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EDITORIAL COMMENT

Fixing the Valve, But Injuring the Kidneys, With Transcatheter Aortic Valve Replacement

Collateral Damage With Serious Consequences*

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Most risk prediction models for outcomes after transcatheter aortic valve replacement (TAVR) have identified renal impairment as an important risk factor for earlier mortality (1,2). Moreover, several studies have shown how post-procedure damage to the kidneys, acute kidney injury (AKI), is associated with worse clinical outcomes (3). Of course, these findings are not unique to TAVR. Baseline renal impairment and AKI are consistently associated with worse clinical outcomes for a variety of cardiovascular conditions and procedures.

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In this issue of *JACC: Cardiovascular Interventions*, Gupta et al. (4) add to this existing body of published reports by providing data from the very large National Inpatient Sample, the largest publicly available all-payer inpatient care database in the United States. Contextually, these are data from 2012 to 2014, when TAVR was largely confined (outside of clinical trials) to patients at high or extreme risk for surgery. A particular strength of the study is the large number of patients with end-stage renal disease (ESRD). Chronic kidney disease (CKD) was identified by International Classification of Diseases-9th Revision (ICD-9) codes, which have reasonable sensitivity and very high specificity for the disease. It is not clear how coding influenced the identified rate of AKI. The authors indicated that ICD-9 codes have very low sensitivity for AKI, yet the rate of AKI reported in this analysis is higher (18.8%) than in clinical trials to date. Nevertheless, a wide range of AKI rates after TAVR have been reported (3). These differences may be related to inaccuracies in coding, different definitions of AKI used by trials and hospital coders, and variation in patient populations. The coding-based data do not provide insight on how the stage of AKI (1, 2, or 3) influences the outcome.

There are several important takeaways from this study. First, the prevalence of CKD and ESRD among patients undergoing TAVR slightly increased during the study period; perhaps as intermediate- and low-risk populations undergo TAVR, these rates will decline simply due to the lower prevalence of CKD and ESRD in those populations. Second, mortality rates in patients with CKD and ESRD declined, but were still higher than for those without CKD. Third, although ESRD does increase risk of a poor outcome, by itself, it is not a marker of futility for TAVR; further work is needed to identify those patients with ESRD for whom the risk of TAVR is likely to outweigh any anticipated benefit. Fourth, AKI rates are quite high in patients undergoing TAVR (1 in 10 of those without CKD and 1 in 3 of those with CKD) and rates of AKI are not decreasing over time. Finally, patients who develop AKI (particularly AKI with dialysis) have a markedly higher in-hospital mortality rate; the excess mortality associated with AKI was particularly pronounced among those without baseline CKD. In patients without CKD, the adjusted odds of

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TABLE 1 Roadmap for Reducing AKI After TAVR

1. What factors are associated with the development of AKI after TAVR? • When do these factors occur (pre-procedure, periprocedure, or post-procedure)? • Are these factors modifiable?
2. What are the most promising interventions to reduce AKI after TAVR? • Gather insights on potential interventions from retrospective analyses, preclinical studies, and other cardiovascular procedures
3. Test potential interventions in randomized controlled trials • These trials could target a subset of patients undergoing TAVR who are at highest risk for AKI to increase event rates and decrease sample size
4. Implement strategies proven to reduce AKI into clinical practice • Provide user-friendly point-of-care tools to identify subjects at risk for AKI • Feedback and accountability on how well providers incorporate proven interventions into the care of patients at highest risk

AKI = acute kidney injury; TAVR = transcatheter aortic valve replacement.

in-hospital mortality associated with AKI was 7.40 (95% confidence interval [CI]: 6.36 to 8.60), whereas in those with baseline CKD, the adjusted odds of in-hospital mortality associated with AKI was 3.61 (95% CI: 2.99 to 4.35). The adjusted odds of in-hospital mortality were roughly doubled in those with and without baseline CKD when AKI required dialysis.

Although none of these findings is necessarily surprising, the high rates of AKI and the markedly higher mortality rates linked to the occurrence of AKI are sobering and merit further attention. Pre-existing renal impairment will be an ongoing reality in this patient population when they are sent for treatment of their aortic stenosis. The pressing question is what can be done to decrease the risk of AKI and its adverse consequences.

