Meta-Analysis of Randomized Controlled Trials of Preprocedural Statin Administration for Reducing Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Catheterization

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Preprocedural statin administration may reduce contrast-induced acute kidney injury (CI-AKI), but current evidence is controversial. Randomized controlled trials (RCTs) comparing preprocedural statin administration before coronary catheterization with standard strategies were searched in MEDLINE/PubMed, EMBASE, Scopus, Cochrane Library, Web of Science, and ScienceDirect databases. The outcome of interest was the incidence of postprocedural CI-AKI. Prespecified subgroup analyses were performed according to baseline glomerular filtration rate (GFR), statin type, and N-acetylcysteine use. Eight RCTs were included for a total of 4,984 patients. The incidence of CI-AKI was 3.91% in the statin group (n = 2,480) and 6.98% in the control group (n = 2,504). In the pooled analysis using a random-effects model, patients receiving statins had 46% lower relative risk (RR) of CI-AKI compared with the control group (RR 0.54, 95% confidence interval [CI] 0.38 to 0.78, p = 0.001). A moderate degree of non-significant heterogeneity was present (I^2 = 41.9%, chi-square = 12.500, p = 0.099, τ^2 = 0.100). In the subanalysis based on GFR, the pooled RR indicated a persistent benefit with statins in patients with GFR <60 ml/min (RR 0.67, 95% CI 0.45 to 1.00, p = 0.050) and a highly significant benefit in patients with GFR ≥60 ml/min (RR 0.40, 95% CI 0.27 to 0.61, p <0.0001). Statin type and N-acetylcysteine or hydration did not significantly influence the results. In conclusion, preprocedural statin use leads to a significant reduction in the pooled RR of CI-AKI. **(Am J Cardiol 2014;114:541−548)**

In the last years, several protocols have been applied for reducing contrast-induced acute kidney injury (CI-AKI), but there is still no agreement on the optimal prevention strategy.[1−3] Current guidelines highly recommend periprocedural intravenous hydration, whereas the recommendation for adjunctive measures such as N-acetylcysteine (NAC) or sodium bicarbonate is low.[4] Statins exert pleiotropic effects beyond being cholesterol-lowering drugs, influencing inflammation response, oxidative stress, endothelial function, plaque stability, thrombus formation, and apoptotic pathways.[5,6] All these effects concur in decreasing the risk of cardiovascular disease events.[5,6] Several randomized controlled trials (RCTs) and observational studies investigated the effectiveness of statin pretreatment in reducing the incidence of CI-AKI with mixed results.[7−16] Therefore, we aimed at performing a comprehensive meta-analysis of RCTs evaluating the nephron-protective role of statins to assess whether their administration before coronary angiography or percutaneous coronary intervention (PCI) can reduce the incidence of CI-AKI in patients exposed to contrast media administration.

Methods

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[17] The MEDLINE/PubMed, EMBASE, Scopus, Cochrane Library, Web of Science, and ScienceDirect electronic databases were searched with the following keywords: "statin," "3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor," "HMG-CoA," "CI AKI," "CI-AKI," "contrast induced acute kidney injury," "CIN," "contrast induced nephropathy," "contrast nephropathy," "AKI," "acute kidney injury," "ARF," "acute renal failure," "contrast media," and "contrast agent." Tangential electronic examination of related reports using links to related references and extensive hand searches of bibliographies of relevant reviews were also performed. No language, filter, or publication date restrictions were applied. Only published reports were considered. The last search was performed on February 10, 2014. The retrieved items were first screened at the title and abstract levels by 2 investigators (DG and PA). Screened citations that were clearly not pertinent were discarded. The inclusion criteria were the following: (1) RCTs of patients who were statin-naïve or not who did not consume statins in the 30 days before coronary angiography or PCI; (2) control group consisting of patients who did not

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See page 547 for disclosure information.

