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Effects of high doses of statins to prevent contrast-induced acute kidney injury, based on cystatin C levels: A meta-analysis

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Abstract

Objective: The potential benefit of measures to prevent contrast-induced acute kidney injury (CIAKI) remains uncertain. This uncertainty is partly due to the reliance on serum creatinine, a biomarker influenced by non-renal factors such as muscle mass, hydration status, and age. Therefore, this study aims to evaluate CIAKI prevention based on cystatin C levels—a more stable and earlier biomarker of renal dysfunction, which may improve diagnostic precision and the assessment of therapeutic efficacy.

Methods: We performed a systematic review and meta-analysis of all randomized clinical trials (RCTs) on preventive measures of contrast-induced acute kidney injury, based on cystatin C levels, in patients who underwent percutaneous procedures. We searched PubMed, Scopus, and Cochrane Central for studies comparing the use of high-dose statins in prevention. The outcome of interest was an acute kidney injury based on increased serum cystatin C after the procedure. Statistical analysis was performed using RevMan 5.4. This systematic review with meta-analysis was registered in the

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International Prospective Register of Systematic Reviews (PROSPERO) under protocol (CRD42023441815).

Results: We included four studies with a total of 1167 patients, of whom 594 (50.8%) received high-dose statins (atorvastatin or rosuvastatin). On the baseline characteristics of the study population, 65% were male; 79.2% had hypertension; 44.3% had diabetes; 35.7% had dyslipidemia, and 35.4% were currently smokers. Overall, high doses of statins were associated with a lower incidence the CIAKI (OR 0.31; 95% CI [0.19,0.53]; $P < .0001$).

Conclusion: Our findings suggest that high doses of statins may play an important role as a measure to prevent CIAKI. If this result is confirmed, we will be able to set up CIAKI prevention protocols, thus expanding the number of patients who will undergo contrast-enhanced exams.

Keywords

CIAKI, high-dose statin, percutaneous intervention, cystatin C, kidney biomarker

Introduction

The administration of iodine-based contrast media is recognized as a classical cause of acute kidney injury (AKI). These media are frequently used in state-of-the-art, minimally invasive cardiac interventions, which have rapidly gained popularity over traditional surgical techniques in recent decades. Advanced imaging technology, crucial for visualizing the vascular system and other anatomical structures via iodinated intravenous contrast, has been fundamental in these procedures. Research has thus focused on developing novel contrast agents with reduced nephrotoxicity and enhancing peri-procedural management strategies.

Statins are posited to reduce the risk of contrast-induced acute kidney injury (CIAKI) by enhancing endothelial function, sustaining nitric oxide production, and alleviating oxidative stress. The antioxidant and anti-inflammatory properties of statins may protect the kidneys from contrast-induced damage, crucial in preventing the apoptosis of renal tubular epithelial cells, a key mechanism in CIAKI development.[1] However, previous studies have shown inconsistent results, largely due to reliance on creatinine as a biomarker, which is affected by muscle mass, age, and hydration status. Addressing these limitations, this study focuses on cystatin C as a more sensitive and specific biomarker.

According to kidney disease: Improving Global Outcomes (KDIGO), CIAKI is defined as an increase in serum creatinine (sCr) levels of ≥ 0.3 mg/dl (26.5 μmol/l) above baseline within 48 hours, or an increase of at least 1.5 times the baseline value within 7 days following the intravascular injection of contrast media, peaking between the third and the fifth day and returning to baseline within 10–14 days.[2] Furthermore, the increase in sCr is not only indicative of a reduction in glomerular filtration but also reflects systemic accumulation influenced by non-renal factors such as age, sex, muscle mass, and

hydration status, thus rendering serum creatinine increases nonspecific for CIAKI diagnosis.[2] Consequently, there is a growing interest in biomarkers that allow earlier and more sensitive detection of kidney damage. This is particularly relevant, as previous studies have demonstrated that the classification of CIAKI may vary significantly—with statistical relevance—depending on the criterion used for sCr measurement.[3]

