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Efficacy Evaluation of High-Dose Atorvastatin Pretreatment in Patients with Acute Coronary Syndrome: A Meta-Analysis of Randomized Controlled Trials

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: It is unclear whether high-dose atorvastatin pretreatment benefits acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). To clarify this issue, we performed a meta-analysis of the published literature.

Material/Methods: Randomized controlled trials (RCTs) assessing high-dose atorvastatin pretreatment in ACS patients undergoing PCI were enrolled. Short-term major adverse cardiac events (MACEs), changes in serum high-sensitivity C-reactive protein (hs-CRP), peak creatine kinase-myocardial band (CK-MB) level, and thrombolysis in myocardial infarction (TIMI) grade 3 flow after PCI were studied as clinical outcomes.





Results: Seventeen RCTs including 10 072 patients were retrieved. High-dose atorvastatin showed greater benefits in reducing the incidence of short-term MACEs (OR 0.72; 95% CI: 0.56 to 0.94; $P=0.01$) and hs-CRP level (SMD -1.59 ; 95% CI: -2.38 to -0.80 ; $P<0.0001$) among ACS patients after PCI. No significant difference was found between the 2 groups in terms of peak CK-MB (SMD -0.34 ; 95% CI: -0.79 to 0.10 ; $P=0.13$) or final TIMI flow grade 3 (OR 1.31; 95% CI: 0.73 to 2.36; $P=0.36$) after PCI. High-dose atorvastatin therapy also was not associated with alanine aminotransferase (ALT) elevation (OR 1.95; 95% CI: 0.95 to 4.03; $P=0.07$).

Conclusions: The results of this meta-analysis suggest that high-dose atorvastatin pretreatment reduces the incidence of short-term MACEs and hs-CRP level without increasing drug-induced hepatotoxicity in ACS patients after PCI.

MeSH Keywords: **Acute Coronary Syndrome • Percutaneous Coronary Intervention • Treatment Outcome**

Abbreviations: **OR** – odds ratio; **CI** – confidence interval; **MACEs** – major adverse cardiac events; **SMD** – standard mean difference; **PCI** – percutaneous coronary intervention; **CK-MB** – creatine kinase-myocardial band; **TIMI** – thrombolysis in myocardial infarction; **ALT** – alanine aminotransferase

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/912544>

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Background

The acute coronary syndrome (ACS) spectrum includes patients with ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina. Percutaneous coronary intervention (PCI) has become one of the most important treatment modalities for ACS patients [1]. In recent years, several studies reported that high-dose atorvastatin pretreatment improves cardiovascular outcomes after PCI in ACS patients. Mechanistic studies have suggested that the possible protective effects of high-dose atorvastatin pretreatment in ACS patients reduce inflammatory cascade and anti-thrombotic activity and enhances coronary atherosclerotic plaque stability [2–4].

However, the beneficial effects of intensive atorvastatin therapy are still controversial. Recently, several studies have reported that high-dose atorvastatin pretreatment improves clinical outcomes for ACS patients undergoing PCI. A few studies have found atorvastatin significantly reduced the risk of major adverse cardiovascular events (MACEs) at 30 days in ACS patients treated with PCI when given a loading dose [5–8]. However, other investigations have yielded conflicting results and raised doubts about the usefulness of high-dose (≥ 80 mg daily) atorvastatin before PCI [9–11]. Whether intensive treatment with atorvastatin is an effective way to reduce hard cardiovascular events among ACS patients remains unclear. To shed further light on this issue, we performed a meta-analysis based on the current literature to determine whether ACS patients undergoing PCI benefit from high-intensity atorvastatin therapy.

Material and Methods

Search strategy

An extensive literature search was conducted in PubMed, Embase, Cochrane CENTRAL, and Web of Science databases up to May 2018 to identify randomized controlled trials (RCTs) comparing high-dose atorvastatin preloading with control (placebo or low-dose atorvastatin therapy) in ACS patients undergoing PCI. The following keywords were used in searching: “atorvastatin”, “acute coronary syndrome”, “percutaneous coronary intervention”, or “PCI”, and “randomized” and “randomly”. Additionally, we checked the references of the selected articles to find additional eligible publications. The studies selected included only those published in English language.

