

Statins role in preventing contrast-induced acute kidney injury: a scoping review

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ABSTRACT

Background: Acute renal failure secondary to contrast-induced acute kidney injury (CI-AKI) is one of the most commonly encountered problems in hospitalised patients. The CI-AKI may lead to the development of persistent renal disease, causing significant morbidity and mortality in high-risk patients. Statins are increasingly recognised as effective in preventing CI-AKI. In this review, we reviewed the literature on statin use for prophylaxis of CI-AKI, its potential benefits, and adverse effects. The aim of the present review was to reveal gaps and discrepancies in the available literature, and to identify areas for future research.

Methods: We searched PubMed for articles published up to 2018, using keywords including: “Statins AND contrast-induced kidney injury”, “3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors AND contrast-induced kidney injury”, and “HMG-CoA reductase inhibitors AND contrast induced nephropathy”.

Results: Various trials and reviews have yielded promising results in terms of statin efficacy. However, conflicting results and a lack of homogeneity in the protocols of these trials have limited the applicability of statin-based therapy in clinical practice. Despite

the reported beneficial therapeutic effects of short-term high-dosage statin use in preventing CI-AKI, statin therapy is not yet the standard prophylactic regimen due to widespread heterogeneity in the clinical trials.

Conclusion: Statin therapy can be used as an adjunct to usual prophylactic measures such as adequate hydration and use of low-volume contrast media. Large well-designed trials on the effects of short-term high-dose statin use in preventing CI-AKI should be conducted, to eliminate any form of discrepancy among results, and to clarify any potential adverse effects.

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Introduction

Acute renal failure secondary to contrast-induced acute kidney injury (CI-AKI) is one of the most commonly encountered problems in hospitalised patients.^{1,2} The CI-AKI is generally defined as an increase of at least 0.5 mg/dL in the plasma creatinine level from the basal value within 24 to 48 hours of contrast exposure.³ The rising incidence of CI-AKI in recent decades is concurrent with the increasing use of diagnostic and therapeutic procedures requiring contrast administration, such as coronary angiography (CAG) and percutaneous coronary intervention (PCI). Recent studies have suggested that CI-AKI may lead to the development of persistent renal disease⁴ and is thus a cause of significant morbidity and mortality,⁵ particularly in patients with pre-existing chronic diseases.⁶ Thus, there is an urgent need to design effective prophylactic regimens for CI-AKI to improve the long-term outcomes in patients undergoing such procedures.

The complex pathways involved in the pathogenesis of CI-AKI are not fully understood. Contrast media are known to cause reduced perfusion of renal medulla, owing to an increase in the release of vasoconstrictive mediators and decrease in the vasodilator substances.^{7,8} This leads haemodynamic changes in the renal vasculature that contribute to CI-AKI. Other mechanisms include direct tubular injury by contrast agents and free-radical mediated injury.⁹ Both direct cellular injury and ischaemia act in concert to increase the production of free radicals that can cause cellular injury themselves and thus cause cumulative damage to tubular cells.¹⁰

An appropriate preventative strategy is the sole means of lowering the risk of contrast-induced nephropathy in high-risk patients, because no intervention is effective once exposure to the contrast medium has already occurred.³ Despite extensive research, the best prophylactic approach for acute kidney injury is yet to be discovered. The current recommended strategy is adequate hydration and

intravascular volume expansion prior to contrast administration.³ Although routinely practised, this strategy has not resulted in substantial reduction of CI-AKI; thus, research on optimal prophylactic regimens for CI-AKI is necessary.

In recent years, there has been increasing interest in statins for prophylaxis of CI-AKI, although the results to date are controversial.¹¹

The aim of the present scoping review was to summarise existing evidence on the efficacy of statins in preventing CI-AKI, to identify discrepancies and gaps in the available literature, and to recommend areas for future research.

Methods

We conducted a review of the literature from PubMed for articles published up to May 2018. A variety of keywords were employed including “Statins AND contrast-induced kidney injury”, “3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors AND contrast-induced kidney injury”, “HMG-CoA reductase inhibitors AND contrast-induced kidney injury”, “Statins AND contrast-induced nephropathy”, “3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors AND contrast-induced nephropathy”, “HMG-CoA reductase inhibitors AND contrast induced nephropathy”, “Statins AND CI-AKI”, “HMG-CoA reductase inhibitors AND CI-AKI”, and “3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors AND CI-AKI”. No language restriction was placed. The abstracts of all the articles were reviewed to assess their relevance to the aims of our study. Our review was conducted in accordance with the PRISMA Extension for Scoping Reviews.¹²

Discussion

In the past decade, there has been growing interest in discovering the renoprotective effects of statins. The cholesterol-lowering properties of statins are well recognised, supporting their widespread use for the prevention of cardiovascular diseases.¹³ However, studies have also revealed a number of pleiotropic effects of statins which are not directly related to lipid metabolism.¹⁴ Though the exact mechanism has not been discovered, it has been speculated that statins act by modulation of immune and inflammatory responses, reduction of oxidative stress, prevention of plaque rupture, and improvement in endothelial function.^{15,16} Since aberrations in these responses are thought to be responsible for CI-AKI, statins can potentially be used to effectively prevent CI-AKI.

