided information on the validity of these codes. The data in administrative databases are typically collected for non-research purposes, and without appropriate re-abstraction and validation, the diagnosis may be inaccurate(188). Even a diagnosis recorded by the surgeon intra-operatively may be inaccurate as the index joint may have an appearance more consistent with OA, and be recorded as such(186). While these patients may have joint and/or bone characteristics more similar to OA, they will still have the other risk factors for complications associated with RA, and should be classified as such. The misclassification of RA patients as having OA would reduce our ability to find differences between these groups. Thus, we may have underestimated differences in TJA outcomes between OA and RA, where they exist.

Despite the large numbers of patients included in the studies reviewed, variable adjustment for confounders limited our ability to pool results, and ultimately lowered our statistical power. Most of the studies reviewed (29/40 or 72.5%) did not, or were inadequately powered to, adjust for potential confounders, including age, sex and co-morbidity. It has been established that younger patients (<70y) have a higher revision rate following TJA, hypothesized to be due to increased activity leading to wearing out of the prosthesis(111). While this assumption may not
apply to younger patients with RA, who may have more activity-limiting polyarticular joint involvement than patients with OA at a comparable age, lack of control for the effect of age is a significant limitation (219). Increased co-morbidity, including specific conditions such as diabetes, are associated with early infection and subsequent revision, while cardiovascular disease may increase the risk for mortality following TJA (220). RA is a systemic disease characterized by an increased risk for cardiovascular disease (221), while OA is associated with a high co-prevalence of obesity, diabetes, hypertension and heart disease (222, 223). Although our focus was on elective primary TJA procedures, where patients are typically medically fit for surgery, the presence of co-morbid contribute to differential risks for TJA complications in patients with RA versus OA. Adequate consideration of, and control for co-morbidity is warranted in future studies examining the rates of revision, and other complications in RA versus OA patients.

Since none of our meta-analyses pooled together ten or more studies, we did not assess funnel plots for asymmetry. However, we did assess differences between studies via the I² values, which describe the percentage of total variation across studies that is due to heterogeneity rather than chance (224). I² values of 25%, 50% and 75% are considered low, moderate, and high, respectively. We had a broad range of I² values (0-85%), although most of our meta-analyses (8/11) had values of 50% of less. This degree of heterogeneity is consistent with our pooling of studies that utilized a diverse set of implants, variable surgical approaches and techniques, and variable use of diagnostic criteria to define RA versus OA.

In summary, compared with TJA recipients with OA, we found that those with RA were at higher risk of dislocation following THA, and higher risk for infection following TKA. However, after adjustment for covariates, we found no difference regarding risk for revision,
90-day-mortality, or VTE within 90 days of either THA or TKA. Adequately powered studies, which incorporate validated definitions for RA and OA diagnosis and control for appropriate confounders and other covariates, are required to confirm these findings. Where differences are confirmed, further research is warranted to elucidate potential explanations, including the role of prosthesis type, medication use (e.g. biologic therapies), co-morbidity, and bone quality. The results of such studies would be useful to guide decision-making regarding TJA in the setting of RA.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Good evidence for or against an association between the complication and RA</td>
</tr>
<tr>
<td></td>
<td><em>Determined by:</em> consistent results across studies; &gt; three studies; at least one study graded as ‘low’ bias</td>
</tr>
<tr>
<td>Fair</td>
<td>Fair evidence for or against an association between the complication and RA</td>
</tr>
<tr>
<td></td>
<td><em>Determined by:</em> consistent results across studies but limited by quantity (three studies) or quality (no studies graded as ‘low’ bias)</td>
</tr>
<tr>
<td>Inconsistent</td>
<td>Inconsistent evidence for or against an association between the complication and RA</td>
</tr>
<tr>
<td></td>
<td><em>Determined by:</em> studies had conflicting results</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Insufficient evidence for or against an association between the complication and RA</td>
</tr>
<tr>
<td></td>
<td><em>Determined by:</em> inadequate number of studies evaluating the risk factor (&lt; three studies)</td>
</tr>
</tbody>
</table>
Table 2.2: characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allam (2006) (207)</td>
<td>THA revision</td>
<td>1990</td>
<td>RA: not described</td>
<td>OA: not described</td>
<td># of hospitals: 22. Trent regional arthroplasty study</td>
<td>Survival defined as:</td>
</tr>
<tr>
<td>JBJS (B) 88(10):1293–8</td>
<td># of patients: 1198 (1042 OA + 84 RA)</td>
<td></td>
<td>Follow-up: 10y</td>
<td>- RA: HR 3.33 (95CI 0.45-24.5); p=0.24 (ref OA)</td>
<td></td>
<td>Case definition: 2 (as per database)</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Implants: cemented, Charnley</td>
<td></td>
<td></td>
<td>Patient selection: 2</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Approach: lateral or transtrochanteric</td>
<td></td>
<td></td>
<td>Follow-up: 2</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Outcomes: survival</td>
<td></td>
<td></td>
<td>Outcome: 2 (revision)</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA:  </td>
<td></td>
<td></td>
<td>Analysis: 3 (multivariate)</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- OA: 307 hinged</td>
<td></td>
<td></td>
<td>Database: 1 (no mention of validation)</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA: 594 hinged</td>
<td></td>
<td></td>
<td>Total: 12/13 (low risk)</td>
</tr>
<tr>
<td>Bongartz (2008) (159)</td>
<td>THA infection</td>
<td>1975-1985</td>
<td>RA: diagnostic code</td>
<td>OA: diagnostic code</td>
<td># of hospitals: multiple, Swedish register</td>
<td>Revision defined as:</td>
</tr>
<tr>
<td>Acta Orthopaedica Scandinavica 62(4): 301-311</td>
<td></td>
<td></td>
<td># of patients: 11,777 TKA (7,534 OA + 4,243 RA)</td>
<td></td>
<td></td>
<td>- Revision of acetabular component and/or</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Follow-up: median 6y (mean flu not provided)</td>
<td></td>
<td></td>
<td>- Revision of femoral component</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Implants: hinged and non-hinged</td>
<td></td>
<td></td>
<td>- Any re-operation on the index hip</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- OA: 307 hinged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA: 594 hinged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Prophylaxis:</td>
<td></td>
<td></td>
<td>Deep infection defined as:</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Systemic antibiotics: 229 cases</td>
<td></td>
<td></td>
<td>- One of:</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Antithrombotic cement alone: 12 cases</td>
<td></td>
<td></td>
<td>- Sinus from joint or adjacent bone,</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Systemic + cement: 63 cases</td>
<td></td>
<td></td>
<td>- Three or more positive intra-operative biopsies</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Outcomes: infection</td>
<td></td>
<td></td>
<td>- Septicemia with same organism as knee aspirate</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA: 4243 TKA   187 infections</td>
<td></td>
<td></td>
<td>- &gt;2 positive knee aspirates</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- OA: 7534 TKA   128 infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berry (2002) (226)*</td>
<td>THA revision</td>
<td>1969-1971</td>
<td>RA: referral Ds from rheumatologists or internists**</td>
<td>OA: radiographic</td>
<td># of hospitals: 1, Mayo Clinic</td>
<td>Revision defined as:</td>
</tr>
<tr>
<td>JBJS (Am) 84-A(2): 171-177</td>
<td></td>
<td></td>
<td># of patients: 2000 (1647 OA + 166 RA)</td>
<td></td>
<td></td>
<td>- Revision of acetabular component and/or</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Follow-up: 20y</td>
<td></td>
<td></td>
<td>- Revision of femoral component</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Implants: all cemented, Charnley</td>
<td></td>
<td></td>
<td>- Any re-operation on the index hip</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Approach: transtrochanteric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Outcomes: Revision:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- None in RA; unclear for OA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA 25y survivorship: 91.8% (95CI 83.0-95.2); test of group 80.1% (95CI 77.4-82.8) p=0.047</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Multivariate analysis relative to OA (adjusted for age and sex)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Revision of femur: OR 0.2 (0.1-0.6); p=0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Revision of acetab: OR 0.3 (0.1-1.0); p=0.049</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Revision of either: OR 0.3 (0.1-0.6); p=0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>**Not stated in text – communication with primary author</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis &amp; Rheumatism 59(12): 1713-1720</td>
<td></td>
<td></td>
<td># of patients: 657 RA TJA (328 THA + 329 TKA)</td>
<td></td>
<td></td>
<td>- At least one of:</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– 1:1 matching to OA for age (+/-5y), time of surgery, gender, site of surgery</td>
<td></td>
<td></td>
<td>- Isolation of the same microorganism from at least 2 cultures of joint aspirates or intraoperative tissue specimens</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Follow-up: 1y</td>
<td></td>
<td></td>
<td>- Acute inflammation consistent with infection on histopathologic examination (as determined by the pathologist)</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Implants: heterogeneous</td>
<td></td>
<td></td>
<td>- Catarrhal sinus tract communicating with the joint prosthesis, and/or purulence in the joint space (as determined by the surgeon)</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Prophylaxis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Perioperative systemic antibiotics: 656 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Antithrombotic impreg cement: 209 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Outcomes: infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Infection: 12 hip + 11 knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Univariate (risks within RA):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Revision: HR 2.99 (1.02-8.75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- Prev infection: HR 5.49 (1.87-16.14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- OR time: HR 1.36 per 60min increase (1.02-1.81)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Compared to OA:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Within 1st year: OR 10.30 (1.31-80.26) (ref OA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Within 5y: adjusted HR 3.74 (95CI 1.23-11.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– Ref: OA, adjusted for prev infection in index joint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA:  </td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- OA: 379 TKA   45 superficial   14 deep (59 total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA: 71 &gt; 3 superficial   2 deep (5 total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chesney (2008) (227)</td>
<td>TKA infection</td>
<td>1998-2005</td>
<td>RA: not described</td>
<td>OA: not described</td>
<td># of hospitals: 1 unit, Newcastle</td>
<td>Superficial wound infection defined as:</td>
</tr>
<tr>
<td>Journal of Arthroplasty 23(3): 355-359</td>
<td></td>
<td></td>
<td># of patients: 1,206 TKA (1,235 OA + 71 RA)</td>
<td></td>
<td></td>
<td>- A wound discharge, which yielded organisms from the culture of aseptically aspirated fluid or tissue, or from a swab</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Follow-up: up to 5y (no mean provided)</td>
<td></td>
<td></td>
<td>Deep infection defined as:</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Implants: Heterogeneous</td>
<td></td>
<td></td>
<td>- An infection which required a second procedure</td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Prophylaxis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>– One dose of Ceftriaxone or gentamycin on induction of anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>Outcomes: infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- OA: 1235 &gt; 45 superficial   14 deep (59 total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td></td>
<td></td>
<td>- RA: 71 &gt; 3 superficial   2 deep (5 total)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* included in quantitative synthesis
<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corroy (2008)</td>
<td>TKA dislocation</td>
<td>1999-2004</td>
<td>RA: diagnostic code; OA: diagnostic code</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td>Dislocation defined as: - Documented positioning of the femoral head outside the acetabular socket resulting in revision arthroplasty</td>
<td>Case definition: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Revision defined as: - Revision of acetabular component and/or - Revision of femoral component</td>
<td>Analysis: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total: 7/11 (moderate risk)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domsic (2010)</td>
<td>Mortality</td>
<td>1993-2006</td>
<td>RA: diagnostic code; SLE: diagnostic code; OA: diagnosis of exclusion</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td>Mortality defined as: - Death during hospital admission</td>
<td>Case definition: 1 (OA defined by exclusion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient selection: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analysis: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Database: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total: 9/13 (moderate risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elke (1995)</td>
<td>TKA revision</td>
<td>1982-1989</td>
<td>RA: not described; OA: not described</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td>Revision defined as: - Removal, realignment or replacement of femoral, tibial, or polyethylene components Survival analysis - End-point: revision - Censored: lost to follow-up, death</td>
<td>Case definition: 0 (not discussed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient selection: 2 (Case series)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 2 (described)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: 2 (revision)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analysis: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total: 7/11 (moderate risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furnes (2001)</td>
<td>TKA revision</td>
<td>1987-1999</td>
<td>RA: diagnostic code; OA: diagnostic code</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td>Revision defined as: - Revision of acetabular component and/or - Revision of femoral component 1986-1987</td>
<td>Case definition: 2 (as per database)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient selection: 2 (Case series)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: 2 (revision)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analysis: 3 (proportions)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Database: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total: 12/13 (low risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gill (2003)</td>
<td>Mortality</td>
<td>1976-1996</td>
<td>RA: not described; OA: not described</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td>Mortality defined as: - Death within 90d of TKA</td>
<td>Case definition: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient selection: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analysis: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total: 7/11 (moderate risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hedlundh (1995)</td>
<td>TKA dislocation</td>
<td>1979-1991</td>
<td>RA: not described; OA: not described</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td>Dislocation defined as: - Documented positioning of the femoral head outside the acetabular socket</td>
<td>Case definition: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient selection: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analysis: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total: 7/11 (moderate risk)</td>
</tr>
</tbody>
</table>
### Table 2.2: characteristics of included studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acta Orthopaedica 76(1): 85-88</td>
<td></td>
<td></td>
<td>OA: diagnostic code</td>
<td># of patients: 8,467 TKA; 6,306 OA + 2,161 RA Follow-up: 3.2 y in OA, 5.2 y for RA Implants: AGC prosthesis Approach: not described Outcomes: loosening</td>
<td>- RA: RR 1.25 (95CI 0.87-1.80) (p=0.2) (ref: OA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Adjusted for age, sex, cement RA patients: 5y survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Age (p=0.007)</td>
<td>- &lt;60: 95.8 (94.1-97.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- &gt;60: 97.9 (96.7-98.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Sex (p=0.004)</td>
<td>- Female: 97.5 (96.5-99.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Male: 94.0 (90.4-96.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Cement (p=0.5)</td>
<td>- Used: 97.0 (95.6-97.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Not used: 96.9 (95.4-97.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OA patients: 5y survival</td>
<td>- Age (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- &lt;60: 95.9 (93.3-97.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- &gt;60: 97.5 (97.0-98.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Sex (p=0.01)</td>
<td>- Female: 97.7 (97.1-98.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Male: 96.1 (94.5-97.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Cement (p=0.4)</td>
<td>- Used: 97.5 (96.8-98.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Not used: 97.6 (95.9-98.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infection defined as:</td>
<td>Re-operation performed secondary to infection</td>
</tr>
<tr>
<td>JBJS (Am) 91(1): 38-47</td>
<td></td>
<td></td>
<td>OA: diagnostic code</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: adjusted HR for reoperation secondary to infection 1.86 (1.31-2.63) (ref OA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Adjusted for age, sex, constrain of prosthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infection defined as:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Re-operation performed secondary to infection</td>
</tr>
<tr>
<td>JBJS (B) 88(10): 1303-1308</td>
<td></td>
<td></td>
<td>OA: diagnostic code</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: 27942 ≥ 113 revisions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: 925 ≥ 5; RR: 1.3 (0.6-2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Adjusted RR 1.3 (0.5-3.3) Failure from 31d to 6mths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- OA: 27716 ≥ 102</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: 915 ≥ 2; RR: 0.6 (0.2-2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Adjusted RR 0.6 (0.1-2.3) Failure from 6mths to 9y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- OA: 26804 ≥ 253</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: 882 ≥ 24; RR: 1.1 (0.8-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted for age, sex, fixation technique, hospital type Unadjusted totals:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- OA: 27942 ≥ 468 revisions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: 925 ≥ 31 revisions</td>
</tr>
</tbody>
</table>

* included in quantitative synthesis
<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No information on sensitivity or positive predictive value available.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90d re-admission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RA: adjusted OR 1.37 (95CI 1.09-1.74) (ref OA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted for co-morbidity score, hospital level, teaching status, geographic region, surgeon’s age</td>
</tr>
<tr>
<td>Kesters (1998) (232)*</td>
<td>THA revision</td>
<td>1983-1994</td>
<td>RA: not described</td>
<td>OA: not described</td>
<td># of hospitals: 1, Lund University Hospital</td>
<td># of patients: 1,660 (1,021 OA + 259 RA + 473 other)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>THA: all cemented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Scan Hip Classic I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approach: posteroanterior or anterior (only for RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcomes: Revision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- OA: 24 hips</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RA: 6 hips</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No information on sensitivity or positive predictive value available.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Implants: heterogeneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approach: heterogeneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcomes: dislocation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Dislocations: 14 OA + 4 RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Adjusted OR: 3.8 (95CI 1.1-13.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Adjusted for age, sex, AS Ascore, procedure (primary vs revision), head size (28mm vs &gt;=32mm), surgeon volume, approach</td>
</tr>
<tr>
<td>Laskin (1997) (234)*</td>
<td>TKA revision</td>
<td>1982-1990</td>
<td>RA: not described</td>
<td>OA: not described</td>
<td># of hospitals: 2, HSS, US</td>
<td># of patients: 790 TKA (674 OA + 116 RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 8 deceased (2 OA + 6 RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 85 lost to f/u (73 OA + 12 RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implants: cruciate-retaining</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approach: not described</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcomes: revision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 104 RA + 13 revisions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 603 OA + 2 revisions</td>
</tr>
<tr>
<td>Mallory (1999) (235)*</td>
<td>THA dislocation</td>
<td>1992-1996</td>
<td>RA: not described</td>
<td>OA: not described</td>
<td># of hospitals: 2, Sweden</td>
<td># of patients: 1,518 THA (1,205 OA + 51 RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Implants: heterogeneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approach: anterolateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcomes: dislocation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 1,205 OA THA 3 dislocations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 51 RA THA 1 dislocation</td>
</tr>
<tr>
<td>Naflis (1996) (236)*</td>
<td>TKA revision</td>
<td>1979-1982</td>
<td>RA: not described</td>
<td>OA: not described</td>
<td># of hospitals: 1, Aarhus Hospital, Denmark</td>
<td># of patients: 348 TKA (184 OA + 164 RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Implants: all cemented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approach: not described</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcomes: revision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 184 OA 3 revisions, survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 164 RA 3 revisions, survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Survival analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- End-point: revision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Censored: lost to follow-up, death</td>
</tr>
</tbody>
</table>

* included in quantitative synthesis
<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patino (1994)</td>
<td>THA revision</td>
<td>1979-1983</td>
<td>RA: not described OA: not described</td>
<td># of hospitals: 1, Finland Central Hospital # of patients: 444 (316 OA + 84 RA + 44 other) Follow-up: 8-12y Implants: high viscosity cement Laboratory: curved SP Approach: posterior Outcomes: Survival at 10 yrs - OA: 88.7 % (84.7 - 92.8) - RA: 91% (84.1 – 97.9)</td>
<td>Revision defined as: Removal, realignment or replacement of femoral, tubial, or polyethylene components</td>
<td>Case definition: 0 (not described) Patient selection: 2 (case series) Follow-up: 2 (described; none lost) Outcome: 2 (revision; hard outcome) Analysis: 3 (survival curves; Mantel Cox) Database: 1 Total: 9/11 (moderate risk)</td>
</tr>
<tr>
<td>Paterson (2010)</td>
<td>Can J Surg. 2010 Jun 33(3):175-83.</td>
<td>2000-2004</td>
<td>RA: diagnostic code OA: diagnostic code</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td># of hospitals: 86, admission database, Ontario, Canada # of patients: 20.290 THA (17,649 OA + 2,641 RA) Follow-up: 1y Implants: heterogeneous implants and use of cement Approach: mixed Outcomes: revision Adjusted OR (age, sex, co-morbidity) within 1y - THA: 1.11 (0.82-1.51) - TKA: 1.08 (0.78-1.50) THA: OA: 17,649 → 16.49 per 1000 → 291 revisions RA: 2,641 → 18.55 per 1000 → 49 revisions TKA: OA: 23,417 → 10.81 per 1000 → 253 revisions RA: 3,805 → 12.61 per 1000 → 50 revisions</td>
<td>Revision (THA) defined as: Removal of acetalbular component and/or revision of femoral component Revision (TKA) defined as: Removal or replacement of femoral, tubial, or polyethylene components</td>
</tr>
<tr>
<td>Pedersen (2010)</td>
<td>JBJS (Am) 92(12): 2156-2164.</td>
<td>1995-2006</td>
<td>RA: diagnostic code OA: diagnostic code</td>
<td>No information on sensitivity or positive predictive value available.</td>
<td># of hospitals: multiple, Danish National Health Service # of patients: 68,863 THA (52,359 OA + 1,841 RA) Follow-up: 90y Implants: heterogeneous Prophylaxis: Dalteparin: 24,467 cases (36.5%) Enoxaparin: 24,976 cases (37.0%) Tinzaparin: 12,670 (18.9%) Fondaparinux: 2,322 cases (3.4%) Combination: 2,428 cases (3.6%) Outcomes: VTE RA: Adjusted OR 0.47 (0.25-0.90) (ref OA) Adjusted for age, sex, Charlson score, specific co-morbidities, year or surgery, type of prophylaxis</td>
<td>VTE defined as: Hospitalization for VTE within 90d of index arthroplasty</td>
</tr>
</tbody>
</table>