Study selection

The inclusion criteria were: (1) the RCTs included a direct comparison of high-dose atorvastatin versus low-dose atorvastatin or placebo therapy in humans; (2) patients with ACS (ST-segment elevation myocardial infarction [STEMI], unstable

angina pectoris, or non-ST-segment elevation myocardial infarction [NSTEMI]); (3) patients who were undergoing current therapy with atorvastatin; (4) the study reported information on MACEs, change in serum high-sensitivity C-reactive protein (hs-CRP), peak creatine kinase-myocardial band (CK-MB) level, and TIMI grade 3 after PCI; and elevated liver transaminases as the main safety endpoint; and 5) the follow-up time was at least 30 days. Exclusion criteria were: (1) ongoing studies; (2) no control studies; (3) duplicate reports without additional or updated data; and (4) studies lacking baseline or follow-up data.

Data extraction

Data were extracted independently by 2 authors and cross-checked to reach a consensus. The following variables were obtained from each article: first author, publication year, study regions, study design, total number of subjects, clinical presentation, atorvastatin intervention and control measures before PCI, follow-up duration, clinical endpoints, and definition of MACEs.

Quality assessment

Study quality for RCTs was evaluated using the Cochrane Collaboration’s tool for assessing risk of bias [12,13]. This tool includes questions related to random-sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other biases. Each aspect can further be classified as low, high, or unclear risk.

Statistical analysis

Statistical analyses were performed using Rev-Man5.3 software (Cochrane Collaboration, Copenhagen, Denmark) and STATA software, version 12.0 (STATA Corp., College Station, TX). The Cochrane χ^2 test and the I^2 test were used to evaluate heterogeneity among studies, with a threshold value of $P < 0.10$ being considered significant [14]. A random effects model was used when heterogeneity was present. Sensitivity analysis was performed to evaluate the stability of the results. Publication bias was assessed by funnel plot and Egger’s regression test. Results were considered statistically significant at $P < 0.05$. All P -values are 2-tailed.

Results

Selected studies and baseline characteristics

The flow diagram of the study analysis is shown in Figure 1. Of 397 potentially relevant articles initially screened, 17 RCTs [3,5–11,15–23] met the inclusion criteria and were

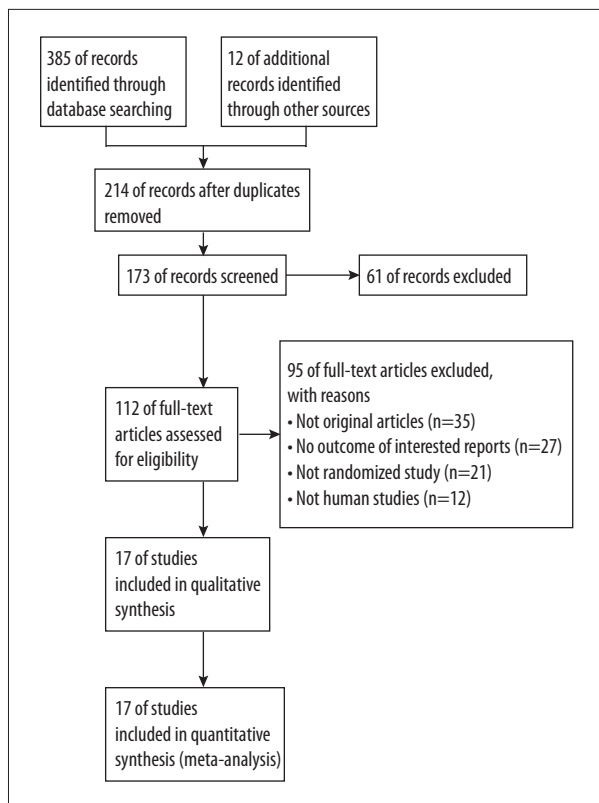


Figure 1. Flow chart of the literature search for this meta-analysis.

included in the final meta-analysis consisting of a total of 10 072 ACS patients, of which 5024 were randomized to the high-dose atorvastatin group and 5048 were randomized to the control group. The clinical characteristics of patients included in the meta-analysis are reported in Table 1. All studies were published in English.

Risk of bias in included studies

Judgments on each risk of bias item for all studies are shown in Figures 2 and 3. Most of the included trials had a potential risk of allocation concealment, selective reporting, and other biases. Due to the small number of eligible studies, none were excluded.

Effect of high-dose atorvastatin preloading on short-term MACEs in ACS patients undergoing PCI

Nine trials [5–11,18,22] evaluated the effects of high-dose atorvastatin pretreatment on the incidence of MACEs in ACS patients who had PCI. The overall pooled results of the random-effects model showed that high-dose atorvastatin therapy led to a 28% relative reduction in MACEs compared with the control medical therapy (OR=0.72, 95% CI: 0.56 to 0.94, P=0.01; I²=51%, P_{het}=0.04; Figure 4).

