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Statins for the Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis

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Key Words
Contrast-induced nephropathy · Statins · Systematic review · Meta-analysis

Abstract
Background: Retrospective and prospective studies have demonstrated that statins have a protective effect in preventing contrast-induced nephropathy (CIN), but there are currently no established guidelines for statin timing or dosage. A systematic review and meta-analysis was performed to determine whether statin administration is protective and the magnitude of their effect. ***Methods:*** We searched MEDLINE, EMBASE, Cochrane Library, CNKI and ISI Proceedings for cohort studies comparing the CIN incidence in a chronic statin pretreatment group and a statin-naïve group, as well as for randomized controlled trials (RCTs) comparing short-term high-dose to short-term low-dose statin treatment or placebo. CIN was defined as an increase in serum creatinine >25% or 0.5 mg/dl (44.2 μmol/l). Qualitative analysis of cohort studies and quantitative analysis of RCTs to estimate pooled risk ratios were performed. ***Results:*** Among 6 cohort studies, 4 showed chronic statin pretreatment had a preventive effect against CIN. From 6 RCTs, 1,194 patients were included in the meta-analysis. Under the fixed-effects model, a nonsignificant protective trend toward decreased incidence of CIN with periprocedural short-term high-dose statin treatment was seen (RR: 0.70; 95% CI: 0.48–1.02). ***Conclusion:*** Current data are not conclusive to whether statins are protective for CIN due to the inherent limitations of the included studies. In the future, large well-designed studies are needed to address the effect of this drug and its longer-term clinical outcomes.

Introduction

Contrast-induced nephropathy (CIN) is an important potential complication of percutaneous coronary intervention. It occurs in approximately 7% of patients undergoing cardiac procedures currently [1–3]. Although the incidence of CIN has decreased due to improved contrast media and better risk prevention measures in the past decade, there are continued substantial increases in CIN cases because of the increasing numbers of patients undergoing percutaneous coronary intervention [4–6]. CIN generally resolves spontaneously in most instances, but patients may have prolonged hospital stay, increased risk of in-hospital death and higher long-term mortality rates [7–9]. There has been considerable interest in searching for effective strategies to prevent CIN.

Tuo Zhang and Ling-Hong Shen contributed equally to this work.

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Besides periprocedural hydration, pharmacological prophylactic strategies have received considerable attention in recent years [10–12]. However, the pathophysiology of CIN is not well known. Some studies have suggested that oxidative stress, inflammation, reduction in renal blood flow and direct tubular cell damage by contrast media might play important roles in the organ injury process [13–15]. Statins are widely used in patients with coronary heart disease due to their cholesterol-lowering effect and cholesterol-independent effects, such as improving endothelial function as well as decreasing oxidative stress and inflammation [16].

Some retrospective and prospective studies have demonstrated that statins have a protective effect in the prevention of CIN, but there are currently no established guidelines on when patients should be given statins or how to use them. In this article, we performed a systematic review and meta-analysis of published human cohort studies and randomized controlled trials (RCTs) to determine whether the administration of statins is protective against CIN and to assess the magnitude of their effects.

Methods

Study Search Strategy

We performed a systematic literature search of MEDLINE (from 1966 to July 2010), EMBASE (from 1974 to July 2010), Cochrane Library (July 2010), CNKI (from 1994 to July 2010) and ISI Proceedings for the last 5 years. We derived two comprehensive search themes that were then combined using the Boolean operator 'AND'. For the theme 'contrast-induced nephropathy', we used combinations of MeSH, entry terms and text words: contrast media, contrast induced nephropathy, iodinated contrast medium, contrast agents, contrast medium, contrast dye, radiographic contrast, radiocontrast media, radiocontrast medium, Iohexol, Iobitridol, Ioxaglate, Ioversol, Iopromide, Iopamidol, Iodixanol, contrast-associated nephropathy, contrast nephropathy, contrast-induced acute renal failure, contrast-induced acute kidney injury, radiocontrast-induced acute kidney injury, radiocontrast-induced acute renal failure and nephrotoxicity. For the theme 'statins', we used: statins, atorvastatin, pravastatin, lovastatin, simvastatin, cerivastatin, fluvastatin, hydroxymethylglutaryl-CoA reductase inhibitors and HMG-CoA inhibitor. To include cohort studies, we did not use the Cochrane highly sensitive search strategy for randomized controlled studies in our search strategy.