Several studies have documented that serum cystatin C (sCys C) may increase 1–2 days earlier than sCr in the context of CIAKI.[4] Importantly, sCys C appears to be independent of race, gender, muscle mass, and hydration status.[5] Its prognostic role has been examined, showing that a rise in sCys C of less than 10% at 24 hours could exclude CIAKI, while a rise greater than 10% at 24 hours is an independent predictor of major adverse events such as all-cause death and dialysis after 1 year.[6]

Despite various strategies targeting the pathophysiological mechanisms of contrast-medium-induced renal damage, those excluding volume expansion generally fail.[7] Although prophylactic intravenous hydration, the use of low-osmolality contrast agents, and reduced contrast agent dosages have been shown to decrease CIAKI occurrence, other medical efforts have proved disappointing.[7] It has been suggested that statins may further reduce the CIAKI risk due to their beneficial effects on endothelial function, nitric oxide production, and oxidative stress reduction.[8]

Therefore, this meta-analysis aims to evaluate the efficacy of high-dose statin therapy in the prevention of CIAKI among patients undergoing percutaneous contrast-enhanced procedures. Additionally, it seeks to assess the predictive value of sCys C as an early biomarker for the detection of CIAKI.

Methods

This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42023441 815 (Date of first submission to PROSPERO: 07 July 2023; Date of registration in PROSPERO: 18 July 2023). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[9]

Although the PROSPERO registration was finalized after the database search had been completed, we confirm that the study protocol, including objectives, eligibility criteria, and planned analyses, was developed and finalized prior to data collection. No modifications were made to the study design, inclusion criteria, or outcomes following the search. This ensures that the methodology remained transparent and was not influenced by the data retrieved. Acknowledging this, we have explicitly addressed the timing of the registration and reaffirmed adherence to the original protocol within this section.

Study eligibility

Eligibility criteria included: (1) randomized controlled trials (RCTs) comparing patients undergoing percutaneous interventions using iodinated contrast with or without high doses of statins. The statin doses in the included studies were 80 mg of atorvastatin or 40 mg of rosuvastatin, administered prior to contrast exposure. These doses were selected

for their established efficacy in reducing oxidative stress and inflammatory responses in patients undergoing percutaneous coronary interventions. Studies that utilized low doses of statins or did not include statin interventions were excluded, as the analysis aimed to evaluate the pronounced renal protective effects of high-dose statins. Prior studies with lower doses showed inconsistent results and were, therefore, excluded; (2) studies that reported the outcomes of interest. No restrictions were placed on publication date, but only articles published in English were included. The rationale for including only RCTs was to minimize bias and ensure the highest level of evidence, as non-randomized studies are more prone to confounding factors and selection bias, potentially compromising result validity.

Search strategy and data extraction

Systematic searches were conducted in the MEDLINE, Cochrane, and Scopus databases on April 22, 2023. The search strategy included the terms: ("intervention" OR "percutaneous coronary intervention") AND (statins OR statin OR "high dose statin" OR atorvastatin OR rosuvastatin) AND ("contrast-induced nephropathy" OR CIN OR "contrast-induced acute kidney injury"). Data were extracted on: (1) serum cystatin dosage; (2) all patients meeting criteria for contrast-induced renal injury. Article selection and data extraction were performed by three independent reviewers (D.F., F.V., L.F.). Disagreements were resolved by consensus.

To assess the methodological quality of the included randomized controlled trials, we conducted an individual evaluation of each study using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach. This method evaluates the certainty of evidence across key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall certainty of evidence for the primary outcome was rated as "moderate" due to some concerns regarding heterogeneity and indirectness across studies. These assessments were independently performed by two reviewers, and discrepancies were resolved through discussion and consensus. The results of the GRADE evaluation are summarized in the supplementary material (Table 2).

