Effect of statin therapy on contrast-induced nephropathy after coronary angiography: A meta-analysis

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ABSTRACT

Background: Although the pleiotropic effects of statins are postulated to be renoprotective, clinical studies have demonstrated conflicting results. We undertook a meta-analysis of published trials to evaluate the impact of statin therapy on the incidence of contrast-induced nephropathy (CIN) in patients undergoing coronary angiography.

Methods: We searched MEDLINE and EMBASE databases through December 2010 for articles evaluating the effect of statins on the incidence of CIN in patients undergoing coronary angiography. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using random effects modeling.

Results: Three randomized controlled trials involving 770 patients (330 in the statin group and 340 in the control group) and 7 non-randomized studies involving 31,959 patients (11,936 statin-pretreated and 20,023 statin-naïve). The definition of CIN varied somewhat among the studies. Based on the pooled estimate across the 3 randomized controlled trials, statin therapy did not significantly reduce the incidence of CIN compared to control (OR = 0.76, 95% CI: 0.41–1.41, p = 0.39). No significant heterogeneity was found in the randomized studies (I² = 0%, p = 0.48). The pooled analysis of the non-randomized studies showed a marginally significant benefit associated with statin therapy (OR = 0.60, 95% CI: 0.36–1.00, p = 0.05). There was significant heterogeneity among the non-randomized studies (I² = 88%, p < 0.00001).

Conclusions: Our meta-analysis suggests that statin therapy might be associated with a significant reduction in the incidence of CIN in patients undergoing coronary angiography. Further studies are warranted to clarify this issue.

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1. Introduction

Contrast-induced nephropathy (CIN) is a well-recognized complication of coronary angiography with a frequency ranging between 5% and 50% depending on the baseline characteristics of the patient population. The highest incidence occurs in those with severe renal dysfunction, diabetes, congestive heart failure, advanced age, and concurrent administration of nephrotoxic drugs [1,2]. CIN is the third leading cause of hospital-acquired acute renal failure, accounting for 12% of all cases [3]. Moreover, the development of CIN is associated with increased morbidity and mortality, length of hospitalization, and chronic renal impairment [4,5].

The pathophysiology of CIN is multi-factorial, complex, and not well understood. Some of the mechanisms of injury that have been described include renal vasoconstriction causing medullary ischemic damage, tubular injury leading to production of oxygen free radicals, decrease in nitrous oxide production, and direct nephrotoxicity [6].

Several strategies to prevent CIN have been studied and these include the use of: theophylline, fenoldopam, mannitol, iloprost, furosemide, dopamine, hemofiltration, ascorbic acid, and N-acetylcysteine (NAC). However, a meta-analysis of trials evaluating the aforementioned agents suggested no benefit in preventing CIN [7]. Moreover, a meta-analysis consisting of 13 randomized trials evaluating the use of NAC prior to coronary angiography concluded that the data was inconclusive, yet NAC is the most widely used preventative strategy [8]. A recent randomized, multi-center trial assessed the use of iso-osmolar versus low osmolar contrast in the prevention of CIN, and concluded that there was no difference between the two agents [9]. Moreover, the optimal hydration strategy either with sodium bicarbonate solution or normal saline also remains controversial in preventing CIN [10,11].

More recently, several trials have been published on the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in preventing CIN, which yielded inconsistent results [12–22]. Apart from the cholesterol-lowering effects, statins have been shown to exhibit the following pleiotropic effects that might target the factors that lead to CIN: scavenging free oxygen radicals (anti-oxidant), increase nitrous oxide production, and enhance vascular smooth muscle relaxation [23].

Although the pleiotropic effects of statins are postulated to be renoprotective, clinical studies have demonstrated conflicting results. In order to summarize the cumulative data to-date, and thereby improve estimation power and precision through the increased
sample size of the cumulative data, we conducted a meta-analysis of published studies to evaluate the impact of statin therapy on the incidence of CIN.