Study Selection, Data Extraction and Quality Assessment

We included cohort studies comparing the incidence of CIN in a chronic statin pretreatment group with a statin-naïve group and RCTs comparing short-term high-dose statin treatment with short-term low-dose statin treatment or placebo, and reported the incidence of CIN in both arms. There was no restriction on language or journal type. The studies were reviewed by 2 independent investigators (T.Z. and L.-H.S.) to determine whether they met the eligibility criteria for inclusion. Discrepancies were resolved by consensus. Using a standardized form, we recorded baseline demographics and clinical and procedural characteristics of each study, including mean age, baseline creatinine, diabetes, average contrast volume, periprocedural hydration, type of radio procedure, type of contrast media, type of statin, statin dose, other prophylactic agents used and the definition of CIN. We evaluated the quality characteristics of the included RCTs using the previously published PRISMA statement [17].

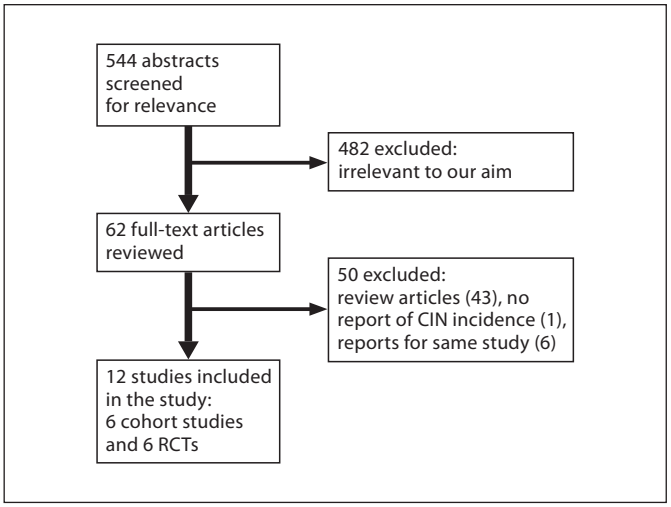

Fig. 1. Process of study selection.

Endpoints, Data Synthesis and Data Analysis

The endpoint was the incidence of CIN, which was defined as an increase in serum creatinine level >25% or 0.5 mg/dl (44.2 μmol/l). We performed qualitative analysis of the cohort studies and quantitative analysis of the RCTs to estimate the pooled risk ratios (RRs) for preventive effect of statins. Quantitative analysis was performed with review manager software (Rev-Man Analyses Version 5.0.4 Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2008). Heterogeneity between studies was analyzed by the Q and I^2 statistics. A p value of Q statistic <0.1 was defined as an indicator of heterogeneity, and I^2 <40% indicated magnitude of the heterogeneity might not be important.

Results

As shown in figure 1, 6 cohort studies and 6 RCTs were identified under our search criteria.

Cohort Studies

The main characteristics of the cohort studies are listed in table 1 [18–23]. The definition of CIN as an increase in serum creatinine >25% or 0.5 mg/dl was used in 4 studies, and the other 2 studies used serum creatinine

Table 1. Design of cohort studies

Author	Year	Design	Total patients	Procedure	Patient character	Statin type	Duration of statins	CIN definition	CM	Hydration
Khanal et al. [20]	2005	retrospective	28,871	PCI	no exclude	NA	NA	(1) SCr ≥0.5 (2) SCr ≥0.5 OR 25%	LOCM, HOCM	NA
Zhao et al. [22]	2008	retrospective	279	emergency-PCI	no exclude	pravastatin (41.1%), simvastatin (37.5%), atorvastatin (21.4%)	chronically	SCr ≥0.5	NA	NA
Patti et al. [23]	2008	prospective	434	PCI	no exclude	atorvastatin (59%), simvastatin (30%), rosuvastatin (7%), pravastatin (4%)	10.6 ± 9.1 months	SCr ≥0.5 OR 25%	iobitridol	CKD
Yoshida et al. [21]	2009	retrospective	431	CAG, PCI	SCr >1.1	pravastatin	>28 days	SCr ≥0.5 OR 25%	nonionic LOCM	yes
Ivanova et al. [18]	2009	retrospective	806	PCI	no exclude	NA	>1 week	SCr ≥0.5	NA	NA
Kandula et al. [19]	2010	retrospective	353	PCI	no exclude	atorvastatin (32.7%), simvastatin (31.0%), pravastatin (22.2%), others	NA	SCr ≥0.5 OR 25%	NA	yes

CAG = Coronary angiography; CKD = chronic kidney disease; CM = contrast medium; HOCM = high-osmolar contrast media; LOCM = low-osmolar contrast media; NA = no data available; PCI = percutaneous coronary intervention; SCr = serum creatinine.