Effect of high-dose atorvastatin preloading on hs-CRP level in ACS patients undergoing PCI

The effects of high-dose atorvastatin pretreatment on hs-CRP level were also analyzed in 9 trials [3,6–9,15,16,18,21]. Overall, high-dose atorvastatin reduced serum hs-CRP level in ACS patients after PCI (SMD –1.59; 95% CI: –2.38 to –0.80; P<0.0001), and statistical heterogeneity was evident among these studies (P<0.00001, I²=97%; Figure 5).

Effect of high-dose atorvastatin preloading on peak CK-MB and final TIMI flow grade in ACS patients undergoing PCI

According to Figure 3C, there were 6 studies [7,9,17–20] used for the quantitative analysis of the level of peak CK-MB in ACS patients after PCI (SMD –0.34; 95% CI: –0.79 to 0.10, P=0.13; I²=84%, P_{het}<0.00001; Figure 6). Regarding the final TIMI flow grade 3 after PCI, the pooling analysis also showed that high-dose atorvastatin did not provide an additional benefit in post-procedural TIMI flow grade 3 (OR=1.31, 95% CI: 0.73 to 2.36, P=0.36; I²=0%, P_{het}=0.54; Figure 7).

Effect of high-dose atorvastatin preloading on serum alanine aminotransferase level

Four studies [5,8,17,18] evaluated whether high-dose atorvastatin treatment increased serum ALT. No significant differences were observed in terms of elevated liver ALT between high-dose atorvastatin therapy and the control group (OR=1.95, 95% CI: 0.95 to 4.03, P=0.07; I²=48%, P_{het}=0.12; Figure 8).

Sensitivity analysis

Sensitivity analysis was performed for the hs-CRP level data with high heterogeneity. After removing each study, sensitivity analysis showed similar results (data not shown). Sensitivity analysis confirmed the stability of our results.

Publication bias diagnostics

The result of the funnel plot suggested that no publication bias was present based on the MACEs results (Figure 9), which was also statistically supported by Begg’s test (p=0.119) and Egger’s test (p= 0.125).

Discussion

This meta-analysis of 10 072 individuals from 17 RCTs shows that high-dose atorvastatin pretreatment significantly reduced the incidence of short-term MACEs and lowered hs-CRP levels in ACS patients after PCI. However, high-dose atorvastatin pretreatment did not improve TIMI myocardial perfusion grade or

Table 1. Details of included studies and extracted statistics used in the meta-analysis.

Study	Study design (trials)	Location	Clinical feature	Loading dose and timing before PCI	Patients number statin loading/control	Outcomes	Definition of the MACEs	The main results of study
Schwartz (2001)	RCT (MIRACL)	International multi-center	Unstable angina or NSTEMI-ACS	Atorvastatin 80 mg/day before PCI vs. placebo pretreatment	1538/1548	MACEs at 16 weeks	Death, non-fatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency re-hospitalization	Atorvastatin 80 mg/day significantly reduced the risk of recurrent ischemic events
Patti (2007)	RCT (ARMYDA-ACS)	Multi-center in Italy	NSTEMI-ACS	Atorvastatin 80 mg then 40 mg/day before PCI vs. placebo pretreatment	86/85	MACEs at 30 days	Death, MI, target vessel revascularization	High-dose atorvastatin pretreatment conferred an 88% risk reduction of 30-day major adverse cardiac events by multivariable analysis
Ordulu (2008)	RCT	Turkey	Unstable angina or NSTEMI-ACS	Atorvastatin 80 mg/day before PCI vs. placebo pretreatment	20/20	Post-PCI hs-CRP level	–	High-dose atorvastatin pretreatment significantly reduced hs-CRP levels
Zhao (2009)	RCT	China	Unstable angina	Atorvastatin 80 mg/day before PCI vs. 20 mg atorvastatin pretreatment	85/79	Post-PCI hs-CRP level	–	80 mg/day atorvastatin therapy significantly reduced the levels of inflammatory factors (hs-CRP, IL-6 and TNF- α), improved vascular endothelial function compared with the 20 mg/day atorvastatin-treated group
Kim (2010)	RCT (The STATIN STEMI trial)	Multi-center in Korea	STEMI	Atorvastatin 80 mg/day before PCI vs. 10 mg atorvastatin pretreatment	86/85	MACEs at 30 days, hs-CRP level, peak CK-MB, Final TIMI flow grade	Death, non-fatal MI, and target vessel revascularization	High-dose atorvastatin pretreatment before PCI did not show a significant reduction of MACEs compared with low-dose atorvastatin but did show improved immediate coronary flow after primary PCI
Sun (2010)	RCT	China	NSTEMI-ACS	Atorvastatin 80 mg then 60 mg/day before PCI vs. 40 mg atorvastatin pretreatment	20/20	MACEs at 30 days, hs-CRP level, peak CK-MB	Cardiac death, MI and revascularization treatment	High-dose pre-PCI atorvastatin therapy reduced the incidence of MACEs, the post-PCI hs-CRP and CK-MB levels
Hahn (2011)	RCT	Multi-center in Korea	STEMI	Atorvastatin 80 mg/day before PCI vs. 10 mg atorvastatin pretreatment	89/84	Final TIMI flow grade, ALT elevation	–	High-dose atorvastatin pretreatment before PCI did not reduce infarct size measured by SPECT
Yu (2011)	RCT	China	NSTEMI-ACS	Atorvastatin 80 mg then 40 mg/day before PCI vs. placebo pretreatment	41/40	MACEs at 30 days, hs-CRP level, peak CK-MB, ALT elevation	Cardiac death, MI and target vessel revascularization	High-dose atorvastatin pretreatment before PCI reduced the incidence of MACEs, the post-PCI hs-CRP and CK-MB levels

