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A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes

Giancarlo Marenzi [a,*,1], Nicola Cosentino [a,1], José P. Werba [a,1], Calogero C. Tedesco [a,1], Fabrizio Veglia [a,1], Antonio L. Bartorelli [a,b,1]

[a] Centro Cardiologico Monzino, I.R.C.C.S., Milan
[b] University of Milan, Italy

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ABSTRACT

Objectives: We assessed whether short-term, pre-procedural, intensive statin treatment may reduce contrast-induced acute kidney injury (CI-AKI) incidence in patients with and without acute coronary syndromes (ACS) undergoing coronary angiography (CA) and percutaneous coronary intervention (PCI).
Background: Statins may exert renal-protective effects through their pleiotropic properties. However, there have been conflicting reports on the CI-AKI preventive effect of pre-procedural statin administration.
Methods: Randomized controlled trials published between January 1st, 2003 and February 28th, 2014 comparing the preventive effects against CI-AKI of pre-procedural statins vs. control (lower statin dose, no statin, or placebo) in patients undergoing CA/PCI were included.
Results: Data were combined from 9 clinical trials enrolling 5212 patients (age 65 ± 5 years, 63% males). Pooled analysis showed that intensive, short-term statin pre-treatment significantly reduced the risk of CI-AKI as compared to control (relative risk [RR] 0.50; 95% confidence interval [CI] 0.39 to 0.64; $P < 0.001$). Pre-specified subgroup analysis showed that intensive statin pre-treatment significantly reduced CI-AKI risk in patients with ACS (RR 0.37; 95% CI 0.25 to 0.55; $P < 0.0001$), with only a non-significant positive trend in patients without ACS (RR 0.65; 95% CI 0.41 to 1.03; $P = 0.07$). No evidence of publication bias was detected.
Conclusions: Short-term, pre-procedural, intensive statin treatment significantly reduced CI-AKI incidence in ACS patients, and may contribute to the overall clinical benefit associated with the early use of these drugs in this clinical setting. Its role in non-ACS patients warrants further investigation.

1. Introduction

Patients undergoing coronary angiography (CA) and percutaneous coronary intervention (PCI) may variably experience contrast-induced acute kidney injury (CI-AKI), which is associated with prolonged hospitalization, progression to end-stage renal disease, and increased short- and long-term morbidity and mortality [1,2]. The best approach to reduce the risk of CI-AKI remains still unclear, and the current guidelines recommend prophylactic intravenous hydration, use of low- or iso-osmolar contrast media and reduced volume of contrast agents [3].

A growing amount of data suggests that 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors (statins) may reduce CI-AKI incidence after CA/PCI thanks to several pleiotropic properties, including anti-oxidant, anti-inflammatory, and anti-thrombotic effects [4–8]. However, previous investigations and meta-analyses provided conflicting results and raised doubts about the usefulness of statin administration before contrast exposure for CI-AKI prevention [9–13]. Patients with acute coronary syndromes (ACS), who are characterized by an increased pro-inflammatory and pro-thrombotic systemic activity, along with an ongoing endothelial dysfunction, have a higher risk of developing CI-AKI [14]. Therefore, they represent a subset of patients who could benefit the most from the potential pleiotropic effects of statins [15–18]. However, whether pre-procedural intensive statin treatment against CI-AKI is more beneficial in patients with ACS has not been clarified yet. Thus,

* Corresponding author at: Centro Cardiologico Monzino, Via Parea 4, 20138 Milan, Italy.
E-mail address: giancarlo.marenzi@ccfm.it (G. Marenzi).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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we performed a meta-analysis of randomized clinical trials aiming at determining whether pre-procedural, short-term, intensive statin administration is superior to conventional-dose statin, no statin, or placebo for CI-AKI prevention in both ACS patients undergoing urgent or emergency CA/PCI and in those without ACS electively referred to CA and, if suitable, to PCI.

2. Methods

2.1. Search strategy

The study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19]. PubMED, MEDLINE, ISI Web of Science, and EMBASE databases were searched for articles published between January 1st, 2003 and February 28th, 2014 combining the following search terms: "statins AND (contrast OR radiocontrast OR contrast media) AND (contrast-induced nephropathy OR nephropathy OR AKI OR acute renal failure)". Our decision to include all studies published since January 1st, 2003 was based on the consideration that the first evidence showing a beneficial effect of statin pre-treatment on CI-AKI occurrence in patients undergoing CA was reported in 2004 [20].

2.2. Study selection

Study inclusion criteria were: 1) age at randomization >18 years; 2) randomized allocation to treatment groups; 3) prospective studies of individuals randomized to statins vs. a control group (who received either lower statin dose, or no statin, or placebo before contrast administration); 4) pre-procedural administration, described as immediately prior to or at least within 24 h before the planned contrast exposure; 5) English language literature only restriction; 6) trials reporting the incidence of CI-AKI as the end point at 48 h or later after contrast administration. Data published in the form of abstracts without peer-reviewed publication of the manuscripts or accepted as short communications or brief reports were excluded.

2.3. Data extraction and quality assessment

Papers identified in the literature search were screened by 2 independent reviewers (NC and JPW) to assess their eligibility for the analysis. Discrepancies were resolved by two senior authors (GM and AB). From each study, information about year of publication, methods and entry criteria, number of patients in treatment and control arms, age, sex, clinical presentation (ACS vs. non-ACS patients), diabetes mellitus rate, baseline renal function, statin type and dose, contrast medium type and volume, and CI-AKI definition and incidence were extracted, tabularized and analyzed with SAS version 9.2, SAS Institute, North Carolina, USA. The pre-specified outcome assessed from selected trials was the difference in the incidence of CI-AKI between the two groups, defined as an absolute increase in serum creatinine (sCr) concentration >0.5 mg/dL or as a relative increase >25%. Notably, when included studies reported CI-AKI incidence both in terms of absolute and relative increase in sCr, the outcome based on the relative change was chosen for analysis due to the advantages of this approach [21]. Furthermore, when CI-AKI incidence was reported both at 48 h and other time periods, the 48-hour incidence was considered for analysis, since this is the most common time point used for CI-AKI definition. A pre-specified subgroup analysis according to the clinical presentation (ACS vs. non-ACS) was performed including eight studies: four enrolling ACS patients only [15–18] and four enrolling non-ACS patients only [5,9,10,12]. The study by Han et al. [4], included in the pooled analysis, was not considered in the subgroup analysis because a mixed population of ACS and non-ACS patients participated in this study and no information about the CI-AKI incidence according to the clinical presentation was available.

2.4. Statistical analysis

2.4.1. Data synthesis and analysis

Categorical variables were summarized as frequencies and quantitative variables as means ± standard deviation or median (interquartile range). Binary outcomes from individual studies were combined with Mantel Haenszel method according to a fixed effect model, leading to pooled relative risks (RR) with their corresponding 95% confidence intervals (CI) [22]. Cochrane's Q via the χ^2 test and I^2 were computed to explore statistical heterogeneity and inconsistency, respectively. A two-tailed P value <0.05 was considered statistically significant. Analyses were performed using Review Manager (RevMan; version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and SAS (version 9.2, SAS Institute, North Carolina, USA).

2.4.2. Sensitivity analysis

To verify the consistency of meta-analysis results regarding patients' outcome, the influence of each individual study on the summary effect estimate was assessed by the 1-study removed sensitivity analysis [23]. To explore the influence of potential effect modifiers on outcome, weighted random-effect meta-regression analysis was performed to test demographic characteristics of the study population (age and gender), CI-AKI risk factors (including diabetes mellitus and chronic kidney disease [CKD]), dose of statin, and volume of contrast medium [24,25].

2.4.3. Publication bias

Publication bias was explored by visual inspection of a funnel plot of precision (standard error of logRR) against the treatment effect (RR on a logarithmic scale) and using the asymmetry linear regression of Egger's test [26].

3. Results

3.1. Characteristics of included trials

The flow of study selection for inclusion in the meta-analysis is shown in Fig. 1. Briefly, we identified 1326 citations from the initial literature search. After the initial screening, 9 randomized controlled trials (4, 5, 9, 10, 12, 15–18) with a total of 5212 patients (2593 assigned to high-dose statin and 2619 assigned to the control arm), satisfying the inclusion criteria, were identified and analyzed.

The main characteristics of the studies are listed in Table 1. There were no significant differences in the baseline characteristics between intensive statin and control groups in terms of age (64 ± 4 and 64 ± 4 years; P = 0.90), diabetes rate (34% and 33%; P = 0.90), CKD prevalence (45% in both groups), sCr levels (1.01 ± 0.1 and 1.07 ± 0.1 mg/dL; P = 0.90), and total contrast volume (139 ± 32 and 135 ± 39 mL; P = 0.82), respectively.

3.2. Outcome analysis

CI-AKI occurred in 92 (3.5%) subjects allocated to the intensive statin group and in 186 (7%) subjects allocated to the control group. The RR for the development of CI-AKI was 0.50 (95% CI 0.39 to 0.64; P < 0.001) for short-term intensive statin treatment vs. controls (Fig. 2). No significant heterogeneity among studies was detected (I2 = 1%; P heterogeneity = 0.42). Subgroup analysis according to clinical subset (ACS vs. non-ACS patients) was based on 4 randomized clinical trials in ACS patients (a total of 1134 patients: 563 assigned to intensive statins and 571 assigned to the control arm) (15–18), and 4 randomized clinical trials in non-ACS patients (a total of 1080 patients: 532 assigned to intensive statins and 548 assigned to the control arm) (5, 9, 10, 12). In patients with ACS, CI-AKI occurred in 31 (5.5%) subjects allocated to the intensive statin group and in 85 (15%) subjects allocated to the control group. The RR for CI-AKI occurrence in intensive statin vs. control groups was 0.37 (95% CI 0.25 to 0.55; P < 0.0001) (Fig. 3). No