The efficacy of statins in preventing CI-AKI has been demonstrated in various trials; however, results have been contradictory. One of the earliest meta-analyses by Zhang et al¹⁷ showed no statistically significant benefits (relative risk [RR]=0.76) of

他汀類藥物在預防造影劑引起的急性腎損傷中的作用：範圍審查

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背景：繼發於造影劑引起的急性腎損傷（CI-AKI）的急性腎功能衰竭是住院患者中其中一個最常見的問題。CI-AKI可導致持續性腎病，造成高風險患者的顯著發病率和死亡率。他汀類藥物逐漸被認為可有效預防CI-AKI。本綜述回顧有關他汀類藥物對預防CI-AKI的潛在益處和不良反應的文獻。本回顧旨在揭示現有文獻中的差距和差異，並確定未來研究的領域。

方法：我們在PubMed搜索截至2018年發表的文章，並使用關鍵詞包括：“Statins AND contrast-induced kidney injury”、“3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors AND contrast-induced kidney injury”以及“HMG-CoA reductase inhibitors AND contrast induced nephropathy”。

結果：多篇試驗和回顧文章在他汀類藥物療效方面報告可喜的結果。然而，這些試驗方案中相互矛盾的結果和缺乏同質性限制了他汀類藥物治療在臨床實踐中的適用性。儘管報導短期高劑量他汀類藥物用於預防CI-AKI的有益治療效果，但由於臨床試驗中廣泛的異質性，他汀類藥物治療尚未成為標準預防方案。

結論：他汀類藥物治療可作為常規預防措施的輔助手段，如充分補水和使用低容量造影劑。建議進行大型精心設計的短期高劑量他汀類藥物CI-AKI預防方案試驗，以消除不同結果之間任何形式的差異，並澄清任何潛在的不良反應。

statin pretreatment in preventing CI-AKI. The only significant difference between the treatment arm and the control arm in that study was serum creatinine levels, which were slightly more elevated in patients treated with statins. However, this meta-analysis included only four trials and a total of 752 subjects, increasing the likelihood of bias and rendering the results of the analysis inconclusive. In contrast, several meta-analyses, with greater numbers of trials and patients included, have yielded promising results with pre-procedural statin administration.¹⁸⁻²⁰

A recent meta-analysis by Li et al²¹ that included 21 randomised controlled trials and 7746 patients observed a significant decrease (RR=0.57) in the likelihood of CI-AKI with statin pretreatment in patients undergoing CAG and PCI. This analysis had some major strengths over previous analyses; for example, the risk of bias in all included studies was gauged using Cochrane Collaboration’s tool. This contrasts with earlier analyses^{22,23} which used the Jadad scoring system.²⁴ The Jadad scoring system has several inherent shortcomings; for example, it does not account for bias arising from the absence of allocation concealment, which limits its reliability for the assessment of methodological quality of trials.

Another major strength of the meta-analysis by Li et al²¹ was the use of subgroup analysis to discover

differences in the effectiveness of statin use with respect to statin type, dosages, duration of therapy, pre-existing diseases, hydration protocols, and definition of CI-AKI. Although the need for better quality trials was emphasised, the authors of that study recommended the use of statins in patients undergoing CAG and PCI, particularly those at high risk of CI-AKI.

The most recent review on statins by Verdoodt et al¹¹ concluded that, although statins are useful for the prevention of cardiovascular diseases, their effectiveness in acute kidney injury and chronic kidney disease (CKD) remains unclear. There is a considerable lack of homogeneity in trials of statin use for preventing CI-AKI, not only in the protocols and methodological designs, but also in the clinical settings in which contrast administration was required. This has limited the validity and reliability of the results of the meta-analyses that have been performed using these trials.

