Published in final edited form as:

Arthritis Rheumatol. 2014 February 1; 66(2): 250–253. doi:10.1002/art.38236.

Arthroplasty outcomes are improving, but why isn't my patient with Rheumatoid Arthritis doing as well?

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This issue of the Arthritis and Rheumatism has two new studies of outcomes after arthroplasty by Ravi et al. (ref Ravi) and Lalmahomed et al. (ref Lalmahomed). Findings from these epidemiological studies can help us better understand the evolving trends in arthroplasty outcomes and the associated risk factors in patients undergoing total knee or hip arthroplasty (TKA or THA).

Ravi et al. reported that compared to patients with osteoarthritis (OA), the risk of infection after TKA and dislocation after THA were higher in patients with rheumatoid arthritis (RA) (ref). In a time-trend study, Lalmahomed et al. examined the Danish nationwide cohort from 1989 to 2007 and found that over time 60-day post-arthroplasty mortality rates declined 60% after primary elective THA and 63% after primary elective TKA in 2003–2007 (incidence in each time period not provided) (ref). Several interesting findings from these studies have important implications that merit further discussion.

Some key principles, common to both studies, deserve recognition. Both studies analyzed a large group of patients, used the state-of-the-art statistical approaches adjusting for important covariates and confounders and controlling for the competing risks, examined clinically meaningful outcomes, defined the cohorts using validated definitions and performed sensitivity analyses that confirmed the main findings. While there is an abundance of well designed epidemiological and outcome studies in the rheumatology literature, many arthroplasty studies in the past had had a small sample size, used non-validated outcomes and/or were single-center studies. By using a sound methodology, a large sample and validated outcomes, these studies succeeded in overcoming key limitations of previous studies.

In the first study, Ravi et al. studied 43,997 eligible THA and 71,793 eligible TKA patients, identified using the hospital discharge and Canadian physician claims databases, who

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Financial Conflict: There are no financial conflicts related directly to this study. J.A.S. has received research and travel grants from Takeda and Savient and consultant fees from Savient, Takeda and Regeneron.

received their first primary elective THA or TKA between 2002 and 2009 (Ravi et al.). They compared patients with osteoarthritis (OA) to those with RA using a previously validated algorithm of the presence of a diagnosis code for RA during a hospital stay 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 two-year period. The authors used multivariable-adjusted Cox proportional hazard models to assess the risk of venous thromboembolism (VTE), death, infection, dislocation, fracture and revision surgery within 2 years of primary elective THA or TKA. Most outcomes were validated. Analyses were adjusted for potential confounders including age, sex, income, rural residence, Charlson comorbidity score, frailty, surgeon and hospital volume and teaching hospital status. Patients with RA had twice the hazard of dislocation after THA and 1.5-times the hazard of joint infection following TKA, compared to patients with OA.

To put these findings in perspective, Chen et al. performed a recent meta-analysis of twelve cohort or case-control studies that found 548 persons with deep knee infection among 57,223 people who underwent TKA (1). RA was associated with an odds ratio of 1.83 for deep knee infection (incidence, 6.96% vs. 3.33%); other significant factors were obesity, diabetes, hypertension, and steroid therapy (1). Cram et al. used 5% Medicare data and found that the presence of rheumatic conditions was associated with a hazard ratio of 1.71 for periprosthetic joint infection after THA (incidence, 4.23% vs. 2.36%) (2). The consistency of the previously reported estimates of risk of joint infection after arthroplasty with the odds ratio of 1.5 reported by Ravi et al. (incidence, 1.64% vs. 0.84%), supports the robustness of these findings. These are important findings. On the other hand, one must also consider the study limitations while interpreting these findings from observational studies. These include residual confounding due to unmeasured variables (including body mass index), inclusion of some outcomes (revision, fractures and VTE) for which validated algorithms were not used and the lack of treatment data for RA patients. The likelihood of a future large randomized trial to answer this question is somewhat limited and therefore the best evidence for this question may in fact come from well-done, high-quality observational studies.

