



Efficacy of high-dose atorvastatin or rosuvastatin loading in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials with GRADE qualification of available evidence

Josip A. Borovac^{1,2} · Mette Leth-Olsen¹ · Marko Kumric¹ · Domenico D'Amario³ · Konstantin Schwarz⁴ · Duska Glavas² · Josko Bozic¹

Received: 20 May 2021 / Accepted: 26 July 2021 / Published online: 23 August 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Purpose We aimed to summarize current evidence regarding the impact of a high-dose statin loading before percutaneous coronary intervention (PCI) on short-term outcomes in patients presenting with the acute coronary syndrome (ACS).

Methods This meta-analysis was based on a search of the MEDLINE, Cochrane Central Register of Controlled Trials, Ovid Journals, and SCOPUS for randomized controlled trials that compared high-dose atorvastatin or rosuvastatin with no or low-dose statin administered before planned PCI in statin-naïve patients with ACS. The primary endpoints were major adverse cardiovascular and cerebrovascular events (MACCE), myocardial infarction (MI), and all-cause mortality at 30 days. Prespecified subanalyses were performed with respect to statin and ACS type.

Results A total of eleven trials enrolling 6291 patients were included, of which 75.4% received PCI. High-dose statin loading was associated with an overall 43% relative risk (RR) reduction in MACCE at 30 days (RR 0.57, 95% CI 0.41–0.77) in whole ACS population. This effect was primarily driven by the 39% reduction in the occurrence of MI (RR 0.61, 95% CI 0.46–0.80). No significant effect on all-cause mortality reduction was observed (RR 0.92, 95% CI 0.67–1.26). In the setting of ST-elevation myocardial infarction (STEMI), atorvastatin loading was associated with a 33% reduction in MACCE (RR 0.67, 95% CI 0.48–0.94), while in non-ST-elevation myocardial infarction ACS (NSTEMI-ACS), rosuvastatin loading was associated with 52% reduction in MACCE at 30 days (RR 0.48, 95% CI 0.34–0.66). The level of evidence as qualified with GRADE was low to high, depending on the outcome.

Conclusion A high-dose loading of statins before PCI in patients with ACS reduces MACCE and reduces the risk of MI with no impact on mortality at 30 days. Atorvastatin reduces MACCE in STEMI while rosuvastatin reduces MACCE in NSTEMI-ACS at 30 days.

Keywords Acute coronary syndrome · Major adverse cardiovascular and cerebrovascular events · Percutaneous coronary intervention · Statin loading

Key points

- Early loading of high-dose statins in patients with the acute coronary syndrome (ACS) naïve to statin treatment and before percutaneous coronary intervention was associated with a reduction in major adverse cardiovascular and cerebrovascular events during the 30 days.
- This effect was primarily driven by the reduction in recurrent myocardial infarctions with no impact on all cause mortality. These effects were observed for the rosuvastatin use in the setting of non-ST-elevation ACS and atorvastatin in ST-elevation ACS.
- Caution in interpreting these findings should be exercised due to the possibility of publication and geographical bias as well as the small sample size of the most of included trials.

✉ Josip A. Borovac
jborovac@mefst.hr

¹ Department of Pathophysiology, School of Medicine, University of Split, Split, Croatia

² Clinic for Heart and Cardiovascular Diseases, University Hospital of Split (KBC Split), Split, Croatia

³ Department of Cardiovascular and Thoracic Sciences, IRCCS Fondazione Policlinico A. Gemelli, Università Cattolica Sacro Cuore, Rome, Italy

⁴ Department of Internal Medicine 3, Karl Landsteiner University of Health Sciences, University Hospital St. Pölten, Krems, Austria

Introduction

Statins are widely prescribed for lipid-lowering management in the setting of primary and secondary prevention of coronary artery disease (CAD). Among patients with the acute coronary syndrome (ACS) such as those with ST-elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTEMI-ACS), statins hold IA class of recommendation (CoR) in major guidelines and are stipulated to be initiated as early as possible, in the absence of contraindications and regardless of baseline cholesterol levels at the time of the acute event [1–3]. In North-American guidelines for STEMI management from 2013, high-dose atorvastatin of 80 mg daily is recommended in all STEMI patients without contraindications (IB CoR) [4].

However, the exact timing of statin initiation and clinical benefit of high-dose statin loading (pretreatment) before primary or delayed percutaneous coronary intervention (PCI) among patients presenting with ACS is unclear. The biological rationale supporting the early or very early [5] use of statins during the initial (unstable) phase of the acute thrombotic event is based on pleiotropic effects beyond lipid lowering that might act early while awaiting PCI [6–10]. Data corroborates that, among patients with both stable angina and ACS, a high-dose statin loading before PCI was associated with improvement in clinical outcomes, mainly driven by the reduction in periprocedural MIs and major adverse cardiovascular and cerebrovascular events (MACCE) during the vulnerable short-term period [11–13]. The largest-to-date randomized controlled trial (RCT) evaluating the effect of high-dose atorvastatin loading before planned PCI in the population of ACS patients provided mixed results; however, significant MACCE reduction was observed among patients that received PCI and had STEMI [14, 15].

Due to the present evidence gap for this problem and the fact that none of the previous systematic reviews qualified evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE), we performed a meta-analysis with GRADE evidence qualification. We included all relevant RCTs to date that assessed the efficacy of early high-dose statin loading *vs.* no statin/low-dose statin/placebo before PCI among statin-naïve patients with ACS on endpoints of MACCE, recurrent MIs, and all-cause death during 30-day follow-up. Secondly, we undertook to determine the effects of high-dose statin loading before PCI on 30-day MACCE concerning statin used (atorvastatin or rosuvastatin) and ACS subtype.

Methods

The PRISMA [16] (preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. Methods used to construct this analysis are elaborated to detail and provided in Appendix A.

Results

Search results

A total of 1520 records were identified from electronic databases. After duplicated were removed, 931 records were screened for eligibility, of which 893 were considered irrelevant. We obtained full texts for the 38 records and excluded 27 for reasons provided (Supplementary Table S1). This resulted in 11 randomized controlled trials being included in this review. The flowchart of study selection is shown in Fig. 1 according to updated PRISMA 2020 statement [17].

Included trials

We included 11 parallel design RCTs in this review, of which 5 were conducted in China [18–22], one in China and Korea [23], two in Italy [24, 25], one in the Netherlands [26], one in Korea [27], and one in Brazil [14]. Detailed information about the included studies is provided in Table 1. All included RCTs took place at the hospital setting and were reported between 2007 and 2018 while studies were conducted from 2005 to 2017. All studies were powered for at least 30-day follow-up.

Participants and clinical features

Overall, 11 RCTs enrolled a total of 6291 statin-naïve patients with ACS that were scheduled to undergo PCI, of which 3132 were randomized to high-dose statin loading before the procedure and 3159 comprised control group. Trials that examined rosuvastatin loading enrolled a total of 1300 patients of which 649 were randomized to high-dose rosuvastatin and 651 received no statin or placebo while trials involving atorvastatin loading enrolled a total of 4991 patients of which 2483 were randomized to high-dose atorvastatin while 2508 comprised control group. A total of 4743 (75.4%) patients received PCI while percutaneous coronary revascularization was planned in all enrolled patients. Among the remaining 1548 patients that did not receive PCI, the most common cause for not utilizing PCI was an indication for conservative medical treatment

or referral to coronary artery bypass graft (CABG) surgery. In 9 out of 11 studies, 100% of patients received PCI, while in one study, PCI receipt was 66% [25], and in another one, PCI receipt was 64.7% [14].

Across studies, mean age of enrolled patients ranged from 58 to 66.2 years, and a majority of those in the treatment group were men while similar distribution was present in the control group. Two trials enrolled only patients with STEMI, and eight trials enrolled only patients with NSTEMI-ACS while one trial included both patients with STEMI and NSTEMI-ACS (Table 2). Patients in both the treatment and control group were well-balanced in terms of distribution of comorbidities and global systolic function at baseline (Supplementary Table S2; Supplementary Figure S1). Likewise, the use of beta-blockers, ACE inhibitors and ARBs, and GPIIb/IIIa inhibitors during hospitalization was similar between two studied groups and across trials (Supplementary Table S3; Supplementary Figure S2).