2. Methods

2.1. Literature search

We searched MEDLINE (1966 to December 2010), EMBASE (1947 to December 2010), and the Cochrane Library databases for articles evaluating the effect of statin therapy on the incidence of CIN in patients undergoing coronary angiography. Using the terms contrast-induced nephropathy, statins, contrast, contrast media, cardiac catheterization, and coronary angiography, we searched for articles indexed as randomized or non-randomized trials. We also searched published abstracts presented at the meetings of the American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), American Society of Nephrology (ASN), and International Society of Nephrology (ISN) from 1998 to 2010. No language restrictions were used.

2.2. Study selection

Two investigators (RP and SS) independently screened all titles and abstracts of identified articles. Full-text articles of potentially relevant studies were reviewed by both investigators to determine their eligibility. Disagreements were resolved through discussion between the authors in accordance with our selection criteria. Randomized and non-randomized trials comparing the use of statins versus intravenous hydration and/or placebo in the prevention of CIN were included. Studies that incorporated NAC were included only if both arms were administered NAC. Trials directly comparing two different doses of a statin were excluded from this review.

2.3. Data extraction and quality assessment

Two investigators (RP and SS) independently abstracted data from eligible studies and resolved controversies by discussion. The abstracted data included patient characteristics, inclusion/exclusion criteria, intravenous hydration protocol, type of contrast media used, statin dosing regimen, and baseline creatinine. The primary endpoint was the incidence of CIN. The quality of eligible studies was assessed using criteria that were previously published [24].

2.4. Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the respective outcomes in each study (according to the intention-to-treat principle). A summary OR with 95% CI was calculated by combining information from multiple 2 x 2 tables, according to the DerSimonian and Laird random effects modeling approach [25]. The Q statistic was calculated and a formal test of heterogeneity was conducted. The I2 index was used to calculate and a formal test of heterogeneity was conducted. The Q statistic was used to determine the presence of heterogeneity. The I2 index was used to determine the presence of heterogeneity. The I2 index was used to determine the presence of heterogeneity.

2.5. Meta-analysis

The percentage of diabetic patients ranged widely from 16% to 73%. The mean baseline serum creatinine level ranged from 0.68 to 1.71 mg/dL. Table 1 also describes the intravenous hydration protocol and the statin regimen that was administered to the patients. The percentage of diabetic patients ranged widely from 16% to 73%. The mean baseline serum creatinine level ranged from 0.68 to 1.71 mg/dL. Table 1 also describes the intravenous hydration protocol and the statin regimen that was administered to the patients. In one of the randomized trials, the statin arm was compared to placebo [12] whereas in the other two trials the control arm included the use of NAC [14,16]. In the non-randomized studies, patients on statins were compared to those not on statins. The definition of CIN varied slightly among the studies; however, the majority of the studies defined CIN as an increase in serum creatinine of either at least 0.5 mg/dL or >25% from baseline at 24 h–1 week after the administration of contrast.

3. Results

3.1. Eligible studies

The electronic database searches identified 184 potentially relevant articles. After independently reviewing the title and abstract of all potential articles, 12 articles were retrieved and reviewed in full-text. Of these, one study which evaluated the effect of statin therapy on renal function in patients undergoing elective coronary angiography was excluded because it did not provide data on the incidence of CIN [22]. Another study was excluded because it compared two different doses of a statin to each other [27]. Therefore, 10 studies (3 randomized and 7 non-randomized) involving 32,729 patients (12,266 statin-pretreated and 20,363 statin-naive) met the inclusion criteria and were included in the analysis [12–21]. Our search strategy is outlined in Fig. 1.

3.2. Patient characteristics and interventions

The characteristics of the 10 eligible studies and the associated patient characteristics are summarized in Tables 1 and 2, respectively. Three studies were randomized controlled trials [12,14,16], whereas 7 were non-randomized studies [13,15,17–21]. In 4 studies, statin therapy was administered acutely 1–2 days before and after coronary angiography [12,14,16,18], whereas in the remaining studies the patients were already on chronic statin therapy [13,15,17,19–21]. The 3 randomized trials involved a total of 770 patients (330 in the statin group and 340 in the control group). The 7 non-randomized studies involved 11,936 patients who were either chronically on statins or acutely received statins prior to the procedure and 20,023 patients who were not on any statins. The study participants were mostly middle-aged or elderly men. The percentage of diabetic patients ranged widely from 16% to 73%. The mean baseline serum creatinine level ranged from 0.68 to 1.71 mg/dL. Table 1 also describes the intravenous hydration protocol and the statin regimen that was administered to the patients. In one of the randomized trials, the statin arm was compared to placebo [12] whereas in the other two trials the control arm included the use of NAC [14,16]. In the non-randomized studies, patients on statins were compared to those not on statins. The definition of CIN varied slightly among the studies; however, the majority of the studies defined CIN as an increase in serum creatinine of either at least 0.5 mg/dL or >25% from baseline at 24 h–1 week after the administration of contrast.