Table 1 continued. Details of included studies and extracted statistics used in the meta-analysis.

Study	Study design (trials)	Location	Clinical feature	Loading dose and timing before PCI	Patients number statin loading/control	Outcomes	Definition of the MACEs	The main results of study
Post (2012)	RCT	Netherlands	STEMI	Atorvastatin 80 mg/day before PCI vs. placebo pretreatment	20/22	Peak CK-MB level and Final TIMI flow grade after PCI	–	High-dose atorvastatin pretreatment before PCI did not result in an improved cardiac function, microvascular perfusion, or decreased myocardial infarct size
Liu HL (2013)	RCT	China	STEMI	Atorvastatin 80 mg/day before PCI vs. placebo pretreatment	32/32	Peak CK-MB level and Final TIMI flow grade after PCI	–	High-dose atorvastatin pretreatment before PCI reduced the levels of inflammatory factors (hs-CRP, BNP and MMP-9), and improved cardiac function
Jang (2014)	RCT (ALP-ACS)	Korea and China	NSTE-ACS	Atorvastatin 80 mg then 40 mg/day before PCI vs. 40 mg atorvastatin pretreatment	247/252	MACEs at 30 days	Death, MI, and target vessel revascularization	High-dose atorvastatin pretreatment before PCI did not reduce the incidence of MACEs and with higher LV systolic function
Shehata (2015)	RCT	Egypt	NSTE-ACS	Atorvastatin 80 mg/day before PCI vs. 10 mg atorvastatin pretreatment	58/60	hs-CRP level and Final TIMI flow grade	–	High-dose atorvastatin pretreatment before PCI was associated with better biochemical outcome in terms of lower hs-CRP and LDL-C levels after PCI and with higher left ventricular systolic function
Yang (2015)	RCT	China	Unstable angina	Atorvastatin 80 mg/day before PCI vs. 20 mg atorvastatin pretreatment	48/48	Final TIMI flow grade	–	High-dose atorvastatin pretreatment before PCI reduced the inflammatory response in monocytes via PPARγ activation
Liu Z (2016)	RCT (CLEAN)	China	ACS	Atorvastatin 80 mg before PCI then 40 mg thereafter vs. 20 mg atorvastatin pretreatment	276/280	MACEs at 30 days, hs-CRP level, ALT elevation	Cardiovascular death, spontaneous MI, and unplanned revascularization	High-dose atorvastatin pretreatment before PCI reduced the incidence of MACEs
Gavazzi (2017)	RCT	Italy	STEMI	Atorvastatin 80 mg/day before PCI vs. 20 mg atorvastatin pretreatment	26/26	hs-CRP level	–	High-dose atorvastatin pretreatment before PCI improved endothelial function and vascular inflammation
Periti (2017)	RCT	India	STEMI	Atorvastatin 80 mg/day before PCI vs. 10 mg atorvastatin pretreatment	512/515	MACEs at 30 days	Death from any cause, myocardial infarction, documented NSTEMI-ACS requiring readmission, ischemia driven revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting, and stroke	High-dose atorvastatin pretreatment before PCI did not reduce the incidence of MACEs, but showed significant improvement in immediate coronary flow depicted by ST-segment resolution

Table 1 continued. Details of included studies and extracted statistics used in the meta-analysis.