Interventions

Patients were randomized to either receive high-dose atorvastatin or rosuvastatin. In all studies, statin was administered per os and before PCI. Atorvastatin was administered in at least 80-mg cumulative dose before PCI in all trials while rosuvastatin was administered in 40 mg cumulative dose before PCI in all trials except in a trial by Wang et al. [21] in which 20 mg rosuvastatin was administered at 2 to

4 h prior to PCI. Regarding the control group, patients in 6 trials [18, 20, 23–26] received no statin, and patients in 4 trials [14, 19, 21, 22] received placebo, while in one study [27], a low-dose statin (10 mg atorvastatin) was used as a control. Details of intervention vs. comparator across trials are shown in Table 1.

The timing of oral statin loading varied across trials—in most trials, loading dose was administered at 12 h before invasive management, whereas in some trials, this was commenced within few hours before the procedure. Furthermore, the concomitant standard of care antithrombotic treatment for ACS consisting of P₂Y₁₂ receptor antagonist (dominantly clopidogrel) and acetylsalicylic acid was administered to all patients before invasive management with the elective use of glycoprotein IIb/IIIa inhibitors (GPI) at the discretion of the operator. Maintenance antithrombotic and statin therapy were similar across trials and prescribed to all patients post-PCI (Supplementary Table S4).

Outcomes

The primary outcomes of this review were rates of MACCE, recurrent MI, and all-cause mortality at 30 days after ACS. MACCE at 30 days was explicitly stated or eligible for calculation in all included trials, as well as rates of recurrent MI and all-cause mortality, in a whole ACS population.

Fig. 1 Flow diagram of study selection

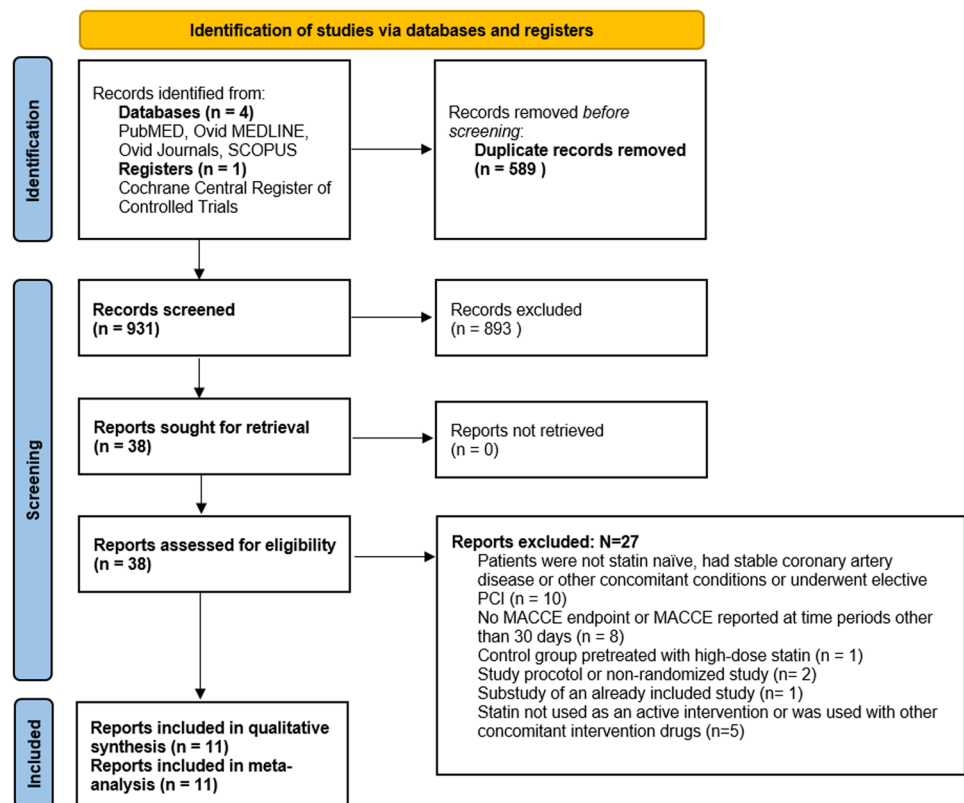


Table 1 Baseline characteristics of included studies encompassing PICOS components and other elements

Study	Patient population	Statin type	Intervention vs comparator	Primary outcome measured	Study design, single center or multicenter	ITT analysis/sample size calculation/COI declared	Funding	Country of origin
Patti et al. [24]	NSTE-ACS	Atorvastatin	80 mg at 12 h + 40 mg at 2 h per os before PCI vs. no statin	MACE at 30 days	RCT (DB) Multicenter	No/yes/no	No external funding received	Italy
Yun et al. [18]	NSTE-ACS	Rosuvastatin	40 mg per os before PCI vs. no statin treatment	MACE at 30 days	RCT (open label) single center	No/yes/no	Supported by grants from the Wonkwang University in 2008 and the Cardiovascular Research Foundation, Asia	China
Kim et al. [27]	STEMI	Atorvastatin	80 mg per os before PCI vs. 10 mg per os before PCI	MACE at 30 days	RCT (DB) multicenter	No/yes/no	Supported in part by a grant from the Korea Health 21 R&D Project, the Ministry of Health and Welfare and Republic of Korea (0412-CR02-0704–0001), and grants from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (No. A085012, A000385, and A085136), and Cardiovascular Research Center, Seoul	Korea
Yu et al. [19]	NSTE-ACS	Atorvastatin	80 mg per os at 12 h + 40 mg per os at 2 h before PCI vs. placebo	MACCE at 30 days	RCT (DB) Single center	No/no/no	No external funding received	China
Luo et al. [20]	NSTE-ACS	Rosuvastatin	20 mg per os 12 h before PCI + 20 mg per os at 2 h before PCI vs. no statin treatment	MACCE at 30 days	RCT (blinded to outcomes) Single center	No/no/no	Funding not stated in the manuscript	China

Table 1 (continued)

Study	Patient population	Statin type	Intervention vs comparator	Primary outcome measured	Study design, single center or multicenter	ITT analysis/sample size calculation/COI declared	Funding	Country of origin
Post et al. [26]	STEMI	Atorvastatin	80 mg per os before PCI vs. no statin treatment	End-systolic volume index	RCT (DB) Multicenter	No/yes/no	Departments of Research and Development of University Medical Centre Utrecht and St. Antonius Hospital Nieuwegein, The Netherlands. Grant sponsors: Berkalis Foundation, Pfizer Inc	Netherlands
Leoncini et al. [25]	NSTE-ACS	Rosuvastatin	40 mg per os on admission following by 20 mg/day per os vs. no statin treatment	Incidence of contrast-induced AKI	RCT (open label) Single center	No/yes/no	Study supported by the Centro Cardiopatici Toscani, Italy	Italy
Wang et al. [21]	NSTE-ACS	Rosuvastatin	20 mg per os at 2–4 h before PCI vs. placebo	MACCE at 30 days	RCT (DB) Single center	No/no/no	Qingdao Science and Technology Support Program [2012-1-3-1-(2)-nsh]	China
Jang et al. [23]	NSTE-ACS	Atorvastatin	80 mg per os at 12 h + 40 mg per os at 2 h before PCI vs. no statin	MACCE at 30 days	RCT (open label) Multi center	Yes/yes/yes*	Study was funded by Pfizer Inc	China and Korea
Xie et al. [22]	NSTE-ACS	Rosuvastatin	20 mg per os 12 h + 20 mg per os at 2 h before PCI vs. placebo	MACCE at 30 days	RCT (unclear blinding) Single center	No/yes/no	Study was supported by the Science and Technology Development Plan of Yulin (grant no. Yu Ke Ji 20,141,002)	China

Table 1 (continued)

Study	Patient population	Statin type	Intervention vs comparator	Primary outcome measured	Study design, single center or multicenter	ITT analysis/sample size calculation/COI declared	Funding	Country of origin
Berwanger et al. [14]	ACS	Atorvastatin	One loading 80 mg dose per os prior to PCI and second 80 mg dose at 24 h after first one vs. placebo	MACCE at 30 days	RCT (DB) Multicenter	Yes/yes/yes**	Funding/support: This study was funded by and conducted as part of the Program to Support Institutional Development of Universal System of the Brazilian Ministry of Health, Brazil Role of the funder/sponsor: the funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication	Brazil

AKI acute kidney injury, COI conflict of interest, DB double-blinded, ITT intention to treat, MACCE major adverse cardiovascular and cerebrovascular events, NSTEMI non-ST-elevation myocardial infarction, NSTEMI non-ST-elevation myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-elevation myocardial infarction