Statistical analysis

Treatment effects for binary endpoints were compared using pooled odds ratios (OR) with 95% confidence intervals (CI). Heterogeneity was assessed using Cochran's Q test, I^2 statistics, and Tau-square with the restricted maximum-likelihood estimator. Heterogeneity was reported as low ($I^2 = 0$–25%), moderate ($I^2 = 26$–50%), or high ($I^2 > 50\%$). All statistical analyses were conducted using R statistical software, version 4.2.1 (R Foundation for Statistical Computing).

Endpoints and subgroup analyses

The primary endpoint was the occurrence of CIAKI, defined as a $\geq 10\%$ increase in sCys C concentration from baseline within 24 hours after contrast media administration.

Results

Study selection and baseline characteristics

Our systematic search initially identified 725 potential articles, as detailed in Figure 1. Following the removal of duplicates and the exclusion of studies based on title and abstract reviews, seven articles were thoroughly assessed for inclusion and exclusion criteria. Ultimately, four RCTs were included, comprising a total of 1167 patients. Of these, 594 patients were assigned to receive high-dose statins (either atorvastatin or rosuvastatin), while 573 patients were subjected to conventional prevention measures for CIAKI. Detailed characteristics of these studies are presented in Table 1.

Pooled analysis of all studies

In assessing the primary endpoint, a statistically significant reduction in the incidence of CIAKI was observed in the group receiving high-dose statins compared to the control group (OR 0.31; 95% CI 0.19–0.53; $P < .0001$; $I^2 = 31\%$). The details of this analysis are depicted in Figure 2.

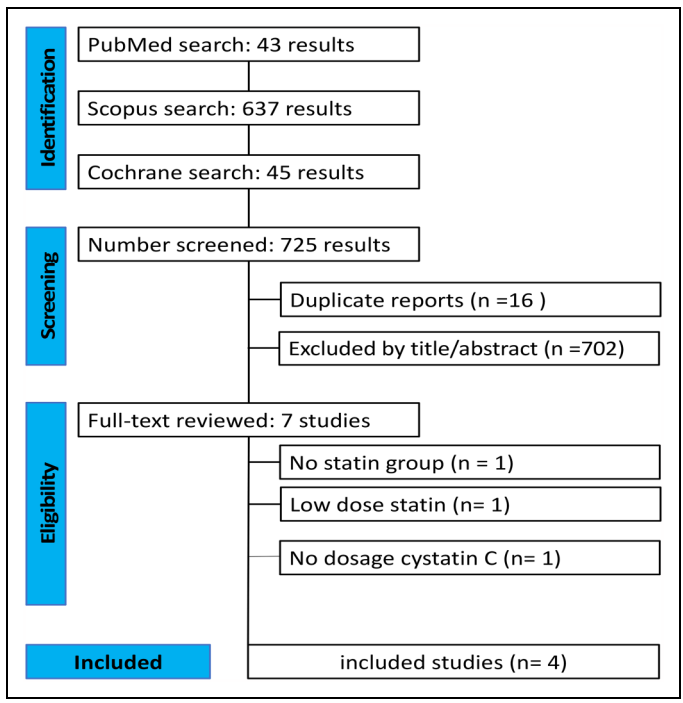

Figure 1. PRISMA flow diagram of study screening and selection.

Table 1. Baseline characteristics of included studies.

Study	Design	Patients SG/CG	Male,% SG/CG	Age, y SG/CG	HYP,% SG/CG	DM,% SG/CG	DYS,% SG/CG	MI,% SG/CG	CV,ml SG/CG	Statin dose	Hydration method	diagnostic or interventional
Li 2012	RCT	83/78	74,4/77,1	66/65	78,2/ 83,1	26,9/28,9	24,4/ 30,1	52,6/53	100/103	Atorvastatin 80 mg	IV saline (0.9%)	Interventional
Quintavalle 2012	RCT	202/208	51/58	70/70	85,5/ 87,5	44/38,5	NA	NA	177/184	Rosuvastatin 40 mg	IV saline and sodium bicarbonate	Diagnostic
Qiao 2015	RCT	60/60	68,3/73,3	80/80	80/80	100/100	10/5	25/26,7	204/212	Atorvastatin 80 mg	IV saline (0.9%)	Diagnostic
Naikuan Fu 2018	RCT	249/247	65,9/67,2	68,7/ 70,4	68,7/ 70,4	37,3/36,8	42,2/ 38,1	20,1/19,8	158/158	Atorvastatin 80 mg	IV saline (0.9%)	Interventional

SG: statin group; CG: control group; mean or median; HYP: hypertension; DM: diabetes mellitus; DYS: dyslipidemia; MI: myocardial infarction; CV: contrast volume.