The path to reducing the risk and consequences of AKI in patients undergoing TAVR is not an uncharted one insofar as AKI has been examined in the context of other cardiovascular procedures. Nonetheless, although there may be areas of overlap, it is worth considering the potentially unique aspects of AKI in patients undergoing TAVR (**Table 1**). First, it is critical to know what factors are associated with the development of AKI. This is important both to identify those at highest risk in whom preventative measures ought to be focused, but also for highlighting what interventions might be helpful to reduce the incidence of AKI. Some of these risk factors will be modifiable (e.g., reducing contrast administration), whereas others will not be modifiable (e.g., baseline renal function). Risk factors may differ in those with versus without baseline renal impairment and may be identified at the pre-procedural, periprocedural, and post-procedural time points, which influences when and what preventive strategies may be used. Prior studies have identified several factors associated with AKI after TAVR, including baseline renal impairment, diabetes, increased contrast load, blood transfusions, hypotension, systemic inflammatory response syndrome, more severe heart failure, and increased circulating 5-adenosylhomocysteine, among others (3,5–7). Larger studies focused on identifying factors associated with AKI, including more careful phenotyping with blood and urine samples for omics-based analyses, will be helpful not only in improving our identification of those at risk but in identifying potentially promising therapeutic targets.

Related to the first step, the most promising interventions to reduce AKI need to be determined. Initial insights may come from retrospective analyses, preclinical studies, or research on other cardiovascular procedures. As an alternative approach, one might find sites that have particularly low rates of AKI after TAVR ("favorable outliers") and examine what they may be doing differently at an operational or system level that may yield lower rates of AKI. Several interventions to reduce AKI after cardiac catheterization or cardiac surgery have been pursued with mixed results, most notably statins, *N*-acetylcysteine, and sodium bicarbonate (8–10). For patients undergoing TAVR, a recent study suggested promise of furosemide-induced diuresis with matched fluid replacement to maintain a high urine flow rate (11). At the very least, on the basis of current knowledge, to potentially reduce the risk of AKI after TAVR, it seems prudent to minimize contrast administration and blood transfusions, avoid prolonged or excessive hypotension or hypovolemia, and avoid nephrotoxic drugs, particularly in patients with existing renal impairment.

Whatever the potential preventive strategy, though, these interventions then need to be tested in randomized trials. To make these intervention trials more feasible, it may be helpful to develop accurate risk models for AKI in order to enrich these trials with patients who have higher event rates to decrease the required sample size. As risk models for AKI are refined and validated and as effective interventions to reduce the risk of AKI are described, it will be critical to translate this knowledge into everyday clinical practice. In this regard, user-friendly point-of-care tools will be needed to identify patients at risk and to suggest optimal preventive strategies, perhaps tailored to the characteristics of that patient. Moreover, providers will need feedback and accountability on their rates of AKI and how well they

are incorporating proven preventive strategies into the care of patients at highest risk.

In less than a decade, we have gone from attempting TAVR in the highest-risk patients to now comparing TAVR to surgical aortic valve replacement in low-risk patients. Device iterations have reduced the risk of paravalvular leak and vascular complications, and the need for nontransfemoral approaches. Dissemination of best practices and increasing experience have translated into more successful device implantations and reduced morbidity and mortality. Nonetheless, there is room for improvement to optimize patient-centered outcomes for those undergoing TAVR. Given the high incidence and serious consequences of AKI, reducing the occurrence of AKI now merits more significant investigative attention and resources so that we can avoid damaging the kidneys (and the patient) while fixing the valve.

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REFERENCES

1. Edwards FH, Cohen DJ, O'Brien SM, et al. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. JAMA Cardiol 2016;1:46–52.

2. Iung B, Laouenan C, Himbert D, et al. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. Heart 2014;100:1016–23.

3. Najjar M, Salna M, George I. Acute kidney injury after aortic valve replacement: incidence, risk factors and outcomes. Expert Rev Cardiovasc Ther 2015;13:301–16.

4. Gupta T, Goel K, Kolte D, et al. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2017;10:2050–60.

5. Barbash IM, Ben-Dor I, Dvir D, et al. Incidence and predictors of acute kidney injury after transcatheter aortic valve replacement. Am Heart J 2012;163:1031–6.

6. Sinning JM, Ghanem A, Steinhauser H, et al. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2010;3:1141–9.

7. Elmariah S, Farrell LA, Daher M, et al. Metabolite profiles predict acute kidney injury and mortality in patients undergoing transcatheter aortic valve replacement. J Am Heart Assoc 2016;5:e002712.

8. Han Y, Zhu G, Han L, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. J Am Coll Cardiol 2014;63:62–70.

9. Thiele H, Hildebrand L, Schirdewahn C, et al. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) trial. J Am Coll Cardiol 2010;55:2201–9.

10. McGuinness SP, Parke RL, Bellomo R, Van Haren FM, Bailey M. Sodium bicarbonate infusion to reduce cardiac surgery-associated acute kidney injury: a phase II multicenter double-blind randomized controlled trial. Crit Care Med 2013;41:1599–607.

11. Barbanti M, Gulino S, Capranzano P, et al. Acute kidney injury with the renalguard system in patients undergoing transcatheter aortic valve replacement: the PROTECT-TAVI trial (PROphylactic effecT of furosEmide-induCed diuresis with matched isotonic intravenous hydraTion in Transcatheter Aortic Valve Implantation). J Am Coll Cardiol Intv 2015;8:1595–604.

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