

Contrast-Induced Acute Kidney Injury in the PRESERVE Trial

Lessons Learned

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The prevention of contrast-induced AKI (CI-AKI) has been a long-standing subject of much interest (1), with a recent PubMed search for “contrast nephropathy clinical trial” yielding >1700 references. However, the field has been hindered by underpowered studies with heterogeneous inclusion criteria and trial end points, as well as uncertainty regarding the lasting effect of these interventions.

It is on this landscape that Weisbord *et al.* (2) recently reported the findings of the Prevention of Serious Adverse Events Following Angiography (PRESERVE) Trial. This US Veterans Affairs/National Health and Medical Research Council of Australia–sponsored trial randomized 5177 patients undergoing coronary and noncoronary angiography in a 2×2 factorial design to intravenous isotonic bicarbonate versus saline and oral acetylcysteine versus placebo. The study population was enriched for patients with risk factors, including those with evidence of stage 3B CKD or stage 3A CKD in the presence of diabetes. In a departure from more commonly used outcomes, like AKI, the investigators chose a primary outcome of major adverse kidney events (MAKE), a composite end point of death, dialysis, or a persistent 50% increase in serum creatinine at 90 days (3); 4993 patients were included in the modified intention to treat analysis, with approximately 90% undergoing coronary angiography and about one quarter involving percutaneous interventions. The median volumes of contrast and crystalloid administered were 85 ml and 1 L, respectively.

The trial was stopped after a prespecified interim analysis indicated a low likelihood of seeing a meaningful difference in the primary end point, which was experienced by 4.7% in the saline group versus 4.4% in the bicarbonate group ($P=0.62$). Similarly, no differences were observed between patients receiving acetylcysteine and placebo (4.6% versus 4.5%, respectively; $P=0.88$). Lastly, no differences were observed in the rates of AKI, cardiovascular, or all-cause hospitalizations or adverse events, and there were no differences within key prespecified subgroups (including stratification by baseline eGFR, albuminuria, and contrast volume).

We believe that the findings from the PRESERVE Trial are practice changing and offer the following important lessons.

- (1) Important and well conducted clinical trials can and should be performed in AKI. Attention to the limitations of previous studies allowed the investigators to implement important design elements, including enrollment of higher-risk patients, characterization of baseline kidney function to better anchor end points, use of a primary end point with clear clinical relevance, and powering the study to efficiently test multiple interventions. In addition, their successful collaboration with cardiologists and other interventionists showed that AKI can be effectively tackled as a crossdisciplinary problem.
- (2) Clinical trials in AKI are an important source for future discovery. Although not a “positive” study, data and samples from the PRESERVE Trial will provide opportunities to address future questions, including the following.
 - (a) Can biomarkers improve AKI phenotyping? Current AKI definitions lump heterogeneous phenotypes together. Although nearly 10% of patients in the PRESERVE Trial experienced AKI, only a fraction suffered persistent loss of kidney function or required dialysis, reminding us that, even within homogenous settings, not all AKI is the same. The PRESERVE Trial will provide opportunities to test whether next generation biomarkers of AKI can identify patients at risk for MAKEs, distinguish potential differences between “prerenal” AKI and tissue injury, and determine whether CI-AKI has itself a biomarker “signature.”
 - (b) Are there treatment-responsive “subtypes” of patients? In other complex diseases (e.g., acute respiratory distress syndrome), distinct “sub- or endophenotypes” that may share a common pathophysiology, improve mechanistic understanding, and/or lead to the identification of new therapeutic targets have been proposed (4,5), but they remain relatively unexplored within kidney disease.
 - (c) Are there longer-term risks associated with CI-AKI? The PRESERVE Trial is among the first AKI trials to apply MAKE90 as a primary outcome, and it was on the basis of recommendations by field experts who recognized the need for end points in AKI that “provide reliable signals for the efficacy of the intervention” and that are more “meaningful to patients” (3). These outcomes and similar variants, such as major adverse kidney and cardiac events, have been