3.3. Assessment of study quality

Overall, the quality of the included studies was rather poor. Although the quality of 2 of the randomized studies (Toso et al. [16] and Jo et al. [12]) was excellent, the third randomized study by Ozhan et al. [14] and all the non-randomized studies were characterized by poor quality. Of the randomized studies, only the studies by Toso et al. [16] and Jo et al. [12] used appropriate methods of randomization, were double-blind and reported study withdrawals and drop outs. Although the study by Ozhan et al. [14] was randomized, it did not provide details to assess the appropriateness of randomization, was not double-blind and did not report study withdrawals and drop-outs.

3.4. Outcomes

Fig. 2 summarizes the available information on the incidence of CIN for the randomized studies. Based on the pooled estimate across the 3 studies, statin therapy reduced the incidence of CIN compared to control by 26%, where the difference between the two arms was not statistically significant (OR = 0.76, 95% CI: 0.41–1.41, p = 0.39).
was no significant heterogeneity across the 3 studies (I² = 0%, p = 0.48). No individual study had a major impact on the overall estimated OR or the statistical significance based on the sensitivity analysis. The point estimates for OR ranged from 0.49 to 0.89, with 95% CI ranging from 0.16 to 1.80 when the 3 studies were sequentially excluded 1 at a time.

Table 2
Summary of subject characteristics of 10 trials.

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Type of therapy</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Statin group (n); statin regimen</th>
<th>Mean age (years)</th>
<th>Males (%)</th>
<th>DM (%)</th>
<th>LVEF (%)</th>
<th>Baseline Cr (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo, 2008</td>
<td>Placebo with same regimen as statin arm</td>
<td>CrCl ≤ 60 mL/min or Scr ≥ 1.1 mg/dL</td>
<td>Statin use within past 30 days</td>
<td>124; Simvastatin 40 mg q 12 h 1 day pre &amp; 1 day post-procedure</td>
<td>65.5</td>
<td>73</td>
<td>26</td>
<td>56</td>
<td>1.25</td>
</tr>
<tr>
<td>Ozkan, 2010</td>
<td>Placebo with same regimen as statin arm</td>
<td>CrCl ≤ 60 mL/min or Scr ≥ 1.1 mg/dL</td>
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</table>
Fig. 2. Forest plot of study-specific and pooled odds ratios and 95% confidence intervals (CI) for the incidence of contrast induced nephropathy (CIN) among patients assigned to statin therapy versus control (placebo or active drug) in the randomized trials.

Fig. 3 summarizes the available information on the incidence of CIN for the non-randomized studies. Based on the pooled estimate across the 7 studies, there was a significant benefit associated with statin treatment (OR = 0.60, 95% CI: 0.36–1.00, p = 0.05). There was significant heterogeneity among the studies (I² = 88%, p < 0.00001), with study-to-study variability explaining 88% of the variation in the OR estimates. A sensitivity analysis was performed to determine the effect of individual studies on the pooled estimates. Omitting the studies by Attallah et al. [18], Khanal et al. [20], Yoshida et al. [17] and Zhao et al. [21] did not have a major impact on the overall estimated OR, but affected the statistical significance, suggesting that there is no significant reduction in CIN incidence associated with statin therapy. Moreover, omitting the study by Patti et al. [15] increased the estimated OR value to 0.82 (95% CI: 0.55–1.22), where the statistical significance was also lost.