Type, dosage, duration, and timing of statin therapy

There are inadequate data regarding the differences in the efficacy of different types of statins, mainly because many trials have only compared one type of statin versus placebo. Li et al²¹ used subgroup analysis to determine discrepancies among different statins and found that the prophylactic effect of statins in CI-AKI was seen irrespective of the type of statin used. Most studies have used one of three statins: rosuvastatin, atorvastatin, or simvastatin. Of these, an appreciable amount of evidence exists for rosuvastatin and atorvastatin, but data on simvastatin are insufficient to draw any reliable conclusions. Liu et al²² did not find any difference in the incidence of CI-AKI between patients treated with rosuvastatin and atorvastatin. However, in another experimental study, rosuvastatin was found to yield better outcomes than simvastatin and atorvastatin.²⁵ Yang et al²⁶ performed a meta-analysis of five randomised controlled trials including a total of 4045 patients that compared the effects of rosuvastatin versus placebo and discovered that rosuvastatin administration prior to cardiac catheterisation caused a notable decrease in the risk of CI-AKI. However, since only one type of statin was used, comparisons could not be made among different types of statins. Current evidence indicates that all statin types have similar effects in the prophylaxis of CI-AKI.

Statin have consistently demonstrated higher efficacy at higher doses. In the meta-analysis by Li et al,²¹ compared with lower-dose statin, high-dose statins were associated with an absolute risk reduction of 63% although the quality of the evidence was reportedly low. Cheungpasitporn et al²³ reported that only three out of 13 trials compared high- versus low-dose statins; however, all trials that showed a

decreased risk of CI-AKI with statin pretreatment used moderately high-dose statins. Another meta-analysis that evaluated the statin efficacy in patients undergoing CAG found high-dose statins to be more effective.²⁷ However, significant heterogeneity in the protocols of the trials and differing baseline characteristics of the patients render it difficult to decide on a single-best dosing regimen. This highlights the need to ensure homogeneity in the protocols of the future trials, so that more reliable conclusions can be drawn.

Timing and duration of statin therapy differed markedly across the trials. Most meta-analyses did not perform subgroup analyses based on these parameters. Li et al²¹ studied the effect of short-term statin treatment on the incidence of CI-AKI, but the duration of therapy that qualified as 'short-term' was not specified. This was also the case with the meta-analysis by Ukaigwe et al,²⁷ which had several strengths but did not elaborate on the timing and duration of statin therapy separately. A meta-analysis by Barbieri et al,²⁰ which demonstrated half the risk of CI-AKI in the statin group versus the control group specified the duration of statin therapy (12 hours to 3 days); however, the effect of therapy duration on outcomes was not determined.

Influence of hydration protocols and volume and strength of contrast media

Most studies have shown that the combination of hydration with statins yields optimal results. Verdoodt et al¹¹ concluded that adequate intravenous hydration with iso-osmolar crystalloids is the best preventative measure for acute coronary syndrome or for patients undergoing CAG and PCI. The meta-analysis by Barbieri et al²⁰ reported the administration of periprocedural hydration in all but one study, in which hydration was administered only in patients with serum creatinine level <1.5 mg/dL or creatinine clearance >60 mL/min.²⁸ Quintavalle et al²⁹ primarily used sodium bicarbonate solution for hydration. In contrast, most other studies have reported the use of isotonic saline instead of sodium bicarbonate solution for hydration, with³⁰⁻³² or without³³⁻³⁶ N-acetylcysteine. However, a recent large-scale multi-centre prospective randomised trial (the 'Acetylcysteine for Contrast-induced nephropathy Trial'³⁷) demonstrated the ineffectiveness of N-acetylcysteine in cases of CI-AKI.^{38,39}

High-volume contrast media (>100 mL) are associated with a particularly high risk of adverse renal events and the current recommendation is the use of low-volume contrast media.⁴⁰ However, Li et al²¹ found that the benefit of statin therapy was observed even in patients administered with contrast media volumes as high as ≥140 mL, although the evidence was of moderate quality for this subgroup of patients.

Statins were found to be useful in cases of both low-osmolar (RR=0.42) and iso-osmolar (RR=0.59) contrast media. The quality of evidence for both subgroups was high.²¹ An earlier meta-analysis by Barbieri et al²⁰ also demonstrated the efficacy of statins in CI-AKI which was independent of the strength of contrast media.

Measures of assessment

To assess the efficacy of statin use, different studies assessed renal function via different measures. For example, a number of studies^{28,32,41,42} used an increase in serum creatinine of ≥ 0.5 mg/dL or $>25\%$ from baseline within 48 h after procedure, whereas others^{31,32,43} used the same criteria but within 72 h. Acikel et al⁴² and Toso et al⁴⁴ assessed renal function by an increase in serum creatinine of ≥ 0.5 mg/dL within 5 days after contrast exposure. Those findings suggest significantly lower postprocedural serum creatinine level among patients in the statin-use group than among those in the control group ($P < 0.0001$).²¹ A few studies have excluded patients on the criteria of serum creatinine level of >3 mg/dL.^{28,30} Quintavalle et al²⁹ reported the incidence of CI-AKI on the basis of increases in serum cystatin C $\geq 10\%$ from baseline within 24 hours after contrast exposure. Creatinine clearance is another parameter used to enrol patients in different studies, for example with a creatinine clearance of <60 mL/min^{8,21,22} or <70 mL/min.³² A meta-analysis indicated that, in some studies, postprocedural estimated glomerular filtration rate was higher among patients in the statin-use group than among those in the control group ($P = 0.001$).²¹ However, no restrictions on the basis of renal function were imposed by Li et al.³¹

