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EDITORIAL COMMENT

Do Statins Reduce the Risk of Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Angiography or Percutaneous Coronary Interventions?*

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Contrast-induced acute kidney injury (CI-AKI), also known as contrast-induced nephropathy, is a common complication of intra-arterial administration of iodinated radiographic contrast medium (IRCM) that may prolong the duration of hospitalization and increase the risk of death (1,2). CI-AKI is characterized by an increase in serum creatinine beginning within the first 24 h of IRCM exposure and peaking at up to 5 days after exposure. CI-AKI is defined most commonly as a rise in serum creatinine concentration ≥0.5 mg/dl or 25% above baseline assessed 48 to 72 h after exposure to contrast (1,2). More recently, the Acute Kidney Injury Network defined CI-AKI as a rise in serum creatinine of ≥0.3 mg/dl above baseline with oliguria (1).

See pages 62 and 71

Patients with chronic kidney disease (CKD) are vulnerable to CI-AKI, particularly in the presence of risk factors such as diabetes mellitus and clinical states associated with decreased renal perfusion (1,2). McCullough (1) proposed a pathophysiologic sequence for CI-AKI. He postulated that entry of IRCM into the renal vasculature initially produces endothelium-independent transient vasodilation, followed by adenosine release from the macula densa, endothelin release, and prostaglandin dysregulation (causing decreased nitric oxide synthesis and release). Sustained intrarenal vasoconstriction subsequently occurs leading to prolonged IRCM transit time in the kidneys, increased exposure of IRCM to renal tubular cells, and medullary hypoxia (1). These sequelae are thought to predispose to direct cellular injury and apoptotic death, ischemic cellular injury and cell death, increased oxidative stress and inflammation, ultimately resulting in CI-AKI (1,2). Many of the therapeutic interventions studied to determine their efficacy in reducing the risk of CI-AKI directly or indirectly affect various elements of this pathophysiologic cascade (1,2). Therapies proven to reduce the risk of CI-AKI include periprocedural intravenous hydration and use of low volumes of low osmolality, or isoosmolar, nonionic IRCM (1,2). Use of pre-procedural *N*-acetylcysteine has produced mixed results (1,2). Therapy with theophylline, iloprost, trimetazidine, endovascular cooling, targeted renal therapy with fenoldapam, and removal of IRCM from the coronary sinus have shown promise but require further study (1,2). Conversely, ascorbic acid, various diuretics, dipyridamole, and nonselective antagonism of endothelin receptors have shown no benefit or worsening of renal function following administration of IRCM (1,2).

In recent years there has been increasing interest in the role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in reducing the risk of CI-AKI in patients undergoing coronary angiography (CA) and/or percutaneous coronary interventions (PCI) (3–11). This is due primarily to their anti-inflammatory properties and their abilities to improve endothelial function, but also because of their antiapoptotic effects, which have been demonstrated in pre-clinical and clinical studies (3–11). Since 2005, 5 cohort studies, only 1 of which was prospective, showed a significantly lower incidence of CI-AKI in patients receiving long-term statin therapy than in those not receiving a statin (3–5). Since 2008, 9 randomized clinical trials (RCTs) have prospectively assessed the effects of short-term administration of statins pre- and post-procedure on the development of CI-AKI in patients undergoing CA and/or PCI. Three of these RCTs showed a significantly lower incidence of CI-AKI in patients receiving intermediate-to-high dose statin therapy pre-procedure than in those who did not receive a statin (3–11). Three studies showed a significantly lower incidence of CI-AKI in patients receiving intermediate-to-high dose statin therapy pre-procedure than in those receiving low-dose statin therapy (3–11). In 3 other RCTs, statin therapy had no effect on the incidence of CI-AKI. Results of meta-analyses of these trials tend to support the use of statins to reduce the risk of CI-AKI in this patient population (3–11). However, given the substantial heterogeneity among trials and the fact that several studies reported no reduction in the risk of CI-AKI, the authors of these meta-analyses acknowledged the need for additional RCTs to clarify this issue.