Various factors were postulated as contributing including surgical factors (soft tissue laxity), mechanical factors (less hip abductor strength, protusio acetabuli) and infection susceptibility due to RA as well as due to the use of disease-modifying anti-rheumatic drugs (DMARDs) in RA, including the biologics. Future studies should investigate whether one or more of these risk factors mediate the high infection risk in RA patients undergoing TKA. The 2008 American College of Rheumatology (ACR) guidelines for the treatment of RA recommended that biologics should be held at least one-week before and one-week after arthroplasty in patients with RA (3). In the absence of strong clinical data related to withholding biologics, it is not entirely clear what duration of withholding biologics around arthroplasty provides the best balance between infection risk reduction and avoiding a RA flare. This may depend on the pharmacokinetics of each biologic. This also has practical challenges, since the administration frequency of biologics can range from twice weekly (for etanercept) to every 2 months (for infliximab). More studies are needed to address this important question. On the other hand, no recommendations were made regarding withholding traditional DMARDs (such as methotrexate, sulfasalazine etc.) before or after a

major surgery (such as arthroplasty) in patients with RA, due to the absence of consistent evidence leading to a lack of consensus on this clinical question.

An interesting observation was that the risk associations of RA with infection were only seen in TKA and not in THA. The authors raised the question whether treatment of RA patients may be different between THA and TKA populations. This is unlikely, since the treatment algorithm in RA is not dependent on knee vs. hip joint involvement and no consistent systematic differences in overall disease activity or disease outcome have been identified in patients with RA with knee vs. hip joint involvement. The joint infection rates were higher in THA (1.1%) vs. TKA (0.9%) in the current study, which contrasts with an opposite finding of lower infection risk in THA (1.7%) vs. TKA (2.8%) in a recent study by Song et al. (4). Differences in the outcome (joint infection vs. all surgical site infections), study setting (Canada vs. Korea) and patient characteristics may explain the discrepant findings. The post-THA joint infection rates were somewhat similar in the two studies (1.1% vs. 1.7%), but post-TKA infection rates were far lower in the current study (0.9% vs. 2.8%). A higher risk of post-TKA surgical site infections (as reported previously) may be related to the fact that the knee joint is more vulnerable to surgical site infections compared to the hip joint due to multiple reasons including: (1) less soft tissue protection and a wound that is stretched vigorously during rehabilitation (or the knee gets stiff); (2) a greater risk of hematoma formation beneath a subcutaneous wound; and (3) large bleeding surfaces, etc.

Ravi et al. also reported that the risk of fracture, revision surgery and mortality did not differ by between patients with RA vs. OA, which are important findings as well. This may indicate that patients with RA do just as well as patients with OA with regards to these outcomes. Another possibility is that the sample size may not have been large enough to detect differences in these outcomes that are uncommon or rare after arthroplasty.

So what are the implications for policy makers, patients and their health care providers, including rheumatologists? First, the implication for policy makers is to incorporate this information into their assessments of case-mix and complexity of patients undergoing arthroplasty, which can inform policy decisions regarding the reimbursement payments and bundling the payment for services such as arthroplasty. Second, surgeons, rheumatologists and other health care providers can discuss the absolute and relative risk of post-arthroplasty joint infection and fracture with the patients with RA planning an arthroplasty. This information should be provided to the patients during the informed consent process, so that they can make informed decisions. These discussions are almost mandatory given the consistent findings from the recent studies including the current study (1, 2) and the significant impact of post-arthroplasty joint infection on morbidity and health care utilization (5, 6). Lastly, the higher infection risk in patients with RA raises the question whether we need reconsideration of the type and/or duration of perioperative antibiotics for patients with RA undergoing TKA compared to those with OA, given a different risk profile. In the absence of strong evidence, it's not likely that this change is needed, since patients with diabetes and immunosuppressed patients, both groups at a potentially higher risk of infection, do not currently receive prolonged regimens of antibiotic prophylaxis as compared to an average patient. Given the potential risks of antibiotics, strong evidence is needed before making such a recommendation.

In the Danish population-based study, Lalmahomed et al. found a significant decline in the 60-day mortality rates after elective THA or TKA for OA, with rates declining by 60% between 1989–91 and 2004–07, a reduction that was more significant compared to the trend in the general population (insert ref). They also reported significant reductions in cause-specific 60-day mortality rates related to myocardial infarction, venous thromboembolism, pneumonia and stroke. Most mortality reduction over time was in the first 30-days post-arthroplasty. Cram et al. recently described postoperative mortality and time-trends in the U.S. Medicare population, where patients with OA and RA undergoing THA (7) and TKA (8) were included. Cram et al. reported that inpatient, 30-day and 90-day mortality after THA decreased between 1991 and 2008 by 60%, 42% and 33% respectively (7). Similarly, 30-day mortality after TKA decreased by 40% from 1991 to 2008 (8). Cram et al. presented high-quality data for time-trends in mortality and several other characteristics, yet these findings are only applicable to patients 65 years or older.

A population-based study from the Olmsted county, Minnesota reported a 90-day mortality of 0.7% and 0.4% after primary THA and TKA respectively (9), consistent with findings from Cram et al. (7, 8). Singh et al. noted a decrease in the incidence of cardiac complications in both THA and TKA cohorts over time from 1994 to 2008 (9). The Danish study adds to the existing evidence in several ways: (1) it examined mortality specific to the leading causes of mortality including myocardial infarction, venous thromboembolism, pneumonia and stroke; and (2) it divided time into meaningful time periods coinciding with the introduction and promotion of the use of low molecular weight heparin (LMWH) in orthopedic surgery patients after a pivotal trial in early to mid 1990s in Denmark.

Lalmahomed et al. performed sensitivity analyses by excluding patients who underwent non-elective THA or TKA (fracture, cancer or infection), meaning that most findings are applicable to elective THA/TKA. Interestingly, the authors also excluded patients with RA for some unclear reasons, a limitation of this study. Such data could have helped us understand the time-trends in post-arthroplasty mortality in RA patients and allowed us to compare how these time-trends compare to mortality time-trends in patients with OA.

The authors cited several potential reasons for declining mortality over time including: (1) multimodal analgesia and aggressive early ambulation after TKA/THA that likely reduced postoperative complications and associated mortality; (2) improved surgical techniques that may improved outcomes and reduced mortality; and (3) the introduction of LMWH that likely reduced the risk of thromboembolism. Important factors overlooked as explanations for declining mortality over time include the more careful pre-operative screening in the recent years for mortality risk including better pre- and peri-operative management of patients with regards to cardiac, pulmonary and other comorbidities. A better patient selection for TKA/THA in recent times may also have contributed to a reduced postoperative mortality over time.

These findings by Lalmahomed et al. also have several implications for both patients and providers. These updated mortality risk estimates can inform patients and providers of the risk of this rare, but important harm. The declining postoperative mortality rate is reassuring.

As might be expected, these two studies also raise several questions. What are the modifiable mediators of mortality in THA and TKA patients that can be targeted to further reduce the mortality? Is the mortality also decreasing in RA patients undergoing THA/TKA? What are the mediators of infection and dislocation risk in RA patients undergoing THA/TKA? What strategies could be implemented that can improve these outcomes? These important questions need to be answered and addressed in future studies. Future studies should particularly investigate and identify any modifiable mediators of postoperative mortality and complications, so that further reductions in mortality and complications can be achieved. This will improve the benefit risk ratio of this procedure for the very elderly, the very frail and for patients with multiple comorbidities with higher surgical risk.