Study	Study design (trials)	Location	Clinical feature	Loading dose and timing before PCI	Patients number statin loading/control	Outcomes	Definition of the MACEs	The main results of study
Berwanger (2018)	RCT (SECURE-PCI)	Multi-center in Brazil	ACS	Atorvastatin 80 mg/day before PCI vs. placebo pretreatment	2087/2104	MACEs at 30 days	All-cause mortality, acute MI, stroke, and unplanned coronary revascularization	High-dose atorvastatin pretreatment before PCI did not reduce the incidence of MACEs

RCT – randomized controlled trial; NSTEMI-ACS – non-ST-elevation acute coronary syndrome; STEMI – ST-elevation myocardial infarction; PCI – percutaneous coronary intervention; MACEs – major adverse cardiac events; hs-CRP – high-sensitivity C-reactive protein; CK-MB – creatine kinase-myocardial band; TIMI – thrombolysis in myocardial infarction; MI – myocardial infarction; SPECT – single-photon emission computed tomography.

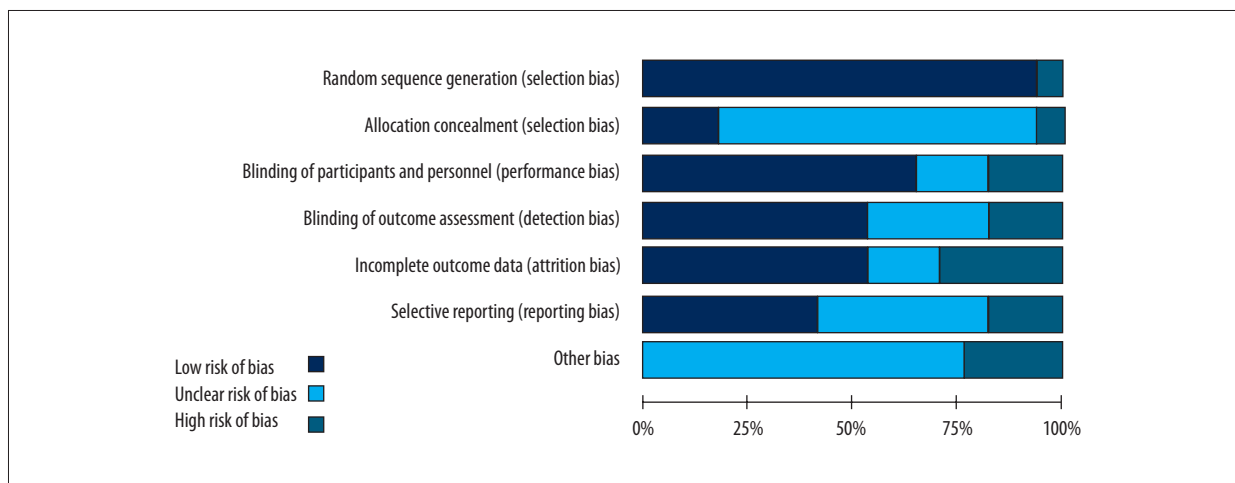


Figure 2. Risk of bias graph of included studies in this meta-analysis.

an additional reduction in peak CK-MB in ACS patients after PCI. In addition, high-dose atorvastatin pretreatment did not increase the risk of hepatotoxicity compared to the placebo/low-dose atorvastatin group.

In recent years, several studies reported that high-dose atorvastatin pretreatment improves cardiovascular outcomes after PCI in ACS patients. However, the beneficial effects of intensive atorvastatin therapy are still controversial. In some studies, such as those by Kim [9] and Jang [10], high-dose atorvastatin pretreatment before PCI did not show a significant reduction of MACEs compared with low-dose atorvastatin, but other studies, such as those by Patti [6], Sun [7], and Liu [8] found that ACS patients benefit from high-dose atorvastatin preloading before PCI. Recently, Berwanger et al. [11] found that high-dose atorvastatin pretreatment in patients with ACS did not reduce the rate of MACEs at 30 days. Considering these conflicting conclusions, a meta-analysis was required to confirm the efficacy and safety of high-dose atorvastatin treatment in ACS patients.

ACS is a complex disorder that encompasses tissue remodeling, necrosis, and thrombosis, and persistent inflammatory processes contribute to the aggravation of atherosclerosis and ACS [24]. hs-CRP is an acute-phase protein synthesized by the liver and is closely related with inflammation. It is reported that serum hs-CRP level can be a postoperative factor to predict future events in ACS patients [25]. As a consequence, intensive atorvastatin treatment during acute myocardial infarction could reduce clinical events by anti-inflammatory effects. In contrast to previous findings [18,26], our results show that the possible reason is mainly due to the distal coronary microembolization and high thrombotic burden associated with ACS.