* included in quantitative synthesis
<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantill (2001) (249)*</td>
<td>THA revision</td>
<td>1987-1993</td>
<td>RA: not described</td>
<td>OA: not described # of hospitals: 1, Rothman Institute</td>
<td>Revision defined as: - Revision of acetabular component and/or - Revision of femoral component</td>
<td>Case definition: 0 Patient selection: 2 (Case series) Follow-up: 1 (well-described) Outcome: 2 (revision) Analysis: 0 Database: n/a Total: 5/11 (high risk)</td>
</tr>
<tr>
<td>Clinical Orthopaedics and Related Research(393): 121-127.</td>
<td></td>
<td></td>
<td></td>
<td># of patients: 185 (123 OA + 62 RA) Follow-up: 5y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implants: cementless Approach: lateral or transtrochanteric Outcomes: Revision - None in RA; 7 in OA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rand (1991) (241)*</td>
<td>TKA revision</td>
<td>1971-1987</td>
<td>RA: not described</td>
<td>OA: not described # of hospitals: 1, Mayo Clinic Joint Registry</td>
<td>Revision defined as: - Removal, realignment or replacement of femoral, tibial, or polyethylene components</td>
<td>Case definition: 2 (as per database) Patient selection: 2 Follow-up: 2 Outcome: 2 Analysis: 3 (Cox PH, Mantel-Cox) Database: 1 (no ref to validation for Dx) Total: 12/13 (low risk)</td>
</tr>
<tr>
<td>JBJS (Am) 73(3): 397-409.</td>
<td></td>
<td></td>
<td></td>
<td># of patients: 8,969 TKA (5,556 OA + 2,513 RA) Follow-up: 5y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implants: Heterogeneous implants and cement Approach: not described Outcomes: revision - OA: 5556 → 382 revisions - RA: 2513 → 325 revisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritter (1994) (242)*</td>
<td>TKA revision</td>
<td>1975-1983</td>
<td>RA: not described</td>
<td>OA: not described # of hospitals: 1, Centre for Hip &amp; Knee Surgery, US</td>
<td>Revision defined as: - Removal, realignment or replacement of femoral, tibial, or polyethylene components</td>
<td>Case definition: 0 (none provided) Patient selection: 2 (Case series) Follow-up: 1 Outcome: 1 Analysis: 2 Total: 6/11 (high risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>139 RA: 49 died, 19 lost to follow-up - no revisions in patients who died</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implants: cruciate- retaining Approach: not described Outcomes: revision - OA: 8427 → 52 revisions - RA: 214 → 1 revision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JBJS (B) 91(6): 745-749.</td>
<td></td>
<td></td>
<td></td>
<td>Implants: PCA knee, mixed cement Approach: not described</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Approach: not described Outcomes: revision - OA: 8427 → 52 revisions - RA: 214 → 1 revision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rud-Sorensen (2010) (163)*</td>
<td>THA revision</td>
<td>1995-2008</td>
<td>RA: diagnostic code</td>
<td>OA: diagnostic code Reference to validation study provided.</td>
<td>Revision defined as: - Revision of acetabular component and/or - Revision of femoral component</td>
<td>Case definition: 2 (as per database) Patient selection: 2 Follow-up: 2 Outcome: 2 (revision) Analysis: 3 (survival analysis) Database: 2 (refers to validation for Dx) Total: 13/13 (low risk)</td>
</tr>
<tr>
<td>Acta Orthopaedica 81(1): 60-65.</td>
<td></td>
<td></td>
<td></td>
<td># of hospitals: 45, Danish Hip Arthroplasty Register # of patients: 66,519 THA (64,858 OA + 1,661 RA) Follow-up: 5y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implants: Heterogeneous implants and use of cement Approach: mixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcomes: revision - OA: 2979 OA, 89 RA - Revisions any cause (Reference group: OA) - Crude RR 1.00 (0.81-1.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.81 (0.65-1.01); p=0.07 Adjusted RR 0.81 (0.65-1.01); p=0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schrama (2010) (164)*</td>
<td>TKA revision</td>
<td>1987-2008</td>
<td>RA: diagnostic code</td>
<td>OA: diagnostic code No information on sensitivity or positive predictive value available.</td>
<td>Revision defined as: - Revision of acetabular component and/or - Revision of femoral component - Resulting from a infection</td>
<td>Case definition: 2 (as per database) Patient selection: 2 Follow-up: 2 Outcome: 2 (revision) Analysis: 3 (survival analysis) Database: 1 (no ref to validation for Dx) Total: 12/13 (low risk)</td>
</tr>
<tr>
<td>Arthritis Care &amp; Research 62(4): 473-479.</td>
<td></td>
<td></td>
<td></td>
<td># of hospitals: 68, Norwegian arthroplasty register</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td># of patients: THA: 84,492 (80,325 OA + 4,167 RA) TK: 24,294 (21,832 OA + 2,462 RA) Follow-up: 6y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implants: Heterogeneous implants and use of cement Approach: mixed Outcomes: revision for infection only THA - RR 0.98 (0.65-1.48); p=0.94 - OA: 80325 → 509 - RA: 4167 → 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TK: RR 1.6 (1.06-2.38); p=0.027 - OA: 21832 → 144 - RA: 2462 → 32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* included in quantitative synthesis
Table 2.2: characteristics of included studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sochoo (2010) (245)*</td>
<td>Venous thromboembolism (VTE) Mortality</td>
<td>1995-2005</td>
<td>RA: diagnostic code OA: diagnostic code No information on sensitivity or positive predictive value available.</td>
<td># of hospitals: multiple, California’s Office of Statewide Health Planning and Development database # of patients: 16,346 THA (8,859 OA + 721 RA) Follow-up: 90d Outcomes: adjusted ORs for RA - 90d VTE risk: OR 1.46 (95CI 0.82-2.61) - 90d mortality: OR 1.88 (95CI 1.17-3.03) - Any complication in 90d: OR1.53 (95CI 1.23-1.91) - 90d infection: OR 1.47 (95CI 0.90-2.41) - 90d dislocation: OR 1.50 (95CI 1.05-2.15) - 90d revision: OR 1.46 (95CI 0.82-2.61) – Ref for all: OA – Adjusted for: age, sex, race, income, co-morbidity, diabetes, peripheral vascular disease, hospital characteristics: teaching status, urban/rural Mortality defined as: - Death within 90d of THA</td>
<td>All complications defined as: - Re-admission within 90d for: - VTE - Infection - Dislocation - Revision Mortality defined as: - Death within 90d of THA Case definition: 2 Patient selection: 2 Follow-up: 2 Outcome: 2 Analysis: 2 Database: 1 Total: 11/13 (low risk)</td>
</tr>
<tr>
<td>Van Heeroved (2001) (246)</td>
<td>Venous thromboembolism (VTE)</td>
<td>1987-1995</td>
<td>RA: not described</td>
<td># of hospitals: 1, The Netherlands # of patients: 103 RA patients (55 THA + 96 TKA) Follow-up: 1y Implants: heterogeneous Prophylaxis: - Standard heparin: 107 cases; 5000 IU 2x/day - Nadroparin: 44 cases; 7500 IC-U 1x/day Outcomes: VTE VTE defined as: - DVT or PE within a year of index procedure</td>
<td>Case definition: 0 Patient selection: 2 Follow-up: 2 Outcome: 2 Analysis: 1 Total: 7/11 (moderate risk)</td>
</tr>
<tr>
<td>West (1996) (247)*</td>
<td>TKA revision</td>
<td>1981-1985</td>
<td>RA: not described OA: not described</td>
<td># of hospitals: 1, Freeman Hospital, Newcastle # of patients: 208 TKA (72 OA + 133 RA) Follow-up: 12y - 44 deceased; 7 lost to fu - no evidence of failure in the deceased Implants: cruciate-retaining, cemented Approaches: not described Outcomes: revision - OA: 72 TKAs 6 revisions - RA: 133 TKAs 15 revisions Survival analysis: 2 (none provided) Database: 1 (no reference to validation for DX) Total: 7/11 (moderate risk)</td>
<td>Revision defined as: - Removal, realignment or replacement of femoral, tibial, or polyethylene components Case definition: 0 (none provided) Patient selection: 2 (case series) Follow-up: 1 Outcome: 2 Analysis: 2 Total: 7/11 (moderate risk)</td>
</tr>
</tbody>
</table>

* included in quantitative synthesis
<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Years of study</th>
<th>Arthritis Diagnosis</th>
<th>Details</th>
<th>Outcome assessment</th>
<th>Bias Score</th>
<th>Characteristics of included studies (continued)</th>
</tr>
</thead>
</table>

* included in quantitative synthesis
**Figure 2.1:** search results and study selection

**MEDLINE, EMBASE, CINAHL, Web of Science (1990-2011)**

4,719 records
- 1,526 duplicates
- 3,193 records
- 1,172 did not discuss THA or TKA
- 2,021 records
- 38 did not have an abstract available (all non-English)
- 1,983 abstracts
- 778 did not mention RA or IA in title or abstract
- 1,205 abstracts
- 642 with different primary outcome
- 563 full-text records
- 346 did not match sample size requirements
- 217 full-text records
- 173 did not stratify the outcome by diagnosis
- 44 full-text records
- 4 studies were redundant (same population and time period as another study)

**40 studies** included:
- THA revision (15 articles)
- TKA revision (11 articles)
- THA dislocation (6 articles)
- TJA infection (5 articles)
- 90d mortality (4 articles)
- VTE within 90d of TJA (5 articles)

**35 studies** in quantitative synthesis:
- THA revision (13 articles)
- TKA revision (11 articles)
- THA dislocation (6 articles)
- TJA infection (0 articles)
- 90d mortality (3 articles)
- VTE within 90d of TJA (2 articles)

* Some studies examined multiple outcomes
Figure 2.2: dislocation of index hip arthroplasty within 5y

**A**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>RA Total</th>
<th>OA Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conroy 2008</td>
<td>0.65232519</td>
<td></td>
<td>1140</td>
<td>58109</td>
<td>37.7%</td>
<td>1.92 [1.13, 3.27]</td>
</tr>
<tr>
<td>Hedlundh 1995</td>
<td>0.84242888</td>
<td></td>
<td>383</td>
<td>2183</td>
<td>34.6%</td>
<td>2.32 [1.30, 4.13]</td>
</tr>
<tr>
<td>Khato 2006</td>
<td>2.11745961</td>
<td></td>
<td>44</td>
<td>1178</td>
<td>11.0%</td>
<td>8.31 [2.30, 30.03]</td>
</tr>
<tr>
<td>Mallory 1999</td>
<td>2.08069076</td>
<td></td>
<td>1205</td>
<td>51</td>
<td>2.6%</td>
<td>8.01 [0.48, 133.21]</td>
</tr>
<tr>
<td>Zwartele 2004</td>
<td>1.30019166</td>
<td></td>
<td>70</td>
<td>340</td>
<td>14.2%</td>
<td>3.67 [1.22, 11.05]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

2842 61861 100.0% 2.74 [1.73, 4.34]

Heterogeneity: $\tau^2 = 0.07$; Chi$^2 = 5.49$, df = 4 ($P = 0.24$); $I^2 = 27$
Test for overall effect: $Z = 4.29$ ($P < 0.0001$)

**B**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>RA Total</th>
<th>OA Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conroy 2008</td>
<td>0.69314718</td>
<td></td>
<td>1140</td>
<td>58109</td>
<td>45.1%</td>
<td>2.00 [1.19, 3.37]</td>
</tr>
<tr>
<td>Hedlundh 1995</td>
<td>0.58778666</td>
<td></td>
<td>383</td>
<td>2183</td>
<td>36.4%</td>
<td>1.80 [1.01, 3.21]</td>
</tr>
<tr>
<td>Khato 2006</td>
<td>1.33500107</td>
<td></td>
<td>44</td>
<td>1178</td>
<td>7.7%</td>
<td>3.80 [1.08, 13.41]</td>
</tr>
<tr>
<td>Zwartele 2004</td>
<td>1.30833282</td>
<td></td>
<td>70</td>
<td>340</td>
<td>10.7%</td>
<td>3.70 [1.27, 10.76]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

1637 61810 100.0% 2.16 [1.52, 3.07]

Heterogeneity: $\tau^2 = 0.00$; Chi$^2 = 2.21$, df = 3 ($P = 0.53$); $I^2 = 0$
Test for overall effect: $Z = 4.31$ ($P < 0.0001$)

Figure 2.2a: dislocation of index hip arthroplasty within 5y without adjustment for confounders
Figure 2.2b: dislocation of index hip arthroplasty within 5y with adjustment for confounders
Figure 2.3: revision of index arthroplasty following total hip replacement

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>RA Total</th>
<th>OA Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random</td>
<td>95% CI</td>
</tr>
</tbody>
</table>

**Figure 2.3a:** revision of index arthroplasty within 5y without adjustment for confounders

**Figure 2.3b:** revision of index arthroplasty between 6-10y without adjustment for confounders

**Figure 2.3c:** revision of index arthroplasty after 10y without adjustment for confounders
Figure 2.4: revision of index arthroplasty following total knee replacement

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>RA Total</th>
<th>OA Total</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Himanen 2005</td>
<td>0.13102826</td>
<td>0.15355132</td>
<td>2161</td>
<td>6306</td>
<td>16.1%</td>
<td>1.14 [0.84, 1.54]</td>
</tr>
<tr>
<td>Paterson 2010</td>
<td>0.19803085</td>
<td>0.16141172</td>
<td>3805</td>
<td>23412</td>
<td>14.6%</td>
<td>1.22 [0.89, 1.67]</td>
</tr>
<tr>
<td>Rand 1991</td>
<td>0.2390169</td>
<td>0.0739674</td>
<td>2513</td>
<td>5556</td>
<td>69.3%</td>
<td>1.27 [1.10, 1.47]</td>
</tr>
</tbody>
</table>

Total (95% CI): 8479 35274 100.0%

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.42$, df = 2 ($P = 0.81$); $I^2 = 0$

Test for overall effect: $Z = 3.50$ ($P = 0.0005$)

Figure 2.4a: revision of index arthroplasty within 5y without adjustment for confounders

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>RA Total</th>
<th>OA Total</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elke 1995</td>
<td>0.41871034</td>
<td>0.48113314</td>
<td>43</td>
<td>300</td>
<td>20.1%</td>
<td>1.52 [0.59, 3.90]</td>
</tr>
<tr>
<td>Laskin 1997</td>
<td>3.75621095</td>
<td>0.87667839</td>
<td>116</td>
<td>674</td>
<td>11.6%</td>
<td>42.79 [7.67, 238.52]</td>
</tr>
<tr>
<td>Partio 1994</td>
<td>0.15700375</td>
<td>0.359086</td>
<td>193</td>
<td>167</td>
<td>23.4%</td>
<td>1.17 [0.58, 2.37]</td>
</tr>
<tr>
<td>Ritter 1994</td>
<td>0.01980263</td>
<td>0.94733981</td>
<td>88</td>
<td>270</td>
<td>10.5%</td>
<td>1.02 [0.16, 6.53]</td>
</tr>
<tr>
<td>Ritter 2009</td>
<td>-0.54472718</td>
<td>1.23974806</td>
<td>214</td>
<td>6427</td>
<td>7.2%</td>
<td>0.58 [0.05, 6.59]</td>
</tr>
<tr>
<td>Schrama 2010</td>
<td>0.68309684</td>
<td>0.20600957</td>
<td>2462</td>
<td>21832</td>
<td>27.2%</td>
<td>1.98 [1.32, 2.96]</td>
</tr>
</tbody>
</table>

Total (95% CI): 3116 29670 100.0%

Heterogeneity: $\tau^2 = 0.50$; $\chi^2 = 16.01$, df = 5 ($P = 0.007$); $I^2 = 69$

Test for overall effect: $Z = 1.84$ ($P = 0.07$)

Figure 2.4b: revision of index arthroplasty between 6-10y without adjustment for confounders

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>RA Total</th>
<th>OA Total</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nafei 1996</td>
<td>1.63510566</td>
<td>0.72782109</td>
<td>164</td>
<td>184</td>
<td>43.5%</td>
<td>5.13 [1.23, 21.36]</td>
</tr>
<tr>
<td>Weir 1996</td>
<td>0.33647224</td>
<td>0.55694856</td>
<td>133</td>
<td>72</td>
<td>56.5%</td>
<td>1.40 [0.47, 4.17]</td>
</tr>
</tbody>
</table>

Total (95% CI): 297 256 100.0%

Heterogeneity: $\tau^2 = 0.42$; $\chi^2 = 2.01$, df = 1 ($P = 0.16$); $I^2 = 50$

Test for overall effect: $Z = 1.40$ ($P = 0.16$)

Figure 2.4c: revision of index arthroplasty after 10y without adjustment for confounders
III. CHAPTER 3 – PATIENTS WITH RHEUMATOID ARTHRITIS ARE AT INCREASED RISK FOR COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY

Bheeshma Ravi\textsuperscript{1}
Ruth Croxford\textsuperscript{2}
Simon Hollands\textsuperscript{2}
J. Michael Paterson\textsuperscript{2,3}
Earl Bogoch\textsuperscript{1,4}
Hans Kreder\textsuperscript{1,3}
Gillian A Hawker\textsuperscript{2,3,5}

From the \textsuperscript{1}Division of Orthopaedic Surgery, Department of Surgery, University of Toronto, the \textsuperscript{2}Institute for Clinical Evaluative Sciences, the \textsuperscript{3}Institute of Health Policy, Management and Evaluation, University of Toronto, the \textsuperscript{4}Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada, and the \textsuperscript{5}Division of Rheumatology, Department of Medicine, Women's College Hospital, Toronto, Canada.

Currently \textit{in press} in \textit{Arthritis & Rheumatism} (accepted July 9, 2013)
ABSTRACT

Background and objectives: Most of the evidence regarding complications following total hip arthroplasty (THA) and total knee arthroplasty (TKA) are based on patients with osteoarthritis (OA); less is known about outcomes in rheumatoid arthritis (RA). Using a validated algorithm for identifying individuals with RA, we compared the rates of complications among THA and TKA recipients with versus without RA.

Methods: In patients with a first primary elective THA or TKA between 2002 and 2009, those with RA were identified with a validated algorithm: hospitalization with a RA diagnosis or 3 RA billing claims with at least 1 claim by a specialist (rheumatologist, orthopedic surgeon or internist) over a 2y period. Recipients with diagnostic codes suggesting an inflammatory arthritis (IA), but not meeting RA criteria, were classified as having IA. All remaining patients were deemed to have OA. Cox proportional hazards, censored on death, were used to determine the relationship between arthritis type and the occurrence of specific complications adjusting for potential confounders (age, sex, co-morbidity and provider volume).

Results: We identified 43,997 eligible THA recipients (3% RA) and 71,793 eligible TKA recipients (4% RA). TJA recipients with RA had higher age & sex-standardized rates of dislocation following THA (OA: 1.21%, RA: 2.45%) and infection following TKA (OA: 0.84%, RA: 1.26%). Controlling for potential confounders, recipients with RA remained at increased risk for dislocation within two years of THA (adjusted HR 1.91, p=0.001), and infection within two years of TKA (adjusted HR 1.47, p=0.03), relative to recipients with OA.

Conclusions: Patients with RA are at higher risk for dislocation following THA and infection following TKA relative to those with OA. Further research is warranted to elucidate explanations, including the role of medication profile, implant choice, post-operative antibiotic protocol and method of rehabilitation following joint replacement.
INTRODUCTION

Rationale

Total joint arthroplasty (TJA) is the surgical treatment for end-stage arthritis of the hip and knee, a stage defined as ongoing pain, limitation in function and reduced quality of life resulting from joint disease, despite appropriate medical management (4, 5). Over the last decade, the age-sex standardized rates of total hip arthroplasty (THA) and total knee arthroplasty (TKA) have increased in North America by approximately 25% and 65%, respectively (20). This increase appears to be largely driven by persons with OA (250), with rates in patients with RA remaining largely static (251-253), although there is some evidence to suggest that the rates of TKA are increasing in persons with RA as well (254). On average, patients report significant and sustained improvement in function and quality of life following THA and TKA (9). However, there is a small risk for serious complications, including early revision, infection, dislocation, venous thromboembolism (VTE) and death (all <2%) (8, 196, 255).

However, the estimated rates of these outcomes are largely based on the experiences of patients with osteoarthritis (OA), who comprise the majority of TJA recipients (197, 198). TJA is also used to treat patients with rheumatoid arthritis (RA), a systemic autoimmune disease, which differs fundamentally from OA in terms of pathogenesis, prognosis and medical management. As such, the risk for complications following TJA, and their predictors, may differ between RA and OA. Therefore, the degree to which TJA outcomes based on the experience of patients with OA may be generalized to recipients with RA is unclear.

We performed a systematic review and meta-analysis to examine TJA complication rates for individuals with RA versus OA (256). We found evidence for an increased risk of hip dislocation following THA and infection following TKA in patients with RA. However, these results were
based on the findings of studies that had several limitations. The majority of these studies used variable definitions for RA diagnosis, which raised concerns about misclassification bias. Some studies combined primary and revision procedures, which limited their generalizability, and precluded meta-analysis. Finally, there was variable adjustment for confounders, with several studies not accounting for any of the systematic differences between RA and OA patients. Thus, it remains unclear whether or not the risks of dislocation following THA and infection following TKA are increased in patients with RA versus OA. Confirmation of these findings is important.

In addition to the significant morbidity associated with these complications (88, 257), if joint replacement recipients with RA are found to be at greater risk for surgical complications, this may have implications for surgical decision-making. The current study sought to overcome the limitations of prior studies. Capitalizing on the availability of a recently validated algorithm for RA using administrative data, with a high sensitivity and specificity, we compared the rates of surgical complications, following THA and TKA in recipients with RA versus OA, controlling for potential confounders.

METHODS

Study sample

The main data sources were hospital discharge abstracts from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), and physician claims from the Ontario Health Insurance Plan (OHIP). Using specific procedure and diagnostic codes from the Canadian version of the 10th revision of the International Statistical Classification of Diseases and the Canadian Classification of Health Interventions (ICD-10-CA/CCI), we defined a cohort of patients who received their first primary elective THA or TKA between April 1, 2002 and March 31, 2009 (Appendix 3.1). The last date for follow-up was March 31, 2011. We excluded the records of individuals who underwent primary or revision TJA prior to April 1, 2002 (i.e.
pre-baseline), those for whom the first procedure was non-elective (e.g. for cancer, fracture, or external cause of injury) or for revision, and those with a history of joint infection, bilateral procedures in the index admission, or for whom the operating surgeon could not be identified (Figure 3.1).

**Main Effect: Arthritis Diagnosis**

The diagnosis of RA was defined using the following validated algorithm: a hospitalization with a diagnosis code for RA or three physician-billing claims with a diagnosis code for RA, with at least one claim by a specialist (rheumatologist, orthopedic surgeon or internist), in a 2 year period (sensitivity 78%, specificity 100%) (258). TJA recipients with at least two diagnostic codes for RA, but not meeting our criteria for diagnosis were classified as having an inflammatory arthritis (IA). Patients with at least one diagnostic code for psoriasis or gout from a rheumatologist or internist, or a diagnostic code for ankylosing spondylitis or systemic lupus erythematosus from any physician, were also classified as having IA. All remaining patients were deemed to have OA.