We then examined the effects of statin therapy when administered acutely prior to a planned PCI, as opposed to chronic statin use. All 4 studies which involved acute statin administration suggested that statin pre-treatment is associated with a decreased risk, although not statistically significant. There was no heterogeneity across the studies (I² = 0%, p = 0.68). Based on the pooled estimate across the 4 studies, acute statin administration before planned PCI was associated with a 37% decrease in the incidence of CIN, which had a trend towards statistical significance (OR = 0.73, 95% CI: 0.53–1.01, p = 0.06). On the other hand, chronic statin use was associated with a non-significant reduction in the incidence of CIN (OR = 0.56, 95% CI: 0.28–1.13, p = 0.11). There was significant heterogeneity across the studies (p < 0.00001), with study-to-study variability explaining 90% of the variation in the OR estimates (I² = 90%).

Summary data for specific subgroups were available in only two studies [12,16]. The following subgroups were analyzed: diabetes, age > 75, left ventricular ejection fraction < 40% and creatinine clearance < 30 ml/min. None of the subgroups showed a significant benefit with statin use (OR = 0.76, 95% CI: 0.28–2.12, p = 0.61; OR = 1.01, 95% CI: 0.43–2.38, p = 0.98; OR = 0.38, 95% CI: 0.12–1.20, p = 0.10; OR = 0.36, 95% CI: 0.08–1.65, p = 0.19, respectively). However, these data should be interpreted cautiously given the limited number of studies and the limited number of patients in each subgroup.

Fig. 3. Forest plot of study-specific and pooled odds ratios and 95% confidence intervals (CI) for the incidence of contrast induced nephropathy (CIN) in non-randomized studies comparing statin therapy versus control (non-statin).

4. Discussion

This meta-analysis of the currently available published data suggests that statin therapy might be associated with a significant reduction in the incidence of CIN in patients undergoing coronary angiography. Moreover, our analysis suggests that statin therapy, even when administered acutely prior to coronary angiography may prevent CIN. This finding is extremely important because of the availability and low cost associated with this preventative approach. However, it should be acknowledged that most of the studies included in this meta-analysis are non-randomized and potentially biased; therefore these results cannot be considered definitive, but rather hypothesis-generating. In fact, a major conclusion of our study is the lack of large randomized trials adequately powered to address this clinically important issue. Nonetheless, it is encouraging to note that the pooled estimate for the randomized trials showed a clinically significant, albeit non-statistically significant reduction (with a wide confidence interval, reflecting the limited statistical power) in the incidence of CIN with the use of statins.

The biologic plausibility of these results is supported by a body of evidence suggesting that statins exhibit pleiotropic effects that might target the factors that lead to CIN. Although the pathogenesis of CIN is not completely understood, multiple mechanisms may be involved. After contrast exposure, there is a brief period of vasodilation followed by renal vasoconstriction, and various molecules (i.e., angiotensin, vasopressin, and endothelin) appear to mediate this decrease in renal blood flow [28]. Because statins induce down-regulation of angiotensin receptors and decrease endothelin synthesis [29], these drugs may prevent CIN by decreasing the period of renal hypoperfusion and ischemia through vasodilation due to vascular smooth muscle relaxation. Another mechanism responsible for CIN is direct damage to tubular cells mediated by oxygen-free radicals, pro-inflammatory cytokines, and complement activation, leading to tubular obstruction by protein precipitates [28]. Statins may decrease inflammation and improve endothelial function by inhibiting nuclear factor B, a transcription factor that acts on genes encoding for pro-inflammatory mediators [30], decreasing expression of endothelial adhesion molecules, increasing...
nitric oxide bioavailability, attenuating production of reactive oxygen species, and protecting against complement-mediated injury [31]. In addition, experimental data have shown that statins exert renoprotective effects in a rat model of long-term inhibition of nitric oxide synthesis by amelioration of vascular endothelial growth factor expression and decrease of RhoA activity [32].

There is evidence that statin treatment has beneficial effects other than possibly reducing the incidence of CIN in patients undergoing coronary angiography. The ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) trial demonstrated that pre-treatment with atorvastatin was associated with an 81% reduction in the risk of peri-procedural MI in patients with stable angina undergoing elective coronary angiography and percutaneous coronary intervention [33]. Moreover, the ARMYDA-ACS trial revealed that pre-treatment with atorvastatin was associated with an absolute risk reduction of 12% in 30 day major adverse cardiac events (death, myocardial infarction, target vessel revascularization) in patients with acute coronary syndromes undergoing early percutaneous coronary intervention [34].