*Conflict of interest declared: Professor Kim has worked as study investigator for Novartis, Pfizer, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Sanofi-Aventis, and acted as a consultant for Pfizer and Merck Sharp & Dohme. Professor Zhu has been a study investigator for Novartis, Sanofi-Aventis, Eli Lilly, and GlaxoSmithKline. Dr Ji was a full-time employee of Pfizer Ltd. Dr Lam is a full-time employee

**Conflict of interest declared: Dr Berwanger reports receipt of grants and/or personal fees from AstraZeneca, Amgen, Bayer, Novo Nordisk, Boehringer Ingelheim, Roche Diagnostics, and Sanofi. Dr Alexander reports receipt of grants and/or personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, CryoLife, CSL Behring, Janssen Pharmaceuticals, Merck, the National Institutes of Health, the US Food and Drug Administration, Novo Nordisk Pharmaceuticals, Pfizer, Portola Pharmaceuticals, Tenax Therapeutics, the VA Cooperative Studies Program, VoluMetrix, Zaifgen, Sanofi, Cempira, and VasoPrep Surgical. Dr Granger reports receipt of grants and/or personal fees from Pfizer, Abbvie, Armetheon, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, the US Food and Drug Administration, Gilead Scientific, GlaxoSmithKline, Janssen, Medscape, Medtronic, Medtronic Foundation, Merck, the National Institutes of Health, Novartis Pharmaceuticals, Rho Pharmaceuticals, Sirtex, and Verseon. Dr Lopes reports receipt of grants and/or personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, and Portola

In a secondary analysis stratified by ACS type, MACCE at 30 days in the setting of NSTEMI-ACS was available for analysis in all trials except in the Post et al. [26] and Kim et al. [27] that both investigated high-dose atorvastatin loading. On the other hand, in the setting of STEMI, 30-day MACCE could be analyzed only in 3 studies [14, 26, 27] that investigated high-dose atorvastatin loading while no studies examining the use of high-dose rosuvastatin in STEMI were available.

Funding

A majority of trials were free of industry-sponsored grants or funds. Six trials [14, 18, 21, 22, 25–27] reported receiving full funding, or at least partial grants from the government, universities, or private foundations. Two trials [19, 24] reported no external funding received while one trial [20] did not declare funding within the manuscript. Two trials [23, 26] declared receiving funds from the pharmaceutical industry (Pfizer Inc.).

RoB in included trials

Results of the RoB assessment in the included trials along with judgments and the supporting explanations are shown in Supplementary Table S5. Included trials generally had a low risk of bias with respect to performance, detection, attrition, reporting, and other potential biases while, on the other hand, most trials had unclear risk with respect to selection bias (random sequence generation and allocation concealment). Supplementary Figure S3 presents the summary of the RoB for each included trial. The percentage of high, low, or unclear risk of bias judgments across included trials is presented in Supplementary Figure S4.

Publication bias assessment and funnel plot asymmetry analysis were performed separately for the endpoints of MACCE, MI, and all-cause mortality at 30 days that included all 11 trials. This analysis revealed funnel plot asymmetry (Supplementary Figure S5) that was significant for the endpoint of MACCE at 30 days (Egger's $Z = -3.23$, $p = 0.001$; Kendall's $\tau = -0.24$, $p = 0.359$) and MI at 30 days (Egger's $Z = -2.34$, $p = 0.020$; Kendall's $\tau = -0.31$, $p = 0.218$) thus indicating a possibility of publication bias. Analysis of all-cause mortality at 30 days did not reveal significant funnel plot asymmetry (Egger's $Z = -0.64$, $p = 0.521$; Kendall's $\tau = -0.16$, $p = 0.54$). Funnel plot asymmetry appeared to be largely driven by the absence of negative or neutral trials with respect to designated outcomes in trials that examined rosuvastatin loading (Supplementary Figure S6).

GRADE qualification of evidence

The quality of evidence for each primary and secondary outcome was qualified using GRADE. High, moderate, and low quality of evidence were determined for the primary outcomes of MI, MACCE, and all-cause death at 30 days, respectively. MACCE at 30 days endpoint was downgraded from high to moderate quality due to inconsistency—47% heterogeneity was detected and effects estimates from studies differed, especially concerning the study size. For the all-cause death endpoint, the level of certainty was downgraded to low quality due to imprecision—a very low number of events was observed; thus, the confidence intervals were large. Finally, findings that high-dose statin loading before PCI reduces the risk of MACCE at 30 days in NSTEMI-ACS and STEMI were based on the high and moderate quality of evidence, respectively. For the latter endpoint, the level of certainty was downgraded from high to moderate due to imprecision—only three studies were included in the analysis. The summary of findings based on GRADE qualification is provided in Table 3.

Effects of interventions

MACCE at 30 days

All studies contributed to effect estimates with an overall of 6291 patients. High-dose statin loading was associated with an overall 43% risk reduction of MACCE at 30 days (RR 0.57, 95% CI 0.44–0.71) in the whole ACS population (Fig. 2). This was predominantly driven by the effects of rosuvastatin (54% risk reduction) while atorvastatin reduced the risk of MACCE by 31%, although this was of borderline significance ($p = 0.08$). Low heterogeneity was detected while no differences between subgroups were observed ($p = 0.15$). Taken together, by combining the results of the meta-analysis and considering the level of certainty of the evidence, we found that high-dose statin loading before PCI reduces MACCE at 30 days.

Myocardial infarction at 30 days

All studies contributed to effect estimates with an overall of 6291 patients. High-dose statin loading before PCI was associated with an overall 39% risk reduction of MI at 30 days (RR 0.61, 95% CI 0.46–0.80) in the whole ACS population compared to the control group (Fig. 3). No significant heterogeneity across studies and no subgroup differences were detected ($p = 0.33$). Results of meta-analysis along with the certainty of evidence qualification together show that high-dose statin loading before PCI reduces the risk of MACCE at 30 days.

Table 2 Clinical characteristics of included studies indicating study size, period of enrollment, follow-up period, distribution of acute coronary syndrome subtypes, mean age, sex distribution, PCI receipt proportion, and number of patients evaluated vs. randomized to treatment

Study	Unstable angina N/total N (%)	NSTEMI N/total N (%)	STEMI N/total N (%)	PCI (% of total N)	Age years ± SD intervention/ control group	% of men intervention vs control group	Total N (Int/Cntrl)	N evaluated/N randomized %	FU	Trial period
Patti et al. [24]	110/171 (64.3%)	61/171 (35.7%)	0/171 (0.0%)	100%	64 ± 11/67 ± 10	79% vs. 79%	171 (86/85)	171/191 90%	30 days	Jan 2005–Dec 2006
Yun et al. [18]	330/445 (74.2%)	115/445 (25.8%)	0/445 (0.0%)	100%	64 ± 10/63 ± 11	60% vs. 62%	445 (225/220)	445/510 87%	30 days	Mar 2005–Dec 2007
Kim et al. [27]	0/171 (0%)	0/171 (0%)	171/171 (100%)	100%	61 ± 11/59 ± 11	77% vs. 78%	171 (86/85)	171/179 96%	30 days 9 months	Mar 2007–Dec 2008
Yu et al. [19]	54/81 (66.7%)	27/81 (33.3%)	0/81 (0%)	100%	63.3 ± 10.5/64.4 ± 11.6	61% vs. 58%	81 (41/40)	81/95 85%	30 days	Jun 2009–Mar 2010
Luo et al. [20]	67/67 (100%)*	0/67 (0%)	0/67 (0%)	100%	58 ± 12/61 ± 9	90% vs. 78%	67 (31/36)	67/78 86%	30 days	Jan 2011–Jan 2012
Post et al. [26]	0/42 (0%)	0/42 (0%)	42/42 (100%)	100%	63.3 ± 10.5/64.4 ± 11.6	61% vs. 58%	42 (20/22)	42/55 76%	1 week 30 days 3 months	Mar 2006–Nov 2007
Leontini et al. [25]	39/504 (7.7%)	465/504 (92.3%)	0/504 (0%)	66%	66.2 ± 12.4/66.1 ± 13.5	66% vs. 66%	504 (252/252)	504/543 93%	30 days 6 months	Aug 2010–Jul 2012
Wang et al. [21]	105/125 (84.0%)	20/125 (16.0%)	0/125 (0%)	100%	65.4 ± 10.2/64.8 ± 11.6	65% vs. 65%	125 (62/63)	125/167 75%	30 days	Mar 2011–Jun 2012
Jang et al. [23]	199/335 (59.4%)	136/335 (40.6%)	0/335 (0%)	100%	60 ± 10.0/61 ± 9.2	71% vs. 73%	335 (163/172)	335/449 75%	30 days	Sep 2008–Apr 2010
Xie et al. [22]	159/159 (100%)*	0/159 (0%)	0/159 (0%)	100%	61.5 ± 11.4/59.8 ± 10.5	75% vs. 70%	159 (79/80)	159/218 73%	24 h 30 days	Sep 2011–Jan 2014
Berwanger et al. [14]	591/4191 (14.1%)	2477/4191 (59.1%)	1012/4191 (24.1%)	64.7%	61.7 ± 11.3/61.9 ± 11.7	76% vs. 73%	4191 (2087/2104)	4191/4191 100%	30 days	Apr 2012–Oct 2017