The present meta-analysis has several features that distinguish it from a similar meta-analysis [27]. First, the prior meta-analysis, by Liu et al., was based on 9 RCTs and enrolled 3 studies published in Chinese, so the quality of the articles may not be as high as studies published in English journals. To limit bias in the selection of included studies, we only included RCTs published in English. Second, although our meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Berwanger 2018	+	?	+	+	+	+	?
Gavazzoni 2017	+	?	-	-	?	-	?
Hahn 2011	+	?	-	+	+	+	?
Jang 2014	+	+	+	+	+	+	?
Kim 2010	+	+	+	+	+	+	-
Liu HL 2013	+	?	+	?	+	?	-
Liu Z 2016	+	?	+	-	+	?	?
Ordulu 2008	-	?	+	?	-	?	-
Patti 2007	+	-	+	+	+	+	?
Post 2012	+	?	+	+	-	?	?
Priti 2017	+	?	+	+	+	?	?
Schwartz 2001	+	?	+	+	-	+	?
Shehata 2015	+	+	+	+	+	?	?
Sun 2010	+	?	-	-	+	+	-
Yang 2015	+	?	?	?	?	-	?
Yu 2011	+	?	?	?	?	?	?
Zhao 2011	+	?	?	?	-	-	?

Figure 3. Risk of bias summary of included studies in this meta-analysis.

yielded a similar overall reduction in the incidence of MACEs, we included 2 additional RCTs. Third, this meta-analysis found that high-dose atorvastatin reduced hs-CRP level after PCI, but post-PCI TIMI 3 flow was not improved.

The present study is one of the largest systematic reviews of the literature that used meta-analysis to study whether high-dose atorvastatin pretreatment before PCI improves clinical endpoints in ACS patients undergoing PCI. This study has certain limitations. Firstly, different doses and durations of atorvastatin treatment in ACS patients from different regions may

have various effects on clinical outcomes. Secondly, most included trials were not long enough. Hence, more RCTs with high quality and longer follow-up periods are required to identify the beneficial cardiac effects of atorvastatin preloading before PCI. Thirdly, MACEs were not uniformly defined. Therefore, reporting bias is possible in our study.

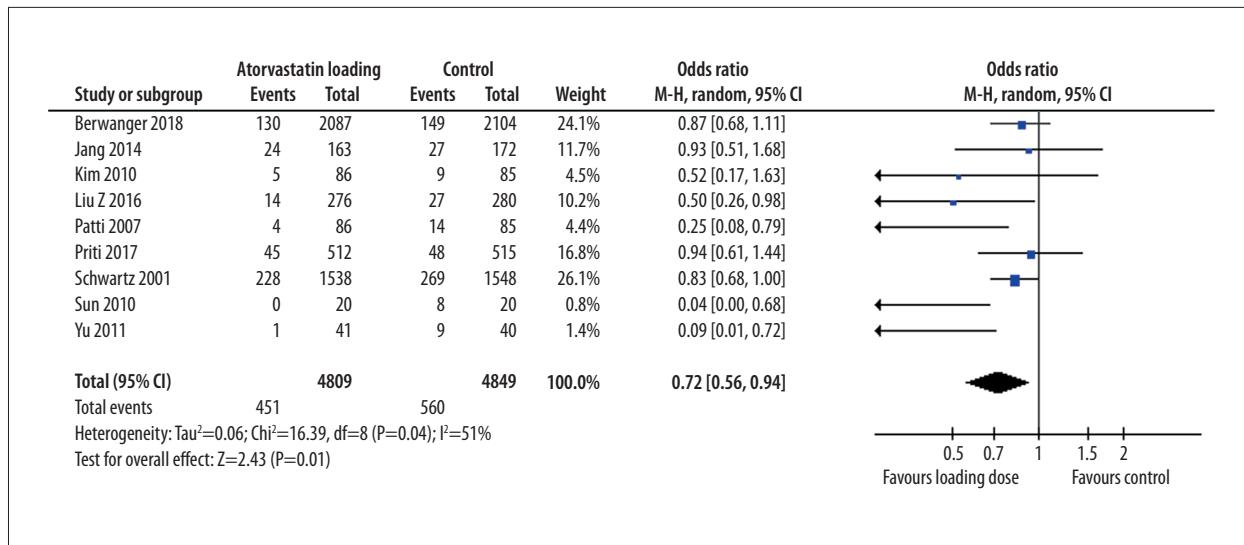


Figure 4. Pooled ORs for MACEs in the high-dose atorvastatin pretreatment versus control in ACS patients undergoing PCI.

