The development of acute kidney injury is not an uncommon complication of invasive cardiovascular procedures requiring administration of radiocontrast, and it is associated with high acute and long-term morbidity and mortality.1-3 Recognized mechanism of acute kidney injury include embolization of atheroma (cholesterol embolism), which has been shown to occur in up to 1.4% of cases in clinical studies4 and in as high as 30% of cases in pathological series,3 and a direct toxic effect of contrast media on renal tubular cells (contrast-induced acute kidney injury). In the absence of cutaneous findings associated with cholesterol embolism, and in the absence of other symptoms and signs of distal embolization, it is difficult to determine the relative contribution of cholesterol embolism to the development of acute kidney injury when compared with contrast-induced acute kidney injury.

The pathophysiology of contrast-induced acute kidney injury is complex and includes a direct toxic effect on tubular cells as well as the production of reactive oxygen species.6,7 Reactive oxygen species, by acting as scavengers of NO, lead to a reduction in Po2 and to increased vascular reactivity to various vasoconstrictors including angiotensin II, thromboxane, endothelin, adenosine, and norepinephrine.

During the past 2 decades, we have made substantial progress in the identification of risk factors for the development of contrast-induced acute kidney injury7,8 and in the identification of interventions that can lead to a reduction of its incidence. As of today, minimization of the total amount of contrast by modification of procedure strategies and appropriate preprocedure hydration are mainstays in the prevention of contrast-induced acute kidney injury.9-11 In addition, the use of low-osmolar and iso-osmolar contrast media has been found to be beneficial when compared with high-osmolar contrast media.12 However, substantial differences also exist within the group of low-osmolar contrast media, where iohexol and ioxaglate seem to be associated with a higher risk of contrast-induced acute kidney injury when compared with other low-osmolar or iso-osmolar contrast media.13 With regard to pharmacological interventions, the results have been disappointing so far. The initial enthusiasm with antioxidants, dopamine receptor agonists, aminophylline, N-acetyl cysteine, and many other pharmacological interventions was met by disappointing results when the same interventions were tested in randomized clinical trials. Similar to other pharmacological interventions, retrospective registry analysis and the results of small randomized clinical trials have suggested that statins might be beneficial in preventing contrast-induced acute kidney injury.14-16 It has been suggested that these effects might be mediated by the nonlipid-lowering, pleiotropic effect of statins on inflammatory pathways, endothelial reactivity, and apoptosis. However, also for statins there is currently no conclusive evidence about their efficacy in the prevention of contrast-induced acute kidney injury.


In the December 18 article of Circulation, Quintavalle et al17 report the results of an analysis of a subset of patients with chronic kidney disease enrolled in the NAPLES II trial. In the NAPLES II trial, patients undergoing elective coronary angiography or percutaneous coronary intervention in a native coronary artery were randomly assigned to receive atorvastatin treatment at a dose of 80 mg daily before the intervention or placebo. In addition to randomization to atorvastatin or placebo, patients with chronic kidney disease received prophylactic treatment for the prevention of contrast-induced acute kidney injury including the administration of (1) N-acetyl cysteine 1200 mg PO twice daily the day before and the day of administration of contrast media and (2) aggressive hydration with sodium bicarbonate solution with an initial intravenous bolus of 3 mL/kg per hour for 1 hour immediately before contrast media injection, followed by 1 mL/kg per hour during contrast exposure and for 6 hours thereafter. The primary end point was the development of contrast-induced acute kidney injury, which was defined as an increase in serum Cystatin-C concentration of 10% above the baseline value at 24 hours from contrast administration. The authors found that pretreatment with atorvastatin in patients with chronic kidney disease was associated with a significant reduction in the development of contrast-induced acute kidney injury. In additional in vitro experiments, they showed that pretreatment with atorvastatin of nonhuman tubular epithelial cells and of human embryonic proximal tubules cells prevents renal cell apoptosis induced by exposure to contrast media. This effect seemed to be mediated by a reduction in stress kinases activation and by restoring survival signals.

