Contrast-associated acute kidney injury signifies a severe and usually reversible decline in kidney function that may develop within 72 hours after intravascular administration of iodinated contrast material.1 The condition is usually defined as an increase in the serum creatinine level of more than 0.5 mg per deciliter (44 μmol per liter) or an increase of at least 25% in the level from baseline. Contrast-associated acute kidney injury occurs most commonly after contrast-enhanced computed tomography, coronary angiography, or percutaneous coronary interventions, circumstances in which the volume of contrast material that is administered is large or the administration is intraarterial.

The incidence of contrast-associated acute kidney injury varies widely, depending on well-described risk factors, such as chronic kidney disease, diabetic nephropathy, an age of more than 75 years, and congestive heart failure, and is associated with important short-term and long-term complications and increased mortality.1,2 Furthermore, subsequent long-term decline in the estimated glomerular filtration rate after an episode of contrast-associated acute kidney injury has been shown to be associated with progressive chronic kidney disease.3 Contrast-associated acute kidney injury also has economic consequences, including an increased duration of hospitalization and increased hospital costs.

Prevention of contrast-associated acute kidney injury has centered on its multifactorial pathogenesis, which includes renal vasoconstriction and tissue hypoxia, direct cytotoxicity, increased oxidative stress, and increased blood viscosity.5 Various preventive strategies have been developed, with recent interest centering on the periprocedural administration of intravenous sodium bicarbonate or oral acetylcysteine rather than on intravenous saline hydration, which has been the standard of care since the 1990s.6 Small initial studies showed benefit from the use of sodium bicarbonate and acetylcysteine in the prevention of contrast-associated acute kidney injury.7,8 However, after the publication of these initial studies, numerous small and underpowered trials, as well as meta-analyses, raised doubt about these approaches. Indeed, there are a staggering number of small, generally less-than-informative trials in this area, with a recent literature search turning up more than 100 studies of acetylcysteine and more than 50 studies of sodium bicarbonate. Such conflicting data have left clinicians with confusing choices about the most effective preventive approach.

In this issue of the Journal, Weisbord et al.9 report the results of the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial, which compared intravenous saline,

intravenous sodium bicarbonate, and oral acetylcysteine for the prevention of the primary end point, which was a composite of death, the need for dialysis, or a persistent increase in the serum creatinine level of at least 50% from baseline at 90 days after the procedure. Contrast-associated acute kidney injury was a secondary end point. This multicenter, randomized, controlled trial enrolled 5177 patients in 2-by-2 factorial design to receive intravenous 1.26% sodium bicarbonate or intravenous 0.9% sodium chloride and 5 days of oral acetylcysteine or oral placebo. Patients were at moderate risk for contrast-associated acute kidney injury (defined as chronic kidney disease stage 3 or worse, with or without diabetes), and the rate of acute kidney injury of approximately 9% in the trial was consistent with this risk stratification. Higher-risk patients, such as those undergoing emergency procedures, were not included in the trial, and the majority of the studies were diagnostic, not interventional. The trial was stopped early for futility after a prespecified interim analysis showed that there was no between-group difference in the primary end point and that complete enrollment was not likely to alter the results. Thus, the trial investigators concluded that there was no additional benefit of sodium bicarbonate over saline, no benefit of acetylcysteine over placebo, and no interactions between these therapies. Subgroup analyses across several different parameters also showed no benefits.

It is important to note that the authors used a primary end point that reflects the sequelae of contrast-associated acute kidney injury rather than focusing on small changes in the serum creatinine level. Their strategy is more clinically relevant, and the finding that neither the primary nor the secondary end point was affected by these therapies strongly suggests that these interventions have no clinical efficacy over saline.

The trial has some limitations. One of the greatest is that the protocol allowed for wide discretion in the amount of intravenous fluid that was administered to patients. Furthermore, clinicians were aware of the patients' clinical characteristics. Thus, one could wonder whether higher-risk patients received more fluids for longer durations, thereby biasing the results. However, the volume of the administered fluid was similar in all groups. In addition, patients at the highest risk for contrast-associated acute kidney injury, such as those with diabetic nephropathy and those receiving large volumes of contrast material for interventional procedures, constituted a very small percentage of the enrolled patients. Despite these and other limitations, this large, well-designed trial should prompt clinicians to focus on the periprocedural use of intravenous saline and abandon the use of sodium bicarbonate and acetylcysteine for the prevention of contrast-associated acute kidney injury. The results of the PRESERVE trial remind us that small, underpowered, single-center studies may be regarded with skepticism until the findings can be confirmed in well-designed, randomized, controlled clinical trials.