Two studies reported in this issue of the *Journal* provide new insights into the role of statins in reducing the risk of renal injury in patients at high risk for CI-AKI (12,13). Both studies are well designed prospective RCTs and are the

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first large-scale trials to assess the effects of rosuvastatin on the development of CI-AKI.

In the study by Leoncini et al. (12), 504 statin-naive patients with non-ST segment acute coronary syndromes (NST-ACS) were studied to assess the effect of high-dose pre-procedure rosuvastatin on the development of CI-AKI. All patients were selected to undergo an early invasive strategy and underwent CA alone or CA with PCI. One group received rosuvastatin, 40 mg, on admission, followed by 10 to 20 mg of rosuvastatin daily (depending on renal function) until discharge. The other group received no statin therapy during hospitalization. Both groups received rosuvastatin after discharge. The incidence of CI-AKI was 6.7% in patients receiving rosuvastatin during their hospitalization compared to 15.1% in those not treated with a statin during their hospitalization ($p = 0.003$). The absolute reduction in CI-AKI risk in rosuvastatin-treated patients was 8.3%, and the number needed to treat to prevent CI-AKI was 12. The results were consistent using multiple alternative definitions of CI-AKI and after adjusting for age, sex, creatinine clearance, left ventricular ejection fraction, and Mehran risk score. The 30-day composite endpoint of death, dialysis, myocardial infarction (MI), stroke, or persistent renal damage occurred in 3.6% of patients receiving rosuvastatin and in 7.9% of those who did not receive rosuvastatin during hospitalization. At 6 months, the incidence of death or nonfatal MI was 3.6% in patients who received periprocedural rosuvastatin and 7.9% in those who did not receive a statin while hospitalized ($p = 0.07$).

Han et al. (13) studied 2,998 patients with type 2 diabetes mellitus and stage 2 or 3 CKD, scheduled to undergo CA, PCI, peripheral arterial angiography, or peripheral arterial intervention to determine the effects of periprocedural rosuvastatin therapy on the development of CI-AKI. Of the 2,998 patients, 84.5% underwent cardiac procedures and >70% presented with NST-ACS. All patients were either statin naive or had not received a statin for at least 2 weeks prior to entry. One group was randomized to receive rosuvastatin, 10 mg daily, for 2 days prior to their procedure and daily for 3 days thereafter. The other group received no statin during this 5-day period. Both of the groups received statin therapy after 5 days. CI-AKI occurred in 2.3% of patients receiving periprocedural rosuvastatin and 3.9% of patients who did not receive periprocedural statin therapy ($p = 0.01$). The beneficial effect on CI-AKI occurred exclusively in patients with stage-2 CKD (1.5% vs. 3.3%, respectively; $p = 0.01$; number needed to treat = 62). Independent predictors of CI-AKI were rosuvastatin therapy, NST-ACS, New York Heart Association functional class, blood hemoglobin, and estimated glomerular filtration rate <60 ml/min/1.73 m^2. High-sensitivity C-reactive protein levels were significantly higher in patients who developed CI-AKI than in those who did not. At 30 days, worsening heart failure was present in 2.6% of patients who had received periprocedural rosuvastatin and in 4.3% of those who did not ($p = 0.02$), whereas the incidence of all-cause deaths or dialysis/hemofiltration was similar between the two groups.

As previously noted, the studies by Leoncini et al. (12) and Han et al. (13) are the first large-scale studies assessing the effect of rosuvastatin on CI-AKI risk. Rosuvastatin is a hydrophilic statin with potent anti-inflammatory properties independent of its cholesterol-lowering effect (14). Like other statins, it improves endothelial function, probably by increasing nitric oxide synthetase bioavailability, and decreases oxidative stress (14). All of these properties counteract specific pathophysiologic mechanisms that promote the development of CI-AKI. Whether these properties of rosuvastatin were responsible for the benefits noted in these studies is uncertain. Moreover, there are no large head-to-head studies involving rosuvastatin to determine whether it is superior to other statins in reducing the risk of CI-AKI and its intermediate and long-term sequelae.

Both of these studies focused on patients who were at high risk for CI-AKI, specifically those with NST-ACS and diabetics with varying degrees of CKD (12,13). Both selected patients who were statin naive or those who had not recently received statin therapy (12,13).

The study by Leoncini et al. (12) suggested that rosuvastatin was most effective in reducing the risk of CI-AKI in patients with mild to moderate renal dysfunction (12), whereas the results of the study by Han et al. (13) showed that only patients with stage 2 CKD benefited from rosuvastatin therapy. Leoncini et al. (12) emphasized the importance of administration of high-dose statin therapy prior to exposure to IRCM, as have other studies assessing the effects of short-term statin therapy on CI-AKI (3–12). However, the dose of rosuvastatin used in the study by Han and colleagues (13) was low (10 mg), yet the incidence of CI-AKI was also significantly lower than in those who did not receive periprocedural statin therapy. Although >70% of patients in the study by Han et al. (13) presented with NST-ACS, the incidence of CI-AKI was substantially lower in both statin-treated and non-statin-treated groups than in the study by Leoncini et al. (12). This may be due to differences in patient composition between the two studies. Both of the studies underscored the fact that risk of adverse renal and cardiovascular outcomes does not end at 5 days in patients with CI-AKI (12,13).

Results of these studies support the use of short-term periprocedural statin therapy to reduce the risk of CI-AKI and its intermediate to long-term sequelae in patients at high risk for this disorder who undergo CA or PCI (12,13). Future studies should attempt to focus on relatively homogeneous patient populations or those large enough to support pre-specified subset analysis. Such studies should attempt to determine which stages of CKD are benefited most by periprocedural statin therapy. Head-to-head comparison of commercially available hydrophilic and lipophilic statins at both high and low doses would help to determine whether differences exist in their abilities to reduce CI-AKI risk and whether dose matters. Prospective

randomized trials should be conducted to determine if long-term statin therapy at the time of exposure to IRCM mitigates the risk of CI-AKI in at-risk patients. Finally, the mechanisms by which statins reduce the risk of CI-AKI in the clinical setting should be further explored.

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REFERENCES

1. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol 2009;51:1419–28.
2. Weisbord SD, Palevsky PM. Contrast-induced acute kidney injury: short and long-term implications. Semin Nephrol 2011;31:300–9.
3. Zhang T, Shen LH, Hu LH, He B. Statins for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Am J Nephrol 2011;33:344–5.
4. Zhang BC, Li WM, Xu YW. High-dose statin pre-treatment for the prevention of contrast induced nephropathy: a meta-analysis. Can J Cardiol 2011;27:851–8.
5. Pappy R, Stavrakis Hennebry TA, Abu-Fadel MS. Effect of statin therapy on contrast-induced nephropathy after coronary angiography: a meta-analysis. Int J Cardiol 2011;151:348–53.
6. Li Y, Liu Y, Mei LFC, Dai B. Efficacy of short-term high-dose statin in preventing contrast-induced nephropathy: a meta-analysis of seven randomized controlled trials. PLOS One 2012;7:e34450.
7. Zhou Y, Yuan WJ, Zhu, Wang L. Short term, high-dose statins in the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Clin Nephrol 2011;76:475–83.
8. Zhang L, Zhang L, Liu Y, et al. Efficacy of statin pre-treatment for the prevention of contrast-induced nephropathy: a meta-analysis of randomized controlled trials. Int J Clin Pract 2011;65:624–30.
9. Munoz MA, Maxwell PR, Green K, Hughes DW, Talbert RL. Pravastatin versus simvastatin for prevention of contrast-induced nephropathy. J Cardiovasc Pharmacol Ther 2011;6:376–9.
10. Li W, Fu X, Wong Y, et al. Beneficial effects of high-dose atorvastatin pretreatment on renal function in patients with acute ST segment elevation myocardial infarction undergoing emergency percutaneous intervention. Cardiology 2012;122:195–202.
11. Quintavelle C, Flore D, DeMicco F, et al. Impact of high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation 2012;126:3008–16.
12. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome. Results from the PRATO-ACS study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome). J Am Coll Cardiol 2014;63:71–9.
13. 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.
14. Luvai A, Mbagaya W, Hall AS, Barth JH. Rosuvastatin: a review of the pharmacology and clinical effectiveness in cardiovascular disease. Clin Med Insights Cardiol 2012;6:17–23.

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