Most articles, including meta-analyses and reviews, have not commented on whether different effects of statins were observed in different populations. However, a meta-analysis conducted by Mao and Huang¹⁹ included trials consisting of Caucasian and Asian populations. The authors reported that the effect of statins in both groups was equally significant.¹⁹ A meta-analysis by Li et al²¹ was the first to report better outcomes in East Asian and statin-naïve patients. Another meta-analysis that performed subgroup analysis for different populations found that there were no differences in the efficacy of statins among different racial populations, suggesting that genetic polymorphisms may not have an important role in determining the efficacy of statins in CI-AKI.²⁷

Effect of underlying diseases/risk factors on statin efficacy

Most previous studies recruited patients who already had some underlying disease or precipitating risk factor for CI-AKI. Advanced age, type and volume of contrast, pre-existing disease such as congestive

heart failure and CKD, and haemodynamic instability are reportedly more likely to influence the development of CI-AKI.¹¹ Chyou et al⁴⁵ demonstrated that increased age, diabetes mellitus, acute coronary syndrome, and CKD are the factors responsible for precipitating the hazard for contrast-induced nephropathy. Further, Chung et al⁴⁶ confirmed that there is a 13% increased risk of developing severe renal failure with statin treatment among the high-risk population. Quintavalle et al²⁹ found lower rates of CI-AKI occurrence in patients with CKD, whereas Toso et al⁴⁴ did not find decrease in the occurrence of CI-AKI in patients with existing CKD with high-dose atorvastatin; however, high-dose rosuvastatin was effective in these patients.⁴⁴

The study by Li et al²¹ was the first to assess the benefits of statin therapy in patients with diabetes mellitus, acute coronary syndrome, CKD, or congestive heart failure and those requiring higher-volume contrast media. The authors observed that statins proved useful regardless of these risk factors, although the quality of evidence varied from low to high. The authors found that the risk of CI-AKI was 4.4% in the diabetes mellitus subgroup compared with 6.5% in control group (RR=0.70).²¹ The overall risk reduction was 5.0% in the statin pretreatment arm compared with 8.4% in the control arm (RR=0.61).²¹ Thus, the results of these meta-analysis indicate that statins are effective prophylactic agents for CI-AKI even in patients with risk factors such as CKD and diabetes mellitus.

Adverse effects

As most trials reviewed did not have a long-term follow-up, the frequency of adverse events with statin use for prophylaxis of CI-AKI is not accurately known.⁴³ A recent updated review published by Verdoodt et al¹¹ was sceptical of the beneficial effects of statins owing to the wide range of potential adverse effects. A large retrospective cohort study from Taiwan found that high-efficacy statins increased the risk of severe renal failure by 13% compared with low-efficacy statins, such as lovastatin, pravastatin, simvastatin, and fluvastatin.⁴⁶ Myopathy is a common adverse effect of statin use and its risk is further increased by concomitant CKD. Statin-induced myopathy clinically manifests as a mild increase in creatinine kinase levels, myalgia, myositis, and rhabdomyolysis. The incidences of these effects have not been reported in most trials that have focused on CI-AKI. Thompson et al⁴⁷ reviewed data from two databases and revealed that the incidence of myalgia ranged from 6% to 14% in one database and from 19% to 25% in the other. However, the clinical trials rarely report on the incidence of myalgia. In almost all trials and meta-analyses that explored the efficacy of statin use for the prevention of CI-AKI, adverse effects of statin use were not documented.

This highlights the need for long-term follow-up of patients undergoing statin prophylaxis, so that the potential adverse effects of statin use can be clarified.

Conclusion

Although several studies have implied beneficial therapeutic effects of short-term high-dose statin use in preventing CI-AKI, statin therapy is not yet the standard prophylactic regimen. Widespread heterogeneity in clinical trials has resulted in inconclusive and contradictory findings regarding the efficacy of statin use for preventing CI-AKI. Large and well-designed trials with more homogeneous protocols should be conducted to minimise discrepancies among the results. Statin therapy can be used as an adjunct to usual prophylactic measures such as adequate hydration and use of low-volume contrast media. However, further controlled trials are required to clarify the harmful potential of statin use in the context of CI-AKI, before this treatment is adopted in clinical practice.

Author contributions

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Concept and design of study: I Anjum.

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Conflicts of interest

All authors have declared no conflicts of interest.

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