Patients undergo elective TKA or THA to achieve relief of pain and improvement in function and quality of life, with the anticipation of minimal risks or complications. The literature is replete with studies that have demonstrated improvement in these patient-reported outcomes (PROs). Recent studies have also shown that the improvement in function and pain is not the same for all patients (10–12). On the other hand, high-level evidence regarding the risks and complications of arthroplasty and associated predictors of these risks/complications (including psychological comorbidity and coping mechanisms) is accumulating from high-quality studies (such as two studies in the current issue) and this area of research is rapidly expanding. The new knowledge will allow a better assessment of benefits and risks of arthroplasty for various patient populations undergoing TKA or THA.

In conclusion, these two studies in the current issue shed more light on arthroplasty outcomes and time-trends. Several key findings should help to inform policy makers and help to enrich the informed consent discussions, leading to better-informed and prepared patients. Future studies need to focus on how to intervene and modify factors associated with increased morbidity and mortality and improve patient outcomes after TKA and THA.

Acknowledgments

Grant support: This material is the result of work supported by the resources and use of facilities at the Birmingham VA Medical Center, Alabama, USA. J.A.S. is also supported by grants from the Agency for Health Quality and Research Center for Education and Research on Therapeutics (AHRQ-CERTs), the National Institute of Aging (NIA), the National Cancer Institute (NCI) and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS).

I thank Dr. Terrence Gioe, MD from the University of Minnesota and the Minneapolis Veterans Affairs Medical Center for reviewing and providing comments on an earlier version of the editorial.

References

1. Chen J, Cui Y, Li X, Miao X, Wen Z, Xue Y, et al. Risk factors for deep infection after total knee arthroplasty: a meta-analysis. *Arch Orthop Trauma Surg.* 2013; 133(5):675–87. [PubMed: 23558519]
2. Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, et al. Patient-related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. *J Bone Joint Surg Am.* 2012; 94(9):794–800. [PubMed: 22552668]
3. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008; 59(6):762–84. [PubMed: 18512708]

4. Song KH, Kim ES, Kim YK, Jin HY, Jeong SY, Kwak YG, et al. Differences in the risk factors for surgical site infection between total hip arthroplasty and total knee arthroplasty in the Korean Nosocomial Infections Surveillance System (KONIS). *Infect Control Hosp Epidemiol*. 2012; 33(11):1086–93. [PubMed: 23041805]
5. Leone JM, Hanssen AD. Management of infection at the site of a total knee arthroplasty. *Instr Course Lect*. 2006; 55:449–61. [PubMed: 16958480]
6. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. *J Arthroplasty*. 2008; 23(7):984–91. [PubMed: 18534466]
7. Cram P, Lu X, Kaboli PJ, Vaughan-Sarrazin MS, Cai X, Wolf BR, et al. Clinical characteristics and outcomes of Medicare patients undergoing total hip arthroplasty, 1991–2008. *JAMA*. 2011; 305(15):1560–7. [PubMed: 21505134]
8. Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR. Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. *JAMA*. 2012; 308(12):1227–36. [PubMed: 23011713]
9. Singh JA, Jensen MR, Harmsen WS, Gabriel SE, Lewallen DG. Cardiac and thromboembolic complications and mortality in patients undergoing total hip and total knee arthroplasty. *Ann Rheum Dis*. 2011; 70(12):2082–8. [PubMed: 22021865]
10. Franklin PD, Li W, Ayers DC. The Chitranjan Ranawat Award: functional outcome after total knee replacement varies with patient attributes. *Clin Orthop Relat Res*. 2008; 466(11):2597–604. [PubMed: 18810570]
11. Singh JA, Gabriel S, Lewallen D. The impact of gender, age, and preoperative pain severity on pain after TKA. *Clin Orthop Relat Res*. 2008; 466(11):2717–23. [PubMed: 18679762]
12. Singh JA, Lewallen DG. Predictors of activity limitation and dependence on walking aids after primary total hip arthroplasty. *J Am Geriatr Soc*. 2010; 58(12):2387–93. [PubMed: 21143444]