**Patient and provider characteristics**

We controlled for patient and provider factors that have previously been linked with complications following joint replacement. Relevant patient demographic information was obtained from the OHIP Registered Persons Databases (RPDB); these included age, sex, income quintile, and rurality (9, 122, 259). Co-morbidities listed on hospital discharge abstracts in the 3 years before the index TJA admission were coded according to the Deyo adaptation of the Charlson Comorbidity Index (260-262). The presence of specific co-morbidities (chronic obstructive pulmonary disease, congestive heart failure, baseline cardiovascular disease risk,
diabetes and hypertension) were identified by validated criteria using hospital discharge abstracts (263-265) and a look-back period of two years.

Additionally, Adjusted Clinical Groups (ACGs), based on diagnosis codes from hospitalizations and physician visits in the 2 years before the index TJA admission were used to classify recipients as frail (yes/no)(266). Frailty is associated with a decline in physical activity and muscle strength, as well as immune system dysfunction(127-130). Frailty may therefore increase risk for falls leading to fracture or dislocation and infection following TJA.

For each of TKA, the volume of arthroplasties performed for each surgeon and each hospital was defined as the number of primary and revision knee replacement procedures performed in the 365 days prior to the index TKA procedure. This was repeated for each index THA procedure. We defined teaching hospitals as those who were members of the Council of Academic Hospitals of Ontario (www.cahohospitals.com).

Surgical Complications

All patients were followed from the date of their index TJA to examine for the occurrence of venous thromboembolism (VTE), and death within 90 days, and infection of the replaced joint, dislocation of the replaced joint (only for THA), peri-prosthetic fracture, and revision of the index arthroplasty within 2 years. We also compared groups on the occurrence of a composite outcome encompassing all of the above complications (VTE, death, infection, dislocation, fracture and revision). We limited follow-up to two years, as revision during this period is considered a catastrophic complication (8, 267, 268). We identified death within 90 days of operation using the OHIP Registered Persons Database (Appendix 3.1). Occurrence of a VTE was defined as the presence of a diagnostic code for a deep vein thrombosis or pulmonary
embolism in the DAD or National Ambulatory Care Reporting System (NACRS) database. Infections were identified using three methods: 1) occurrence of an ICD-10-CA diagnostic code for intra-articular infection, with a confirmatory code for an irrigation and debridement; 2) occurrence of an OHIP code for a spacer insertion; and/or 3) occurrence of a procedure code for a peripheral intravenous central catheter (PICC) line after the TJA, where the referring physician was an orthopaedic surgeon. Dislocations were defined as the occurrence of a diagnostic code for dislocation, or a procedure code for closed/open hip reduction. Peri-prosthetic fractures were defined as the occurrence of a diagnostic code for fracture following insertion of an implant. Revision procedures were identified using ICD-10-CA/CCI procedure codes accompanied by the supplementary status attribute “R”.

Statistical analyses

Age-sex standardized rates for each complication by the type of arthritis were determined using indirect standardization. Univariate analysis was used to compare demographics of TJA recipients at the time of their index surgical admission by arthritis type (RA versus OA). Wilcoxon rank-sum tests were used to compare non-normally distributed continuous variables. Chi-square and Fisher exact tests were used to compare categorical variables. Cox proportional hazards models, censored on death and accounting for clustering of patients within surgeons, were used to estimate the hazard of each outcome for patients with RA and IA, relative to those with OA. Age and sex were included in all multivariable models. Other variables were included if in the univariate analyses he covariate was associated with the outcome at a p-value of ≤0.4. Other potential variables included: income quintile, rurality, Charlson co-morbidity score, frailty, surgeon and hospital volume in the year preceding the surgery, and performance of the TJA at a teaching hospital. We performed two sensitivity analyses: 1) repeating the multivariate analysis after excluding persons with a prior code for osteonecrosis, and 2) repeating the
analyses after limiting the definition of infection to cases managed specifically by an irrigation and debridement. Where appropriate, unadjusted hazard ratios and adjusted hazard ratios with 95% confidence intervals (95%CI) are reported. All analyses were performed using SAS version 9.2 for UNIX (SAS Institute, Cary NC). The type I error probability was set to 0.05 for all analyses.

RESULTS

Cohort characteristics

Between April 1, 2002 and March 31, 2009, there were 60,305 THAs and 89,713 TKAs were performed in Ontario, Canada (Figure 3.1). Of these, 43,997 eligible THA (OA: 37,881 – 86%; IA: 4,953 – 11%; RA: 1,163 – 3%) and 71,793 eligible TKA recipients (OA: 59,564 – 83%; IA: 9,537 – 13%; RA: 2,692 – 4%) were identified. THA and TKA recipients with RA were younger, more likely to be female, have greater co-morbidity, and to be frail relative to recipients with OA (Tables 3.1 and 3.2 for THA and TKA, respectively). The IA group was made up of a variety of inflammatory arthritides: 58% had diagnostic codes for RA but did not meet the criteria set out by our algorithm, the remaining 42% met the described criteria for psoriatic arthritis, systemic lupus erythematosus, or ankylosing spondylitis. Individuals classified as having IA tended to have demographic characteristics intermediate between OA and RA (Tables 3.1 and 3.2).

Surgical Complication Rates following THA in Individuals with RA versus OA

A total of 2,119 THA recipients (4.8%) experienced one of more surgical complications: 569 (1.3%) hip dislocations; 612 (1.4%) VTEs; 487 (1.1%) joint infections; 515 (1.2%) revision THAs; 160 (0.4%) peri-prosthetic fractures; and 220 (0.5%) post-operative deaths (Table 3.1). Compared with THA recipients with OA, those with RA were more likely to experience any
surgical complication (5.7% versus 4.7%, p=0.01), and hip dislocation (2.6% versus 1.2%, p<0.001), and less likely to experience a VTE (0.4% versus 1.4%, p=0.02). Additionally, the age-sex standardized rates for dislocation were higher in patients with RA, and the rates of VTE were lower in patients with RA, relative to those with OA (Table 3.3). Controlling for other factors, RA diagnosis remained an independent and significant risk factor for dislocation following THA (adjusted HR 1.91, 95%CI 1.29-2.82, p=0.001) (Table 3.4) and was protective for VTE (adjusted HR 0.35, 95%CI 0.15-0.82, p=0.02). No differences were found for THA recipients with RA versus OA with respect to risk for infection, revision, peri-prosthetic fracture, or death following THA. Among those that had a dislocation in the two years following their THA, the median time to the dislocation was shortest for recipients with RA [OA: 263 (IQR 129-420); IA: 383 (IQR 210-567); RA: 211 (IQR 35-234)] (Figure 3.2).

Surgical Complication Rates following TKA in Individuals with RA versus OA

A total of 2,577 TKA recipients (3.6%) experienced one of more surgical complications: 1,160 (1.6%) VTEs; 637 (0.9%) joint infections; 850 (1.2%) revision TKAs; 60 (0.1%) peri-prosthetic fractures; and 299 (0.4%) post-operative deaths (Table 3.2). There was no difference between TKA recipients with RA versus OA with respect to the occurrence of our composite outcome (3.6% versus 3.6% experienced 1+ complication, p=0.58), or in risk for VTE, revision, peri-prosthetic fracture, or death following TKA. Unadjusted for other factors, TKA recipients with RA were at increased risk for infection relative to recipients with OA (1.2% versus 0.8%, p=0.02). The age-sex standardized rate for infection was higher in patients with RA than those with OA (Table 3.3). Controlling for potential confounders, RA diagnosis remained significantly and independently predictive of increased infection risk following TKA (adjusted HR 1.52, 95%CI 1.11-2.09, p=0.03)(Table 3.4). Among those that had an infection in the two
years following their TKA, the median time to the infection was shortest for recipients with RA [OA: 468 (IQR 199-732); IA: 429 (IQR 229-717); RA: 196 (IQR 98-403)] (Figure 3.2).

Sensitivity Analyses

We repeated our analyses after excluding persons who had a diagnostic code for osteonecrosis; and persons with RA remained at an increased risk for dislocation following THA (adjusted HR 1.90, 95%CI 1.26-2.87, p=0.002) and infection following TKA (adjusted HR 1.47, 95%CI 1.05-2.05, p=0.02). We also repeated our analyses after limiting the definition of infection specifically to the occurrence of an irrigation and debridement procedure, and the elevated risk for infection following TKA in persons with RA persisted (adjusted HR 1.61, 95%CI 1.01-2.57, p=0.04).

DISCUSSION

In a large population cohort, and controlling for previously identified predictors of TJA complications, we found that TJA recipients with RA were approximately twice as likely to experience a dislocation following THA, and one-and-a-half times as likely to experience an infection following TKA, relative to recipients with OA. THA recipients with RA were also one-third as likely to experience a VTE, relative to those with OA. No differences were found with respect to risk of infection following THA, VTE following TKA, or fracture or death following either procedure.

The increased risk for dislocation is consistent with the findings of previous studies by Khatod et al (2006) and Conroy et al (2008)(89, 212), and remained robust after controlling for systematic differences in health status between THA recipients with RA versus OA (including a measure of frailty) that were associated with increased dislocation risk. Dislocation following
THA is a serious complication. In addition to being very painful, and necessitating revision arthroplasty and/or aggressive rehabilitation following closed reduction(87), it is estimated that dislocations increase the hospital costs of a primary THA by over 300%(88). Potential explanations for our findings include systematic differences in the size of implants used for patients with RA versus OA. On average, patients with RA, have a lower body-mass-index (BMI) than patients with OA(271, 272); this smaller body size may result in a tendency by surgeons to use a smaller femoral head component, which may increase the risk for dislocation(89, 90). However, in their study examining dislocation following THA, Khatod et al (2006) controlled for head size, and still found an elevated risk in RA patients(212). Dislocation risk in RA may also be the result of anatomic differences at the level of the hip joint between individuals with RA versus OA. For example, studies have suggested that the prevalence of protrusio acetabuli is increased in patients with RA(91, 92). Acetabular protrusion may increase the risk of impingement and subsequent dislocation. Additionally, there is an increased prevalence of osteoporosis in persons with RA(273), which may increase the risk for fracture-dislocations. There may also be a systematic difference in surgical approach between arthritis types that accounts for our results(274-276). Finally, increased susceptibility to dislocation in patients with RA may result from poorer soft tissue quality relative to patients with OA(177) resulting in suboptimal hip abductor strength and soft-tissue laxity post-operatively(93). Further research is warranted to elucidate the effect of these and other factors on the risk for dislocation in patients with RA.

The documented reduced risk for VTE following THA in patients with RA versus OA was not expected. Previous studies have demonstrated an increased risk for DVT and PE in patients with RA relative to the age- and sex-matched general population without RA, likely due to the effects of systemic inflammation and endothelial dysfunction(277, 278). Our findings may be the result
of selection bias, such that healthier patients with RA are selected for THA, and/or an overall higher risk for VTE among individuals with advanced OA relative to the general age- and sex-matched non-OA population (279).

The increased risk for infection following TKA in patients with RA versus OA persisted after adjusting for systematic differences between these groups in terms of health status (co-morbidity and frailty) (280). In addition to being a source of considerable morbidity, each infected arthroplasty is estimated to cost over $30,000 (USD), on average, to manage (257). Foremost amongst the potential explanations for this increased risk is that RA is a systemic autoimmune disorder, and it is managed with immunomodulatory drugs that have been linked to increased risk for infection (DMARDs, systemic corticosteroids, anti-malarials, and biologic therapies) (155, 159, 281, 282). However, to our knowledge, the impact of biologics on the risk for infection following TJA has not been examined. It is also unclear why this increased risk for infection occurs following TKA, but not following THA. Future studies are required to determine if use of specific medications contribute to the elevated risk for infection in TKA recipients with RA.

A major strength of our study was its use of a validated algorithm for identification of RA patients using administrative data. RA is a challenging diagnosis to establish clinically (218). The algorithm used in this study has been shown to have very high specificity (100%), which allowed us to be confident that these patients had RA. Further, to increase the specificity of our OA diagnosis group, we classified TJA recipients who had had codes for RA, but did not meet our criteria, as well as those who had diagnostic codes suggestive of other inflammatory arthritides into an IA group. The results in our IA group were intermediate between those of RA and OA. This suggests that pooling of this group with either the RA or OA patients, as some
studies have done, would lead to an under-estimation of the surgical risk differences between RA and OA.

Although the risks of dislocation and infection were more common in recipients with RA after THA and TKA, respectively, we did not find a concomitant increased risk for revision. It is possible that in patients with RA, surgeons may preferentially manage hip dislocations with closed reduction and activity modification (217), and knee infections with antibiotics or irrigation and debridement, instead of revision arthroplasty, for either complication.

Other strengths of our study include its large sample size and adjustment for potential confounders. However, there are also important limitations. First, we did not have information regarding patient-reported outcomes, and thus cannot comment on whether the observed increased risks for dislocation and infection translated into worse patient reported pain or disability following THA and TKA, respectively. Second, we did not have information on the types of implant used, and thus could not determine if systematic differences in use of specific implants might explain the observed differences in complication risk. Finally, although we had access to information regarding several potentially important confounders, there are others for which we had no information, such as body-mass-index. Thus, we cannot exclude the possibility that our results were due to lack of control for important unmeasured confounders.

In summary, compared to recipients with OA, we found that those with RA were at significantly greater risk of dislocation following THA and infection following TKA. As both dislocation and infection lead to significant morbidity, and drastically increase health-care costs, research is warranted to elucidate explanations for this increased risk among patients with RA. This
information will be valuable to inform patient management decisions, including the
development and implementation of strategies designed to target modifiable risk factors.
## Table 3.1: Characteristics of Eligible THA Recipients by Arthritis Type

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OA</th>
<th>IA</th>
<th>RA</th>
<th>TOTAL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>N=37,881</td>
<td>N=4,953</td>
<td>N=1,163</td>
<td>N=43,997</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y) [Median (IQR)]</td>
<td>68 (58-75)</td>
<td>68 (59-76)</td>
<td>64 (54-73)</td>
<td>68 (58-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex [N (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>20,372 (53.9%)</td>
<td>2,818 (57.0%)</td>
<td>850 (73.5%)</td>
<td>24,040 (54.8%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17,423 (46.1%)</td>
<td>2,122 (43.0%)</td>
<td>306 (26.5%)</td>
<td>19,851 (45.2%)</td>
<td></td>
</tr>
<tr>
<td>Income Quintile [N (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Lowest</td>
<td>6,114 (16.2%)</td>
<td>868 (17.6%)</td>
<td>199 (17.2%)</td>
<td>7,181 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7,257 (19.2%)</td>
<td>938 (19.4%)</td>
<td>228 (19.7%)</td>
<td>8,443 (19.3%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7,375 (19.5%)</td>
<td>939 (19.4%)</td>
<td>235 (20.4%)</td>
<td>8,571 (19.5%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7,909 (20.9%)</td>
<td>1,053 (21.3%)</td>
<td>246 (21.2%)</td>
<td>9,208 (21.0%)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>9,105 (24.1%)</td>
<td>1,096 (22.2%)</td>
<td>249 (21.5%)</td>
<td>10,450 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>Rural [N (%)]</td>
<td>6,509 (17.2%)</td>
<td>801 (16.2%)</td>
<td>196 (16.9%)</td>
<td>7,506 (17.1%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Frail [N (%)]</td>
<td>1,953 (5.2%)</td>
<td>367 (7.4%)</td>
<td>99 (8.5%)</td>
<td>2,419 (5.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior joint injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6mths prior to THA</td>
<td>995 (2.6%)</td>
<td>176 (3.6%)</td>
<td>55 (4.7%)</td>
<td>1,226 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>6-12mths prior</td>
<td>696 (1.8%)</td>
<td>136 (2.7%)</td>
<td>30 (2.6%)</td>
<td>862 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>1-5years prior</td>
<td>777 (2.1%)</td>
<td>169 (3.4%)</td>
<td>67 (5.8%)</td>
<td>1,013 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt;5years prior to THA</td>
<td>35,413 (93.5%)</td>
<td>4,472 (90.3%)</td>
<td>1,011 (86.9%)</td>
<td>40,896 (93.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteonecrosis [N (%)]</td>
<td>1,530 (4%)</td>
<td>313 (6.3%)</td>
<td>61 (5.3%)</td>
<td>1,904 (4.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline CVD Risk [N (%)]</td>
<td>2,376 (6.3%)</td>
<td>390 (7.9%)</td>
<td>83 (7.1%)</td>
<td>2,849 (6.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes [N (%)]</td>
<td>5,668 (15.0%)</td>
<td>836 (16.9%)</td>
<td>196 (16.9%)</td>
<td>7,600 (15.2%)</td>
<td></td>
</tr>
<tr>
<td>HTN [N (%)]</td>
<td>22,865 (60.4%)</td>
<td>3,305 (66.7%)</td>
<td>625 (56.1%)</td>
<td>26,823 (61.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD [N (%)]</td>
<td>6,117 (16.1%)</td>
<td>990 (20.0%)</td>
<td>209 (18.0%)</td>
<td>7,316 (16.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF [N (%)]</td>
<td>1,933 (5.1%)</td>
<td>363 (7.3%)</td>
<td>92 (7.9%)</td>
<td>2,388 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson Score [N (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>34,500 (91.1%)</td>
<td>4,341 (87.6%)</td>
<td>904 (77.7%)</td>
<td>39,745 (90.3%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,700 (4.5%)</td>
<td>306 (6.2%)</td>
<td>145 (12.5%)</td>
<td>2,151 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>1,681 (4.4%)</td>
<td>306 (6.2%)</td>
<td>114 (9.8%)</td>
<td>2,101 (4.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Admission characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching hospital [N (%)]</td>
<td>12,978 (34.3%)</td>
<td>1,834 (37.0%)</td>
<td>483 (41.5%)</td>
<td>15,295 (34.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgeon volume [Median (IQR)]</td>
<td>67 (35-85)</td>
<td>55 (35-87)</td>
<td>59 (37-97)</td>
<td>55 (35-86)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospital volume [Median (IQR)]</td>
<td>211 (150-341)</td>
<td>212 (153-334)</td>
<td>222 (160-373)</td>
<td>211 (150-340)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication [N (%)]</td>
<td>1,776 (4.7%)</td>
<td>276 (5.6%)</td>
<td>67 (5.7%)</td>
<td>2,119 (4.8%)</td>
<td>0.01</td>
</tr>
<tr>
<td>VTE within 90d [N (%)]</td>
<td>533 (1.4%)</td>
<td>74 (1.5%)</td>
<td>5 (0.4%)</td>
<td>612 (1.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>2y infection [N (%)]</td>
<td>407 (1.1%)</td>
<td>63 (1.3%)</td>
<td>17 (1.5%)</td>
<td>487 (1.1%)</td>
<td>0.23</td>
</tr>
<tr>
<td>2y revision [N (%)]</td>
<td>429 (1.1%)</td>
<td>66 (1.3%)</td>
<td>20 (1.7%)</td>
<td>515 (1.2%)</td>
<td>0.09</td>
</tr>
<tr>
<td>2y dislocation [N (%)]</td>
<td>458 (1.2%)</td>
<td>81 (1.6%)</td>
<td>30 (2.6%)</td>
<td>569 (1.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2y # [N (%)]</td>
<td>136 (0.4%)</td>
<td>15 (0.3%)</td>
<td>7 (0.6%)</td>
<td>160 (0.4%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Death within 90d [N (%)]</td>
<td>176 (0.5%)</td>
<td>33 (0.7%)</td>
<td>9 (0.8%)</td>
<td>220 (0.5%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; HTN: hypertension; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; VTE: venous thrombo-embolism; #: peri-prosthetic fracture
<table>
<thead>
<tr>
<th>Table 3.2: Characteristics of Eligible TKA Recipients by Arthritis Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age (y) [Median (IQR)]</td>
</tr>
<tr>
<td>Sex [N (%)]</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Income Quintile [N (%)]</td>
</tr>
<tr>
<td>Lowest</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Highest</td>
</tr>
<tr>
<td>Rural [N (%)]</td>
</tr>
<tr>
<td>Frail [N (%)]</td>
</tr>
<tr>
<td>Prior joint injection &lt;6mths prior to TKA</td>
</tr>
<tr>
<td>6-12mths prior</td>
</tr>
<tr>
<td>1-5years prior</td>
</tr>
<tr>
<td>&gt;5years prior prior to TKA</td>
</tr>
<tr>
<td>Co-morbidities</td>
</tr>
<tr>
<td>Osteonecrosis [N (%)]</td>
</tr>
<tr>
<td>Baseline CVD Risk [N (%)]</td>
</tr>
<tr>
<td>Diabetes [N (%)]</td>
</tr>
<tr>
<td>HTN [N (%)]</td>
</tr>
<tr>
<td>COPD [N (%)]</td>
</tr>
<tr>
<td>CHF [N (%)]</td>
</tr>
<tr>
<td>Charlson Score [N (%)]</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2 or more</td>
</tr>
<tr>
<td>Admission characteristics</td>
</tr>
<tr>
<td>Teaching hospital [N (%)]</td>
</tr>
<tr>
<td>Surgeon volume [Median (IQR)]</td>
</tr>
<tr>
<td>Hospital volume [Median (IQR)]</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Any complication [N (%)]</td>
</tr>
<tr>
<td>VTE within 90d [N (%)]</td>
</tr>
<tr>
<td>2y infection [N (%)]</td>
</tr>
<tr>
<td>2y revision [N (%)]</td>
</tr>
<tr>
<td>2y # [N (%)]</td>
</tr>
<tr>
<td>Death within 90d [N (%)]</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; HTN: hypertension; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; VTE: venous thrombo-embolism; #: peri-prosthetic fracture
<table>
<thead>
<tr>
<th></th>
<th>Rate per 100 recipients (95%CI)</th>
<th>OA</th>
<th>IA</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE within 90days</td>
<td>1.40 (1.29-1.53)</td>
<td>1.49 (1.17-1.87)</td>
<td>0.46 (0.15-1.07)</td>
<td></td>
</tr>
<tr>
<td>Death within 90days</td>
<td>0.47 (0.40-0.54)</td>
<td>0.65 (0.45-0.92)</td>
<td>0.95 (0.43-1.80)</td>
<td></td>
</tr>
<tr>
<td>Revision within 2years</td>
<td>1.13 (1.03-1.25)</td>
<td>1.33 (1.03-1.69)</td>
<td>1.65 (1.01-2.54)</td>
<td></td>
</tr>
<tr>
<td># within 2years</td>
<td>0.37 (0.31-0.43)</td>
<td>0.29 (0.17-0.49)</td>
<td>0.55 (0.22-1.13)</td>
<td></td>
</tr>
<tr>
<td>Infection within 2years</td>
<td>1.07 (0.97-1.18)</td>
<td>1.28 (0.98-1.63)</td>
<td>1.50 (0.87-2.40)</td>
<td></td>
</tr>
<tr>
<td>Dislocation within 2years</td>
<td>1.21 (1.10-1.32)</td>
<td>1.62 (1.29-2.02)</td>
<td>2.45 (1.64-3.52)</td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>4.69 (4.47-4.91)</td>
<td>5.55 (4.91-6.24)</td>
<td>5.79 (4.48-7.37)</td>
<td></td>
</tr>
<tr>
<td><strong>TKA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE within 90days</td>
<td>1.63 (1.53-1.73)</td>
<td>1.63 (1.39-1.91)</td>
<td>1.29 (0.89-1.80)</td>
<td></td>
</tr>
<tr>
<td>Death within 90days</td>
<td>0.39 (0.35-0.45)</td>
<td>0.51 (0.38-0.67)</td>
<td>0.59 (0.31-1.00)</td>
<td></td>
</tr>
<tr>
<td>Revision within 2years</td>
<td>1.16 (1.07-1.25)</td>
<td>1.39 (1.17-1.66)</td>
<td>1.02 (0.68-1.46)</td>
<td></td>
</tr>
<tr>
<td># within 2years</td>
<td>0.08 (0.06-0.11)</td>
<td>0.08 (0.04-0.16)</td>
<td>0.14 (0.04-0.35)</td>
<td></td>
</tr>
<tr>
<td>Infection within 2years</td>
<td>0.84 (0.04-0.77)</td>
<td>1.07 (0.87-1.29)</td>
<td>1.26 (0.87-1.77)</td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>3.56 (3.41-3.71)</td>
<td>3.79 (3.41-4.20)</td>
<td>3.59 (2.91-4.39)</td>
<td></td>
</tr>
</tbody>
</table>