Table 2. Baseline characteristics and results of the cohort studies

Author	Group	n	Mean age	Baseline SCr	Baseline CrCl	CKD %	DM %	CM volume	PCI %	LVEF	CHF %	CIN %	Logistic regression
Khanal et al. [20]	statin(+)	10,831	63.6 ± 11.5	1.12 ± 1.09	89.8 ± 40	11.46	32.5	220 ± 105	100	NA	12.4	4.37 (8.8)[a]	OR: 0.86
	statin(–)	18,040	63.6 ± 12.8	1.10 ± 0.61	88.7 ± 41.3	11.06	28.0	221 ± 102	100	NA	11.1	5.93 (11.9)[a]	0.78–0.95
	p		0.84	0.5	0.02	0.30	<0.05	0.915			<0.05	<0.05	
Zhao et al. [22]	statin(+)	56	NA	1.11 ± 0.3	NA	NA	NA	336 ± 165	100	47 ± 17	NA	7.1	
	statin(–)	223	NA	1.09 ± 0.2	NA	NA	NA	358 ± 223	100	48 ± 14	NA	20.6	NA
	p			0.18				0.26		0.36		<0.05	
Patti et al. [23]	statin(+)	260	65 ± 10	1.1 ± 0.3	84 ± 23	15	37.0	221 ± 100	100	54 ± 9	NA	3	OR: 0.10
	statin(–)	147	67 ± 10	1.2 ± 0.3	83 ± 19	17	37.0	234 ± 105	100	55 ± 9	NA	27	0.02–0.18
	p		<0.05	0.18	0.87	0.37	0.99	0.32		0.15		<0.05	
Ivanova et al. [18]	statin(+)	328	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.8	
	statin(–)	478	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.2	NA
	p											0.8	
Yoshida et al. [21]	statin(+)	194	69.9 ± 8.8	1.4 ± 0.3	41.4 ± 16.8	100	24.7	124.1 ± 53.8	51.0	53.9 ± 13.2	NA	4.1	OR: 0.34
	statin(–)	237	70.9 ± 8.9	1.4 ± 0.3	39 ± 17.1	100	30.8	123.6 ± 51.4	44.7	53.9 ± 15.0	NA	11.8	0.15–0.77
	p		0.233	0.179	0.157		0.602	0.915	0.083	0.993		<0.05	
Kandula et al. [19]	statin(+)	239	72.1 ± 10.4	1.15	NA	18	41.0	217.1 ± 106.8	100	NA	15.5	24.7	OR: 1.66
	statin(–)	114	72.7 ± 11.3	1.14	NA	21.5	34.2	182.1 ± 85.4	100	NA	18.4	14	0.68–3.22
	p		0.64	0.98		0.38	0.24	<0.05			0.53	<0.05	

Data are reported as means ± SD or medians (interquartile range) as in the original manuscript. CHF = Chronic heart failure; CrCl = creatinine clearance; DM = diabetes mellitus; LVEF = left ventricular ejection fraction. Other abbreviations as in table 1.

[a] Incidence of CIN, when an increase in SCr >0.5 mg/dl or 25% as definition.

>0.5 mg/dl as a definition. Demographic and baseline characteristics of these studies are listed in table 2. Most risk factors associated with CIN were comparable in both arms. Demographic and baseline characteristics of the two groups were not available in the study by Ivanova et al. [18], but multivariate analysis was performed with these risk factors to adjust the odds ratio (OR) of statin pretreatment.