Quintavalle et al17 should be praised for their further contribution to the body of knowledge related to the prevention of contrast-induced acute kidney injury, for their thorough analysis, and for their attempt to link clinical findings with the
result of in vitro experiments to identify a pharmacodynamic mechanism for the observed clinical effect. There are several points that are relevant to the current practice of interventional cardiology and that deserve further discussion. First, traditional definitions of contrast-induced acute kidney injury have included an increase in serum creatinine of 0.5 mg/dL over baseline or an increase of serum creatinine of 25% over baseline. Previous studies have shown that these definitions have clinical relevance because they have been found to be associated with an increased risk of in-hospital and long-term mortality. However, it has also been shown that the definitions based on serum creatinine might not be as sensitive as in the assessment of renal function and in detecting acute deterioration of renal function. More recently, Cystatin-C has emerged as a new marker of renal function that is more sensitive than serum creatinine, and which seems to be independent of age, sex, dietary intake, and muscle mass. Cystatin-C is a low molecular mass protein produced by all human nucleated cells and it is freely filtered through the normal glomerular membrane. After filtration, 99% of the filtered Cystatin-C is degraded by tubular cells. It has been shown that the renal plasma clearance of Cystatin-C is linearly related to the plasma clearance of $^{51}$Cr-EDTA, with a regression equation close to the identity line. Although Quintavalle et al were able to show an effect of atorvastatin on renal function as measured by Cystatin-C levels, the study was not powered to detect an effect according to the more traditional (and less sensitive) definitions of contrast-induced acute kidney injury. However, they confirmed a relationship between Cystatin-C increases and adverse long-term outcomes (morbidity and dialysis), which has been previously suggested in other studies, and which confirms the value of Cystatin-C as a sensitive, surrogate end point to predict adverse long-term outcomes. Yet, no information was provided in the present study on whether the observer effect of atorvastatin treatment on Cystatin-C levels was translated into a beneficial effect with regard to those same hard outcomes. Inadequate sample size for a detection of an effect on hard outcomes is a plausible explanation for such omission. Second, it is disappointing to see that the benefit of atorvastatin was observed only in patients at intermediate risk, ie, with a glomerular filtration rate $>30$ and $<60$, but not in high-risk patients with a glomerular filtration rate $<30$. It remains to be determined why no benefit was observed in the higher risk group. Third, all patients in the present study were pretreated with N-acetylcysteine. The possibility of an interaction or a synergistic effect between N-acetylcysteine and atorvastatin cannot be ruled out, and it is indirectly supported by the results of the in vitro experiments. Unfortunately, based on a recent large randomized clinical trial and a registry analysis, the use of N-acetylcysteine has been removed from the most recent American College of Cardiology/American Heart Association guidelines for percutaneous coronary intervention, and it is classified now as a class III indication. Thus, the application of the results of this study to current practice in the context of the most recent guidelines remains to be defined. Finally, from a mechanistic perspective, the pleiotropic effect of statins includes among others plaque stabilization. Thus, whether the effect of statins in this patients’ population is also mediated by stabilization of atheroma and by a reduction in cholesterol embolism is an intriguing though unproven hypothesis.

Despite these perceived limitations, the study by Quintavalle et al adds an important chapter to our understanding of contrast-induced acute kidney injury and its prevention, and it provides a stimulus for further investigations. It suggests that statins use can result in additional benefit as adjunctive therapy to optimal prevention including appropriate hydration and the use of less nephrotoxic contrast media. In addition, it provides indirect support for broadening or at least maintaining the current American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for percutaneous coronary intervention that recommend preprocedure statins as a class IIa indication for the prevention of periprocedural myocardial infarction in patients undergoing percutaneous coronary intervention, regardless the potential role of other adjunctive therapy.

Disclosures

None.

References


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