#: peri-prosthetic fracture
Table 3.4: Results for Cox Proportional Hazards - Fully Adjusted Models

<table>
<thead>
<tr>
<th></th>
<th>Dislocation within 2y of THA</th>
<th>VTE within 90d of THA</th>
<th>Infection within 2y of TKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95%CI)</td>
<td>p-value</td>
<td>Adjusted HR (95%CI)</td>
</tr>
<tr>
<td><strong>Age (per year)</strong></td>
<td>1.00 (0.99-1.01)</td>
<td>0.39</td>
<td>1.01 (1.01-1.02)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.96 (0.81-1.12)</td>
<td>0.58</td>
<td>1.12 (0.95-1.32)</td>
</tr>
<tr>
<td>Female</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Income Quintile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>1.25 (0.92-1.70)</td>
<td>0.16</td>
<td>0.98 (0.75-1.29)</td>
</tr>
<tr>
<td>2</td>
<td>1.09 (0.84-1.41)</td>
<td>0.54</td>
<td>0.97 (0.76-1.24)</td>
</tr>
<tr>
<td>3</td>
<td>1.05 (0.79-1.40)</td>
<td>0.74</td>
<td>0.98 (0.77-1.25)</td>
</tr>
<tr>
<td>4</td>
<td>1.19 (0.89-1.58)</td>
<td>0.24</td>
<td>1.20 (0.96-1.49)</td>
</tr>
<tr>
<td>Highest</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Rural</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.40 (1.16-1.69)</td>
<td>0.0006</td>
<td>0.77 (0.61-0.97)</td>
</tr>
<tr>
<td>No</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Frail</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.65 (1.24-2.19)</td>
<td>0.0006</td>
<td>1.06 (0.75-1.51)</td>
</tr>
<tr>
<td>No</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td><strong>Charlson</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>1</td>
<td>1.98 (1.50-2.60)</td>
<td>&lt;0.0001</td>
<td>0.85 (0.56-1.28)</td>
</tr>
<tr>
<td>2+</td>
<td>1.39 (0.96-2.01)</td>
<td>0.09</td>
<td>1.01 (0.67-1.53)</td>
</tr>
<tr>
<td><strong>Hospital Volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.62 (0.43-0.90)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Surgeon Volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.50 (0.38-0.67)</td>
<td>&lt;0.0001</td>
<td>0.86 (0.64-1.14)</td>
</tr>
<tr>
<td><strong>Teaching Hospital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.92 (0.69-1.21)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>REF</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td><strong>Arthritis Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>IA</td>
<td>1.37 (1.09-1.71)</td>
<td>0.006</td>
<td>1.14 (0.89-1.46)</td>
</tr>
<tr>
<td>RA</td>
<td>1.91 (1.29-2.82)</td>
<td>0.001</td>
<td>0.37 (0.16-0.88)</td>
</tr>
<tr>
<td>RA vs OA</td>
<td>Unadjusted HR (95%CI)</td>
<td>p-value</td>
<td>Unadjusted HR (95%CI)</td>
</tr>
<tr>
<td></td>
<td>2.05 (1.41-2.99)</td>
<td>0.0002</td>
<td>0.35 (0.15-0.82)</td>
</tr>
</tbody>
</table>

**VTE:** venous thrombo-embolism; #: fracture; Variables that did not meet selection criteria in univariate analyses were not included in the relevant multivariable model(s)

*Log to the base 10
Figure 3.1: Selection of patients for inclusion

Received a primary TJA between 2002-2009
TKA: N=89,713
THA: N=60,305

Received a TJA prior to 2002
N=18,935

Pre-existing joint infection, cancer, fracture, or non-elective procedure
N=8,029

≥2 TJA procedure at index admission
N=4,960

No information on laterality
N=82

Not eligible for OHIP
N=911

Not performed by an Orthopaedic surgeon
N=18

Unable to identify operating surgeon
N=1,293

Final Cohort
TKA: N=71,793
THA: N=43,997
**Figure 3.2:** Cumulative survival curves for the occurrence of a dislocation following THA (2A) and infection following TKA (2B), both within two years.
IV. CHAPTER 4 – INCREASED SURGEON EXPERIENCE WITH RHEUMATOID ARTHRITIS REDUCES THE RISK FOR COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY

Bheeshma Ravi
Ruth Croxford
Peter C Austin
Simon Hollands
J Michael Paterson
Earl Bogoch
Hans Kreder
Gillian A Hawker

From the Division of Orthopaedic Surgery, Department of Surgery, University of Toronto, the Institute for Clinical Evaluative Sciences, the Institute of Health Policy, Management and Evaluation, University of Toronto, the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada, and the Division of Rheumatology, Department of Medicine, Women's College Hospital, Toronto, Canada.

Currently in press in Arthritis & Rheumatism (accepted September 18, 2013)
ABSTRACT

Background and objectives: Total joint arthroplasty (TJA) presents unique surgical challenges in persons with rheumatoid arthritis (RA). We determined the relationship between surgeon experience with, and complications following, TJA in persons with RA.

Methods: Using administrative data, a cohort of RA patients with at least one primary elective hip or knee replacement between 2002 and 2009 was assembled. Cox proportional hazards, censored on death, and accounting for clustering of patients within surgeons, were used to determine the relationship between overall and ‘RA-specific’ surgeon TJA volume and the occurrence of a composite ‘complication’ outcome (revision, infection, dislocation or peri-prosthetic fracture within 2 years of the initial TJA), controlling for potential confounders (patient age, sex, co-morbidity, and disease severity).

Results: We identified 4,762 eligible TJAs (1,515 THAs and 3,247 TKAs) in persons with RA. Of these, 152 (3.3%) experienced a surgical complication within 2 years of their procedure. Controlling for patient and hospital factors, greater surgeon TJA volume in persons with RA, but not overall TJA volume, was associated with a reduced risk for complications (adjusted HR per additional 10 cases: RA volume 0.81, 95%CI 0.71-0.93, p=0.002; overall volume: 0.98, 95%CI 0.97-1.00, p=0.09).

Conclusions: In a cohort of hip and knee TJA recipients with RA, we found that increased surgeon experience performing TJA in patients with RA, irrespective of their overall TJA experience and hospital factors, was associated with a decreased risk of surgical complications. These findings have potential implications for surgeon training and the referral practices of rheumatologists.
INTRODUCTION

Rationale

Volume-outcome relationships have been demonstrated for total joint arthroplasty (TJA)\(^{(8, 212, 283, 284)}\), with the risk for surgical complications roughly inversely proportional to the annual surgeon volume, where surgeon volume is defined as the number of TJA procedures performed by the surgeon in the 365d prior to the index procedure\(^{(285)}\). While most patients undergoing TJA have osteoarthritis (OA), ~3-5\% have rheumatoid arthritis (RA). For the latter, it is not known if the protective benefit of high surgeon TJA volume applies, or if specific surgical experience in persons with RA is required.

RA differs from OA in pathogenesis, prognosis, and medical management\(^{(286, 287)}\). We have recently shown that TJA recipients with RA are at a higher risk for early surgical complications relative to recipients with OA\(^{(256, 288)}\). These findings are not surprising as TJA in persons with RA may pose unique surgical challenges. Relative to patients with OA, those with RA have, on average, more severe synovitis\(^{(173, 174)}\), more delicate soft tissues\(^{(175-177)}\), weaker tendons\(^{(178)}\), ligaments\(^{(173, 174)}\), and bone-tendon attachments\(^{(179, 180)}\). Patients with RA are also more likely to have osteopenic bone\(^{(181-183)}\), and altered periarticular bony anatomy\(^{(91, 92, 184, 185)}\). These anatomic differences have implications for soft tissue handling, joint alignment, implant fixation, and successful joint mechanics following TJA. The particular challenges in this subgroup of patients may require specific experience on the part of the surgeon.

We set out to determine if surgeon experience performing TJA in patients with RA is associated with lower risk for post-TJA complications, after controlling for overall TJA surgeon experience and hospital TJA volume. Specifically, the goals of our study were to: 1) determine the
correlation between annual overall surgeon volume (i.e. ‘all TJA’) and annual surgeon volume specifically in patients with RA (i.e. ‘RA TJA’); 2) determine the proportion of RA TJA recipients that received their surgery at a teaching hospital; and 3) determine the impact of surgeon ‘RA TJA’ volume on the risk of a surgical complication within 2 years of TJA in recipients with RA. We hypothesized that 1) increased surgeon ‘RA TJA’ volume would be highly correlated with surgeon ‘all TJA’ volume; 2) most RA TJA recipients will have received their surgery from a surgeon with high ‘all TJA’ volumes and at a teaching hospital; and 3) that, controlling for other factors, increased surgeon ‘RA TJA’ volumes would independently predict a lower risk for complications.

METHODS

Study sample

Health administrative databases from Ontario, Canada (the country’s most populous province, with a population of 13.5 million in 2012) were used. Ontarians are insured under a single payer system, which covers all medically necessary procedures, including TJAs. The main data sources were hospital discharge abstracts from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), and physician claims from the Ontario Health Insurance Plan (OHIP). These data sets were held securely in a linked, de-identified form and analyzed at the Institute for Clinical Evaluative Sciences. Using specific procedure and diagnostic codes from the Canadian version of the 10th version of the International Statistical Classification of Diseases and the Canadian Classification of Health Interventions (ICD-10-CA/CCI), we created a cohort of primary elective hip and knee TJA recipients (1.VA.53 and 1.VG.53, respectively) with RA, with the index procedure occurring between April 1, 2002 and March 31, 2009. The diagnosis of RA was established using the following validated algorithm: a
hospitalization with a diagnosis code for RA or three physician-billing claims with a diagnosis code for RA in a 2 year period, with at least one claim by a specialist (rheumatologist, orthopedic surgeon or internist) (sensitivity: 78%, specificity: 100%)(258). We excluded the records of individuals for whom the index procedure was not elective, or if it was performed secondary to trauma, fracture or cancer. We also excluded those with a prior history of joint infection or revision arthroplasty, and those who were receiving nursing care immediately prior to surgery, or for whom the operating surgeon could not be identified (Figure 4.1). If a patient underwent multiple procedures, only the first procedure during the study period was included.

**Primary outcome: Surgical complications**

All patients were followed from the date of their index TJA until the occurrence of a composite outcome of surgical complication (infection, dislocation, peri-prosthetic fracture, or revision). Patients were censored after two years of follow-up if they were still event free. Dislocations were defined as the occurrence of a diagnostic code for dislocation, or a procedure code for closed/open reduction. To maximize sensitivity, we identified infections as one of more of: occurrence of an ICD-10-CA diagnostic code for intra-articular infection, with a confirmatory code for an irrigation and debridement; occurrence of an OHIP code for a spacer insertion; or occurrence of a procedure code for a peripheral intravenous central catheter (PICC) line after the TJA, where the referring physician was an orthopaedic surgeon. Peri-prosthetic fractures were defined as the occurrence of a diagnostic code for fracture following insertion of an implant. Revision procedures were identified using ICD-10-CA/CCI procedure codes accompanied by the supplementary status attribute “R.”

**Main exposure variable: Surgeon ‘all TJA’ and ‘RA TJA’ volume**
For each TJA, annual surgeon ‘all TJA’ volume was defined as the number of hip and knee arthroplasty procedures (both primary and revision) performed by the surgeon in the 365 days prior to the procedure (regardless of whether the patient had RA or not), while surgeon ‘RA TJA’ volume was defined as the number of TJA procedures the surgeon had performed on persons with RA over the same time period. The physician claims differentiate between the surgeon who performed the surgery (the ‘primary surgeon’) and the assisting physician (if any). As the primary surgeon typically makes the key decisions regarding surgical approach, choice of implant, and degree of soft tissue tension, our definition of surgeon volume only included TJAs for which the surgeon acted as the primary surgeon.

Patient and hospital covariates

Patient and provider factors that have previously been shown to affect the risk of occurrence of complications following joint replacement were assessed as follows: relevant patient demographic information was obtained from the OHIP Registered Persons Databases (RPDB) (age, sex, neighbourhood income quintile, and rurality); co-morbidities listed on hospital discharge abstracts in the three years before the index TJA admission were categorized according to an adaptation of the Charlson Co-morbidity Index; Adjusted Clinical Groups (ACGs), based on diagnosis codes from hospitalizations and physician visits in the two years before the index TJA admission were used to classify TJA recipients as ‘frail’ (yes/no) at the time of the index procedure; and the number of times each TJA recipient had seen a rheumatologist in the two years prior to the index TJA was assessed as a proxy for RA severity. For each patient, the occurrence of a primary TJA before April 1, 2002 (pre-baseline) was identified from the CIHI-DAD using the appropriate ICD-9 procedure codes (THA: 93.51 and 93.59; TKA: 93.41). Hospital TJA volume was defined as the number of primary and revision TJA procedures performed at the hospital in the 365 days prior to the RA patients’
index procedure. We defined teaching hospitals as those who were members of the Council of Academic Hospitals of Ontario (www.caho-hospitals.com).

**Statistical analyses**

Spearman's rank correlation coefficients were used to quantify the association between surgeon ‘RA TJA’ volume and each of surgeon ‘all TJA’ volumes and hospital TJA volume. Since surgeon volume was defined as the number of procedures performed in the year prior to that index procedure, and thus might vary between TJA procedures performed by the same surgeon at different points in the study period, we used the TJA procedure (and not the surgeon) as the unit of analysis in these correlation analyses. We elected to set the threshold for high surgeon ‘all TJA’ volume at 100 cases/year (high: 100+, low: <100) based on a recent systematic review that classified ‘high’ volumes as >50 TKA procedures per year(290). In the absence of prior studies examining surgeon RA TJA volume, we defined high surgeon ‘RA TJA’ volume as at or above the median value (high: ≥ median, low: <median). Standardized rates of complications (standardized for age, sex, and the joint being replaced) were determined for each surgeon volume category (low ‘ALL’ + low ‘RA’; high ‘ALL’ + low ‘RA’; low ‘ALL’ + high ‘RA’; high ‘ALL’ + high ‘RA’) using indirect standardization.

Univariate Cox proportional hazards regression models, with patients censored on the occurrence of death, were used to determine the relationship between each covariate and the risk of complication. A multivariable Cox proportional hazards model was used to determine the relationship between surgeon ‘RA TJA’ volume and the risk for a surgical complication after adjusting for relevant confounders. As above, patients were censored at the time of death if this occurred prior to the occurrence of the composite outcome. A robust ‘sandwich-type’ variance estimator was used to account for the clustering of patients within the surgeon performing the
procedure. Restricted cubic splines were used to allow for a non-linear relationship between surgeon ‘RA TJA’ volume and the log-hazard of a complication. While patient age and sex at the time of surgery were included in the multivariable model \textit{a priori}, additional covariates were controlled for if, in the univariate regression, they were associated with the composite outcome at a p-value of $\leq 0.4$. These additional covariates considered were: number of visits to a rheumatologist in the two years pre-index TJA, neighbourhood income quintile, rurality, Charlson co-morbidity index, frailty, surgeon ‘all TJA’ volume and hospital TJA volume. We also checked for interactions between surgeon ‘RA TJA’ volume and surgeon volume (dichotomized as ‘high’ or ‘low’), as well as occurrence of the TJA at a teaching hospital. All analyses were performed at the Institute for Clinical Evaluative Sciences (www.ices.on.ca) using SAS version 9.3 for UNIX (SAS Institute, Cary NC). The type I error probability was set to 0.05 for all analyses.

\textbf{RESULTS}

\textit{Cohort characteristics}

Between April 1, 2002 and March 31, 2009, there were 7,472 TJAs (2,814 THAs and 4,658 TKAs) performed in persons with RA in Ontario, Canada (Figure 4.1); of these, 4,762 were eligible primary elective TJA procedures (1,515 THAs and 3,247 TKAs) (Table 4.1). The median age of eligible RA TJA recipients was 66 years (IQR 57-74); most were female (75.3%), with a Charlson score of ‘0’ (78.3%), and only 8.2% were classified as ‘frail’.

\textit{Surgeon and hospital characteristics}

The 4,762 eligible primary elective TJAs were performed by 423 orthopaedic surgeons in 65 hospitals. Approximately 84\% of the surgeries had an assistant; 68\% of these assistants were general practitioners, 17\% were orthopaedic surgeons, and the remainder was a mix of general
surgeons and other assorted surgical specialties. Approximately 40% of these cases were performed in teaching hospitals. The median surgeon ‘all TJA’ and ‘RA TJA’ volumes were 130 cases (IQR 86-200) and 10 cases (IQR 6-19), respectively. The median hospital TJA volume was 549 cases (IQR 370-824). Surgeon ‘all TJA’ volume was significantly correlated with their ‘RA TJA’ volume [Spearman correlation 0.76, p<0.0001] (Figure 4.2), while the correlation between surgeon ‘RA TJA’ volume and hospital TJA volume was 0.41 (p<0.0001).

Approximately two-thirds of the RA TJA recipients received their surgery from a surgeon with high ‘all TJA’ volumes, as we defined it; of the one third who received their TJA from a low volume surgeon, the majority (72%) also received their TJA from a surgeon with a low RA TJA volume. A small cluster of surgeons (approximately 5% of the RA TJA recipients’ surgeons) had low overall TJA volumes but high numbers of TJAs among patients with RA (up to more than 70 in the previous year).

*Surgical complications within two years of TJA – Univariate analysis*

Among the 4,762 TJA recipients with RA, 152 (3.2%) experienced at least one surgical complication within 2 years of their index TJA: 42 (0.9%) dislocations; 53 (1.1%) infections; 43 (0.9%) peri-prosthetic fractures; and 52 (1.1%) revisions (Table 4.1). The 152 cases that had a surgical complication were performed by 105 surgeons. The highest number of complications for a single surgeon was 6, out of a total of 79 cases performed by this surgeon in persons with RA over the study period. Most surgeons (91 out of 105) had 1-2 complications over the study period. The age- and sex-standardized rates of complications ranged from a low of 2.75 per 100 cases (RA patients whose surgeons had low ‘all TJA’ volumes but high ‘RA TJA’ volumes) to a high of 3.41 per 100 cases (RA patients whose surgeons had high ‘all TJA’ volumes but low RA TJA volumes) (Table 4.2). Restricted cubic splines demonstrated an approximately linear relationship between surgeon ‘RA TJA’ volume and the log-hazard of a complication (Figure 4.2).
Consequently, we modified the regression model so that a linear term was used to relate surgeon ‘RA TJA’ volume to the log-hazards of a complication (thereby allowing us to report a uniform hazard ratio). In univariate analysis, there was an increased risk for complications if the index procedure was a hip replacement (unadjusted HR 3.47, 95%CI 2.45-4.90, p<0.0001, ref: index knee replacement), if the patient was frail (unadjusted HR 1.81, 95%CI 1.15-2.86, p=0.01), and if the patient had a Charlson co-morbidity score of 2 or more (unadjusted HR 1.73, 95%CI 1.02-2.93, p=0.04). We did not find a significant interaction between surgeon ‘RA TJA’ volume and surgeon ‘all TJA’ volume (dichotomized as ‘high’ or ‘low’) (p=0.42) or performance of the procedure at a teaching hospital (p=0.95).