Cntrl control group, FU follow-up, Int intervention group, NSTEMI non-ST-elevation myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-elevation myocardial infarction
*Authors did not discriminate patients with NSTEMI and unstable angina in the study

All-cause death at 30 days

All studies contributed to effect estimates with an overall of 6291 patients. Overall results obtained in the analysis suggested an 8% reduction of death at 30 days; however, due to imprecise results, no significant difference between high-dose statin loading and control group was found (RR 0.92, 95% CI 0.67–1.26; Fig. 4). No significant differences between subgroups were found ($p=0.34$), and no heterogeneity was detected across included studies. This result of meta-analysis along with qualification of certainty of evidence shows that high-dose statin loading before PCI does not reduce the risk of all-cause death at 30 days, compared to no statin loading.

MACCE at 30 days in NSTE-ACS

Nine studies contributed to the effect estimates with an overall of 4955 patients. High-dose statin loading before PCI was associated with a cumulative 45% risk reduction of MACCE

at 30 days in the NSTE-ACS (RR 0.55, 95% CI 0.38–0.80; Fig. 5A). This effect was significantly driven by rosuvastatin (52% risk reduction) while atorvastatin was associated with 35% risk reduction, although of borderline significance. No significant difference between subgroups treated with two different statins was detected in this population ($p=0.38$, $I^2=0\%$). There was a moderate heterogeneity (60%) present among studies in this setting, largely due to the study of Yu et al.; however, we excluded this study in the sensitivity analysis, and similar effect estimates were obtained. Such results combined with a high level of certainty of evidence show that high-dose statin loading, particularly that with rosuvastatin, reduces the risk of MACCE at 30 days in the NSTE-ACS population.

MACCE at 30 days in STEMI

Three studies of which all studied atorvastatin as intervention contributed to the effect estimates with an overall of

Table 3 Summary of findings showing quality of evidence with respect to studied outcomes, as assessed by the GRADE methodology

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statin loading	Control	Relative (95% CI)	Absolute (95% CI)		
MACCE at 30 days												
11	randomised trials	not serious	serious ^a	not serious	not serious	none	210/3132 (6.7%)	308/3159 (9.7%)	RR 0.57 (0.41 to 0.77)	42 fewer per 1,000 (from 58 fewer to 22 fewer)	⊕⊕⊕○ MODERATE	
All-cause death at 30 days												
11	randomised trials	not serious	not serious	not serious	very serious	none	72/3132 (2.3%)	81/3159 (2.6%)	RR 0.92 (0.67 to 1.26)	2 fewer per 1,000 (from 8 fewer to 7 more)	⊕⊕○○ LOW	
MI at 30 days												
11	randomised trials	not serious	not serious	not serious	not serious	none	132/3132 (4.2%)	210/3159 (6.6%)	RR 0.61 (0.46 to 0.80)	26 fewer per 1,000 (from 36 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	
MACCE at 30 days in STEMI												
3	randomised trials	not serious	not serious	not serious	serious ^b	none	49/601 (8.2%)	76/624 (12.2%)	RR 0.67 (0.48 to 0.94)	40 fewer per 1,000 (from 63 fewer to 7 fewer)	⊕⊕⊕○ MODERATE	
MACCE at 30 days in NSTE-ACS												
9	randomised trials	not serious	not serious	not serious	not serious	none	158/2475 (6.3%)	226/2480 (9.1%)	RR 0.55 (0.38 to 0.80)	41 fewer per 1,000 (from 56 fewer to 18 fewer)	⊕⊕⊕⊕ HIGH	

ACS acute coronary syndrome, CI confidence interval, MACCE major adverse cardiovascular and cerebrovascular events, NSTE-ACS non-ST-elevation ACS, RR risk ratio, STEMI ST-elevation myocardial Infarction

^a47% heterogeneity, effects estimates from studies differing, especially in relation to the study size

^bLow number of events, only three studies included

MACCE at 30 days in ACS

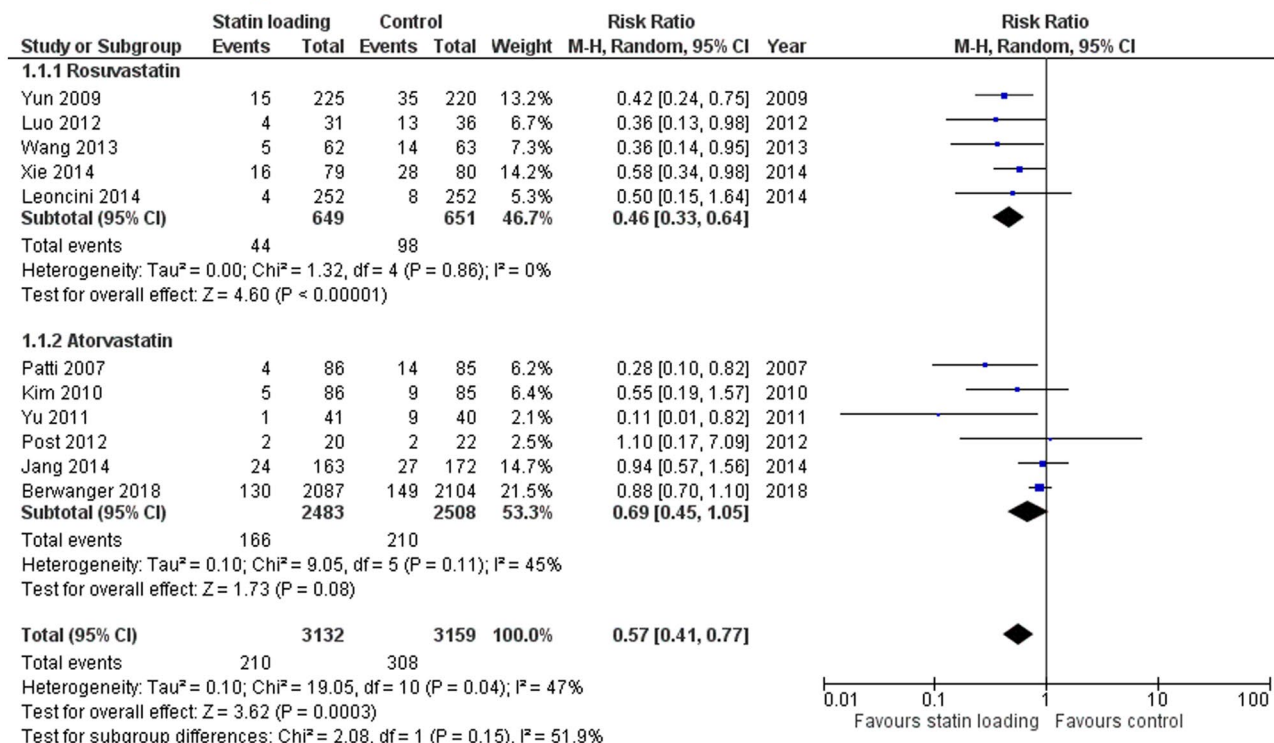


Fig. 2 Cumulative risk ratio (RR) of high-dose statin loading vs. control before PCI for major adverse cardiovascular events (MACCE) at 30 days

1255 patients. No studies for rosuvastatin were eligible for the analysis. No significant heterogeneity across studies was detected. Taken together with qualification of certainty of the evidence, a result of this meta-analysis shows that high-dose atorvastatin loading before PCI reduces MACCE at 30 days in the STEMI population, and this was attributed to 33% relative risk reduction (RR 0.67, 95% CI 0.48–0.94; Fig. 5B).