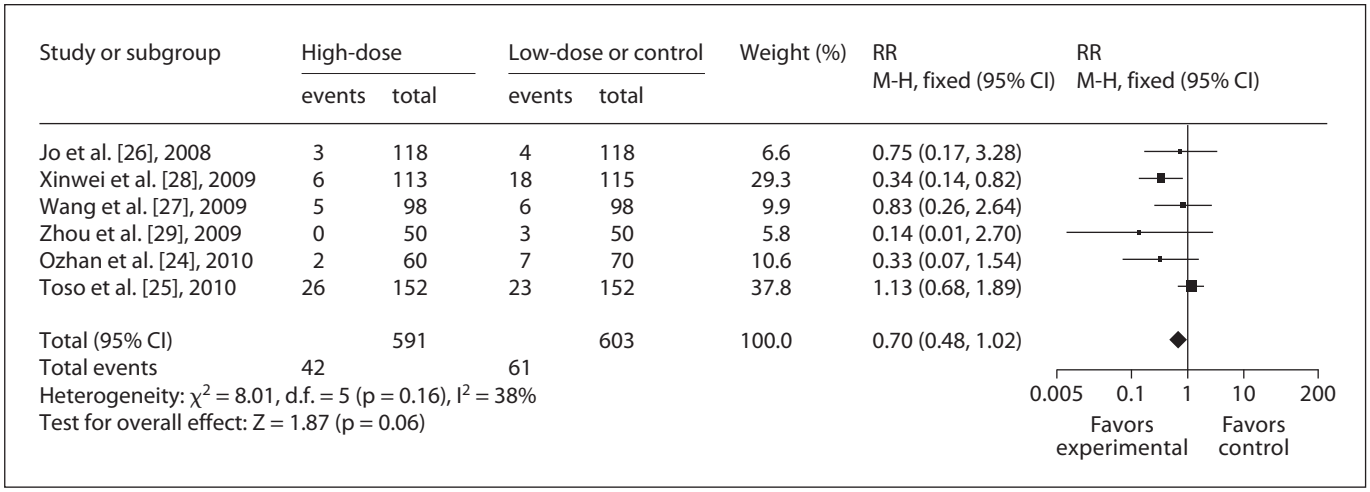

Fig. 2. Summary of all RCTs. M-H = Mantel-Haenszel.

Results of the cohort studies are listed in table 2. The incidence of CIN was available in all the studies. Four studies reported adjusted ORs of statin pretreatment. According to these results, 4 studies supported that chronic statin pretreatment significantly reduced the incidence of CIN. In the study by Yoshida et al. [21], even high-risk patients combined with renal insufficiency defined as baseline serum creatinine >1.1 mg/dl also benefited from statin pretreatment. Although there was no significant difference in the incidence of CIN between the two groups in the study by Ivanova et al. [18], multivariate analysis indicated that only statin treatment was nephroprotective and was a significant variable in predicting the rise in serum creatinine. In the study by Kandula et al. [19], a higher incidence of CIN was observed in patients pretreated with statins, but there was no significant difference between the groups after adjusting for the propensity of receiving statins.

In addition, Khanal et al. [20] reported a significant reduction in the need for renal dialysis in the statin group (0.32 vs. 0.49%, p = 0.03). In the study by Patti et al. [23], 430 of 434 patients (99%) were followed up for 4 years, and no patient required dialysis. Moreover, the incidence of late major adverse cardiac events were significantly lower in the statin group (6 vs. 36%, $p < 0.05$). Actuarial life-table analysis showed that 4-year event-free survival was similar between statin-pretreated patients with CIN and statin-naïve patients without CIN (72 vs. 71%).

Randomized Control Trials

The main characteristics of RCTs are listed in table 3, and the demographic and baseline characteristics of the RCTs are listed in table 4. Overall, 1,194 patients were included: 591 patients who received short-term high-dose statin treatment and 603 patients who received short-term low-dose statin treatment or placebo [24–29]. Two statins were used, and the duration of statin treatment ranged from 2 to >7 days. The total statin dose ranged from 140 to >460 mg. All of the patients received low-osmolar or iso-osmolar contrast media and periprocedural hydration. Patients in 2 studies received oral N-acetylcysteine as a prophylactic agent. Two studies included high-risk patients combined with chronic kidney disease, which means baseline serum creatinine was higher than the other studies. The quality characteristics of the studies are shown in table 5.

Figure 2 shows the results from all RCTs with corresponding RRs. The fixed-effects model was chosen as a test for heterogeneity, and showed p = 0.16 and I^2 = 38%. The overall effect was a nonsignificant protective trend toward decreased incidence of CIN with periprocedural short-term high-dose statin treatment (RR: 0.70; 95% CI: 0.48–1.02). Further, similar results were shown under a random-effects model (RR: 0.63; 95% CI: 0.36–1.33).

Two studies followed up long-term effects. In the study by Toso et al. [25], there was 1 death in the statin group and 1 patient undergoing temporary hemofiltration in the control group within 1 month. No differences were observed between the 2 groups at the 6-month follow-up in the study by Jo et al. [26].