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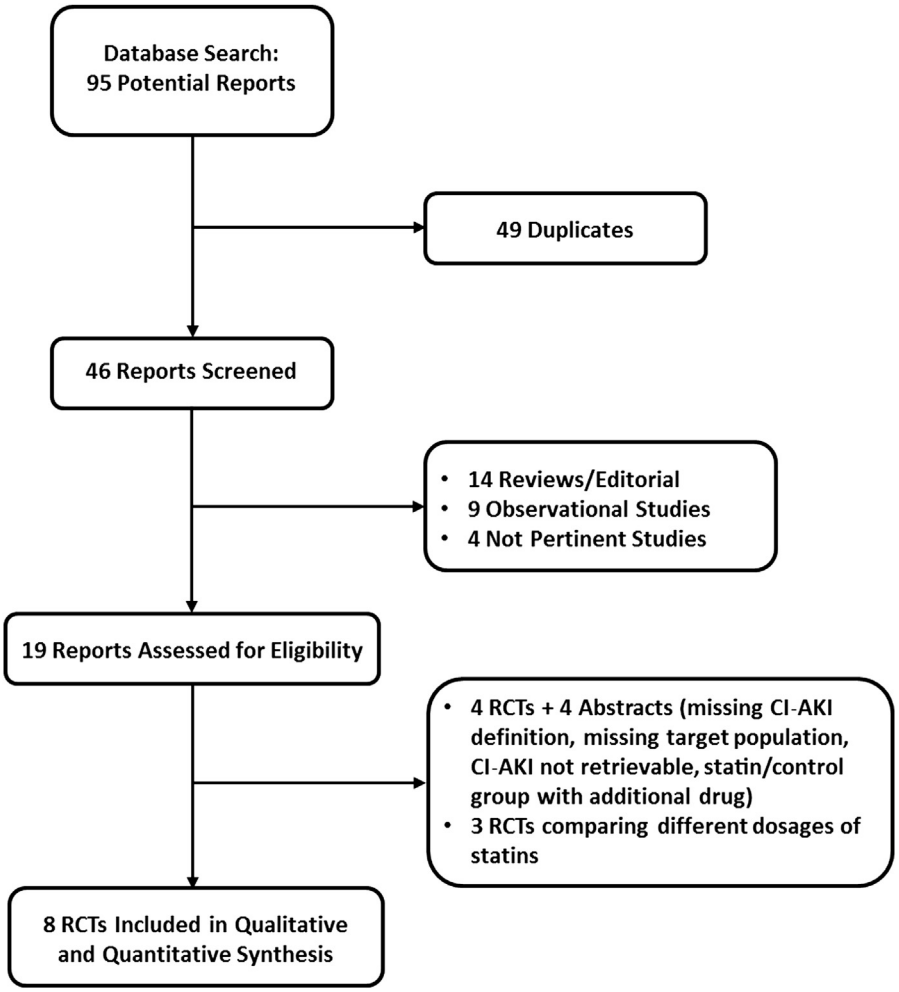

Figure 1. Trial flowchart: the chart shows the number of studies identified and the selection process accounting for the final number of RCTs included in the present study.

consume statins and received placebo or standard therapy, defined as saline solution or NAC and/or sodium bicarbonate (other drugs were excluded); (3) CI-AKI reported and defined as serum creatinine increase from baseline $\geq$25% or $\geq$0.5 mg/dl within the first 48 to 72 hours; and (4) studies investigating statin use in patients undergoing coronary angiography or PCI. Studies not satisfying the aforementioned criteria were excluded. Eligibility assessment and data extraction were performed by 2 investigators (DG and PA), and discordances were solved by consensus. Participants of any age, with or without chronic kidney disease, undergoing coronary angiography or PCI were considered. No statin type and dosage limitations were imposed. CI-AKI was prespecified as the outcome of interest. Planned subanalyses included stratification based on baseline renal function (glomerular filtration rate [GFR] $<$60 ml/min or $\geq$60 ml/min), statin type (lipophilic or hydrophilic), and type of adjunctive treatment (saline solution or NAC). Statistical analysis was performed using the Comprehensive Meta-Analysis (version 2.2.064; Biostat Inc., Englewood, New Jersey). A DerSimonian-Laird random-effects model was used.[18] The primary end point measure was quantified and reported as pooled relative risk (RR) ratio with 95% confidence interval (CI). The influence of removal of 1 study each time on RR was measured to establish the impact of each individual trial on the pooled effect size.[19] Additional analyses were performed to identify the relative weight of each trial and to describe the pooled RR trend over time. Heterogeneity was graded using the I^2 statistic with I^2 $<$25%, 25% to 50%, and I^2 $>$50% representing mild, moderate, and severe inconsistencies, respectively.[20] The extent of publication bias was assessed by visual inspection of funnel plots. Additionally, Egger's regression asymmetry test was performed to explore the potential publication bias and Orwin's fail-safe N formula was used to evaluate whether the entire effect was a bias-driven artifact.[19] To quantify the potential impact of bias on the pooled RR, Duval and Tweedie's trim and fill method was used.[21]

Results

The search strategy retrieved a total of 95 citations. After duplicates were removed, 46 reports remained. Of these, 38 were discarded after full text reading because they were not pertinent or did not meet the eligibility criteria