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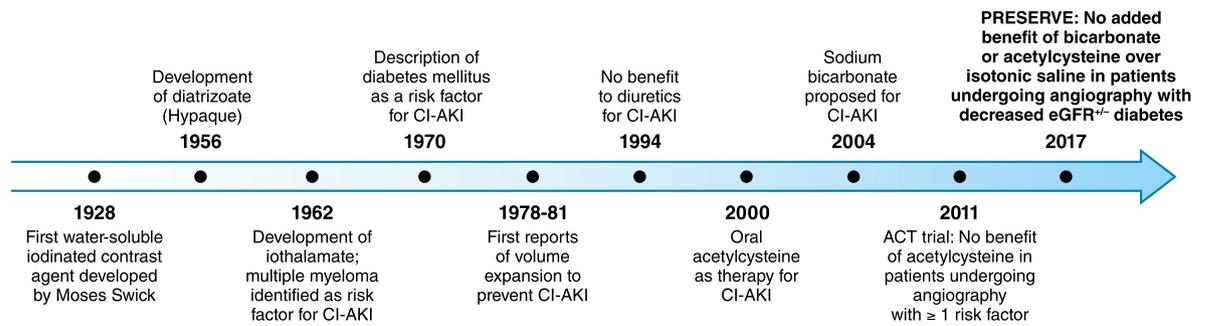


Figure 1. | There has been interest for many years in the prevention of CI-AKI, and the PRESERVE trial tested two interventions that have been common in clinical practice for many years.

adapted from the cardiology literature and will provide opportunities to strengthen understanding of the transition between AKI and persistent kidney dysfunction in CI-AKI. The integrated health care systems in which the trial was performed may also provide opportunities to understand the long-term ramifications of CI-AKI, including cardiovascular disease.

- (3) Evolving practice standards for CI-AKI prophylaxis may also be reducing serious kidney-related events. The key finding from the PRESERVE Trial is that adequate volume expansion with isotonic saline alone remains a key element of best practice for intra-arterial contrast prophylaxis during elective procedures. However, it is worth highlighting the potentially equally important effect of changing practice patterns on this evolving standard. Recent literature suggests that the incidence of AKI in patients with acute myocardial infarction is decreasing despite increases in coronary angiography and percutaneous intervention (6). In the PRESERVE Trial, the contrast agents used were exclusively either low or iso-osmolar, and the amounts were modest (7), reflecting a significant departure from earlier seminal studies (8). These changes are an often overlooked aspect of the evolving story of CI-AKI and may partially explain why few patients experienced serious kidney sequelae in the PRESERVE Trial. Importantly, a recent large negative clinical trial of acetylcysteine suggests that there may be still room for widespread adoption of some strategies, such as routine use of low or iso-osmolar contrast (9). With the continued exploration of ultralow-contrast volumes and alternative agents, it is reasonable to expect that kidney complications after angiography may continue to decrease.
- (4) Decision making regarding the risk-benefit of angiography can be better informed for this patient population. The PRESERVE Trial provides the clinical community with valuable prognostic information. That is, although serious complications can and do occur, the likelihood of experiencing lasting serious kidney-specific adverse sequelae seems to be low in moderate-risk patients when available prevention strategies are applied and should be placed in context when discussing the potent benefits of elective angiography (10).

Some questions were not directly addressed by the PRESERVE Trial. Specifically, patients with acute coronary syndromes undergoing urgent procedures (thought to be at higher risk of CI-AKI) were not included, and the proportion of patients at

highest risk for CI-AKI (*e.g.*, eGFR < 30 ml/min per 1.73 m²) was limited. Differences in setting and patient mix also make direct extrapolation to other forms of contrast exposure (*e.g.*, intravenous) challenging; however, it is difficult to hypothesize that the pathophysiology of CI-AKI in these settings would be so different as to make a benefit more likely when none was observed in the PRESERVE Trial. Furthermore, given recent studies suggesting that the risk of CI-AKI has been overinflated in the context of modern intravenous contrast agents, the number of patients that would need to be treated would be even larger.

In summary, we should celebrate the PRESERVE Trial for providing robust answers to the potential benefit of two interventions, about which uncertainty has lingered for too long. Yet, in considering this achievement, we are reminded that significant time, effort, and resources have been devoted to studying these interventions in CI-AKI (Figure 1), despite perhaps the lack of a strong mechanistic basis. The relatively common nature of its exposure and its predictable timing have made CI-AKI an attractive area of investigation. However, these findings and other suggest that the contribution of CI-AKI to the overall landscape of severe AKI, which is growing and for which proven therapies remain lacking, may be diminishing. Future studies that focus on resolving the heterogeneity issues that burden the clinical evaluation of AKI may hold the key to improving understanding of its pathogenesis and developing novel targets needed to advance the field and improve outcomes.

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Disclosures

None.

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