Cardiovascular Revascularization Medicine 20 (2019) 632–633

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Statins for Prevention of Contrast-Associated Acute Kidney Injury: Is the Debate a Moot Point?☆

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Contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury (CI-AKI) was first reported in the 1950s as a fatal AKI that occurred after intravenous pyelography in a patient with myeloma kidney. Since then, CIN has been plagued with controversy. There is controversy in the medical literature regarding its incidence, with reported rates ranging from as low as <1% to >30%. Moreover, there is controversy regarding the prognosis of patients who develop CIN, with reported rates of requiring dialysis varying from <0.5% to >5% [1–4]. Even the term CIN is controversial, with strong advocates for the term contrast "associated" AKI (CA-AKI) rather than "induced" given a lack of robust data to support a causal relationship, as most studies on CI-AKI did not include a comparable no-contrast control group. In fact, studies of contrast-enhanced computed tomography (CT) versus non-contrast CT show no difference in the incidence of AKI, suggesting perhaps differences in the incidence of AKI when iodinated contrast media is administered via the intravenous route rather than intra-arterial route [5]. The diagnosis is controversial, with some definitions using absolute increase in creatinine (from 0.3 to 0.5 mg/dL) and others using a relative increase in creatinine (from 25% to 50%), and few others using a relative decrease in estimated glomerular filtration rate (>50%) within 48-72 hours from baseline.

The strategies for prevention of CI-AKI are also controversial, with debates on the utility of sodium bicarbonate and N-acetyl cysteine (NAC) despite multiple randomized clinical trials (RCTs). Similarly, in this issue of the journal, in a single-center observational study of 2055 patients, statin use before coronary angiography was not associated with decreased incidence of CI-AKI when compared with no statin use [6]. The study has a number of limitations, including selection and ascertainment bias. Moreover, no data were available on other strategies (especially saline hydration) and whether they were comparable between the groups. In addition, no data were presented on type of statin, dose of statin, and whether statin was in fact administered on the day of coronary angiography. Moreover, the study was not restricted to statin-naïve patients.

There is variability in guideline recommendations. The 2018 European Society of Cardiology myocardial revascularization clinical practice guidelines give a Class IIa, Level of evidence A recommendation for pre-treatment with high-intensity statins before angiography to prevent CI-AKI in patients with moderate or severe CKD. However, there is no recommendation for such pre-treatment in the American College of Cardiology/American Heart Association guidelines.

There are a number of RCTs on this subject. The inclusion/exclusion criteria, sample size, statin type and dose tested, definition of CI-AKI, and length of follow-up have been highly variable among these trials. The results from these RCTs have therefore not been consistent. Meta-analyses of these trials, which now outnumber the number of RCTs, have also shown variable results, with some showing a benefit of statin pre-treatment and others failing to do so.

In a hierarchical Bayesian network meta-analysis of 124 RCTs with 28,240 patients comparing a total of 10 different CI-AKI prevention strategies, statins reduced the risk of CI-AKI by 58% when compared to saline hydration alone, and this benefit was consistent in multiple sensitivity analyses [7]. Statins were superior to saline and NAC but not to the other comparator (all of which were indirect estimates with no direct head-to-head trials). The saline strategy differed between the RCTs. Another direct-comparison meta-analysis with 21 RCTs and 7746 patients similarly showed that short-term statin treatment significantly reduces the risk of CI-AKI and that high-dose statins are more effective than the lower-dose statins [8]. However, patients with stage 3 or worse CKD were largely underrepresented in these trials [9]. Still another meta-analysis of RCTs showed a benefit of atorvastatin; few others have shown a

https://doi.org/10.1016/j.carrev.2019.07.004
1553-8389/

benefit of rosuvastatin, and a recent network meta-analysis showed a benefit of either atorvastatin or rosuvastatin with no significant difference between the two at reducing the risk of CA-AKI [10]. A few other meta-analyses (largely with fewer RCTs) have shown no benefit of statins at reducing the risk of CA-AKI.

Despite the above data, the debate on the beneficial effect of statins at preventing CA-AKI is probably a moot point for the following reasons: 1) The majority of patients undergoing percutaneous coronary procedures who are at risk for CI-AKI (such as those with diabetes, those presenting with ACS, or those undergoing PCI) are also those who fall into the statin benefit group either because of known atherosclerotic cardiovascular disease (ASCVD) or being at high risk for ASCVD. These patients should be on long-term statin treatment, and pre-treatment before coronary angiography might be one way to start statin treatment if they are not already on one. 2) No trial to date has shown a deleterious effect of statin pre-treatment in such patients.

In conclusion, although there is variability in evidence to support the benefit of statin pre-treatment before coronary angiography to prevent CA-AKI, the results favor statin pre-treatment. Moreover, as discussed above, the debate on whether statin pre-treatment is beneficial is perhaps a moot point given the growing recognition of statin treatment to prevent long-term cardiovascular adverse events.

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