Table 3. Design of RCTs

Author	Year	Total patients	Procedure	Patient characteristics	Statin type	Statin dose, duration (total dose)
Jo et al. [26]	2008	247	CAG ± PCI	SCr >1.1 or CrCl <60	simvastatin	80 mg before, 80 mg after procedure (160 mg)
Zhou et al. [29]	2009	100	CAG ± PCI	normal or SCr <1.7	atorvastatin	high dose: 80 mg·1 day before, 10 mg·6 days after procedure (140 mg); low dose: 10 mg qd·7 days (70 mg)
Wang et al. [27]	2009	196	cerebral artery intervention	no exclude	atorvastatin	80 mg·3 days before procedure (240 mg)
Xinwei et al. [28]	2009	228	PCI	ACS	simvastatin	high dose: 80 mg qd before, 20 mg after procedure (>460 mg); low dose: 20 mg qd (>160 mg)
Toso et al. [25]	2010	304	CAG ± PCI	CrCl <60	atorvastatin	80 mg·2 days before, 80 mg·2 days after procedure (320 mg)
Ozhan et al. [24]	2010	130	CAG ± PCI	SCr <1.5 or eGFR >70	atorvastatin	80 mg before, 80 mg·2 days after procedure (240 mg)

Type of contrast medium	Hydration	Other preventive agents	CIN definition	Follow-up
Iodixanol	yes	N	48 h, SCr ≥0.5; OR 25%	1, 2 days; 1, 6 months
Iopamidol	yes	N	72 h, SCr ≥0.5; OR 25%	1, 3, 5 days
Iohexol	yes	N	48 h, SCr ≥0.5; OR 25%	1, 2, 7 days
Iodixanol for CKD	yes	N	48 h, SCr ≥0.5; OR 25%	1, 2 days
Iohexol for normal				
Iodixanol	yes	NAC	5 days, (1) SCr ≥0.5; (2) ≥25%	1, 2, 3, 5, 10 days; 1 month
Iopamidol	yes	NAC	48 h, SCr ≥0.5; OR 25%	48 h

N = None. Other abbreviations as in tables 1, 2.

Table 4. Baseline characteristics and result of RCTs

Author	Group	n	Mean age	DM %	Interven-tion, %	Quantity of CM	Baseline SCr	Baseline CrCl	SCr after procedure	CIN n
Jo	statin	118	65.0 ± 9.3	28.2	30.6	173.3 ± 99.3	1.286 ± 0.418	53.46 ± 15.63	1.288 ± 0.445 (max)	3
et al. [26]	control	118	66.1 ± 8.2	23.6	26.8	190.9 ± 133.5	1.248 ± 0.364	55.40 ± 16.77	1.265 ± 0.512 (max)	4
Zhou	high-dose	50	59.6 ± 8.2	22.0	NA	118.7 ± 34.3	1.04 ± 0.24	76.88 ± 23.30	1.11 ± 0.24 (72 h)*	0
et al. [29]	low-dose	50	61.2 ± 9.2	18.0	NA	112.9 ± 33.4	1.08 ± 0.24	70.54 ± 21.02	1.21 ± 0.26 (72 h)*	3
Wang	statin	98	54.6 ± 8.1	NA	100	206 ± 85.4	0.99 ± 0.12	NA	1.06 ± 0.17 (48 h)*	5
et al. [27]	control	98	55.7 ± 9.2	NA	100	197.4 ± 77.1	1.01 ± 0.18	NA	1.17 ± 0.15 (48 h)*	6
Xinwei	high-dose	113	65 ± 11	20	100	227 ± 65	0.82 ± 0.24	93.6 ± 36.7	NA*	6
et al. [28]	low-dose	115	66 ± 12	22	100	240 ± 78	0.83 ± 0.19	85.5 ± 30.3	NA*	18
Toso	statin	152	75 ± 8	20	50	151 ± 95	1.20 ± 0.35	NA	1.21 ± 0.39 (72 h)	15 (26)[a]
et al. [25]	control	152	76 ± 7	22	55	164 ± 99	1.18 ± 0.33	NA	1.21 ± 0.42 (72 h)	16 (23)[a]
Ozhan	statin	60	54 ± 10	15.0	13.3	97 ± 7	0.88 ± 0.2	92 ± 21	0.84 ± 0.19 (48 h)*	2
et al. [24]	control	70	55 ± 8	17.1	1.4	93 ± 6	0.88 ± 0.3	89 ± 22	0.95 ± 0.35 (48 h)*	7

Abbreviations as in table 1, 2. * $p < 0.05$. [a] Number of CIN when an increase in SCr is >25% as definition.