Surgical complications within two years of TJA – Multivariable analysis

After controlling for significant covariates, as well as age, sex, neighbourhood income quintile, and occurrence of the procedure at a teaching hospital, surgeon ‘RA TJA’ volume was independently and significantly associated with a reduced risk for our composite outcome (adjusted HR 0.81 per 10 cases, 95%CI 0.71-0.93, p=0.002) (Table 4.3). Collectively, these variables explained 41% of the variance in the outcome(291). Further adjustment for surgeon ‘all TJA’ volume slightly attenuated the effect of surgeon ‘RA TJA’ volume, but the latter remained statistically significant (adjusted HR 0.84 per additional 10 RA TJA cases, 95%CI 0.69-0.95, p=0.009) and no independent effect was seen for ‘all TJA’ volume (adjusted HR 1.00 per additional 10 TJA cases, irrespective of diagnosis, 95%CI 0.98-1.03, p=0.78). Removal of surgeon ‘RA TJA’ volume did not result in a significant association between surgeon ‘all TJA’ volume and the occurrence of a complication (adjusted HR 0.98 per additional 10 TJA cases, 95%CI 0.97-1.00, p=0.09).

DISCUSSION
In a cohort of persons with RA receiving a primary elective TJA of the hip or knee, and taking into consideration previously identified predictors of complications following TJA, we found that greater surgeon experience performing TJA in patients with RA was independently and significantly associated with reduced risk of early surgical complications. This relationship appeared to be linear, with no threshold or cut-point for surgeon ‘RA TJA’ volume identified. Approximately 3.2% of persons in our cohort experienced a complication within 2 years of their TJA; this risk declined by ~20% for every 10 additional RA TJA procedures performed by the surgeon in the year prior to the surgery.

While surgeons who performed more TJA procedures overall were also more likely to have some experience performing TJA in persons with RA, we did not find an independently significant protective benefit of overall surgeon experience once RA TJA experience was accounted for. These findings indicate that specific experience performing TJA in persons with RA is required to adequately prepare surgeons for their associated operative challenges (93, 177, 182, 292-296). To our knowledge, this is the first study to demonstrate that experience in persons with RA, on the part of the surgeon, has a protective benefit for TJA recipients with RA.

As performance of TJA in persons with RA poses unique challenges, both intra-operatively (91, 92, 173-185) and peri-operatively (297-299), we hypothesized that most RA patients would receive TJA in high volume teaching hospitals. This was not the case; only about 40% of our RA TJA recipients received their surgery at an academic centre. We also hypothesized that due to the added complexity of performing TJA in patients with RA versus OA that most RA TJA recipients would be operated on by high volume surgeons. Indeed, two-thirds of our participants received their surgery from a high volume surgeon. However, we identified a small but distinct group of patients who received their TJA from ‘RA TJA expert surgeons’; the latter appeared to
perform TJA predominantly in patients with RA. RA patients who received their TJA from a RA TJA expert had the lowest risk for surgical complications. These findings provide further support for the importance of RA-specific surgical expertise in ensuring optimal surgical outcomes.

In prior work, we have shown that, among patients with RA undergoing TJA, the rate of complications is higher for total hip versus total knee replacement(288). Unfortunately, the relatively small number of RA patients receiving a TJA who experienced a complication precluded analyses of the effect of surgeon RA TJA volume on risk for complications following hip versus knee replacement in patients with RA. The relatively small number of complications also precluded an analysis of specific complications (e.g.: dislocation following THA), and as such we cannot comment on whether the effect of surgeon RA TJA volume varies by complication. Further research in larger samples is warranted to address these issues.

The algorithm used to define the presence or absence of RA had high specificity and sensitivity, but does not provide information on disease severity(289). We controlled for possible proxy measures of RA severity, including frailty(300) and the number of visits to a rheumatologist in the two years prior to surgery(301). While frailty is associated with more severe underlying disease, increased frequency of visits to a rheumatologist may not necessarily indicate increased severity, but rather may indicate appropriate pre-operative management of RA, which may contribute to improved outcomes post-operatively. As such, we cannot rule out the possibility that there are systematic differences in the types of RA patients on which surgeons perform TJA that explain our findings. However, as patients with more severe RA would likely be deemed at higher risk for complications following TJA than those with stable disease, one might expect that these patients would preferentially be operated on by more experienced surgeons. If so,
more complete adjustment for RA severity may serve to accentuate the effect of surgeon RA TJA experience on surgical outcomes. Further research is needed to test this hypothesis.

Our definition of surgeon TJA volume was based on the number of procedures performed by the surgeon in the 365 days immediately preceding each surgery. A similar definition has been used in previous studies (285, 302). Alternatively, some studies have defined surgeon volume as the average caseload for a surgeon over a period of time. While this allows for a uniform volume for each surgeon, it also assumes that there is a benefit on current cases from future experience, which may not be the case, especially if a surgeon’s volume changes over time. The advantage of the ‘surgeon volume’ definition used in the current study is that it allows for fluctuations in a surgeon’s caseload over time (i.e., from early to later in their career). Furthermore, this definition does not assume that a benefit necessarily derives from the surgeon’s years in practice; rather, it evaluates their specific recent experience performing TJAs.

Strengths of our study include the use of population-based health administrative data to assemble a large sample of TJA recipients with RA, defined using a validated algorithm for RA, and consideration of patient, hospital and surgeons predictors of post-TJA complications. However, there were some limitations in addition to those already noted. First, we did not have any information on patient-reported outcomes, including post-TJA pain, functioning and improvements in quality of life. Thus, we do not know whether surgeon experience is also predictive of these outcomes (283, 302). However, since the occurrence of surgical complications has been linked with worse patient-reported outcomes (63, 65), it is likely that greater surgeon experience with RA also contributes to improved patient-reported outcomes in this population. Second, we were unable to capture and thus adjust for technical aspects of the procedure, e.g. surgical approach (86), implant type (303), and use of bone cement (304), which
have been linked with complication rates following TJA. Surgeons with greater experience in performing TJA in patients with RA may systematically differ from those with less experience with respect to surgical techniques; if so, this may account, at least in part, for the RA TJA volume effect. Further research is recommended to confirm or refute these hypotheses.

In summary, among persons with RA who received a primary elective TJA of the hip or knee, those who were operated on by surgeons who performed a greater number of these procedures in patients with RA, experienced fewer complications (revision, infection, dislocation or periprosthetic fracture within 2 years), after controlling for relevant confounders including overall TJA experience. Our findings indicate that overall experience performing TJA is insufficient with respect to optimizing outcomes for patients with RA undergoing this procedure. This has implications for specialty training, as surgeons who wish to establish a practice in RA patients may benefit from specialized training. These findings are also relevant to referring physicians, who should not assume that high-volume surgeons necessarily have the requisite experience in persons with RA.
Table 4.1: Characteristics of Eligible TJA Recipients with RA

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>N=4,762</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (y) [Median (IQR)]</td>
<td>66 (57-74)</td>
</tr>
<tr>
<td>Sex [N (%)]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,573 (75.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>1,173 (24.7%)</td>
</tr>
<tr>
<td>Income Quintile [N (%)]</td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>953 (20.1%)</td>
</tr>
<tr>
<td>2</td>
<td>977 (20.6%)</td>
</tr>
<tr>
<td>3</td>
<td>910 (19.2%)</td>
</tr>
<tr>
<td>4</td>
<td>943 (19.9%)</td>
</tr>
<tr>
<td>Highest</td>
<td>952 (20.1%)</td>
</tr>
<tr>
<td><strong>Arthritis Management</strong></td>
<td></td>
</tr>
<tr>
<td>Prior TJA (before 2002)</td>
<td>1,169 (24.5%)</td>
</tr>
<tr>
<td>Joint replaced – index procedure</td>
<td></td>
</tr>
<tr>
<td>THA</td>
<td>1,515 (31.8%)</td>
</tr>
<tr>
<td>TKA</td>
<td>3,247 (68.2%)</td>
</tr>
<tr>
<td>Saw a rheumatologist in the two years prior to the surgery [N (%)]</td>
<td>2366 (49.7%)</td>
</tr>
<tr>
<td>Number of visits to a rheumatologist in the two years prior to surgery [Median (IQR)]</td>
<td>5 (0-13)</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Frail [N (%)]</td>
<td>389 (8.2%)</td>
</tr>
<tr>
<td>Charlson Score [N (%)]</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3,731 (78.3%)</td>
</tr>
<tr>
<td>1</td>
<td>698 (14.7%)</td>
</tr>
<tr>
<td>2 or more</td>
<td>333 (7.0%)</td>
</tr>
<tr>
<td><strong>Admission characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Teaching hospital [N (%)]</td>
<td>1,894 (39.8%)</td>
</tr>
<tr>
<td>Surgeon ‘all TJA’ volume [Median (IQR)]</td>
<td>130 (86-200)</td>
</tr>
<tr>
<td>High volume (&gt;100 cases/year) [N (%)]</td>
<td>3,329 (67.6%)</td>
</tr>
<tr>
<td>Surgeon ‘RA TJA’ volume [Median (IQR)]</td>
<td>10 (6-19)</td>
</tr>
<tr>
<td>High volume (&gt; 10 cases/year) [N (%)]</td>
<td>2,607 (52.9%)</td>
</tr>
<tr>
<td>Hospital TJA volume [Median (IQR)]</td>
<td>549 (370-824)</td>
</tr>
<tr>
<td><strong>Complications within 2 years of index TJA</strong></td>
<td></td>
</tr>
<tr>
<td>Revision [N (%)]</td>
<td>51 (1.1%)</td>
</tr>
<tr>
<td>Infection [N (%)]</td>
<td>51 (1.1%)</td>
</tr>
<tr>
<td>Dislocation [N (%)]</td>
<td>41 (0.9%)</td>
</tr>
<tr>
<td>Peri-prosthetic fracture [N (%)]</td>
<td>43 (0.9%)</td>
</tr>
<tr>
<td>Any complication [N (%)]</td>
<td>152 (3.3%)</td>
</tr>
</tbody>
</table>

IQR: inter-quartile range
<table>
<thead>
<tr>
<th></th>
<th>‘RA TJA’ volume &lt;10 cases/year</th>
<th>‘RA TJA’ volume ≥10 cases/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘All TJA’ volume &lt;100 cases/year</td>
<td>3.21 (95% CI 2.31-4.36)</td>
<td>2.76 (95% CI 1.11-5.68)</td>
</tr>
<tr>
<td>‘All TJA’ volume ≥100 cases/year</td>
<td>3.41 (95% CI 2.33-4.81)</td>
<td>2.93 (95% CI 2.30-3.69)</td>
</tr>
</tbody>
</table>

*Standardized for age, sex, and the joint being replaced (hip/knee)
Table 4.3: Univariate and multivariate determinants of occurrence of a surgical complication

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.22</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.92 (0.63, 1.35)</td>
<td>0.67</td>
</tr>
<tr>
<td>Female</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Income Quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>1.17 (0.72, 1.90)</td>
<td>0.53</td>
</tr>
<tr>
<td>2</td>
<td>0.85 (0.53, 1.38)</td>
<td>0.52</td>
</tr>
<tr>
<td>3</td>
<td>0.71 (0.40, 1.25)</td>
<td>0.24</td>
</tr>
<tr>
<td>4</td>
<td>0.98 (0.59, 1.62)</td>
<td>0.95</td>
</tr>
<tr>
<td>Highest</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Arthritis Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior TJA (before 2002)</td>
<td>1.07 (0.75, 1.54)</td>
<td>0.69</td>
</tr>
<tr>
<td>Joint replaced – index procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THA</td>
<td>3.47 (2.45, 4.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TKA</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frail</td>
<td>1.81 (1.15, 2.86)</td>
<td>0.01</td>
</tr>
<tr>
<td>Charlson Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>REF</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.10 (0.68, 1.79)</td>
<td>0.70</td>
</tr>
<tr>
<td>2 or more</td>
<td>1.73 (1.02, 2.93)</td>
<td>0.04</td>
</tr>
<tr>
<td>Admission characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching hospital</td>
<td>1.20 (0.85, 1.68)</td>
<td>0.29</td>
</tr>
<tr>
<td>Surgeon ‘all TJA’ volume (per 10 cases)</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hospital TJA volume (per 50 cases)</td>
<td>1.01 (0.98, 1.03)</td>
<td>0.64</td>
</tr>
<tr>
<td>Surgeon ‘RA TJA’ volume (per 10 cases)</td>
<td>0.89 (0.79, 1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Further adjustment for surgeon ‘all TJA’ volume slightly attenuated the effect of surgeon ‘RA TJA’ volume, but the latter remained statistically significant (adjusted HR 0.84 per additional 10 RA TJA cases, 95%CI 0.69-0.95, p=0.009) and no independent effect was seen for ‘all TJA’ volume (adjusted HR 1.00 per additional 10 TJA cases, irrespective of diagnosis, 95%CI 0.98-1.03, p=0.78). Removal of surgeon ‘RA TJA’ volume did not result in a significant association between surgeon ‘all TJA’ volume and the occurrence of a complication (adjusted HR 0.98 per additional 10 TJA cases, 95%CI 0.97-1.00, p=0.09).
Figure 4.1: Selection of patients for inclusion

Person with RA receiving a primary TJA between 2002-2009

TOTAL: N=7,472
TKA: N=4,658
THA: N=2,814

Prior joint infection, revision TJA, or index TJA for cancer or fracture
N=2,065

≥2 TJA procedure at index admission
N=413

Not eligible for health insurance
N=39

received nursing care immediately prior to index TJA
N=89

Unable to identify surgeon
N=104

Final Cohort
TOTAL: N=4,762
TKA: N=3,247
THA: N=1,515
Figure 4.2: Surgeon ‘all TJA’ versus ‘RA TJA’ volume*

* Each point represents an individual patient at the time of their index TJA – the volume variables are those of the patient’s operating surgeon in the 365d prior to the index TJA

* The percentage values refer to the proportion of patients in each quadrant relative to the total number of TJA recipients
**Figure 4.3:** Log-hazards for occurrence of a surgical complication versus surgeon ‘RA TJA’ volume
V. CHAPTER 5 – DISCUSSION

This thesis consists of three projects investigating the occurrence of surgical complications following total joint arthroplasty (TJA) in persons with rheumatoid arthritis (RA). While TJA of the hip (THA) and knee (TKA) are among the most successful health care interventions, there is a low, but very real, risk for subsequent complications – including, but not limited to, venous thrombo-embolic events, dislocation, infection, peri-prosthetic fracture, and revision arthroplasty. Not only do these complications lead to considerable morbidity for the patient, they place a significant burden on the health care system. As the rates of these procedures continue to increase, against a backdrop of diminishing resources, it is increasingly important to identify predictors of complications, as well as strategies to mitigate them. While several risk factors for complications have been identified, the majority of this research has been performed in TJA recipients with osteoarthritis (OA). As RA differs fundamentally from OA in terms of etiology, pathogenesis, and pharmacologic management, it is not clear if the results of these studies are generalizable to TJA recipients with RA. To put this into context, somewhere between 4,000 to 14,000 primary TJAs were performed in persons with RA, in Ontario, over the last decade. Determining if these patients are at increased risk for complications, and identifying specific mitigating factors, may inform patient-physician discussions regarding timing and referral for arthroplasty and may affect surgical decision-making.

The projects that comprise this thesis were undertaken with an eye towards determining the state of the current evidence around TJA in RA, and clarifying the risk for complications following TJA in persons with RA versus OA. The first project examined the current evidence on the risk of complications in TJA recipients with RA relative to those with osteoarthritis (OA). The second project was a retrospective cohort study, which utilized administrative data to determine
if TJA recipients with RA are at increased risk for complications relative to those with OA, after adjusting for potential confounders. The third project examined the impact of surgeon experience performing TJA procedures in persons with RA, and surgeon TJA volume overall, on the likelihood of occurrence of surgical complications following TJA in patients with RA. This discussion consists of three sections. The first section describes the contributions to the literature for each of the three papers. The second section summarizes the implications of our findings, and potential strategies to address the differential risks of complications following TJA, based on arthritis type. The third section summarizes our conclusions.

I. Contributions to the Literature

PAPER 1: A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY FOR RHEUMATOID ARTHRITIS VERSUS OSTEOARTHRITIS

Objective
To quantitatively and qualitatively synthesize the existing evidence on the relative risk of complications following TJA in persons with RA versus OA, and to identify actionable limitations in methodology that may have threatened the validity of prior findings.

Contribution
There was strong evidence for an increased risk for dislocation following THA and fair evidence for an increased risk for infection following TKA, in persons with RA versus those with OA. To our knowledge, this is the first systematic review to assess rates of complications following THA and TKA in patients with RA versus OA. Since its publication, there has been one more study examining peri-operative outcomes in TKA recipients with RA versus OA(305) – this study also noted an increased risk for infection following TKA, in unadjusted analysis. The
increased risk of dislocation following THA in patients with RA was not, to our knowledge, well recognized previously. This study also identified several limitations in previous research that warranted further attention. Less than 10% of studies (3 out of 40) described the criteria that were used to establish the diagnosis of RA. An additional three studies used the diagnosis provided by the referring physician to determine the diagnosis of RA (information not in text, provided via e-mail from corresponding author of relevant study). For 85% of studies (34 out of 40), we did not have, and were unable to obtain, any information on the validity of the definition used to establish RA, making it challenging to compare findings across studies and to interpret results. It is possible that some studies used a less specific definition of RA and OA, increasing the risk of misclassification bias, whereby patients with RA are actually classified as having OA, and possibly vice-versa. This blurring between diagnoses reduces the likelihood of identifying differences between these groups. Furthermore, less than 30% of the studies adjusted for potential confounders – patients with RA are younger, and are more likely to have a heavier burden of co-morbidity, both of which are risk factors for complications following TJA(27, 144, 151, 152). As such, any observed differences between RA and OA in these studies may actually be secondary to systematic differences in socio-demographics (among other characteristics) between these populations, and not necessarily due to differences in the disease process. None of the studies controlled for clustering of patients by surgeons or hospitals. By ignoring the clustered nature of outcomes, one mixes cluster variance with subject variance, which ultimately leads to an underestimate of the overall variance, with inappropriately small p values and overly narrow confidence intervals(306). Furthermore, the majority of these studies were underpowered to detect a difference between groups – the described rates of surgical complications are < 2%, therefore comparative studies require a relatively large sample size to assess for a difference between groups. As such, the lack of an observed difference between RA and OA in terms of the occurrence of revision, infection (following THA), venous thrombo-
embolism or mortality may be a reflection of the inadequate sample size in these studies. For these reasons, we concluded that further work is required to determine if patients with RA are at differential risk for complications following TJA relative to those with OA.

PAPER 2: PATIENTS WITH RHEUMATOID ARTHRITIS ARE AT INCREASED RISK FOR COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY

Objective

To address the methodological complications identified in project 1, above, we used provincial health administrative databases to compare the rates of surgical complications following THA and TKA in recipients with RA versus OA, after controlling for potential confounders and for clustering by surgeons.

Contribution

The rates of occurrence of at least one complication (within 90 days: venous thrombo-embolism, death; within 2 years: revision, periprosthetic fracture, infection, or dislocation) are similar between RA and OA after both THA (OA: 3.5%, RA: 3.6%) and TKA (OA: 4.7%, RA: 5.8%). However, TJA recipients with RA were found to be approximately twice as likely to experience a dislocation following THA, and one-and-a-half times as likely to experience an infection following TKA, relative to recipients with OA. No increased risk was found for other complications, including: infection following THA, death within 90 days, periprosthetic fracture, or early revision following either THA or TKA. This information will help inform both rheumatologists and patients with rheumatoid arthritis on the risks of joint replacement – specifically, that while RA patients are at a higher risk for two specific complications, in general, the risk of complications is rare and similar to that in TJA recipients with OA – arthroplasty remains a relatively safe procedure in RA patients.
The immediate aftermath of this study will take the form of further studies to identify the mediators for the increased risk for dislocation following THA, and increased risk for infection following TKA for patients with RA. Identification of specific mediators could lead to the development of strategies to mitigate the risks, particularly if the mediators are modifiable. In the interim, the findings of the current study may help guide post-operative management and monitoring strategies. In most cases, THA recipients are asked to follow a set of “hip precautions” in the first weeks to months following surgery(307, 308). These precautions detail several motions and positions that the patient is advised not to put their hip through, in a bid to avoid the occurrence of dislocation. Given the results of this study, surgeons may opt to keep RA patients on dislocation precautions for a slightly longer period of time, as the majority of dislocations in the RA group occurred in the first 6 months following surgery. Surgeons may also opt to modify their surgical approach or choice of implants in these patients, in an effort to mitigate the risk of dislocation. In response to the increased risk for infection following TKA in patients with RA, surgeons may opt to extend the course of antibiotics post-operatively, or have more frequent follow-up visits to monitor wound healing. They may also opt for a post-operative rehabilitation protocol that balances the need for complete range-of-motion with potential for delayed wound healing in these patients.

To our knowledge, this is the largest cohort study comparing the rates of complications following TJA in persons with RA versus those with OA, and the first to use a validated algorithm, with high sensitivity and specificity, to identify persons with RA using administrative databases. This is also the first paper to report the age & sex-standardized rates for a range of complications following TJA, for either patients with RA, or those with OA. As we have demonstrated, the rate of complications within 2 years of TJA is likely higher than the often-
stated figure of <2%. Finally, this paper was the first to show that the increased risk for RA patients persists after adjusting for several confounders that have not been previously accounted for (e.g.: presence of frailty, surgeon and hospital volume), and after accounting for the clustering of patients by operating surgeons. Patients with RA also experienced these complications earlier in their post-operative course than patients with OA, suggesting that patients with RA require closer monitoring in the short-term following TJA. These findings suggest that the differential risk in patients with RA is mediated by factors unique to this disease, and its management, and does not solely result from the varying socio-demographics and provider factors between these groups.

PAPER 3: INCREASED SURGEON EXPERIENCE WITH RHEUMATOID ARTHRITIS REDUCES THE RISK OF COMPLICATIONS FOLLOWING TOTAL JOINT ARTHROPLASTY

Objective
We set out to determine if specific experience on the part of the surgeon with respect to performance of TJA procedures in patients with RA has a protective benefit above that provided by high surgeon TJA volume overall (i.e. regardless of the patient’s underlying diagnosis).