Caution is advised when interpreting the results of this analysis due to the non-randomized nature and poor quality of most of the studies and the significant heterogeneity among the studies. The sensitivity analysis for the pooled estimate of the non-randomized studies revealed loss of statistical significance when each of several studies was omitted, further underscoring this notion. We analyzed the randomized and non-randomized studies separately in order to account for between-study heterogeneity. Because of the significant heterogeneity among the non-randomized studies, we analyzed the results using a random effects model, which reflects study-to-study variation in the estimated statin effect. As such, although the study by Khanal et al. [20] comprises 85% and 90% of the overall population included in the meta-analysis and the population included in the non-randomized studies, respectively, it is only weighed 18% by the random effects model. Nonetheless, a random effects model cannot account for poor study quality. Since certain clinical characteristics have been identified as risk factors for CIN, we aimed to evaluate whether statin therapy had a significant effect in those subgroups. Unfortunately, analysis of the effect of statins in specific patient groups that are deemed to be at higher risk for CIN could not be completely evaluated due to the insufficient sample size.

A major limitation of this meta-analysis is the inclusion of both randomized and non-randomized studies. Non-randomized studies are associated with potential bias because it is impossible to completely control for unknown confounding factors, even if statistical adjustment for confounding and modifying factors is used. In this regard, it is promising that the pooled analysis of the 3 randomized trials revealed a reduction (although non-significant) in the incidence of CIN with the use of statins. The slight differences in the definitions of CIN among the studies may also limit our results. Finally, variations in the type, duration, and dose of statins among the included studies might have affected our results, since all statins may not be equal in their pleiotropic effects [35]. Atorvastatin is the most studied statin that has been evaluated in a randomized, controlled fashion [14,16]. The dosing regimen of atorvastatin that was described in these studies was 80 mg once a day, administered from 1 to 2 days prior to the procedure. Other specific statins that have been evaluated include simvastatin [12] and pravastatin [17].

Several strategies to prevent CIN have been evaluated; however, the cumulative data to-date reveals that only intravenous hydration and the avoidance of high osmolality contrast media are consistently associated with renoprotection and decrease in the incidence of CIN [7]. Moreover, the recent Acetylcysteine for the prevention of Contrast-Induced Nephropathy Trial (ACT), which is currently published in abstract form only, indicated that high-dose NAC had no benefit compared to placebo in preventing CIN in patients undergoing coronary or vascular angiography [36]. Nevertheless, despite these preventative strategies, the incidence of CIN ranges from 5% to 50% with an average incidence of 17% based on a recent meta-analysis [8]. This remains an unacceptable risk for patients undergoing coronary angiography, and therefore, it is imperative to investigate optimal preventative strategies.

Our results underscore the need for large randomized trials to further clarify the impact of statins on the incidence of CIN. Furthermore, assessment of the effects of statins on CIN in patients that have high-risk features, i.e., diabetes, age > 75 years, congestive heart failure, and low glomerular filtration rate may be warranted. Of note, it is not conclusive if all patients with chronic kidney disease derive benefit from preventative statin therapy. For instance, a study by Patti et al. [15] suggested that patients with severely impaired baseline renal function (glomerular filtration rate [GFR] < 40 mL/min) had less benefit, probably because multiple non-reversible pathogenetic mechanisms are involved. The most efficacious type, duration, and dose of statin have yet to be determined. A cost–benefit analysis comparing the cost of statin therapy and the cost of managing complications associated with CIN needs further investigation. No trials have suggested significant side effects, however, larger trials assessing the safety profile of acute statin therapy are lacking. The ease of administration, low cost, and potential lack of significant side effects are attributes of statins that make it an appealing preventative strategy to decrease the incidence of CIN pending further investigation.

5. Conclusion

This is the first meta-analysis that consolidates the available information to-date regarding the use of statins in the prevention of CIN after coronary angiography. Although statin therapy had an overall trend towards a beneficial effect among the analyzed studies, caution is advised when interpreting these data because of the non-randomized nature of most of the studies and the significant heterogeneity among the studies. Clinical equipoise remains for the performance of a large randomized trial to determine whether statin therapy reduces the incidence of CIN in patients undergoing coronary angiography.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [37].

References