Quality assessment

The quality of individual RCTs was assessed using the Cochrane Risk of Bias tool for randomized trials (RoB 2)[10] and GRADE Assessment of the Evidence Quality. This assessment was performed by three independent reviewers (D.F., F.V., L.F.). Disagreements were resolved by consensus. The use of the RoB 2 tool enabled a comprehensive evaluation of potential biases, addressing issues related to the randomization process, deviations from intended interventions, missing outcome data, and measurement of outcomes. The results of this assessment are illustrated in Figure 3.

The certainty of the evidence for the primary outcome was rated as moderate according to the GRADE assessment. This rating reflects a reasonable level of confidence in the estimated effect size, while acknowledging some limitations in the body of evidence, such as moderate heterogeneity and concerns related to indirectness. A summary of the GRADE evaluation is provided in Table 2.

Discussion

In this systematic review and meta-analysis of four studies involving 1167 patients, we assessed the effect of high-dose statins on the incidence of CIAKI in patients undergoing

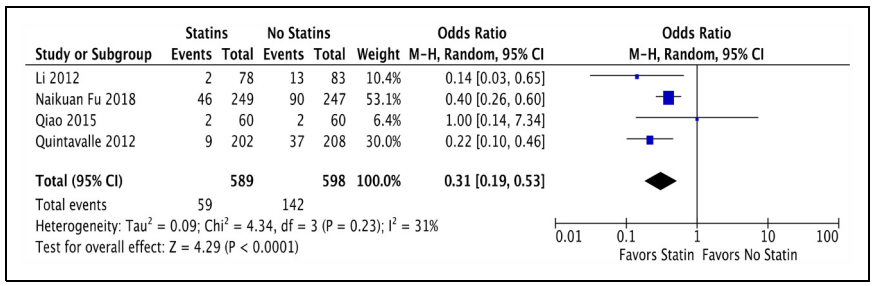

Figure 2. Forest plot for primary outcome.

Study	Bias from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcomes	Bias in selection of the reported result	Overall risk of bias
QUINTAVALLE 2012	Low	Low	Low	Low	Low	Low
LI 2012	Low	Low	Low	Low	Low	Low
Qiao 2015	Low	Low	Low	Low	Low	Low
Naikuan Fu 2018	Low	Low	Low	Low	Low	Low

Figure 3. Risk of bias summary for randomized studies (RoB 2).

Table 2. GRADE assessment of the evidence quality.

Domain	Assessment	Justification	Impact on evidence
Risk of Bias	Not downgraded—all studies low risk (RoB 2)	All four included RCTs were assessed as low risk in all RoB 2 domains.	No impact—evidence remains high.
Inconsistency	Not downgraded—moderate heterogeneity ($I^2 = 31\%$)	Variation across studies was moderate and considered acceptable.	No impact—evidence remains high.
Imprecision	Not downgraded—CI 95% [0.19–0.53] is precise	The confidence interval is narrow and shows a consistent effect.	No impact—evidence remains high.
Indirectness	Not downgraded—applicable population and intervention	Included studies were directly relevant to the research question.	No impact—evidence remains high.
Publication Bias	Downgraded—no formal assessment performed	No funnel plot or statistical analysis for publication bias was performed. Potential bias cannot be ruled out.	Downgraded—evidence reduced to moderate.

Final Grade of Evidence: MODERATE.

percutaneous interventions using iodinated contrast. Our principal finding indicates that high-dose statins significantly reduce the risk of CIAKI as evidenced by sCys C measurements.