Contribution
Greater surgeon experience performing primary TJA in patients with RA was independently and significantly associated with reduced risk of early surgical complications (revision, infection, periprosthetic fracture, or dislocation) in primary elective TJA recipients with RA. Approximately 3% of TJA recipients with RA will experience a surgical complication within two years of their procedure, and this risk declines by 20% (e.g.: from 3% to 2.4%) for every 10 additional TJA procedures performed by the operating surgeon on persons with RA in the year
prior to surgery. While surgeons with high TJA volumes were also likely to have experience performing TJAs in person with RA, there was not a significant protective benefit of overall surgeon experience once RA TJA experience was accounted for. We also identified a small but distinct group of patients who received their TJA from ‘RA TJA expert surgeons’, who appear to perform TJA predominantly in patients with RA, and had the lowest rates of complications. These findings build on those reported in projects 1 & 2, and lends credence to the notion that “surgical factors” are associated with, and are potential moderators of, the occurrence of complications following TJA in persons with RA. It is possible that surgeons with specific experience in this patient population have developed strategies to deal with the unique surgical challenges in patients with RA (i.e.: poorer quality soft-tissues, osteopenic bone, increased likelihood of acetabular protrusion, diminished function at baseline, etc.). It is possible that solicitation (in the form of a survey of higher ‘RA TJA’ volume surgeons) and promulgation of these strategies (in the form of peer-reviewed research and/or specialized training as part of fellowship programs) could help mitigate the complications in patients with RA.

We also noted that while most RA TJA recipients receive their surgery from a high-volume surgeon, >60% receive their surgery at a non-academic centre. We had anticipated that the majority of RA patients – who we assumed would be receiving care from a rheumatologist, who tend to be clustered around academic centres (in Ontario) – would have been referred to a surgeon at a teaching hospital for their TJA. One possible explanation is that these patients are being managed mainly by their family physicians, who refer to orthopaedic surgeons that are in close proximity, not necessarily those working at teaching hospitals. This is consistent with our finding that less than half of the RA patients in our cohort had seen a rheumatologist in the two years prior to their surgery. It is also consistent with recent work that has demonstrated that RA patients, particularly those over the age of 65, are less likely to receive care from a
rheumatologist, and will instead be followed by a family physician (309) – as such, there is no reason to expect that these patients will be referred to a surgeon at an academic centre for their TJA. This further suggests that any guidelines for referral that arise from future studies will need to be targeted to family physicians as well as rheumatologists.

To our knowledge, this is the first paper to demonstrate that specific experience, on the part of the surgeon, operating in persons with RA, has a protective benefit for TJA recipients with RA. Our findings support the notion that surgeons who wish to establish a practice in RA patients may benefit from specialized training. Furthermore, they suggest that referring physicians need to take the specific experience of the surgeon in persons with RA prior to making a referral.

II. Implications of, and potential strategies to address, the differential risks of complications following TJA, based on arthritis type

Despite the increased risk for specific complications (infection following TKA, dislocation following THA) in recipients with RA versus OA, the rates of these complications remain relatively low (<3%) in both groups. This would indicate that despite the fact that patients with RA are, on average, younger, sicker, and more likely to be frail than patients with OA, the rate of complications in patients with RA is not excessive. This speaks to the generally safe nature of this elective procedure, and suggests that the benefits of TJA are not outweighed by the risk for complications. This information, alongside our findings around the impact of surgeon RA experience on the risk of complications, directly informs referring physicians, RA patients, and arthroplasty surgeons.

The increased risk for dislocation following THA in persons with RA may result from anatomic differences in persons with RA and/or from systematic differences in the surgical approach or
implant selection between arthritides. Persons with RA are more likely to have acetabular protrusion(91, 92), which increases the risk of implant-on-bone impingement and subsequent dislocation. These patients are also prone to suboptimal hip abductor strength and soft-tissue laxity post-operatively, secondary to their generally weaker soft-tissues relative to persons with OA(93, 177). Furthermore, patients with RA are generally smaller than those with OA(271, 272); this may result in a tendency by surgeons to use a smaller femoral head component, which in turn increases the risk for dislocation(89, 90). In response to our findings, surgeons should carefully consider their choice of surgical approach, implant offset and tensioning of soft tissues in patients with RA. They may also ask patients with RA to follow ‘hip precautions’ for a longer period of time post-operatively(307, 308) than they would recipients with OA.

Now that we have confirmed that patients with RA are at increased risk for this complication, the next step is to identify specific mediators for this risk. Prosthesis dislocations are very painful, and they require revision arthroplasty and/or aggressive rehabilitation following closed reduction(87). It is estimated that a dislocation increases the hospital costs of a primary THA by over 300%(88). Identification of specific mediators could lead to the development of strategies to mitigate this risk, particularly if these mediators are modifiable. The projects that comprised this thesis were not designed to identify mediators for this risk, but were instead designed to clarify whether RA patients were at increased risk after adjusting for socio-demographic differences between these patients and those with OA. Future studies that aim to identify specific mediators, such as implant size, will need to be adequately powered adjust for these mediators and observe the effect of this adjustment on the coefficient relating RA diagnosis to the hazard for dislocation(310, 311).
There are several potential explanations for the increased risk for infection following TKA in persons with RA. Identification of these mediators may improve targeting of TJA, and aid in the development of strategies to mitigate this risk. In addition to being a source of considerable morbidity, each infected arthroplasty is estimated to cost over $30,000 (USD), on average, to manage\(^{(257)}\). One area that is ripe for exploration is the impact of the pharmacologic therapy for RA – these medications include several immunomodulatory drugs, such as DMARDs, systemic corticosteroids, anti-malarials, and biologic therapies. Most of these medications have been linked to an increased risk for post-operative wound infection\(^{(155, 159, 281, 282)}\), and their use pre-operatively may contribute to the increased risk for infection following TKA in patients with RA. To the best of our knowledge, the impact of biologics on the risk for infection following TJA has not been examined. Less clear, however, is why the risk for infection was greater following TKA, and not in THA. One possible explanation is that the musculocutaneous flap is thinner in TKAs than in THAs – from deep to superficial, the flaps in THA are made up of the hip capsule, the abductor tendons, the fascia lata, and finally the dermis. In contrast, the flap in a TKA has two layers: the extensor tendons, and the dermis. By definition, a thinner flap is more prone to break down\(^{(312)}\); in patients with RA, this risk is exacerbated by the generally weaker quality of the soft tissues\(^{(175-177)}\). It is also possible that RA patients with end-stage arthritis in their knees are more likely to use DMARDs, and other immunomodulatory drugs, relative to those with end-stage hip arthritis. Further studies are required to elucidate this.

The studies described in *Chapters 2 & 3* were not designed to identify mediators of the increased risk for complications in TJA recipients with RA. The systematic review and meta-analysis was focused on comparative studies between RA and OA, not on analyses focused solely on persons with RA. However, these studies were pulled and reviewed as part of the preparation for the project, but none of these studies were designed to identify mediators for
complications following TJA. The retrospective cohort study described in Chapter 3 was designed to compare complication rates between TJA recipients with RA and OA, and to determine any differential risk persisted after adjusting for socio-demographic differences between these groups. We did not include several potential mediators in our model, as we wished to first clarify if a differential risk existed. Ideally, future studies will utilize arthroplasty registers that are linked to administrative databases, and will be able to combine large sample sizes, validated arthritis diagnoses, and a rich reservoir of information on pre-operative morbidity and the procedure itself (e.g.: implants, surgical approach, etc).

While it is not clear if systematic differences in surgical technique account, in part, for the increased risk for complications in TJA recipients with RA versus OA, the findings described in Chapter 4 certainly suggest that ‘surgical factors’ can potentially affect the risk for complications in patients with RA. These factors may include specific surgical approaches, implants, bone cement, etc. Our findings support the notion that increased surgeon experience in persons with RA reduced the risk for complications in TJA recipients with RA. It is possible that these surgeons have developed specific operative strategies for dealing with the surgical challenges in RA patients, and that these strategies involve specific approaches, implants, etc. This also offers potential avenues through which the risk for complications can be minimized: 1) by selective referral from referring physicians to surgeons with specific experience in persons with RA, and 2) the integration of teaching on the unique surgical challenges in these patients as part of arthroplasty fellowship training. Education about the importance of specific surgical experience in persons with RA cannot be solely directed at orthopaedic surgeons and rheumatologists, but must also inform family physicians, and patients with RA. In addition to publication of these findings in peer-reviewed journal and presentations at relevant national and international conferences, these findings could be discussed with the Canadian Rheumatology
Association (CRA), Canadian Orthopaedic Association (COA), Canadian Arthroplasty Society (CAS), etc. These groups may help promulgate these findings to the relevant stakeholders (rheumatologists, family physicians, orthopaedic surgeons). The implementation of further strategies to minimize risk for complications, and maximizing improvement in patient-reported outcomes, requires the identification of specific mediators for this increased risk in TJA recipients with RA.

The studies described in the previous chapters did not examine for differences in pre- and post-operative patient-reported outcomes (pain, function, and quality of life) between TJA recipients with RA versus OA, limiting our ability to comment on these outcomes. While the rates of complications following TJA remain fairly low, it is currently estimated that anywhere from 15% to 30% of TJA recipients report suboptimal improvements, and in some cases worsening, of pain and function following TJA. To put this into context, there were ~110,000 first-time primary elective TJAs performed in Ontario, Canada between 2002-2009, of which up to 33,000 patients experienced suboptimal outcomes. A recent study, the findings of which were reported at EULAR 2013, suggested that THA recipients with RA have significantly worse patient-reported outcomes following THA than recipients with OA(313). As the occurrence of post-operative complications is associated with suboptimal patient-reported outcomes(68, 69, 314), our findings, particularly around the timings of these complications, may account, at least partially, for the differential patient-reported outcomes in patients with RA versus OA. Other risks for suboptimal patient-reported outcomes include worse function at baseline and involvement of multiple joints(9, 13, 315-318). However, no study to date has explored the impact of baseline disease severity (measured by the disease activity score – DAS)(319, 320) on patient-reported outcomes following TJA. Given the inflammatory and poly-articular nature of RA, it is possible that baseline severity has an even greater impact on outcomes than in patients
with OA. Determining if reduced baseline disease severity is associated with greater improvement in patient-reported outcomes following joint replacement in patients with RA will aid patient-physician decision-making around arthroplasty, particularly around the timing of peri-operative pharmacologic management.

III. Conclusions

The principal conclusion of this thesis is that while the risk for complications following TJA in persons with RA is low, these patients are at increased risk relative to those with OA. While there was no significant difference in the occurrence of complications overall, patients with RA were at increased risk for dislocation following THA and infection following TKA versus patients with OA. These complications likely lead to suboptimal patient-reported outcomes, and may account, in part, for the disparity in the outcomes in TJA recipients with RA versus OA. Increased surgeon experience in persons with RA lowers the risks for surgical complications in these patients, suggesting that there are modifiable ‘surgical factors’ that should be used in these patients. Further research is required to identify potential mediators for this increased risk in patients with RA, and to delineate strategies to optimize outcomes in these patients.
REFERENCES


193. Dislocation rate after hip arthroplasty within the first postoperative year: 36mm versus 28mm femoral heads. HIP International. [Journal: Article]. 2011;21(5):559-64.


Appendix 2.1: Eligibility criteria for selected studies

Implants: at least 1 of the following
- Total hip arthroplasty (THA)
- Total knee arthroplasty (TKA)

Outcomes: at least 1 of the following
- Revision surgery
- Dislocation
- Infection
  - Superficial infection necessitating antibiotics
  - Deep infection requiring irrigation and debridement
  - Deep infection requiring revision
- Venous thromboembolism
  - Deep vein thrombosis
  - Pulmonary embolism
- All cause mortality within 90d of surgery

Stratification / adjustment
- Arthritis diagnosis either stratified for in the analysis OR adjusted for in a multivariate model

Sample size
- 200 joints or more
- Sample size requirements refer to individual joints (i.e. hip OR knee), not combinations of THA and TKA

Year of publication
- 1990 to 2011

Population
- Inclusions
  - Humans with total knee arthroplasty or total hip arthroplasty
  - Adult patients (18 years of age or older)
  - Comparison with osteoarthritis (OA)
- Exclusions
  - Patients who have had previous surgical procedures on the index joint (e.g.: realignment osteotomy)
  - Patients who have had a joint arthroplasty as a result of a fracture or malignancy
Appendix 2.2: MeSH keywords and search strategies utilized

Ovid MEDLINE(R)

1. arthritis, rheumatoid/ or caplan syndrome/ or felty's syndrome/ or rheumatoid nodule/ or rheumatoid vasculitis/ or sjogren's syndrome/ or still's disease, adult-onset/ or (rheumatoid adj5 arthrit*).ti,ab.

2. (("Prostheses and Implants"/ or *Arthroplasty/) and (*Hip/ or *Hip Joint/ or *knee/ or *knee joint/)) or *Hip Prosthesis/ or *Joint Prosthesis/ or *arthroplasty, replacement/ or *arthroplasty, replacement, hip/ or *arthroplasty, replacement, knee/ or ((hip* or knee*) adj5 (arthroplast* or replace*))).mp.

3. 1 and 2

4. case-control studies/ or exp cohort studies/ or cross-sectional studies/ or Registries/ or (cohort* or registry or registries).mp. or cohort studies/ or longitudinal studies/ or follow-up studies/ or case-control studies/ or retrospective studies/ or prognosis/ or disease-free survival/ or treatment outcome/ or treatment failure/ or prognosis/ or disease-free survival/ or medical futility/ or pregnancy outcome/ or treatment outcome/ or treatment failure/ or disease progression/ or morbidity/ or incidence/ or prevalence/ or mortality/ or "cause of death"/ or child mortality/ or fatal outcome/ or fetal mortality/ or hospital mortality/ or infant mortality/ or maternal mortality/ or perinatal mortality/ or survival rate/ or survival analysis/ or disease-free survival/ or natural history.mp. or reoperation/ or prosthesis failure/ or postoperative complications/ or pain, postoperative/ or implant capsular contracture/ or prosthesis-related infections/ or surgical wound infection/ or Venous Thrombosis/ or pain measurement/ or pain/ or back pain/ or low back pain/ or headache/ or metatarsalgia/ or neck pain/ or neuralgia/ or sciatica/ or pain, intractable/ or pain, referred/

5. 3 and 4

Embase

1. rheumatoid arthritis/ or adult onset still disease/ or felty syndrome/ or rheumatoid nodule/ or (rheumatoid adj5 (arthrit* or vasculitis)).ti,ab. or pneumoconiosis/ or (Caplan* adj2 (disease* or syndrome*)).ti.ab. or Sjogren syndrome/

2. ((arthroplasty/ or *joint prosthesis/) and (*hip/ or *knee/)) or exp *hip arthroplasty/ or exp *knee arthroplasty/ or *total hip prosthesis/ or ((hip* or knee*) adj5 (arthroplast* or replace*)).mp.

3. 1 and 2

4. cohort analysis/ or cross-sectional study/ or exp case control study/ or longitudinal study/ or prospective study/ or retrospective study/ or hospital based case control study/ or population based case control study/ or cancer recurrence/ or cancer regression/ or cancer relapse/ or disease duration/ or disease exacerbation/ or prognosis/ or recurrent disease/ or reinfection/ or relapse/ or remission/ or tumor recurrence/ or tumor regression/ or survival/ or cancer survival/ or disease free survival/ or overall survival/ or survival rate/ or survival time/ or incidence/ or cancer incidence/ or familial incidence/ or morbidity/ or maternal morbidity/ or perinatal morbidity/ or newborn morbidity/ or mortality/ or cancer mortality/ or childhood mortality/ or embryo mortality/ or fetus mortality/ or infant mortality/ or maternal mortality/ or prenatal mortality/ or surgical mortality/ or perinatal mortality/ or newborn mortality/ or prevalence/ or treatment outcome/ or disease free interval/ or treatment failure/ or drug treatment failure/ or death/ or "cause of death"/ or dying/ or heart death/ or sudden death/ or child death/ or newborn death/ or "evaluation and follow up"/ or
follow up/ or functional assessment/ or functional assessment inventory/ or harris hip score/ or hazard assessment/ or case study/ or reoperation/ or postoperative complication/ or postoperative infection/ or postoperative pain/ or postoperative thrombosis/ or exp prosthesis failure/ or surgical infection/ or prosthesis failure/ or prosthesiology/ or endoprostheses loosening/ or prosthesis loosening/ or prosthesis fixation/ or pain/ or exp backache/ or exp bone pain/ or chronic pain/ or flank pain/ or exp "headache and facial pain"/ or intractable pain/ or jaw pain/ or exp leg pain/ or limb pain/ or musculoskeletal pain/ or exp myalgia/ or neck pain/ or exp neuralgia/ or exp postoperative pain/ or referred pain/ or shoulder pain/ or spinal pain/ or pain assessment/  
5  3 and 4

**CINAHL (EBSCOHost)**

S1 (MH "Arthritis, Rheumatoid") OR (MH "Caplan Syndrome") OR (MH "Felty's Syndrome") OR (MH "Sjogren's Syndrome") OR (MH "Spondylitis, Ankylosing") OR (MH "Still's Disease, Adult-Onset") OR (MH "Pneumoconiosis") OR (TX rheumatoid N3 vasculitis)  
S2 (MH "Arthroplasty") OR (MH "Joint Prosthesis") OR (TX hip N5 arthroplast*) OR (TX knee* N5 arthroplast*) OR (TX hip* N5 replace*) OR (TX knee N5 replace*)  
S3 (S1 AND S2)  

**Web of Science**

1  Arthroplasty OR joint replacement  
2  Rheumatoid arthritis  
3  1 AND 2
Appendix 2.3: Assessment of risk of bias

1. Case definition
   2 = Operational definition of cases/controls including exclusion criteria
   1 = Operational definition of cases/controls but no exclusion criteria
   0 = No explicit definition of cases or can’t tell

2. Patient selection
   2 = Inception cohort, defined in relation to time of primary joint replacement or revision
   1 = Mixed cohort, including a subset of the sample followed from time of primary joint replacement or revision
   0 = Mixed cohort, unable to define subsets within the cohort or can’t tell

3. Follow-up
   2 = Complete follow-up: > 90% of all participants accounted for
   1 = < 90% follow-up with description provided of participants lost to follow-up
   0 = < 90% follow-up with no description of those lost to follow-up

4. Outcome
   2 = Blinded outcome appropriate to the research question with potential for replicability of at least 1 outcome or valid/reliable self-report measure
   1 = Outcome appropriate to the research question with description of how outcome was assessed
   0 = Outcome appropriate to the research question but no description of how outcome was assessed

5. Analysis
   3 = Adjusted proportions provided (e.g., by use of Mantel–Haenzel) or appropriate multivariate techniques used to adjust for any prognostic factor
   2 = Crude proportions but data stratified or presented in a manner that would allow for analysis of subsets
   1 = Crude proportions for at least 1 outcome
   0 = Description of sample only, unclear about statistical methods used or can’t tell

6. Database (for database studies only)
   2 = Any attempt to assess data quality (i.e., double data entry, some reabstraction of primary data, or other quality checks)
   1 = No attempt to assess data quality

7. Total score
   ________/ 11 (question 6 omitted)
   ________/ 13 (question 6 included)
### Appendix 2.4: Summary of comparative studies reporting hip dislocation following THA

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Approach</th>
<th>UAOR [95CI]</th>
<th>Adjusted OR [95CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedlundh (1995)(230)</td>
<td>2y</td>
<td>Mix</td>
<td>2.32 [1.30, 4.11]</td>
<td>1.8 [1, 3.2]</td>
</tr>
<tr>
<td>Conroy (2008)(89)</td>
<td>5y</td>
<td>Mix</td>
<td>1.92 [1.12, 3.24]</td>
<td>2.0 [1.2, 3.4]</td>
</tr>
<tr>
<td>Mallory (1999)(234)</td>
<td>3y</td>
<td>WJ/TG</td>
<td>8.01 [0.32, 88.51]</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Combined Estimate**

- UAOR 2.74 [95CI 1.73, 4.34; 2,842 RA, 61,861 OA patients; $I^2 = 27\%$]

- Adjusted OR 2.16 [95CI 1.52, 3.07; 1,637 RA, 61,810 OA patients; $I^2 = 0\%$]

*WJ = Watson-Jones; TG = transgluteal*
### Appendix 2.5: Summary of studies reporting hip revision

