Prevention of 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)*

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In this issue of JACC: Cardiovascular Interventions, Barbanti et al. (1) report the results of a single-center, prospective, randomized, controlled trial (RCT) investigating the potential protective effect of the RenalGuard system in patients undergoing transcatheter aortic valve replacement (TAVR). Acute kidney injury (AKI) is an important finding after interventional and operative procedures and is associated with a significantly adverse prognosis after percutaneous coronary intervention (PCI) or TAVR. Numerous approaches to prevent post-procedural AKI have been studied, including various contrast agents, renal protective drugs, and hydration regimens. Almost all have failed in large RCTs with the exception of simply limiting contrast dose and ensuring adequate pre-procedural hydration. Patients undergoing TAVR, in particular, are at high risk, not only at risk of AKI but of subsequent cardiac and noncardiac mortality. In the current study, patients were quite typical of those undergoing TAVR in Europe and North America, with a median age older than 80 years and high prevalences of hypertension (75%), diabetes mellitus, dyspnea, previous heart failure, and peripheral vascular disease, all factors associated with a higher risk of AKI. Although the mean estimated glomerular filtration rate (GFR) was not unreasonable, ~10% of patients had severe baseline renal dysfunction (estimated GFR <30 ml/min), and almost 50% had moderate renal dysfunction (estimated GFR 30 to 60 ml/min). The TAVR procedures themselves (majority CoreValve) were well executed by this experienced group with high device success rates and a low incidence of permanent pacemaker implantation. Rapid pacing, which induces hypotension, was used in all cases, and the median contrast volume administered was relatively high at 175 ml (interquartile range up to 230 ml).

Logistically, the trial was a single-center, prospective RCT, and the authors are to be congratulated for this design as opposed to simply performing a consecutive case series. Due to the single-center nature of the trial, a relatively small number of patients were randomized, 56 per group, which, unfortunately, is typical of many early studies in the field of AKI prevention.

The RenalGuard system (RenalGuard Solutions Inc., Milford, Massachusetts) is a unique proprietary technology and is approved for sale in Europe. The
system causes renal flushing by carefully matching intravenous infusion of isotonic saline solution to furosemide-forced diuresis. The current study demonstrated a lower incidence of AKI as assessed by increases in serum creatinine (stage 1 AKI, 5.4% of the treatment group vs. 23.2% of the control group; p = 0.013). Although at first glance this appears impressive, in almost all cases, the creatinine level returned to normal, and no patient required hemodialysis. Moreover, there was no significant difference in other important clinical endpoints, either cardiac or noncardiac, between groups. Stage 3 AKI developed in only 1 patient in the control group. This particular patient received 300 ml of contrast during the procedure and experienced a creatinine peak of almost 6 mg/dl despite a baseline estimated GFR of 63.8 ml/min. It is unclear whether this 84-year-old patient was also diabetic.

These observations lead to a number of interesting questions. First, although the RenalGuard system does appear to lower post-procedural creatinine increases, does it actually prevent renal dysfunction or merely flush serum creatinine? Second, is serum creatinine an appropriate biomarker for AKI in this model? It should be remembered that creatinine is a break-down product of creatine phosphate in muscle tissue, and ~1% to 2% of muscle creatine is converted to creatinine daily. Creatinine is eliminated both by filtration and tubular excretion, and, in a steady state serum creatinine concentrations, reflects underlying GFR. We previously suggested that even hydration may actually be diluting serum creatinine (2). With the RenalGuard system, the effects of renal flushing on kidney physiology need to be accounted for.

Glomerular filtration rate changes constantly to accommodate the variations in the osmolar load. Osmolar load varies based on the diet and the rate of protein breakdown. When a patient is faced with a large osmolar load, the GFR drastically increases, and elimination of the additional osmoles is enhanced. In the kidney, the elimination process is tightly regulated by tubuloglomerular feedback (TGF) (3). During TGF, enhanced sodium chloride delivery to the loop of Henle and distal convoluted tubules results in significant afferent arteriolar vasoconstriction. This mechanism is orchestrated via a chloride-sensitive signaling process through the juxtaglomerular apparatus. As the result, nephrons avoid rapid loss of electrolytes and maintain GFR in the physiological range. Loop diuretics block this signaling process, and afferent arteriolar vasoconstriction is avoided. With RenalGuard, however, the GFR increases significantly due to a rapid load of osmoles received in the form of normal saline. Unlike physiological scenarios, TGF is not able to modulate the enhanced GFR due to the blocking effect of furosemide on the juxtaglomerular apparatus. This results in a significant increase in GFR during RenalGuard use. This hyperfiltration will increase elimination of serum creatinine. When an intervention, such as RenalGuard, directly affects the serum creatinine level, the outcome of interest (renal function) cannot be adequately assessed based on the serum creatinine level alone.

In the current study, patients in the control group are in a disadvantageous position because they likely (data are not provided in the paper) received a much smaller osmolar load because they did not need to reach 300 ml/h of urine output. Therefore, the GFR would not be expected to increase to the same extent in the control group as in the intervention group. Moreover, the control group did not receive furosemide to mitigate TGF, and the chloride load in this group could actually have enhanced afferent arteriolar vasoconstriction. The sum total of these effects in the control group, particularly coupled with the vasoconstrictive characteristics of contrast media, may have resulted in severe vasoconstriction of the afferent arteriole and decreases in the GFR. We suspect that it is this physiological phenomenon that has been detected as stage 1 AKI in the current study. Information regarding osmolar load and elimination (amount of osmoles received and osmolar excretion via urine) in each arm of the study would have helped to delineate this issue. Finally, the extent of tubular cell damage in each group is unclear as there were no renal stress or injury biomarkers measured.

What, then, can we conclude from the current paper? First, the RenalGuard system appears to be safe to use in patients undergoing TAVR and is associated with lower creatinine increases, but there are no differences in important clinical endpoints, including need for hemodialysis. We are not convinced that serum creatinine is an appropriate sole marker for AKI when a renal flushing system is being used for the reasons outlined previously. Finally, the RenalGuard system should be evaluated in a larger multicenter trial enrolling patients at moderate to high risk of post-procedural AKI, whether that be TAVR or PCI. Such a trial should incorporate more robust markers of kidney function, such as isothalamate clearance and cystatin C, in conjunction with kidney stress and injury biomarkers (e.g., insulin-like growth factor binding protein-7 and tissue inhibitor metalloproteinase-2 [4], neutrophil gelatinase-associated lipocalin [5],
kidney injury molecule-1 (KIM-1) (6)). Until such trials are performed, we believe that it is premature to advocate widespread adoption of renal flushing for the prevention of AKI.

REFERENCES


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