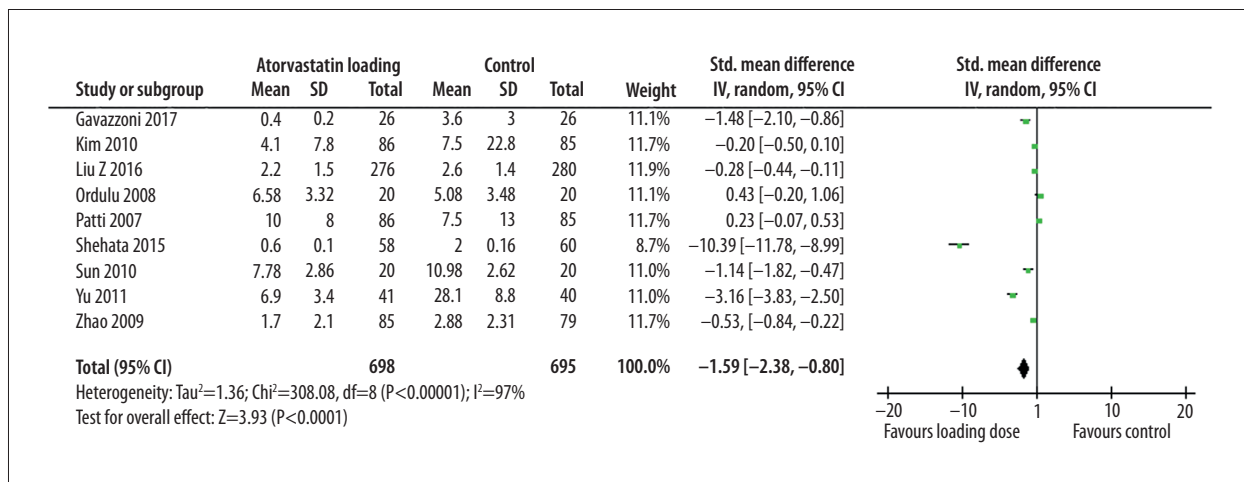


Figure 5. Pooled SMD of change in hs-CRP after PCI in the high-dose atorvastatin pretreatment versus control in ACS patients.

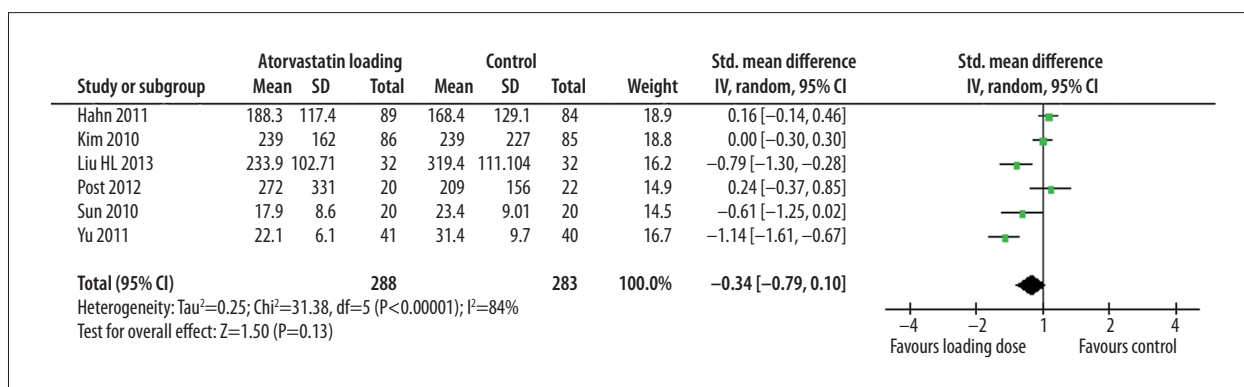


Figure 6. Pooled SMD of change in peak CK-MB after PCI in the high-dose atorvastatin pretreatment versus control in ACS patients.