Although sCr is widely utilized due to its low cost, its sensitivity and specificity are limited, and it reacts slowly to acute kidney dysfunction.[11] In contrast, sCys C is emerging as a superior biomarker for glomerular filtration rate, primarily because it is less influenced by muscle mass and dietary factors.[12] It has been demonstrated that sCys C not only offers better diagnostic accuracy than sCr in detecting acute kidney dysfunction but also responds more swiftly to kidney injury, peaking earlier than creatinine levels. This makes sCys C an ideal biomarker for the early detection of CIAKI, with the optimal measurement time being 24 hours post-contrast exposure.[11]

Cystatin C also presents significant advantages over creatinine by being less affected by age, sex, muscle mass, hydration status, thyroid function, and smoking, thereby providing a more accurate assessment of renal function in acute settings. The quicker response time of cystatin C allows for more timely interventions, underscoring its potential as a preferred biomarker in clinical settings.

Given the growing evidence of sCys C as a sensitive and early biomarker for CIAKI, its routine measurement may be particularly valuable in specific high-risk populations. These include patients with pre-existing chronic kidney disease (CKD), diabetes mellitus, advanced age, or those undergoing procedures involving large volumes of contrast media. In such populations, early detection of subtle changes in renal function is crucial for prompt clinical decision-making and the

implementation of nephroprotective strategies. Therefore, selective use of sCys C in these clinical contexts may enhance diagnostic accuracy and improve patient outcomes.

Moreover, administering a high-loading dose of atorvastatin within 24 hours before contrast exposure has been shown to reduce the incidence of CIAKI by preventing apoptosis in tubular renal epithelial cells and enhancing survival signaling pathways.[13] However, despite the practical application of statins in clinical settings, there remains a lack of precise criteria for robust study designs, which could yield more reliable outcomes regarding their use.[14] There is a need for more specific guidelines for the use of statins in various medical procedures, such as in cardiology, vascular surgery, or neurology, particularly regarding the amounts of iodinated contrast and statin dosages.

Our study faces several limitations: (1) the scarcity of randomized studies that evaluate CIAKI based on sCys C levels; (2) the underutilization of sCys C as a routine biomarker limits the immediate clinical applicability of our findings; (3) moderate heterogeneity in the main outcome ($I^2 = 31\%$) attributed to factors such as differences in patient populations, variation in statin dosages, hydration methods, and types and volumes of contrast used, as well as the criteria for defining CIAKI. Despite these challenges, the significant effects of high-dose statins in preventing CIAKI were demonstrated, though variability across studies should be carefully considered in different clinical contexts.

Future research should aim to standardize statin administration protocols and hydration methods to minimize heterogeneity and improve comparability of results. Additionally, further studies incorporating cystatin C as a biomarker in randomized clinical trials are necessary to more precisely evaluate the efficacy of statins in preventing CIAKI across diverse patient populations.

Conclusion

This meta-analysis demonstrates that high-dose statins, namely atorvastatin and rosuvastatin, significantly reduce the incidence of CIAKI. The use of sCys C as a biomarker allowed for earlier and more accurate detection of renal injury, offering an advantage over traditional measures such as sCr. These findings support the consideration of high-dose statins as a preventive strategy in patients at increased risk undergoing contrast-enhanced procedures.

While the included studies showed consistent benefits, moderate heterogeneity was present, likely due to variations in patient populations, statin dosages, hydration protocols, and contrast media used. Despite this, the overall strength of the evidence supports the potential clinical integration of this preventive approach.

Further randomized controlled trials are warranted to determine the optimal timing and dosing strategies and to confirm efficacy across broader patient populations. Standardizing intervention protocols may also help reduce heterogeneity and enhance reproducibility in future research.

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Ethics considerations

Ethical approval was not required for this study, as it is a systematic review and meta-analysis of previously published data. No new patient data were collected or analyzed.

Author contributions

DF: study design, literature search, and manuscript writing. FV: data extraction and statistical analysis. LF: review and editing. MB: methodological review. MS: final approval and clinical guidance.

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Declaration of conflicting interests

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Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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