Exploratory PCI analysis

The analysis of PCI-only cohorts included a total of 4306 patients of which 2144 received statin loading while 2162 received no statin loading before PCI. We observed that, among patients with ACS, of which all received PCI, statin loading was associated with a 44% relative risk reduction of MACCE at 30 days (RR 0.56, 95% CI 0.43–0.74) (Fig. 6). This effect was consistent and significant for both rosuvastatin (RR 0.46, 95% CI 0.33–0.65) and atorvastatin (RR 0.65, 95% CI 0.44–0.97). Finally, a low degree of overall heterogeneity ($I^2 = 33%$) across studies was detected, and there was no significant difference observed between trials concerning statin type used ($p = 0.20$).

Discussion

Data obtained from 6291 patients from 11 RCTs that were included in this meta-analysis showed that high-dose statin loading before PCI reduces the risk of MACCE and reduces the risk of MI at 30 days in the whole ACS population. High-dose loading of either statin does not reduce the risk of all-cause death at 30 days. These findings are based on evidence of moderate certainty concerning MACCE, high certainty with respect to MI, and low certainty concerning all-cause death. In the context of STEMI, high-dose atorvastatin loading before PCI reduces the risk of MACCE at 30 days, and this is backed by evidence of moderate certainty while no studies with rosuvastatin were available in this setting. In patients with NSTEMI-ACS, evidence of high certainty shows that high-dose rosuvastatin loading before PCI reduced the risk of MACCE at 30 days while atorvastatin had a borderline impact on this endpoint. These findings suggest that high-dose atorvastatin loading before PCI likely confers benefits in STEMI while high-dose rosuvastatin loading reduces adverse events in NSTEMI-ACS patients. These effects seem to be primarily driven by the significant reduction of recurrent MIs during the vulnerable 30-day period which translates to an

Myocardial infarction at 30 days in ACS

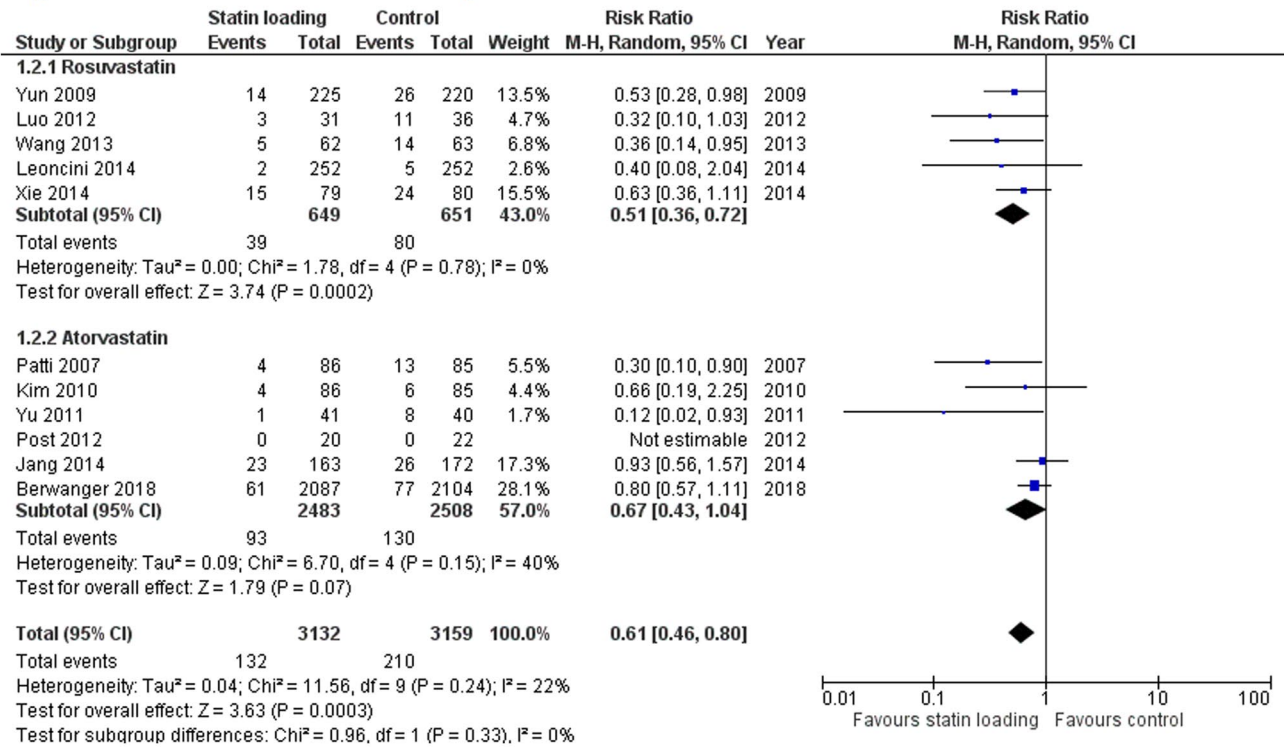


Fig. 3 Cumulative risk ratio (RR) of high-dose statin loading vs. control before PCI for myocardial infarction at 30 days

overall reduction of MACCE, however, without impact on mortality. Of note, trials studying atorvastatin loading had larger patient enrollment compared to those studying rosuvastatin loading thus inferring its use in ACS potentially more valid. Finally, our exploratory analysis focused on patients with ACS, of whom all received PCI, confirmed our main findings since both atorvastatin and rosuvastatin loading consistently reduced MACCE at 30 days in this cohort of patients.

Our findings were derived from RCTs that included patients with ACS that we typically see in real-world clinical practice. Of note, we only included trials that enrolled patients naive to statin treatment and with the unstable disease. Equally important, three-quarters of all included patients underwent PCI while those that did not were in most instances referred to CABG surgery or conservative treatment. However, our exploratory analysis of PCI-only patients was in line with the main findings and showed that both statins reduced MACCE at 30 days.

We also focused our analyses on trials using the two most commonly used high-potency statins in clinical practice, atorvastatin, and rosuvastatin. Previous meta-analyses [28–30] were heterogeneous concerning such clinical parameters—some studies mixed stable and unstable CAD patients or included both statin-naive and chronic statin users. Furthermore, actual receipt of PCI

widely differed in a substantial number of included trials or analyses were focused on one particular or multiple statin types. Thus, the quality of evidence in this setting was never critically evaluated before. Therefore, findings obtained from previous systematic reviews might not entirely apply to real-world ACS patients.

Cardioprotective effects of early high-dose statin loading in ACS patients with planned percutaneous revascularization are not fully elucidated, but it is suggested that statins exert pleiotropic effects that are beneficial to the cardiovascular system and are beyond the dominant lipid-lowering mechanism [31]. The seminal CANTOS trial validated the inflammatory hypothesis of atherothrombosis since monoclonal antibody blocking inflammatory interleukin-1β pathway managed to reduce rates of recurrent cardiovascular events, compared to placebo, among patients that had a history of MI and increased systemic inflammation as evidenced by high-sensitivity C-reactive protein (CRP) levels ≥ 2 mg/L [32]. Drugs interfering with inflammatory and immune pathways such as colchicine, methotrexate as well as drugs antagonizing IL-6 receptors, were tested for the prevention of adverse cardiovascular events with mixed success in clinical trials [33]. Since statins act anti-inflammatory and reduce CRP levels independent of low-density lipoprotein cholesterol (LDL-C) reduction [34], it is plausible that synergistic

All-cause mortality at 30 days in ACS

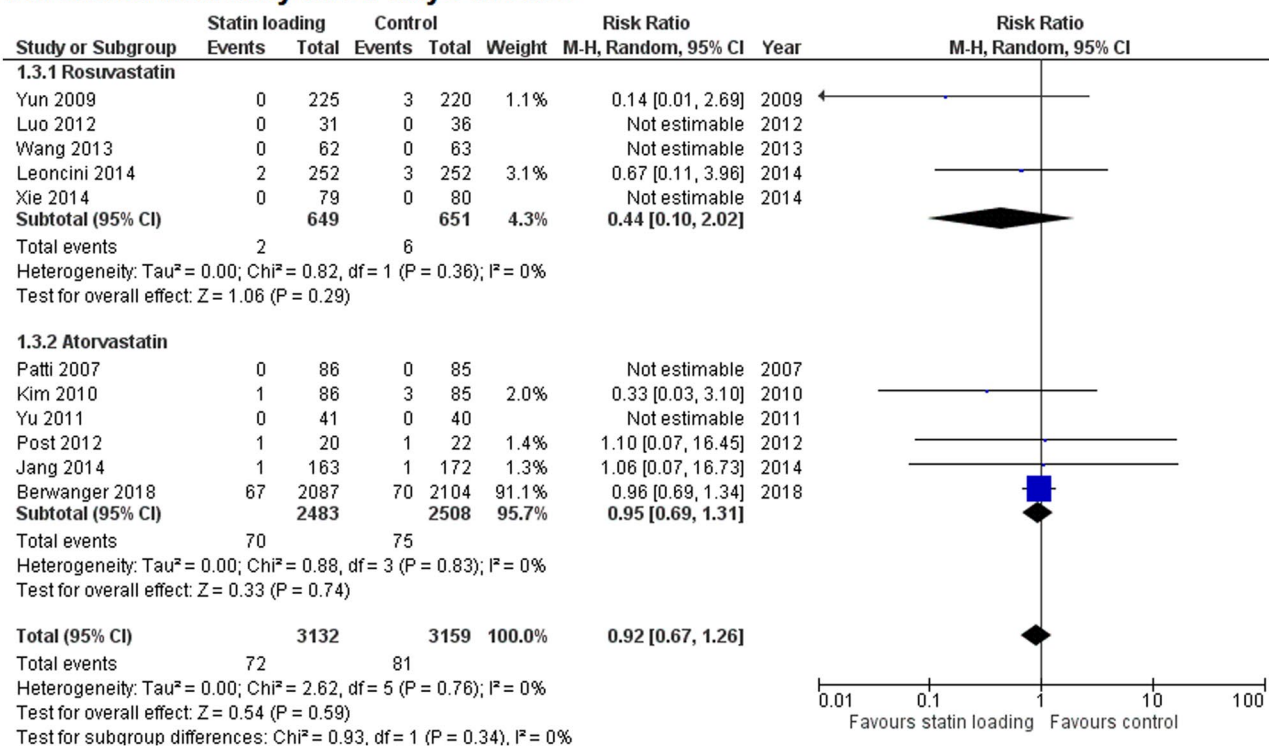


Fig. 4 Cumulative risk ratio (RR) of high-dose statin loading vs. control before PCI for all-cause death at 30 days

anti-inflammatory and lipid-lowering mechanisms of statins administered in high dose during the early phase of ACS may yield beneficial cardiovascular effects, although such mechanisms are yet to be fully explained.

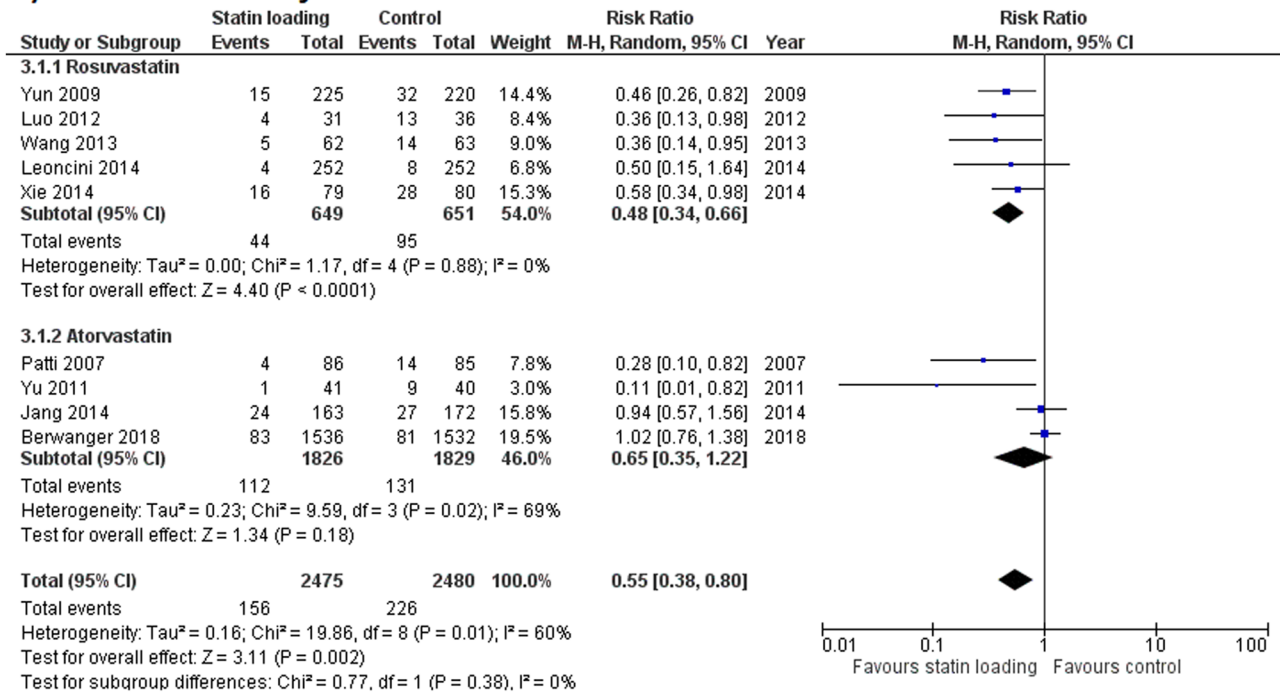
Earlier clinical studies showed that intensive statin use can reduce MACCE in patients with ACS undergoing PCI [35] and prevent procedural myocardial injury in elective PCI among patients with stable CAD [36]. However, questions such as how early to initiate these agents and in which dose during the acute presentation of the coronary event have been less clear [37]. The signal of benefit was more clearly revealed when Patti and colleagues published a collaborative patient-level meta-analysis showing that preprocedural use of statins led to a significant reduction of periprocedural MIs and adverse events at 30 days in a heterogeneous patient cohort receiving PCI [11]. More recent meta-analyses suggested the benefits of atorvastatin [28] and rosuvastatin [29] loading on periprocedural myocardial injury and MACCE among ACS patients undergoing PCI.

Current European and American guidelines for the management and diagnosis of STEMI [2, 4] and NSTEMI-ACS [1, 3] recommend the initiation of statins as early as possible; however, no specific remarks to high-dose loading before PCI and exact timing of statin initiation are made. To answer these questions, the largest-to-date, double-blind,

placebo-controlled, multicenter RCT (SECURE-PCI) that evaluated the use of 80 mg of atorvastatin before and 24 h after coronary angiography among patients with ACS was neutral with respect to the primary outcome of MACCE at 30 days. However, when the data were analyzed concerning those patients that in the end received PCI, it was shown that high-dose atorvastatin loading was associated with a significant 34% reduction in 30-day MACCE (HR 0.66, 95% CI 0.48–0.98), and this effect was sustained in STEMI, but not NSTEMI-ACS patients [15] which is in line with our findings. Similarly, the observed greater impact of rosuvastatin on MACCE reduction in NSTEMI-ACS compared to atorvastatin could be explained by the more robust reduction in systemic and microvascular inflammation by rosuvastatin compared to atorvastatin among patients with ACS [38], and this might translate to improved clinical outcomes. Of note, elevated hs-CRP levels were shown to be a prognostic indicator of new MACE and cardiovascular and all-cause mortality in patients with ACS [39]. However, the mechanistic pathways explaining the potential advantage of rosuvastatin in NSTEMI-ACS have not been fully elucidated yet.

This meta-analysis has some limitations. No protocol was published before this analysis and we only included RCTs in the English language without searching grey literature. While trials were overall at low risk of bias, the majority of studies

A) MACCE at 30 days in NSTE-ACS



B) MACCE at 30 days in STEMI

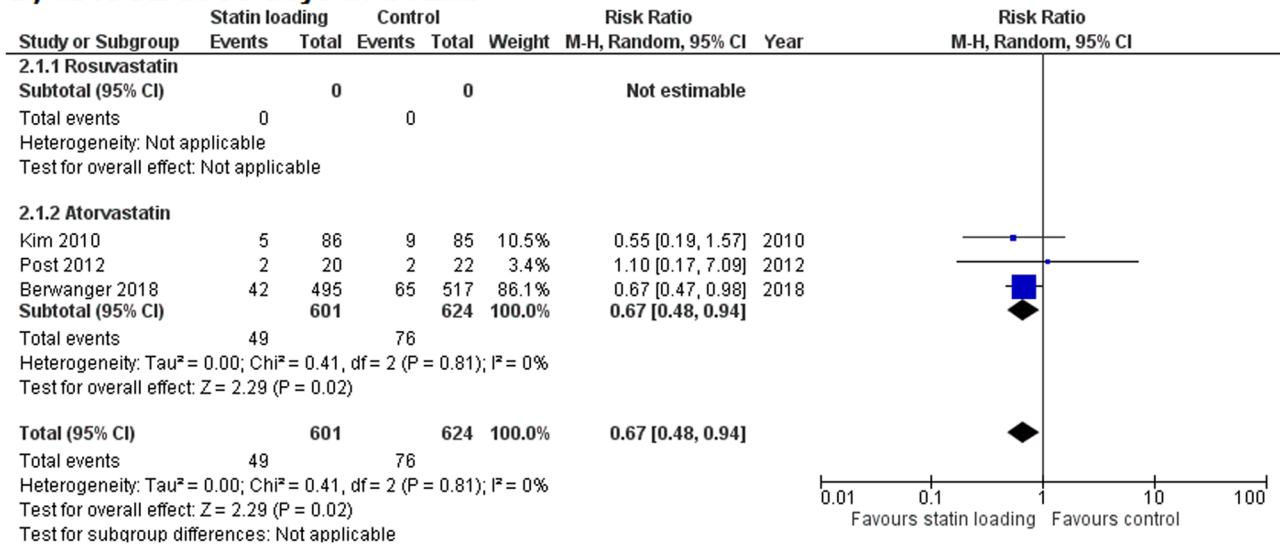
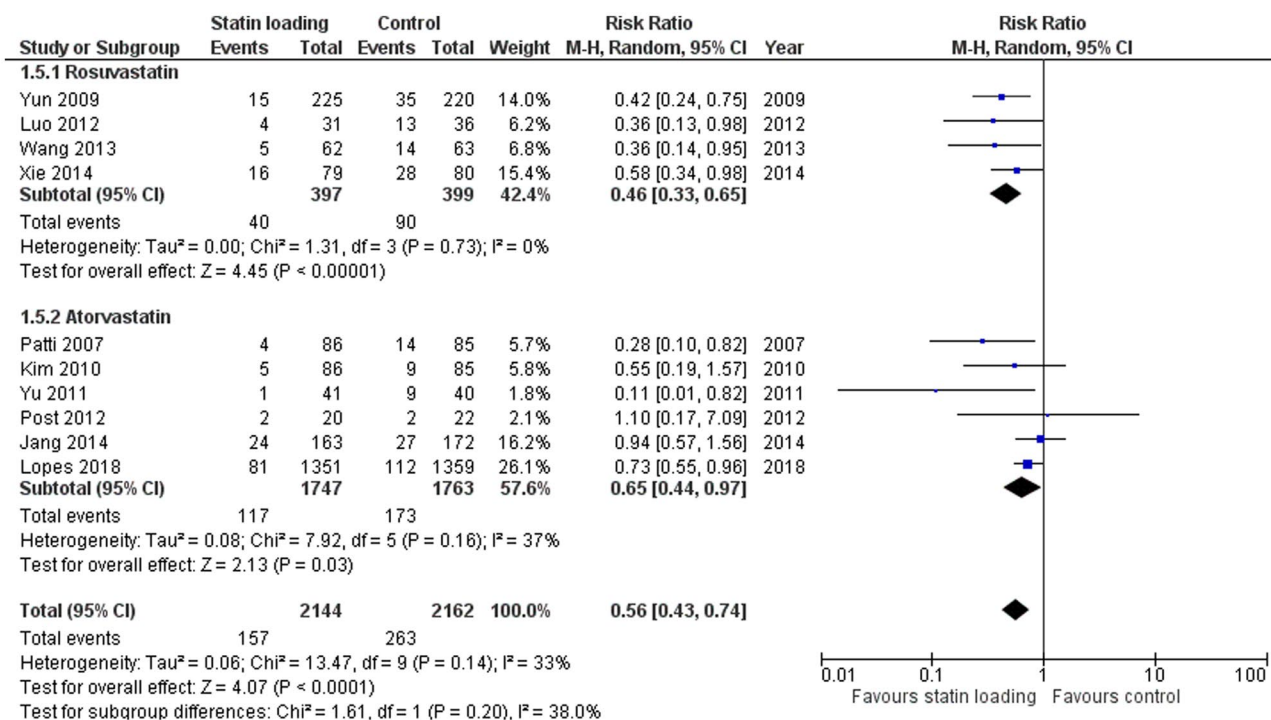


Fig. 5 Risk ratios (RR) of rosuvastatin or atorvastatin high-dose loading vs. control before PCI for MACCE at 30 days in **(A)** patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) and **(B)** patients with ST-elevation myocardial infarction (STEMI)

were of unclear risk concerning selection bias. Similarly, due to the subjective nature of the risk of bias assessment and lack of some information provided by the authors of the studies, uncertainty regarding some evaluations may exist. Moreover, most of the studies had discrepancies concerning a number of analyzed cases vs. those that were randomized to treatment; however, this is in line with the clinical practice since it is expected that not all of the patients randomized

to PCI will receive PCI since they might have other indications. Also, it should be acknowledged that most of the evidence of the benefit of statin loading comes from smaller trials whereas the largest trial included (SECURE-PCI) was neutral concerning the benefit of statin loading in ACS. Due to the predominant weight of this trial and the great number of events compared to other trials, it is likely that it significantly impacted on overall results, although our sensitivity



MACCE at 30 days - PCI only cohort

Fig. 6 Exploratory analysis of statin loading in population of patients with ACS that received PCI (100% receipt of PCI) with respect to the primary outcome of MACCE at 30 days

analyses in which this trial was removed confirmed our initial findings. Similarly, the body of evidence in terms of patient size was more robust for NSTEMI-ACS than STEMI population, and this might have an effect on obtained results. For some endpoints, we encountered moderate heterogeneity and discrepancies between effects of larger vs. small studies; however, to account for this, we used a random-effects statistical model that provides more conservative and generalizable results as opposed to a fixed model. Publication bias might also be present due to the detected funnel plot asymmetry, and this observation was mostly driven by trials examining rosuvastatin loading since there appears to be a lack of studies reporting neutral or negative effects with respect to rosuvastatin loading on outcomes of interest. Finally, we should account for a potential geographical bias since most of the included studies were conducted in East Asia.

Conclusions

The results of this meta-analysis, based on moderate and high certainty of the evidence, suggest that early high-dose loading of atorvastatin and rosuvastatin before planned PCI was in association with a significant reduction of MACCE

and recurrent MI, in particular, during the short-term period, among statin-naïve patients with ACS. This effect seemed to be pronounced among STEMI patients loaded with high-dose atorvastatin and NSTEMI-ACS patients loaded with high-dose rosuvastatin before planned PCI. However, the results from this meta-analysis should be interpreted with caution due to the potential presence of publication bias and limitations such as small studies contributing to most of the observed effects and the largest trial demonstrating an overall neutral effect of statin loading on clinical outcomes, although more granular analyses of this trial suggested a benefit of early atorvastatin loading in patients receiving PCI and particularly if they had STEMI.

Taken together, these findings suggest a personalized, rather than “one size fits all” approach regarding the early high-potency statin loading in ACS. Therefore, to identify which specific ACS populations would benefit the most from early statin loading strategy, future RCTs should enroll a large number of patients receiving high-dose rosuvastatin and atorvastatin loading in NSTEMI-ACS, as well as high-dose rosuvastatin loading in the context of STEMI for which the largest evidence gap currently exists.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00228-021-03196-9>.

Acknowledgements The authors would wish to express gratitude to an independent methodology consultant Tina Poklepovic Pericic (T.P.P.), DMD, PhD, from Cochrane Croatia, for participating in risk of bias assessment performed for this study and help with manuscript preparation.

Author contribution J.A.B. conceived the study and wrote the first original draft of the manuscript in its entirety. J.A.B., M.L.O., and M.K. performed research, data collection, and manuscript preparation. All authors (J.A.B., M.L.O., M.K., D.D., K.S., D.G., and J.B.) commented on the original draft and contributed to the writing of manuscript. All authors participated in the manuscript revision process. All authors read and approved the final version of the manuscript.

Availability of data and material The data that supports the findings of this study are available in the article and the supplementary material of this article.

Code availability Not applicable.

Declarations

Ethical approval This article does not contain any studies with humans or animal subjects performed by any of the authors.

Conflict of interest The authors declare no competing interests.

References

- Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL et al (2021) 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 42(14):1289–1367
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 39(2):119–177
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr et al (2014) 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64(24):e139–e228
- O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA et al (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61(4):485–510
- Angeli F, Reboldi G, Mazzotta G, Garofoli M, Cerasa MF, Verdecchia P (2012) Statins in acute coronary syndrome: very early initiation and benefits. *Ther Adv Cardiovasc Dis* 6(4):163–174
- Hwang DS, Shin ES, Kim SJ, Lee JH, Kim JM, Lee SG (2013) Early differential changes in coronary plaque composition according to plaque stability following statin initiation in acute coronary syndrome: classification and analysis by intravascular ultrasound-virtual histology. *Yonsei Med J* 54(2):336–344
- Banach M, Serban C, Sahebkar A, Mikhailidis DP, Ursoniu S, Ray KK et al (2015) Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies. *BMC Med* 13(1):229
- Taguchi I, Oda K, Yoneda S, Kageyama M, Kanaya T, Toyoda S et al (2013) Evaluation of serial changes in tissue characteristics during statin-induced plaque regression using virtual histology-intravascular ultrasound studies. *Am J Cardiol* 111(9):1246–1252
- Moscardó A, Vallés J, Latorre A, Madrid I, Santos MT (2013) Reduction of platelet cytosolic phospholipase A2 activity by atorvastatin and simvastatin: biochemical regulatory mechanisms. *Thromb Res* 131(4):e154–e159
- Takata K, Imaizumi S, Zhang B, Miura S, Saku K (2016) Stabilization of high-risk plaques. *Cardiovasc Diagn Ther* 6(4):304–321
- Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C et al (2011) Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation* 123(15):1622–1632
- Zhai C, Cong H, Liu Y, Zhang Y, Liu X, Zhang H et al (2015) Effect of high-dose statin pretreatment on the incidence of periprocedural myocardial infarction in patients undergoing percutaneous coronary intervention: grading the evidence through a cumulative meta-analysis. *Clin Cardiol* 38(11):668–678
- Navarese EP, Kowalewski M, Andreotti F, van Wely M, Camaro C, Kolodziejczak M et al (2014) Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Am J Cardiol* 113(10):1753–1764
- Berwanger O, Santucci EV, de Barros ESPGM, Jesuino IA, Damiani LP, Barbosa LM et al (2018) Effect of loading dose of atorvastatin prior to planned percutaneous coronary intervention on major adverse cardiovascular events in acute coronary syndrome: the SECURE-PCI randomized clinical trial. *JAMA* 319(13):1331–1340
- Lopes RD, de Barros ESPGM, de Andrade JI, Santucci EV, Barbosa LM, Damiani LP et al (2018) Timing of loading dose of atorvastatin in patients undergoing percutaneous coronary intervention for acute coronary syndromes: insights from the SECURE-PCI randomized clinical trial. *JAMA Cardiol* 3(11):1113–1118
- Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7):e1000097
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71
- Yun KH, Jeong MH, Oh SK, Rhee SJ, Park EM, Lee EM et al (2009) The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome. *Int J Cardiol* 137(3):246–251
- Yu XL, Zhang HJ, Ren SD, Geng J, Wu TT, Chen WQ et al (2011) Effects of loading dose of atorvastatin before percutaneous coronary intervention on periprocedural myocardial injury. *Coron Artery Dis* 22(1):87–91
- Luo J, Li J, Shen X, Hu X, Fang Z, Lv X et al (2013) The effects and mechanisms of high loading dose rosuvastatin therapy before percutaneous coronary intervention in patients with acute coronary syndrome. *Int J Cardiol* 167(5):2350–2353
- Wang Z, Dai H, Xing M, Yu Z, Lin X, Wang S et al (2013) Effect of a single high loading dose of rosuvastatin on percutaneous coronary intervention for acute coronary syndromes. *J Cardiovasc Pharmacol Ther* 18(4):327–333
- Xie W, Li P, Wang Z, Chen J, Lin Z, Liang X et al (2014) Rosuvastatin may reduce the incidence of cardiovascular events in patients with acute coronary syndromes receiving percutaneous coronary intervention by suppressing miR-155/SHIP-1 signaling pathway. *Cardiovasc Ther* 32(6):276–282

23. Jang Y, Zhu J, Ge J, Kim YJ, Ji C, Lam W (2014) Preloading with atorvastatin before percutaneous coronary intervention in statin-naïve Asian patients with non-ST elevation acute coronary syndromes: a randomized study. *J Cardiol* 63(5):335–343
24. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G et al (2007) Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* 49(12):1272–1278
25. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F (2014) Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: results from the PRATO-ACS Study (protective effect of rosuvastatin and antiplatelet therapy on contrast-induced acute kidney injury and myocardial damage in patients with acute coronary syndrome). *J Am Coll Cardiol* 63(1):71–79
26. Post S, Post MC, van den Branden BJ, Eefting FD, Goumans MJ, Stella PR et al (2012) Early statin treatment prior to primary PCI for acute myocardial infarction: REPERATOR, a randomized placebo-controlled pilot trial. *Catheter Cardiovasc Interv* 80(5):756–765
27. Kim JS, Kim J, Choi D, Lee CJ, Lee SH, Ko YG et al (2010) Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. *JACC Cardiovasc Interv* 3(3):332–339
28. Ma M, Bu L, Shi L, Guo R, Yang B, Cao H et al (2019) Effect of loading dose of atorvastatin therapy prior to percutaneous coronary intervention in patients with acute coronary syndrome: a meta-analysis of six randomized controlled trials. *Drug Des Devel Ther* 13:1233–1240
29. Pan Y, Tan Y, Li B (2015) Li X (2015) Efficacy of high-dose rosuvastatin preloading in patients undergoing percutaneous coronary intervention: a meta-analysis of fourteen randomized controlled trials. *Lipids Health Dis* 14:97
30. Benjo AM, El-Hayek GE, Messerli F, DiNicolantonio JJ, Hong MK, Aziz EF et al (2015) High dose statin loading prior to percutaneous coronary intervention decreases cardiovascular events: a meta-analysis of randomized controlled trials. *Catheter Cardiovasc Interv* 85(1):53–60
31. Oesterle A, Laufs U, Liao JK (2017) Pleiotropic effects of statins on the cardiovascular system. *Circ Res* 120(1):229–243
32. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C et al (2017) Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 377(12):1119–1131
33. Ma J, Chen X (2021) Anti-inflammatory therapy for coronary atherosclerotic heart disease: unanswered questions behind existing successes. *Front Cardiovasc Med* 7:631398
34. Albert MA, Danielson E, Rifai N, Ridker PM (2001) Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 286(1):64–70
35. Gibson CM, Pride YB, Hochberg CP, Sloan S, Sabatine MS, Cannon CP (2009) Effect of intensive statin therapy on clinical outcomes among patients undergoing percutaneous coronary intervention for acute coronary syndrome. PCI-PROVE IT: A PROVE IT-TIMI 22 (pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22) substudy. *J Am Coll Cardiol* 54(24):2290–5
36. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G (2004) Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (atorvastatin for reduction of myocardial damage during angioplasty) study. *Circulation* 110(6):674–678
37. Mega S, Patti G, Cannon CP, Di Sciascio G (2010) Preprocedural statin therapy to prevent myocardial damage in percutaneous coronary intervention: a review of randomized trials. *Crit Pathw Cardiol* 9(1):19–22
38. Kumar B, Shah MAA, Kumar R, Kumar J, Memon A (2019) Comparison of atorvastatin and rosuvastatin in reduction of inflammatory biomarkers in patients with acute coronary syndrome. *Cureus* 11(6):e4898
39. Mani P, Puri R, Schwartz GG, Nissen SE, Shao M, Kastelein JJP et al (2019) Association of initial and serial C-reactive protein levels with adverse cardiovascular events and death after acute coronary syndrome: a secondary analysis of the VISTA-16 Trial. *JAMA Cardiol* 4(4):314–320

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.