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Cement</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paterson (2010)(8)</td>
<td>1y</td>
<td>Both</td>
<td>1.11 [0.82, 1.51]*</td>
</tr>
<tr>
<td>Conroy (2008)(89)</td>
<td>5y</td>
<td>Both</td>
<td>1.64 [1.14, 2.34]</td>
</tr>
<tr>
<td>Zwartele (2004)(248)</td>
<td>2y</td>
<td>Cementless</td>
<td>1.48 [0.31, 6.03]</td>
</tr>
<tr>
<td>Purtil (2001)(240)</td>
<td>5y</td>
<td>Cementless</td>
<td>0.14 [0.00, 1.90]</td>
</tr>
<tr>
<td><strong>Combined Estimate:</strong></td>
<td></td>
<td></td>
<td><strong>UAOR</strong> 1.33 [95CI 1.03, 1.71; 3913 RA, 76,098 OA patients; $I^2 = 6%$]</td>
</tr>
<tr>
<td>Rud-Sorensen (2010)(163)</td>
<td>6y</td>
<td>Both</td>
<td>1.18 [0.94, 1.47]</td>
</tr>
<tr>
<td>Schrama (2010)(164)</td>
<td>6y</td>
<td>Both</td>
<td>0.95 [0.62, 1.44]</td>
</tr>
<tr>
<td>Stea (2009)(203)</td>
<td>7y</td>
<td>Both</td>
<td>1.80 [1.05, 3.07]**</td>
</tr>
<tr>
<td>Johnsen (2006)(111)</td>
<td>9y</td>
<td>Both</td>
<td>2.04 [1.38, 2.98]</td>
</tr>
<tr>
<td>Furnes (2001)(202)</td>
<td>10y</td>
<td>Both</td>
<td>1.10 [0.90, 1.35]*</td>
</tr>
<tr>
<td>Kesteris (1998)(232)</td>
<td>10y</td>
<td>Cemented</td>
<td>0.99 [0.36, 2.57]</td>
</tr>
<tr>
<td>Partio (1994)(237)</td>
<td>10y</td>
<td>Cemented</td>
<td>0.82 [0.37, 1.83]</td>
</tr>
<tr>
<td>Allami (2006)(207)</td>
<td>10y</td>
<td>Cemented</td>
<td>3.33 [0.45, 24.5]***</td>
</tr>
<tr>
<td>Zwartele (2008)(249)</td>
<td>10y</td>
<td>Cementless</td>
<td>1.34 [0.39, 4.48]</td>
</tr>
<tr>
<td><strong>Combined Estimate:</strong></td>
<td></td>
<td></td>
<td><strong>UAOR</strong> 1.16 [95CI 0.94, 1.43; 9,118 RA, 210,674 OA patients; $I^2 = 46%$]</td>
</tr>
<tr>
<td>Sochart (1997)(244)</td>
<td>12y</td>
<td>Cemented</td>
<td>0.27 [0.14, 0.51]</td>
</tr>
<tr>
<td>Berry (2002)(226)</td>
<td>25y</td>
<td>Cemented</td>
<td>0.3 [0.1, 0.6]*</td>
</tr>
<tr>
<td><strong>Combined Estimate:</strong></td>
<td></td>
<td></td>
<td><strong>UAOR</strong> 0.28 [95CI 0.17, 0.47; 229 RA, 1701 OA patients; $I^2 = 0%$]</td>
</tr>
</tbody>
</table>

*Adjusted OR; ** adjusted relative risk; *** adjusted hazards ratio; SE = standard error
**Appendix 2.6: Summary of studies reporting knee revision**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Cement</th>
<th>Cruciate</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paterson (2010) (8)</td>
<td>1y</td>
<td>Both</td>
<td>Both</td>
<td>1.08 [0.78, 1.50]*</td>
</tr>
<tr>
<td>Himanen (2005) (208)</td>
<td>4y</td>
<td>Both</td>
<td>PS</td>
<td>1.25 [0.87, 1.80]**</td>
</tr>
<tr>
<td>Rand (1991) (241)</td>
<td>5y</td>
<td>Both</td>
<td>Both</td>
<td>1.27 [1.10, 1.47]</td>
</tr>
</tbody>
</table>

**Combined Estimate:** UAOR 1.24 [95CI 1.10, 1.40; 8,974 RA, 35,274 OA patients; \( I^2 = 0\% \)]

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Cement</th>
<th>Cruciate</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrama (2010) (164)</td>
<td>6y</td>
<td>Both</td>
<td>Both</td>
<td>1.98 [1.32, 2.96]</td>
</tr>
<tr>
<td>Laskin (1997) (233)</td>
<td>6y</td>
<td>Both</td>
<td>CR</td>
<td>42.79 [8.99, 279.29]</td>
</tr>
<tr>
<td>Elke (1995) (229)</td>
<td>7y</td>
<td>Both</td>
<td>CR</td>
<td>1.52 [0.59, 3.89]</td>
</tr>
<tr>
<td>Ritter (1994) (242)</td>
<td>8y</td>
<td>Both</td>
<td>CR</td>
<td>1.02 [0.14, 5.74]</td>
</tr>
<tr>
<td>Ritter (2009) (243)</td>
<td>7y</td>
<td>Cemented</td>
<td>PS</td>
<td>0.58 [0.03, 3.87]</td>
</tr>
<tr>
<td>Partio (1994) (238)</td>
<td>8y</td>
<td>Cemented</td>
<td>PS</td>
<td>1.17 [0.58, 2.37]</td>
</tr>
</tbody>
</table>

**Combined Estimate:** UAOR 2.03 [95CI 0.96, 4.30; 2,995 RA, 29,476 OA patients; \( I^2 = 69\% \)]

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Cement</th>
<th>Cruciate</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nafei (1996) (235)</td>
<td>12y</td>
<td>Cemented</td>
<td>PS</td>
<td>5.13 [1.35, 23.41]</td>
</tr>
<tr>
<td>Weir (1996) (247)</td>
<td>12y</td>
<td>Cemented</td>
<td>PS</td>
<td>1.40 [0.48, 4.26]</td>
</tr>
</tbody>
</table>

**Combined Estimate:** UAOR 2.46 [95CI 0.70, 8.70; 297 RA, 256 OA patients; \( I^2 = 50\% \)]

*Adjusted OR; ** unadjusted RR; SE = standard error
Appendix 3.1: Diagnostic and procedural codes used to establish the TJA cohorts described in Chapters 3 & 4

TJA OHIP Billing and DAD Procedure Codes

**OHIP** (with FEESUFF= ‘A’)

**HIP**

THA - Primary
R440 Total hip replacement - acetabulum and femur
THA - Revision
R241 Revision total arthroplasty hip - one or both components - acetabular or femoral

**KNEE**

TKA - Primary
R441 Total replacement/both compartments
R248 Total knee replacement with take down of fusion
TKA - Revision
R244 Revision total arthroplasty knee

**DAD**

THA - Primary
Prior to 2002 (ICD9/CCP) – For look back [variable PRCODE1-10].
- 93.51, *total hip replacement with methyl methacrylate*; and 93.59, *other total hip replacement*.

April 1, 2002- March 31, 2010 (ICD10/CCI) [variable INCODE1-20].
- 1.VA.53, *implantation of internal device, hip joint* -- 1.VA.53.LA-PN (open approach) and 1.VA.53.PN-PN (robotics-assisted approach)

THA - Revision
- Prior to 2002 (ICD9/CCP) – For look back
- 93.52, *revision cemented with methyl methacrylate*; and 93.53, *revision uncemented*.

April 1, 2002- March 31, 2010 (ICD10/CCI)
- As for Primary, but with Status Attribute = R [variable INATSTAT1-20].

TKA - Primary
Prior to 2002 (ICD9/CCP) – For look back
- 93.41, *geomedic and polycentric total knee replacement*

April 1, 2002- March 31, 2010 (ICD10/CCI)
- 1.VG.53, *implantation of internal device, knee joint* (includes both TKAs and partial knee replacements (single component prosthetic devices and cement spacers to maintain consistency with above)

TKA - Revision
Prior to 2002 (ICD9/CCP) – For look back
- 93.40, *revision of total knee replacement cemented or uncemented*

April 1, 2002- March 31, 2010 (ICD10/CCI)
- As for Primary, but with Status Attribute = R [variable INATSTAT1-20].
Diagnosis codes for malignancy, fracture, trauma on the index admission (for excluding “unplanned” procedures)

Malignancy ICD10
C402 (malignant neoplasm of long bones of lower limb)
C043 (malignant neoplasm of short bones of lower limb)
C408 (overlapping malignant lesion of bone and articular cartilage of limbs)
C409 (malignant neoplasm of bone and articular cartilage of limb, unspecified)
C795 (secondary malignant neoplasm of bone and bone marrow)

Fracture ICD10
S324 (fracture of acetabulum)
S72 (fracture of femur)
S820 (fracture of patella)
S821 (fracture of upper end of tibia)
S822 (fracture of shaft of tibia)
S824 (fracture of fibula alone)
S827 (multiple fractures of lower leg)
S829 (fracture of lower leg, part unspecified)

Trauma
V01 to V99: transport accidents
W01 to W19: falls

Congenital hip deformity ICD10
Q650 Congenital dislocation of hip, unilateral
Q651 Congenital dislocation of hip, bilateral
Q652 Congenital dislocation of hip, unspecified
Q653 Congenital subluxation of hip, unilateral
Q654 Congenital subluxation of hip, bilateral
Q655 Congenital subluxation of hip, unspecified
Q656 Unstable hip
Q658 Other congenital deformities of hip
Q659 Congenital deformity of hip, unspecified

Osteonecrosis ICD10
M8700 Idiopathic aseptic necrosis of bone, multiple sites
M8705 Idiopathic aseptic necrosis of bone, pelvic region and thigh
M8706 Idiopathic aseptic necrosis of bone, lower leg
M8708 Idiopathic aseptic necrosis of bone, other site
M8709 Idiopathic aseptic necrosis of bone, unspecified site
M8710 Osteonecrosis due to drugs, multiple sites
M8715 Osteonecrosis due to drugs, pelvic region and thigh
M8716 Osteonecrosis due to drugs, lower leg
M8718 Osteonecrosis due to drugs, other site
M8719 Osteonecrosis due to drugs, unspecified site
M8720 Osteonecrosis due to previous trauma, multiple sites
M8725 Osteonecrosis due to previous trauma, pelvic region and thigh
M8726 Osteonecrosis due to previous trauma, lower leg
M8728 Osteonecrosis due to previous trauma, other site
M8729 Osteonecrosis due to previous trauma, unspecified site
M8730 Other secondary osteonecrosis, multiple sites
M8735 Other secondary osteonecrosis, pelvic region and thigh
M8736 Other secondary osteonecrosis, lower leg
M8738 Other secondary osteonecrosis, other site
M8739 Other secondary osteonecrosis, unspecified site
M8780 Other osteonecrosis, multiple sites
M8785 Other osteonecrosis, pelvic region and thigh
M8786 Other osteonecrosis, lower leg
M8788 Other osteonecrosis, other site
M8789 Other osteonecrosis, unspecified site
M8790 Osteonecrosis, unspecified, multiple sites
M8795 Osteonecrosis, unspecified, pelvic region and thigh
M8796 Osteonecrosis, unspecified, lower leg
M8798 Osteonecrosis, unspecified, other site
M8799 Osteonecrosis, unspecified, unspecified site

**Diagnosis codes for joint infection on the index admission**

**Infection ICD10**

M8600, Acute haematogenous osteomyelitis, multiple sites
M8605, Acute haematogenous osteomyelitis, pelvic region and thigh
M8606, Acute haematogenous osteomyelitis, lower leg
M8607, Acute haematogenous osteomyelitis, ankle and foot
M8608, Acute haematogenous osteomyelitis, other site
M8609, Acute haematogenous osteomyelitis, unspecified site
M8610, Other acute osteomyelitis, multiple sites
M8618, Other acute osteomyelitis, other site
M8619, Other acute osteomyelitis, unspecified site
M8620, Subacute osteomyelitis, multiple sites
M8625, Subacute osteomyelitis, pelvic region and thigh
M8626, Subacute osteomyelitis, lower leg
M8628, Subacute osteomyelitis, other site
M8629, Subacute osteomyelitis, unspecified site
M8680, Other osteomyelitis, multiple sites
M8685, Other osteomyelitis, pelvic region and thigh
M8686, Other osteomyelitis, lower leg
M8688, Other osteomyelitis, other site
M8689, Other osteomyelitis, unspecified site
M8690, Osteomyelitis, unspecified, multiple sites
M8695, Osteomyelitis, unspecified, pelvic region and thigh
M8696, Osteomyelitis, unspecified, lower leg
M8698, Osteomyelitis, unspecified, other site
M8699, Osteomyelitis, unspecified, unspecified site
M8630, Chronic multifocal osteomyelitis, multiple sites
M8635, Chronic multifocal osteomyelitis, pelvic region and thigh
M8636, Chronic multifocal osteomyelitis, lower leg
M8638, Chronic multifocal osteomyelitis, other site
M8639, Chronic multifocal osteomyelitis, unspecified site
M8640, Chronic osteomyelitis with draining sinus, multiple sites
M8645, Chronic osteomyelitis with draining sinus, pelvic region and thigh
M8646, Chronic osteomyelitis with draining sinus, lower leg
M8648, Chronic osteomyelitis with draining sinus, other site
M8649, Chronic osteomyelitis with draining sinus, unspecified site
M8650, Other chronic haematogenous osteomyelitis, multiple sites
M8655, Other chronic haematogenous osteomyelitis, pelvic region and thigh
M8656, Other chronic haematogenous osteomyelitis, lower leg
M8658, Other chronic haematogenous osteomyelitis, other site
M8659, Other chronic haematogenous osteomyelitis, unspecified site
M8660, Other chronic osteomyelitis, multiple sites
M8665, Other chronic osteomyelitis, pelvic region and thigh
M8666, Other chronic osteomyelitis, lower leg
M8668, Other chronic osteomyelitis, other site
M8669, Other chronic osteomyelitis, unspecified site
M0000 Staphylococcal arthritis and polyarthritis, multiple sites
M0001 Staphylococcal arthritis and polyarthritis, shoulder region
M0002 Staphylococcal arthritis and polyarthritis, upper arm
M0003 Staphylococcal arthritis and polyarthritis, forearm
M0004 Staphylococcal arthritis and polyarthritis, hand
M0005 Staphylococcal arthritis and polyarthritis, pelvic region and thigh
M0006 Staphylococcal arthritis and polyarthritis, lower leg
M0007 Staphylococcal arthritis and polyarthritis, ankle and foot
M0008 Staphylococcal arthritis and polyarthritis, other site
M0009 Staphylococcal arthritis and polyarthritis, unspecified site
M0010 Pneumococcal arthritis and polyarthritis, multiple sites
M0011 Pneumococcal arthritis and polyarthritis, shoulder region
M0012 Pneumococcal arthritis and polyarthritis, upper arm
M0013 Pneumococcal arthritis and polyarthritis, forearm
M0014 Pneumococcal arthritis and polyarthritis, hand
M0015 Pneumococcal arthritis and polyarthritis, pelvic region and thigh
M0016 Pneumococcal arthritis and polyarthritis, lower leg
M0017 Pneumococcal arthritis and polyarthritis, ankle and foot
M0018 Pneumococcal arthritis and polyarthritis, other site
M0019 Pneumococcal arthritis and polyarthritis, unspecified site
M0020 Other streptococcal arthritis and polyarthritis, multiple sites
M0021 Other streptococcal arthritis and polyarthritis, shoulder region
M0022 Other streptococcal arthritis and polyarthritis, upper arm
M0023 Other streptococcal arthritis and polyarthritis, forearm
M0024 Other streptococcal arthritis and polyarthritis, hand
M0025 Other streptococcal arthritis and polyarthritis, pelvic region and thigh
M0026 Other streptococcal arthritis and polyarthritis, lower leg
M0027 Other streptococcal arthritis and polyarthritis, ankle and foot
M0028 Other streptococcal arthritis and polyarthritis, other site
M0029 Other streptococcal arthritis and polyarthritis, unspecified site
M0080 Arthritis and polyarthritis due to other specified bacterial agents, multiple sites
M0081 Arthritis and polyarthritis due to other specified bacterial agents, shoulder region
M0082 Arthritis and polyarthritis due to other specified bacterial agents, upper arm
M0083 Arthritis and polyarthritis due to other specified bacterial agents, forearm
M0084 Arthritis and polyarthritis due to other specified bacterial agents, hand
M0085 Arthritis and polyarthritis due to other specified bacterial agents, pelvic region and thigh
M0086 Arthritis and polyarthritis due to other specified bacterial agents, lower leg
M0087 Arthritis and polyarthritis due to other specified bacterial agents, ankle and foot
M0088 Arthritis and polyarthritis due to other specified bacterial agents, other site
M0089 Arthritis and polyarthritis due to other specified bacterial agents, unspecified site
M0090 Pyogenic arthritis, unspecified, multiple sites
M0091 Pyogenic arthritis, unspecified, shoulder region
M0092 Pyogenic arthritis, unspecified, upper arm
M0093 Pyogenic arthritis, unspecified, forearm
M0094 Pyogenic arthritis, unspecified, hand
M0095 Pyogenic arthritis, unspecified, pelvic region and thigh
M0096 Pyogenic arthritis, unspecified, lower leg
M0097 Pyogenic arthritis, unspecified, ankle and foot
M0098 Pyogenic arthritis, unspecified, other site
M0099 Pyogenic arthritis, unspecified, unspecified site
M0100 Meningococcal arthritis multiple sites
M0101 Meningococcal arthritis, shoulder region
M0102 Meningococcal arthritis, upper arm
M0103 Meningococcal arthritis, forearm
M0104 Meningococcal arthritis, hand
M0105 Meningococcal arthritis, pelvic region and thigh
M0106 Meningococcal arthritis, lower leg
M0107 Meningococcal arthritis, ankle and foot
M0108 Meningococcal arthritis, other site
M0109 Meningococcal arthritis, unspecified site
M0110 Tuberculous arthritis, multiple sites
M0111 Tuberculous arthritis, shoulder region
M0112 Tuberculous arthritis, upper arm
M0113 Tuberculous arthritis, forearm
M0114 Tuberculous arthritis, hand
M0115 Tuberculous arthritis, pelvic region and thigh
M0116 Tuberculous arthritis, lower leg
M0117 Tuberculous arthritis, ankle and foot
M0118 Tuberculous arthritis, other site
M0119 Tuberculous arthritis, unspecified site
M0120 Arthritis in Lyme disease, multiple sites
M0121 Arthritis in Lyme disease, shoulder region
M0122 Arthritis in Lyme disease, upper arm
M0123 Arthritis in Lyme disease, forearm
M0124 Arthritis in Lyme disease hand
M0125 Arthritis in Lyme disease, pelvic region and thigh
M0126 Arthritis in Lyme disease, lower leg
M0127 Arthritis in Lyme disease, ankle and foot
M0128 Arthritis in Lyme disease, other site
M0129 Arthritis in Lyme disease, unspecified site
M0130 Arthritis in other bacterial diseases classified elsewhere, multiple sites
M0131 Arthritis in other bacterial diseases classified elsewhere, shoulder region
M0132 Arthritis in other bacterial diseases classified elsewhere, upper arm
M0133 Arthritis in other bacterial diseases classified elsewhere, forearm
M0134 Arthritis in other bacterial diseases classified elsewhere, hand
M0135 Arthritis in other bacterial diseases classified elsewhere, pelvic region and thigh
M0136 Arthritis in other bacterial diseases classified elsewhere, lower leg
M0137 Arthritis in other bacterial diseases classified elsewhere, ankle and foot
M0138 Arthritis in other bacterial diseases classified elsewhere, other site
M0139 Arthritis in other bacterial diseases classified elsewhere, unspecified site
M0140 Rubella arthritis, multiple sites
M0141 Rubella arthritis, shoulder region
M0142 Rubella arthritis, upper arm
M0143 Rubella arthritis, forearm
M0144 Rubella arthritis, hand
M0145 Rubella arthritis, pelvic region and thigh
M0146 Rubella arthritis, lower leg
M0147 Rubella arthritis, ankle and foot
M0148 Rubella arthritis, other site
M0149 Rubella arthritis, unspecified site
M0150 Arthritis in other viral diseases classified elsewhere, multiple sites
M0151 Arthritis in other viral diseases classified elsewhere, shoulder region
M0152 Arthritis in other viral diseases classified elsewhere, upper arm
M0153 Arthritis in other viral diseases classified elsewhere, forearm
M0154 Arthritis in other viral diseases classified elsewhere, hand
M0155 Arthritis in other viral diseases classified elsewhere, pelvic region and thigh
M0156 Arthritis in other viral diseases classified elsewhere, lower leg
M0157 Arthritis in other viral diseases classified elsewhere, ankle and foot
M0158 Arthritis in other viral diseases classified elsewhere, other site
M0159 Arthritis in other viral diseases classified elsewhere, unspecified site
M0160 Arthritis in mycoses, multiple sites
M0161 Arthritis in mycoses, shoulder region
M0162 Arthritis in mycoses, upper arm
M0163 Arthritis in mycoses forearm
M0164 Arthritis in mycoses, hand
M0165 Arthritis in mycoses, pelvic region and thigh
M0166 Arthritis in mycoses, lower leg
M0167 Arthritis in mycoses, ankle and foot
M0168 Arthritis in mycoses other site
M0169 Arthritis in mycoses, unspecified sites
M0180 Arthritis in other infectious and parasitic diseases classified elsewhere, multiple sites
M0181 Arthritis in other infectious and parasitic diseases classified elsewhere, shoulder region
M0182 Arthritis in other infectious and parasitic diseases classified elsewhere, upper arm
M0183 Arthritis in other infectious and parasitic diseases classified elsewhere, forearm
M0184 Arthritis in other infectious and parasitic diseases classified elsewhere, hand
M0185 Arthritis in other infectious and parasitic diseases classified elsewhere, pelvic region and thigh
M0186 Arthritis in other infectious and parasitic diseases classified elsewhere, lower leg
M0187 Arthritis in other infectious and parasitic diseases classified elsewhere, ankle and foot
M0188 Arthritis in other infectious and parasitic diseases classified elsewhere, other site
M0189 Arthritis in other infectious and parasitic diseases classified elsewhere, unspecified site
A544 Gonococcal infection of musculoskeletal system

**Arthritis typing for IA and OA**

Inflammatory Arthritis (IA) = any patient with a code for RA that does not meet the established validated criteria, or has any of the following codes (one or more times) all of which should precede the index joint replacement

**ICD9**

711.9, 711.4: Post-infective and reactive arthropathy
696.0: Psoriatic arthritis
274.0: Gout
712: other crystal arthropathies
716.5: unspecified polyarthritis
713.0: Metabolic arthritis

**ICD10**

M02: Reactive arthritis
M07: Psoriatic arthritis
M03: Post-infective and reactive arthropathy
M08, M09: Juvenile arthritis
M10: Gout
M11: Other crystal arthropathies
M12: Other post-rheumatic arthropathy
M13: Unspecified polyarthritis
M14: Metabolic arthritis
M17: Gonarthrosis