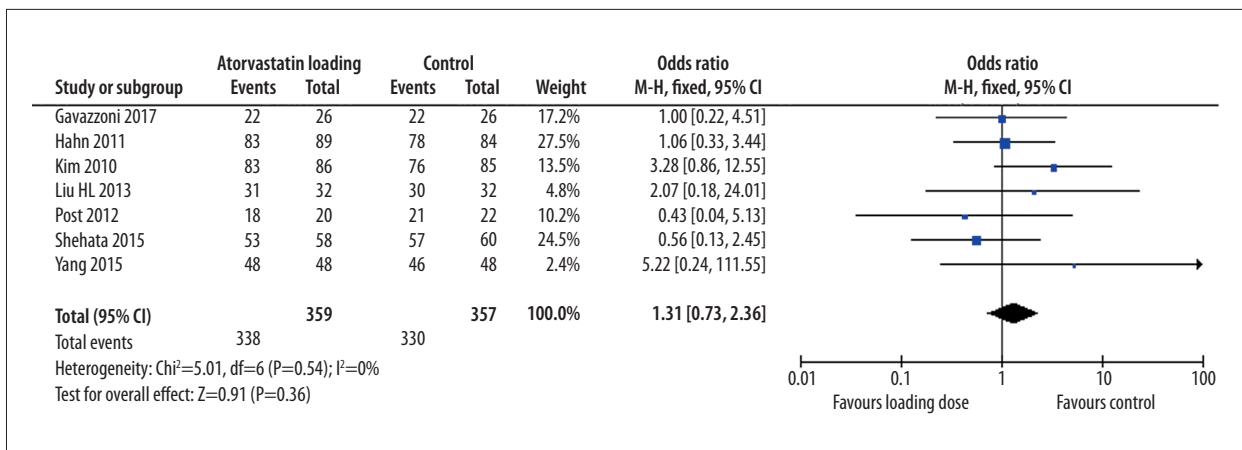


Figure 7. Pooled ORs for final TIMI flow grade 3 after PCI in the high-dose atorvastatin pretreatment versus control in ACS patients.

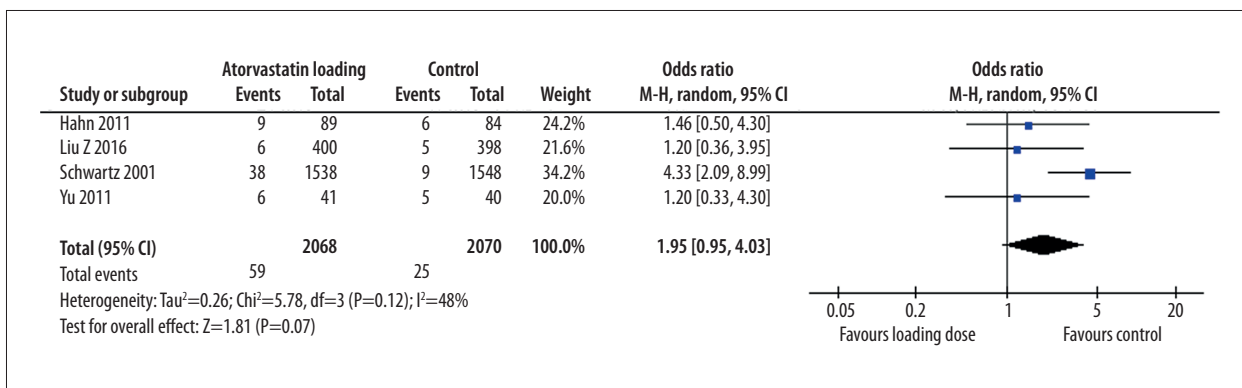


Figure 8. Pooled ORs for elevated ALT in the high-dose atorvastatin pretreatment versus control in ACS patients.

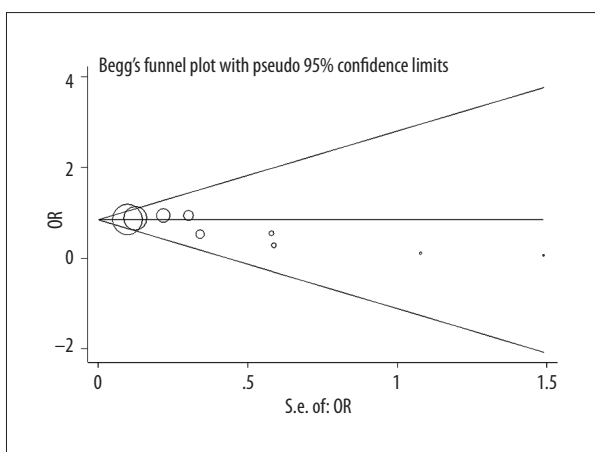


Figure 9. Funnel plot analysis to assess publication bias based on MACEs data.

Conclusions

Our meta-analysis demonstrates that high-dose atorvastatin pretreatment can reduce the rate of short-term MACEs and hs-CRP levels without increasing drug-induced hepatotoxicity in ACS patients after PCI. Larger additional RCTs with larger sample sizes and longer follow-up periods are needed to confirm the clinical benefits of high-dose atorvastatin loading in ACS patients who undergo primary PCI.

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