Table 5. Quality characteristics of the studies

Author	Randomization described	Method for concealment of allocation	Blinding	Randomized patients not analyzed	Power calculation report
Jo et al. [26]	yes	yes	double-blind	7.50%	yes
Zhou et al. [29]	yes	NA	single-blind	NA	no
Wang et al. [27]	no	NA	single-blind	NA	no
Xinwei et al. [28]	yes	yes	no	no	yes
Toso et al. [25]	yes	yes	no	no	yes
Ozhan et al. [24]	no	NA	no	NA	no

Discussion

To the best of our knowledge, this is the first study to pool the current evidence of the preventive effect of statins in CIN.

Statins, which are mainly used as cholesterol-lowering agents, are also known to have pleiotropic effects, such as antioxidative and anti-inflammatory properties [16, 30–32]. Given the potential role of oxidative stress in the pathophysiology of CIN, statins might reduce contrast media nephrotoxicity by removing free radicals. In our study, we included cohort studies comparing the incidence of CIN in a chronic statin pretreatment group to a statin-naïve group.

Most studies have suggested that chronic use of statins have a preventive effect against CIN, and a beneficial effect in reducing the incidence of dialysis and long-term mortality was also reported. Only 1 study has reported a null effect for statin use [19] and an even higher incidence of CIN in the statin group. Higher contrast volume administered in the statin group might have contributed to this result, but when adjusted for the amount of contrast used, no differences in the incidence of CIN were noted. We also performed quantitative analysis of RCTs comparing periprocedural short-term high-dose statins with low-dose statins or placebo. Pooled RR indicated that short-term high-dose statin treatment was associated with a reduction in the incidence of CIN, but there was no statistical significance.

Considering the inherent limitations of cohort studies and meta-analysis, these results must be considered with several caveats. Among the cohort studies included, most risk factors associated with CIN were well balanced in the two arms, and adjusted ORs were also available in 4 studies. But there were still some confounding variables. For instance, there was a higher percentage of patients with diabetes mellitus or chronic heart failure in the statin group than in the statin-naïve group in the study by Khanal et al. [20]. In the study by Kandula [19], the mean total contrast dose per procedure in the statin group was more than that in the statin-naïve group. These characteristics could have introduced clinical heterogeneity and bias against the beneficial effects of chronic statin pretreatment. Consequently, we did not perform quantitative analyses on these studies.

There is also clinical heterogeneity in RCTs associated with the varied study settings. One of the factors is the timing of statin pretreatment. For example, simvastatin was used both in the studies by Jo et al. [26] and Xinwei et al. [28]. Patients in Jo's study received simvastatin 80 mg before and after the procedure (a total of 160 mg), while patients in Xinwei's study received simvastatin pretreatment for more than 5 days (>460 mg in total). The former, however, showed a null effect for this drug and the latter showed a positive effect. The duration of statin use might have been too short to exert an effect in Jo's study. On the other hand, the timing of drug administration might also be important in cohort studies. Chronic statin administration could contribute to the positive effect of statins.

Secondly, other preventive strategies applied in these studies are also related to the effect of statins. In the studies by Toso et al. [25] and Ozhan et al. [24], the patients received oral N-acetylcysteine at the same time. There was no difference between the two arms in CIN frequency. To date, N-acetylcysteine, an anti-oxidant agent, is considered the most effective drug at decreasing the incidence of CIN [33–35]. Statins and N-acetylcysteine might share the same mechanism for renal protection. The preventive effect of statins might be obscured by N-acetylcysteine.

Finally, CIN is associated with poor long-term outcome, but current studies focus primarily on short-term

rather than long-term outcomes of harder endpoints, such as incidence of dialysis requirement, morbidity and mortality. Although 2 RCTs followed up for 1 and 6 months, the sample sizes were too small to detect differences. Thus, a larger multicenter study will be necessary to detect differences in more meaningful outcomes.

Study Limitations

The major limitation of this study is based on the combined data of cohort studies and heterogeneous RCTs. Another potential limitation is the inclusion of low-quality studies for meta-analysis. All the RCTs, except the one by Jo et al. [26], did not report loss to follow-up. We presumed that loss was not significant due to the short duration of observation in these studies. Some studies did not have blinding. However, considering that the endpoint of these studies was objective, we believe that including these studies did not bring any notable bias.

In conclusion, most cohort studies showed chronic using of statins might have a preventive effect against CIN. Short-term high-dose statin treatment was associated with a protective trend toward decreased CIN incidence in RCTs, but there was no statistical significance. Considering the limitations of the included studies, the current data are not conclusive as to whether statins are protective for CIN. Future large well-designed studies are needed to address the effect of these drugs and their longer-term clinical outcomes.

Acknowledgments

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