Canadian Journal of Cardiology 35 (2019) 1085–1087

Editorial

Evaluating Transcatheter Aortic Valve Replacement in Kidney Transplant Recipients: Characterizing Opportunities to Improve Outcomes

Ngan N. Lam, MD, MSc,[a] and Matthew T. James, MD, PhD[b]

[a] Department of Medicine, Division of Nephrology, University of Alberta, Edmonton, Alberta, Canada

[b] Department of Medicine and Department of Community Health Sciences, Libin Cardiovascular Institute of Alberta, O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

See article by Witberg et al., pages 1114–1123 of this issue.

In Canada and other high-income countries, population aging is contributing to an increasing prevalence of multimorbidity, adding considerable complexity to healthcare and creating a growing need to evaluate the effectiveness, appropriateness, and safety of interventions in patients with unique management considerations.[1] Patients with severe aortic stenosis and chronic kidney disease (CKD) exemplify the complexity and treatment challenges that can occur as diseases that accompany aging coincide.[2,3] Outcomes with surgical aortic valve replacement have historically been poorer for patients with advanced CKD, complicated by high rates of worsening kidney function, kidney failure requiring dialysis, major adverse cardiac events, and mortality.[4,5] Given the high perioperative risks of surgical value replacement, transcatheter aortic valve replacement (TAVR) has become an attractive, less-invasive treatment option than surgical aortic valve replacement for many patients. Although patients with CKD have typically been excluded from randomized controlled trials in this area, observational studies have reported that TAVR is associated with better clinical outcomes compared with surgical valve replacement in patients with CKD.[6-8]

Kidney transplant recipients are a particularly unique group of patients with CKD who are at risk of both allograft failure and cardiovascular disease (including valve disease) due to aging, a high prevalence of traditional cardiac risk factors, exposure to CKD-specific risk factors (including those that may be accrued from previous time undergoing dialysis), and transplant-specific factors (many related to the effects of immunosuppressive medications).[9-11] Recent trends illustrate that kidney transplant recipients are becoming older, have more comorbidities at the time of transplant, and are surviving longer with a functioning allograft after transplant, further contributing to their acquisition of comorbidities and complexity.[12,13] Historically (1991-2004), patients with a kidney transplant have been reported to have a 2-year mortality risk of 30% after surgical aortic valve replacement, including a 14% risk of in-hospital death.[14] Despite growing evidence of the efficacy and safety of TAVR in high-, intermediate-, and low-risk patients at large, there has been little information on outcomes to guide TAVR use specifically in kidney transplant recipients who develop aortic stenosis.[15]

In this issue of the *Canadian Journal of Cardiology*, Witberg et al.[16] address an important knowledge gap by reporting on outcomes after TAVR from a multicenter registry (created from 16 centres in Europe, North America, and Israel that performed procedures between 2008 and 2017), including 72 kidney transplant recipients vs 144 matched nontransplant controls with similar levels of kidney function. Kidney transplant recipients made up < 1% of patients undergoing TAVR in this registry. Mean estimated glomerular filtration rate (eGFR) improved by 3 mL/min/1.73 m^2 at 90 days after TAVR in patients with CKD without a transplant, but declined in transplant recipients from a preprocedural mean eGFR of 39 mL/min/1.73 m^2 to a nadir of 32 mL/min/1.73 m^2 at 90 days. One in 4 kidney transplant recipients required initiation of dialysis after TAVR, which was 2 times more common than in matched patients without a transplant. Of note, more than three-quarters of patients who went on to receive dialysis required its initiation during the periprocedural period, and only 1 in 10 patients who started dialysis in this period were able to subsequently discontinue it. This finding indicates that the development of kidney failure was temporally related to events surrounding the TAVR procedure and that kidney function was unlikely to recover subsequently. In multivariable models, the strongest predictor of requiring dialysis was the contrast volume to eGFR ratio, with significant effect modification observed such

Received for publication February 5, 2019. Accepted February 5, 2019.

Corresponding author: Dr Matthew T. James, Division of Nephrology, Department of Medicine, Department of Community Health Sciences, University of Calgary, 3280 Hospital Dr. NW, Calgary, Alberta T2N 4Z6, Canada. Tel.: +1-403-220-6499; fax: +1-403-210-6660.

E-mail: mjames@ucalgary.ca

See page 1087 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.02.002

that the risk of dialysis associated with a higher contrast volume to eGFR ratio was greater among kidney transplant recipients. Other periprocedural and intermediary outcomes were similar between the 2 groups, and over a median follow-up of 2.3 years post-TAVR, the risk of death was similar between the 2 groups, at 29% vs 32%. This study suggests that TAVR may serve as an effective and appropriate treatment strategy for many kidney transplant recipients who develop aortic stenosis; however, recognition of the risk of graft failure requiring dialysis is an important safety consideration that warrants further consideration.

The investigators should be commended for their efforts to collaborate across multiple centers to deliver this cohort study and thereby advance our understanding of the risks and outcomes of TAVR in kidney transplant recipients. Previous studies of TAVR in kidney transplant recipients have been limited by very small sample sizes and sparse data on post-procedure kidney allograft function.[17,18] A strength of the study by Witberg et al.[16] lies in its sample of 72 transplant recipients from across 16 international centers, which provides valuable information on the absolute risks of outcomes that are important to kidney transplant recipients, including acute dialysis initiation, 2-year risk of maintenance dialysis, and death post-TAVR.[16,19] These results can inform the risk and benefit discussions with kidney transplant recipients when weighing management options for severe aortic stenosis.

There are also limitations to the inferences that can be drawn from the information provided in this study that are important to recognize. Although the study provides risk estimates relative to the nontransplant CKD population, what would arguably be most clinically relevant would be a comparison of the effectiveness and safety between all the management approaches that should be presented as treatment options to patients, including conservative medical management, TAVR, and surgical aortic value replacement. One previous study by Fox et al.[17] reported on 8 kidney transplant recipients who underwent TAVR vs 18 recipients who underwent surgical valve replacement and reported 1-year mortality of 0% in the TAVR group vs 17% (based on 3 deaths) in the surgical group. The small number of patients and events, and potential for treatment selection bias for surgery vs TAVR, leaves considerable uncertainty as to the degree that differences in outcomes result from the treatment approaches vs prognostic "case-mix" differences between patients who received the different interventions. This is particularly difficult when attempting to compare outcomes of various treatments, applied to different study populations, reported in separate studies.

In this study of transplant recipients by Witberg et al.,[16] the comparison of outcomes after TAVR with patients without a kidney transplant provides a framework to understand the incremental differences in risk experienced by patients with a kidney transplant above those of patients with comparably reduced eGFR. Although the measured baseline comorbidities between the 2 groups were similar, there are important unmeasured confounders that would have differed between these 2 groups that could contribute to the differences in kidney outcomes observed. Even when matched based on eGFR, kidney transplant recipients (who, in this study, had received their transplant on average 13 years before TAVR) have several unique causes of reduced eGFR, such as chronic rejection and calcineurin inhibitor nephrotoxicity, that place them at risk for progression of chronic allograft nephropathy to kidney allograft failure that necessitates maintenance dialysis. These factors could play an important role in the larger decline in eGFR and higher risk of requiring long-term dialysis among kidney transplant recipients than older patients with CKD without a transplant.

Nonetheless, the particularly high risk of dialysis in the perioperative period and low incidence of recovery of kidney function are noteworthy findings of this study and suggest that the procedural risk of acute kidney injury (which may be related to radiocontrast, hypotension, bleeding, and medication exposures around the time of TAVR) likely plays a prominent role in the development of kidney failure after TAVR. There are several factors that place kidney transplant recipients at particularly high risk of acute kidney injury, including the use of multiple medications that can reduce kidney perfusion (including calcineurin inhibitors, renin-angiotensin system blockers, and diuretics). Further, kidney allografts are particularly prone to developing chronic damage after ischemia–reperfusion injury,[20] increasing the likelihood that those who develop acute kidney injury will progress to kidney failure requiring dialysis rather than recover kidney function. These factors may interact with radiocontrast-induced injury to increase the risk of severe acute kidney injury, which may underlie the stronger relationship between the contrast volume to eGFR ratio and the risk of periprocedural dialysis that was observed in kidney transplant recipients in this study.

There are several important messages from this study by Witberg et al.[16] that can inform clinical care today and research on strategies designed to improve the safety of TAVR in the future for people with CKD. This study highlights that patients with advanced CKD, particularly those with a kidney transplant, should be recognized as being at high risk of kidney failure requiring dialysis after TAVR, and discussion of this risk should be provided to patients in a shared decision-making process. These findings should prompt care teams to include processes that address modifiable factors for kidney protection into preoperative, intraoperative, and postoperative care pathways for cardiac procedures for patients with advanced CKD, including transplant recipients. In the absence of pharmacological interventions for prevention of acute kidney injury, other strategies to reduce the risk of acute kidney injury also need to be evaluated in this patient population, in whom the traditional use of prophylactic intravenous fluids is extremely challenging. Promising strategies include novel imaging techniques and procedural strategies that can be used to reduce the volume of contrast required to complete procedures, as well as refined strategies to improve assessment and optimization of volume status. Because approximately one-third of patients now undergoing TAVR have CKD, and this number can be expected to grow in the future, it would seem that testing these strategies should be a priority. The study by Witberg et al.[16] provides an important foundation for understanding current challenges and identifying opportunities to improve the outcomes of cardiovascular intervention in this complex population.

Funding Sources

M.T.J. is supported by a Canadian Institutes for Health Research (CIHR) New Investigator Award and funded by a

CIHR Foundation Award and CIHR CanSOLVE CKD Strategic Patient Oriented Research Network Grant.

Disclosures

N.N.L. reports no conflicts. M.T.J. is the principal investigator on an investigator-initiated research grant funded by Amgen Canada.

References

1. Forman DE, Maurer MS, Boyd C, et al. Multimorbidity in older adults with cardiovascular disease. J Am Coll Cardiol 2018;71:2149-61.
2. Bello AK, Hemmelgarn B, Lloyd A, et al. Associations among estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes. Clin J Am Soc Nephrol 2011;6:1418-26.
3. Vavilis G, Bäck M, Occhino G, et al. Kidney dysfunction and the risk of developing aortic stenosis. J Am Coll Cardiol 2019;73:305-14.
4. Patel KK, Shah SY, Arrigain S, et al. Characteristics and outcomes of patients with aortic stenosis and chronic kidney disease. J Am Heart Assoc 2019;8:e009980.
5. Pineda AM, Kevin Harrison J, Kleiman NS, et al. Clinical impact of baseline chronic kidney disease in patients undergoing transcatheter or surgical aortic valve replacement. Catheter Cardiovasc Interv 2019;93:740-8.
6. Cheng X, Hu Q, Zhao H, Qin S, Zhang D. Transcatheter versus surgical aortic valve replacement in patients with chronic kidney disease: a meta-analysis. J Cardiothorac Vasc Anesth 2019;33:2221-30.
7. Kumar N, Khera R, Garg N, et al. Comparison of outcomes of transcatheter versus surgical aortic valve replacement in patients with chronic kidney disease. Am J Cardiol 2018;121:343-8.
8. Steinmetz T, Witberg G, Chagnac A, et al. Transcatheter aortic valve implantation versus conservative treatment in chronic kidney disease patients. EuroIntervention 2018;14:e503-10.
9. Lam NN, Klarenbach S, Quinn RR, et al. Renal function, albuminuria, and the risk of cardiovascular events after kidney transplantation. Transplant Direct 2018;4:e389.
10. Weiner DE, Carpenter MA, Levey AS, et al. Kidney function and risk of cardiovascular disease and mortality in kidney transplant recipients: the FAVORIT trial. Am J Transplant 2012;12:2437-45.
11. de Mattos AM, Prather J, Olyaei AJ, et al. Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. Kidney Int 2006;70:757-64.
12. Lam NN, Kim SJ, Knoll GA, et al. The risk of cardiovascular disease is not increasing over time despite aging and higher comorbidity burden of kidney transplant recipients. Transplantation 2017;101:588-96.
13. Knoll G. Trends in kidney transplantation over the past decade. Drugs 2008;68(Suppl 1):3-10.
14. Sharma A, Gilbertson DT, Herzog CA. Survival of kidney transplantation patients in the United States after cardiac valve replacement. Circulation 2010;121:2733-9.
15. Cribier AG. The odyssey of TAVR from concept to clinical reality. Texas Heart Inst J 2014;41:125-30.
16. Witberg G, Shamekhi J, Van Mieghem NM, et al. Transcatheter aortic valve replacement outcomes in patients with native vs transplanted kidneys: data from an international multicenter registry. Can J Cardiol 2019;35:1114-23.
17. Fox H, Büttner S, Hemmann K, et al. Transcatheter aortic valve implantation improves outcome compared to open-heart surgery in kidney transplant recipients requiring aortic valve replacement. J Cardiol 2013;61:423-7.
18. Al-Rashid F, Bienholz A, Hildebrandt HA, et al. Transfemoral transcatheter aortic valve implantation in patients with end-stage renal disease and kidney transplant recipients. Sci Rep 2017;7:14397.
19. Allard J, Durand C, Anthony SJ, et al. Perspectives of patients, caregivers and researchers on research priorities in donation and transplantation in Canada. Transplant Direct 2017;3:e127.
20. Ponticelli C. Ischaemia-reperfusion injury: a major protagonist in kidney transplantation. Nephrol Dial Transplant 2014;29:1134-40.