OA = all patients who do not meet the criteria for RA or IA as listed above

**Codes for surgical complications during the index admission**

a) non-specific surgical complication

**ICD10**

T800, Air embolism following infusion, transfusion and therapeutic injection
T801, Vascular complications following infusion, transfusion and therapeutic injection
T802, Infections following infusion, transfusion and therapeutic injection
T803, ABO incompatibility reaction
T804, Rh incompatibility reaction
T805, Anaphylactic shock due to serum
T806, Other serum reactions
T808, Other complications following infusion, transfusion and therapeutic injection
T809, Unspecified complication following infusion, transfusion and therapeutic injection
T810, Haemorrhage and haematoma complicating a procedure, not elsewhere classified
T811, Shock during or resulting from a procedure, not elsewhere classified
T812, Accidental puncture and laceration during a procedure, not elsewhere classified
T813, Disruption of operation wound, not elsewhere classified
T814, Infection following a procedure, not elsewhere classified
T8150, Adhesions due to foreign body accidentally left in body cavity or operation wound following procedure
T8151, Obstruction due to foreign body accidentally left in body cavity or operation wound following procedure
T8152, Perforation due to foreign body accidentally left in body cavity or operation wound following a procedure
T8158, Other specified complication due to foreign body left in body cavity or operation wound following a procedure
T8159, Unspecified complication due to foreign body accidentally left in body cavity or operation wound following a procedure
T816, Acute reaction to foreign substance accidentally left during a procedure
T817, Vascular complications following a procedure, not elsewhere classified
T818, Complication of inhalation therapy
T8180, Emphysema (subcutaneous) resulting from a procedure
T8181, Persistent postoperative fistula
T8188, Other complications of procedures, not elsewhere classified
T819, Unspecified complication of procedure
T8403, Mechanical complication of hip prosthesis
T8404, Mechanical complication of knee prosthesis
T8409, Mechanical complication of unspecified joint prosthesis
T8413, Mechanical complication of internal fixation device of femur
T8419, Mechanical complication of internal fixation device of bones of limb NOS
T8424, Mechanical complication of internal fixation device of pelvis
T8428, Mechanical complication of internal fixation device of other bones
T843, Mechanical complication of other bone devices, implants and grafts
T844, Mechanical complication of other internal orthopaedic devices, implants and grafts
T8453, Infection and inflammatory reaction due to hip prosthesis
T8454, Infection and inflammatory reaction due to knee prosthesis
T8458, Infection and inflammatory reaction due to other joint prosthesis
T8459, Infection and inflammatory reaction due to unspecified joint prosthesis
T8463, Infection and inflammatory reaction due to internal fixation device of femur
T8468, Infection and inflammatory reaction due to internal fixation device of bones at other site
T8469, Infection and inflammatory reaction due to internal fixation device of bones of limb NOS
T847, Infection and inflammatory reaction due to other internal orthopaedic prosthetic devices, implants and grafts
T848, Other complications of internal orthopaedic prosthetic devices, implants and grafts
T849, Unspecified complication of internal orthopaedic prosthetic device, implant and graft
T880, Infection following immunization
T881, Other complications following immunization, not elsewhere classified
T882, Shock due to anaesthesia
T883, Malignant hyperthermia due to anaesthesia
T884, Failed or difficult intubation
T885, Other complications of anaesthesia
T886, Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T887, Unspecified adverse effect of drug or medicament
T888, Other specified complications of surgical and medical care, not elsewhere classified
T889, Complication of surgical and medical care, unspecified

b) DVT
ICD10
I801, Phlebitis and thrombophlebitis of femoral vein
I802, Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I803, Phlebitis and thrombophlebitis of lower extremities, unspecified
I809, Phlebitis and thrombophlebitis of unspecified site
I822, Embolism and thrombosis of vena cava
I823, Embolism and thrombosis of renal vein
I828, Embolism and thrombosis of other specified veins
I829, Embolism and thrombosis of unspecified vein

c) PE
ICD10
I260, Pulmonary embolism with mention of acute cor pulmonale
I269, Pulmonary embolism without mention of acute cor pulmonale

d) AMI
ICD10
I210, Acute transmural myocardial infarction of anterior wall
I211, Acute transmural myocardial infarction of inferior wall
I212, Acute transmural myocardial infarction of other sites
I213, Acute transmural myocardial infarction of unspecified site
I2140, Acute subendocardial myocardial infarction of anterior wall
I2141, Acute subendocardial myocardial infarction of inferior wall
I2142, Acute subendocardial myocardial infarction of other sites
I2149, Acute subendocardial myocardial infarction, unspecified site
I219, Acute myocardial infarction, unspecified
I220, Subsequent myocardial infarction of anterior wall
I221, Subsequent myocardial infarction of inferior wall
I228, Subsequent myocardial infarction of other sites
I229, Subsequent myocardial infarction of unspecified site

e) pneumonia
ICD10
J100, Influenza with pneumonia, influenza virus identified
J101, Influenza with other respiratory manifestations, influenza virus identified
J108, Influenza with other manifestations, influenza virus identified
J110, Influenza with pneumonia, virus not identified
J111, Influenza with other respiratory manifestations, virus not identified
J118, Influenza with other manifestations, virus not identified
J120, Adenoviral pneumonia
J121, Respiratory syncytial virus pneumonia
J122, Parainfluenza virus pneumonia
J128, Other viral pneumonia
J129, Viral pneumonia, unspecified
J13, Pneumonia due to Streptococcus pneumoniae
J14, Pneumonia due to Haemophilus influenzae
J150, Pneumonia due to Klebsiella pneumoniae
J151, Pneumonia due to Pseudomonas
J152, Pneumonia due to Staphylococcus
J153, Pneumonia due to Streptococcus, group B
J154, Pneumonia due to other streptococci
J155, Pneumonia due to Escherichia coli
J156, Pneumonia due to other aerobic Gram-negative bacteria
J157, Pneumonia due to Mycoplasma pneumoniae
J158, Other bacterial pneumonia
J159, Bacterial pneumonia, unspecified
J160, Chlamydial pneumonia
J168, Pneumonia due to other specified infectious organisms
J180, Bronchopneumonia, unspecified
J181, Lobar pneumonia, unspecified
J182, Hypostatic pneumonia, unspecified
J188, Other pneumonia, organism unspecified
J189, Pneumonia, unspecified

Codes for Index admission diagnosis, or subsequent NACRS/DAD diagnosis within 90 days

f) DVT
ICD10
I801, Phlebitis and thrombophlebitis of femoral vein
I802, Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I803, Phlebitis and thrombophlebitis of lower extremities, unspecified
I809, Phlebitis and thrombophlebitis of unspecified site
I822, Embolism and thrombosis of vena cava
I823, Embolism and thrombosis of renal vein
I828, Embolism and thrombosis of other specified veins
I829, Embolism and thrombosis of unspecified vein

g) PE
ICD10
I260, Pulmonary embolism with mention of acute cor pulmonale
I269, Pulmonary embolism without mention of acute cor pulmonale

h) AMI
ICD10
I210, Acute transmural myocardial infarction of anterior wall
I211, Acute transmural myocardial infarction of inferior wall
I212, Acute transmural myocardial infarction of other sites
I213, Acute transmural myocardial infarction of unspecified site
I2140, Acute subendocardial myocardial infarction of anterior wall
I2141, Acute subendocardial myocardial infarction of inferior wall
I2142, Acute subendocardial myocardial infarction of other sites
I2149, Acute subendocardial myocardial infarction, unspecified site
I219, Acute myocardial infarction, unspecified
I220, Subsequent myocardial infarction of anterior wall
I221, Subsequent myocardial infarction of inferior wall
I228, Subsequent myocardial infarction of other sites
I229, Subsequent myocardial infarction of unspecified site

i) pneumonia
ICD10
J100, Influenza with pneumonia, influenza virus identified
J101, Influenza with other respiratory manifestations, influenza virus identified
J108, Influenza with other manifestations, influenza virus identified
J110, Influenza with pneumonia, virus not identified
J111, Influenza with other respiratory manifestations, virus not identified
J118, Influenza with other manifestations, virus not identified
J120, Adenoviral pneumonia
J121, Respiratory syncytial virus pneumonia
J122, Parainfluenza virus pneumonia
J128, Other viral pneumonia
J129, Viral pneumonia, unspecified
J13, Pneumonia due to Streptococcus pneumoniae
J14, Pneumonia due to Haemophilus influenzae
J150, Pneumonia due to Klebsiella pneumoniae
J151, Pneumonia due to Pseudomonas
J152, Pneumonia due to Staphylococcus
J153, Pneumonia due to Streptococcus, group B
J154, Pneumonia due to other streptococci
J155, Pneumonia due to Escherichia coli
J156, Pneumonia due to other aerobic Gram-negative bacteria
J157, Pneumonia due to Mycoplasma pneumoniae
J158, Other bacterial pneumonia
J159, Bacterial pneumonia, unspecified
J160, Chlamydial pneumonia
J168, Pneumonia due to other specified infectious organisms
J180, Bronchopneumonia, unspecified
J181, Lobar pneumonia, unspecified
J182, Hypostatic pneumonia, unspecified
J188, Other pneumonia, organism unspecified
J189, Pneumonia, unspecified

**Dislocation, infection, peri-prosthetic fracture (within 2y, or time-to)**

j) dislocation (Note: Hospital admission not required as many will be OP.)

**OHIP**
D042, D043, R628, D038, D039, D040, D031, R403

**ICD10**
S730x, x=0,1,8,9; S8310x, x=0,1,2,3,8,9; S83000 or S83001
S73000, Posterior dislocation of hip, closed
S73001, Posterior dislocation of hip, open
S73010, Obturator dislocation of hip, closed
S73011, Obturator dislocation of hip, open
S73080, Other anterior dislocation of hip, closed
S73081, Other anterior dislocation of hip, open
S73090, Unspecified dislocation of hip, closed
S73091, Unspecified dislocation of hip, open
S83000, Dislocation of patella, closed
S83001, Dislocation of patella, open
S83100, Anterior dislocation of knee, closed
S83101, Anterior dislocation of knee, open
S83110, Posterior dislocation of knee, closed
S83111, Posterior dislocation of knee, open
S83120, Medial dislocation of knee, closed
S83121, Medial dislocation of knee, open
S83130, Lateral dislocation of knee, closed
S83131, Lateral dislocation of knee, open
S83180, Other dislocation of knee, closed
S83181, Other dislocation of knee, open
S83190, Unspecified dislocation of knee, closed
S83191, Unspecified dislocation of knee, open

k) Diagnosis of joint infection (with accompanying confirmatory hip/knee procedure)
First I/P hospitalization with an infection diagnosis which must be confirmed by a procedure.
NB: Some infection codes in the index admission cause the case to be excluded from the cohort (APPENDIX 3).

**ICD10**
M8610, Other acute osteomyelitis, multiple sites
M8618, Other acute osteomyelitis, other site
M8619, Other acute osteomyelitis, unspecified site
M8620, Subacute osteomyelitis, multiple sites
M8625, Subacute osteomyelitis, pelvic region and thigh
M8626, Subacute osteomyelitis, lower leg
M8628, Subacute osteomyelitis, other site
M8629, Subacute osteomyelitis, unspecified site
M8630, Chronic multifocal osteomyelitis, multiple sites
M8635, Chronic multifocal osteomyelitis, pelvic region and thigh
M8636, Chronic multifocal osteomyelitis, lower leg
M8638, Chronic multifocal osteomyelitis, other site
M8639, Chronic multifocal osteomyelitis, unspecified site
M8660, Other chronic osteomyelitis, multiple sites
M8665, Other chronic osteomyelitis, pelvic region and thigh
M8666, Other chronic osteomyelitis, lower leg
M8668, Other chronic osteomyelitis, other site
M8669, Other chronic osteomyelitis, unspecified site
M8680, Other osteomyelitis, multiple sites
M8685, Other osteomyelitis, pelvic region and thigh
M8686, Other osteomyelitis, lower leg
M8688, Other osteomyelitis, other site
M8689, Other osteomyelitis, unspecified site
M8690, Osteomyelitis, unspecified, multiple sites
M8695, Osteomyelitis, unspecified, pelvic region and thigh
M8696, Osteomyelitis, unspecified, lower leg
M8698, Osteomyelitis, unspecified, other site
M8699, Osteomyelitis, unspecified, unspecified site
T802, Infections following infusion, transfusion and therapeutic injection
T814, Infection following a procedure, not elsewhere classified
T8453, Infection and inflammatory reaction due to hip prosthesis
T8454, Infection and inflammatory reaction due to knee prosthesis
T8458, Infection and inflammatory reaction due to other joint prosthesis
T8459, Infection and inflammatory reaction due to unspecified joint prosthesis
T8463, Infection and inflammatory reaction due to internal fixation device of femur
T8468, Infection and inflammatory reaction due to internal fixation device of bones at other site
T8469, Infection and inflammatory reaction due to internal fixation device of bones of limb NOS
T847, Infection and inflammatory reaction due to other internal orthopaedic prosthetic devices, implants and grafts
A4888 Other specified bacterial diseases
A490 Staphylococcal infection, unspecified site
A491 Streptococcal infection, unspecified site
A492 Haemophilus influenzae infection, unspecified site
A493 Mycoplasma infection, unspecified site
A498 Other bacterial infections of unspecified site
A499 Bacterial infection, unspecified
B672 Echinococcus granulosus infection of bone
B673 Echinococcus granulosus infection, other and multiple sites
B674 Echinococcus granulosus infection, unspecified
B676 Echinococcus multilocularis infection, other and multiple sites
B677 Echinococcus multilocularis infection, unspecified
L081 Erythrasma
L088 Other specified local infections of skin and subcutaneous tissue
L089 Local infection of skin and subcutaneous tissue, unspecified
M0097 Pyogenic arthritis, unspecified, ankle and foot
M0098 Pyogenic arthritis, unspecified, other site
M0099 Pyogenic arthritis, unspecified, unspecified site
M0100 Meningococcal arthritis multiple sites
M0101 Meningococcal arthritis, shoulder region
M0102 Meningococcal arthritis, upper arm
M0103 Meningococcal arthritis, forearm
M0104 Meningococcal arthritis, hand
M0105 Meningococcal arthritis, pelvic region and thigh
M0106 Meningococcal arthritis, lower leg
M0107 Meningococcal arthritis, ankle and foot
M0108 Meningococcal arthritis, other site
M0109 Meningococcal arthritis unspecified site
M0110 Tuberculous arthritis, multiple sites
M0111 Tuberculous arthritis, shoulder region
M0112 Tuberculous arthritis, upper arm
M0113 Tuberculous arthritis, forearm
M0114 Tuberculous arthritis, hand
M0115 Tuberculous arthritis, pelvic region and thigh
M0116 Tuberculous arthritis, lower leg
M0117 Tuberculous arthritis, ankle and foot
M0118 Tuberculous arthritis, other site
M0119 Tuberculous arthritis, unspecified site
M0120 Arthritis in Lyme disease, multiple sites
M0121 Arthritis in Lyme disease, shoulder region
M0122 Arthritis in Lyme disease, upper arm
M0123 Arthritis in Lyme disease, forearm
M0124 Arthritis in Lyme disease hand
M0125 Arthritis in Lyme disease, pelvic region and thigh
M0126 Arthritis in Lyme disease, lower leg
M0127 Arthritis in Lyme disease, ankle and foot
M0128 Arthritis in Lyme disease, other site
M0129 Arthritis in Lyme disease, unspecified site
M0130 Arthritis in other bacterial diseases classified elsewhere, multiple sites
M0131 Arthritis in other bacterial diseases classified elsewhere, shoulder region
M0132 Arthritis in other bacterial diseases classified elsewhere, upper arm
M0133 Arthritis in other bacterial diseases classified elsewhere, forearm
M0134 Arthritis in other bacterial diseases classified elsewhere, hand
M0135 Arthritis in other bacterial diseases classified elsewhere, pelvic region and thigh
M0136 Arthritis in other bacterial diseases classified elsewhere, lower leg
M0137 Arthritis in other bacterial diseases classified elsewhere, ankle and foot
M0138 Arthritis in other bacterial diseases classified elsewhere, other site
M0139 Arthritis in other bacterial diseases classified elsewhere, unspecified site
M0140 Rubella arthritis, multiple sites
M0141 Rubella arthritis, shoulder region
M0142 Rubella arthritis, upper arm
M0143 Rubella arthritis, forearm
M0144 Rubella arthritis, hand
M0145 Rubella arthritis, pelvic region and thigh
M0146 Rubella arthritis, lower leg
M0147 Rubella arthritis, ankle and foot
M0148 Rubella arthritis, other site
M0149 Rubella arthritis, unspecified site
M0150 Arthritis in other viral diseases classified elsewhere, multiple sites
M0151 Arthritis in other viral diseases classified elsewhere, shoulder region
M0152 Arthritis in other viral diseases classified elsewhere, upper arm
M0153 Arthritis in other viral diseases classified elsewhere, forearm
M0154 Arthritis in other viral diseases classified elsewhere, hand
M0155 Arthritis in other viral diseases classified elsewhere, pelvic region and thigh
M0156 Arthritis in other viral diseases classified elsewhere, lower leg
M0157 Arthritis in other viral diseases classified elsewhere, ankle and foot
M0158 Arthritis in other viral diseases classified elsewhere, other site
M0159 Arthritis in other viral diseases classified elsewhere, unspecified site
M0160 Arthritis in mycoses, multiple sites
M0161 Arthritis in mycoses, shoulder region
M0162 Arthritis in mycoses, upper arm
M0163 Arthritis in mycoses forearm
M0164 Arthritis in mycoses, hand
M0165 Arthritis in mycoses, pelvic region and thigh
M0166 Arthritis in mycoses, lower leg
M0167 Arthritis in mycoses, ankle and foot
M0168 Arthritis in mycoses other site
M0169 Arthritis in mycoses, unspecified sites
M0180Arthritis in other infectious and parasitic diseases classified elsewhere, multiple sites
M0181Arthritis in other infectious and parasitic diseases classified elsewhere, shoulder region
M0182Arthritis in other infectious and parasitic diseases classified elsewhere, upper arm
M0183Arthritis in other infectious and parasitic diseases classified elsewhere, forearm
M0184Arthritis in other infectious and parasitic diseases classified elsewhere, hand
M0185Arthritis in other infectious and parasitic diseases classified elsewhere, pelvic region and thigh
M0186Arthritis in other infectious and parasitic diseases classified elsewhere, lower leg
M0187Arthritis in other infectious and parasitic diseases classified elsewhere, ankle and foot
M0188Arthritis in other infectious and parasitic diseases classified elsewhere, other site
M0189Arthritis in other infectious and parasitic diseases classified elsewhere, unspecified site
M0300 Postmeningococcal arthritis, multiple sites
M0301 Postmeningococcal arthritis, shoulder region
M0302 Postmeningococcal arthritis, upper arm
M0303 Postmeningococcal arthritis, forearm
M0304 Postmeningococcal arthritis, hand
M0305 Postmeningococcal arthritis, pelvic region and thigh
M0306 Postmeningococcal arthritis, lower leg
M0307 Postmeningococcal arthritis, ankle and foot
M0308 Postmeningococcal arthritis, other site
M0309 Postmeningococcal arthritis, unspecified site
M0310 Postinfective arthropathy in syphilis, multiple sites
M0311 Postinfective arthropathy in syphilis, shoulder region
M0312 Postinfective arthropathy in syphilis, upper arm
M0313 Postinfective arthropathy in syphilis, forearm
M0314 Postinfective arthropathy in syphilis, hand
M0315 Postinfective arthropathy in syphilis, pelvic region and thigh
M0316 Postinfective arthropathy in syphilis, lower leg
M0317 Postinfective arthropathy in syphilis, ankle and foot
M0318 Postinfective arthropathy in syphilis, other site
M0319 Postinfective arthropathy in syphilis, unspecified site
M0320 Other postinfectious arthropathies in diseases classified elsewhere, multiple sites
M0321 Other postinfectious arthropathies in diseases classified elsewhere, shoulder region
M0322 Other postinfectious arthropathies in diseases classified elsewhere, upper arm
M0323 Other postinfectious arthropathies in diseases classified elsewhere, forearm
M0324 Other postinfectious arthropathies in diseases classified elsewhere, hand
M0325 Other postinfectious arthropathies in diseases classified elsewhere, pelvic region and thigh
M0326 Other postinfectious arthropathies in diseases classified elsewhere, lower leg
M0327 Other postinfectious arthropathies in diseases classified elsewhere, ankle and foot
M0328 Other postinfectious arthropathies in diseases classified elsewhere, other site
M0329 Other postinfectious arthropathies in diseases classified elsewhere, unspecified site
M0360 Reactive arthropathy in other diseases classified elsewhere, multiple sites
M0361 Reactive arthropathy in other diseases classified elsewhere, shoulder region
M0362 Reactive arthropathy in other diseases classified elsewhere, upper arm
M0363 Reactive arthropathy in other diseases classified elsewhere, forearm
M0364 Reactive arthropathy in other diseases classified elsewhere, hand
M0365 Reactive arthropathy in other diseases classified elsewhere, pelvic region and thigh
M0366 Reactive arthropathy in other diseases classified elsewhere, lower leg
M0367 Reactive arthropathy in other diseases classified elsewhere, ankle and foot
M0368 Reactive arthropathy in other diseases classified elsewhere, other site
M0369 Reactive arthropathy in other diseases classified elsewhere, unspecified site

Confirmatory procedures
OHIP
Hexarthohip: R415, R443, R488, R547
Kexarthohip: R412, R496, R497
ICD10CCI
hexarth: 1VA55x, x=LAPM, LAPN, LAPNN, LAXXN
kexarth: 1VG55

Peri-prosthetic fracture
ICD10CCI
M966 Fracture of bone following insertion of orthopaedic implant, joint prosthesis, or bone plate

Codes for readmission associated with amputation, fusion, or excision
OHIP
hampohip: R631, R630
kampohip: R625, R626
hfuseohip: R470
Kfuseohip: R468
Hexarthohip: R443, R488
Kexarthohip: R496, R497

ICD10CCI
hamp: 1VA93 or 1VC93
kamp: 1VG93
hfuse: 1VA75
kfuse: 1VG75
hexarth: 1VA55x, x=LAPM, LAPN, LAPNN, LAXXN
kexarth: 1VG55
COPYRIGHT ACKNOWLEDGEMENTS

Chapter 2 was reprinted from:


Chapter 3 was reprinted from:


Chapter 4 was reprinted from: