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META-ANALYSIS

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Effect of High-Dose Statin Pretreatment for Myocardial Perfusion in Patients Receiving Percutaneous Coronary Intervention (PCI): A Meta-Analysis of 15 Randomized Studies

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: For coronary artery disease, percutaneous coronary intervention (PCI) is the preferred treatment. Reperfusion injury is a common and serious complication of PCI. Studies showed that early statin therapy has a favorable prognostic impact for patients undergoing PCI. However, the effects of statins on improving post-PCI myocardial perfusion are still unclear. In this study we evaluated the potential effect of high-dose statin pretreatment on postprocedure myocardial perfusion and MACE rate in patients receiving PCI.

Material/Methods: We searched randomized controlled trials that evaluated the effect of high-dose statin pretreatment on post-PCI TIMI flow grade and MACE in patients undergoing PCI from the databases of PubMed, Embase, and Cochrane Library. All data were pooled for analysis and were stratified by type of statin, clinical presentation, and current statin therapy status in subgroup.

Results: Fifteen RCTs with 4240 individuals were selected. The pooled analysis showed that high-dose statin pretreatment before PCI significantly improved the final TIMI flow grade compared with the control group (OR=0.61, 95% CI: 0.46 to 0.80, p=0.0005), and showed reduced incidence of MACE (OR=0.53, 95%CI: 0.39 to 0.71, p<0.0001). In subgroup analysis, the beneficial effect of high-dose statin was significant in statin-naive treatment patients, ACS patients, and patients on atorvastatin therapy, but no difference occurred in rosuvastatin, previous statin therapy, and stable angina patients.

Conclusions: High-dose statin pretreatment has an important effect on postprocedure myocardial perfusion by improving the TIMI flow in patients undergoing PCI, and high-dose statin preloading also reduces the incidence of MACE.

MeSH Keywords: Cardiology • Myocardial Perfusion Imaging • Nephrology

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Background

Coronary artery disease is the most common heart disease and is a leading cause of mortality worldwide. Percutaneous coronary intervention (PCI) is regarded as the most important reperfusion treatment for coronary artery disease, which rescues myocardial tissues through restoring epicardial blood flow. However, reperfusion injury after reopening the epicardial coronary artery worsens the clinical outcome after PCI [1,2]. Therefore, numerous therapies have been explored to avoid myocardial reperfusion injury and improve the prognosis.

Statins, which are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme, can reduce the risk of all major vascular events. Studies showed that obestatin had a beneficial role in cardiomyocyte injury induced by ischemia-reperfusion [3]. A combination of low-dose atorvastatin and losartan improved aortic ring relaxation and diminished ischemic-reperfusion injury in isolated rat hearts [4]. Simvastatin also reduced infarct size in a model of acute myocardial ischemia and reperfusion in rats [5]. Early initiation of statin therapy in acute coronary syndrome patients has a favorable prognostic impact for patients undergoing PCI because of the antithrombotic and antioxidant function, inhibiting inflammation, improving vascular endothelial function, and stabilizing atherosclerotic plaque [6,7]. However, the effects of statins on improving post-PCI myocardial perfusion and decreasing the incidence of no-flow phenomenon are still disputed due to inconsistent results [8–10]. To clarify this issue, we performed a meta-analysis to assess the effect of high-dose statin therapy preloading before PCI on post-PCI TIMI flow grade and MACE in patients who received PCI.

Material and Methods

Search strategy

Two of the present authors independently searched studies from the electronic databases PubMed, Embase, and Cochrane Library up to January 2018. Three search themes were used for searching: statins, percutaneous coronary intervention, and myocardial perfusion. The search terms for "statins" were: hydroxymethylglutaryl-CoA, statin, atorvastatin, rosuvastatin, pravastatin, simvastatin, lovastatin and fluvastatin. For "percutaneous coronary intervention", we used percutaneous coronary intervention, angioplasty, revascularization, stent, and PCI. For "myocardial perfusion" the key words were: TIMI flow, TIMI frame count, TIMI myocardial perfusion grades, myocardial blush grades, index of microcirculatory resistance, coronary blood flow, and no-flow. The 3 themes were combined with the Boolean operator "AND". All randomized controlled trails were selected that compared the post-PCI blood flow and clinical outcome of different dosages of statins. Previous related meta-analyses and all references of selected articles were also screened. No language or journal type was limited.

Records through other sources

Randomized controlled trials (RCTs) were selected. Patients with ACS (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina pectoris) or stable angina undergoing PCI were enrolled in our study. Patients with CABG, previous myocardial infarction, PCI history during the recent 6 months, statin intolerance, serious adverse effects, and with severe organ failure were excluded. The interventions included high-dose statins and non-statin or low-dose statins treatment before PCI.

Data extraction

Two analysts collected the title and abstract of all selected studies and extracted the following data from the eligible studies: authors, organization, journal, study design, country, patient characteristics, clinical condition (STEMI, NSTEMI, and unstable angina or stable angina pectoris), details of intervention (type of statin, dose, and time of duration), and clinical outcomes (TIMI flow grade and MACE) independently. Thrombolysis in myocardial infarction (TIMI) flow grade was defined as the blood flow in the epicardial vessels. TIMI grade 0/1 as no flow, grade 2 as slow flow, and grade 3 as normal flow [11]. Major adverse cardiac events (MACE) were death, myocardial infarction (MI), target vessel revascularization (TVR), or left ventricular dysfunction any disagreements were resolved through discussion with the third professional analyst.

Quality assessment

We evaluated the quality of these studies and assessed the bias risk of enrolled trials according to Cochrane Collaboration's Tool, including random sequence generation, allocation concealment, blinding methods (blinded to participant and outcome assessment), incomplete outcome data, selective reporting, and other bias. The quality assessment was completed by 2 analysts independently.

Data analysis

Primary analysis

Dichotomous variables of measurement were used to evaluate the effects of pretreatment of statin for patients undergoing primary PCI. The pooled odds ratio (OR) with 95% confidence interval (CI) was presented for the dichotomous outcomes (the incidence of post-PCI TIMI flow 3 and MACE). The test of heterogeneity among all studies was performed using the I2 statistic,

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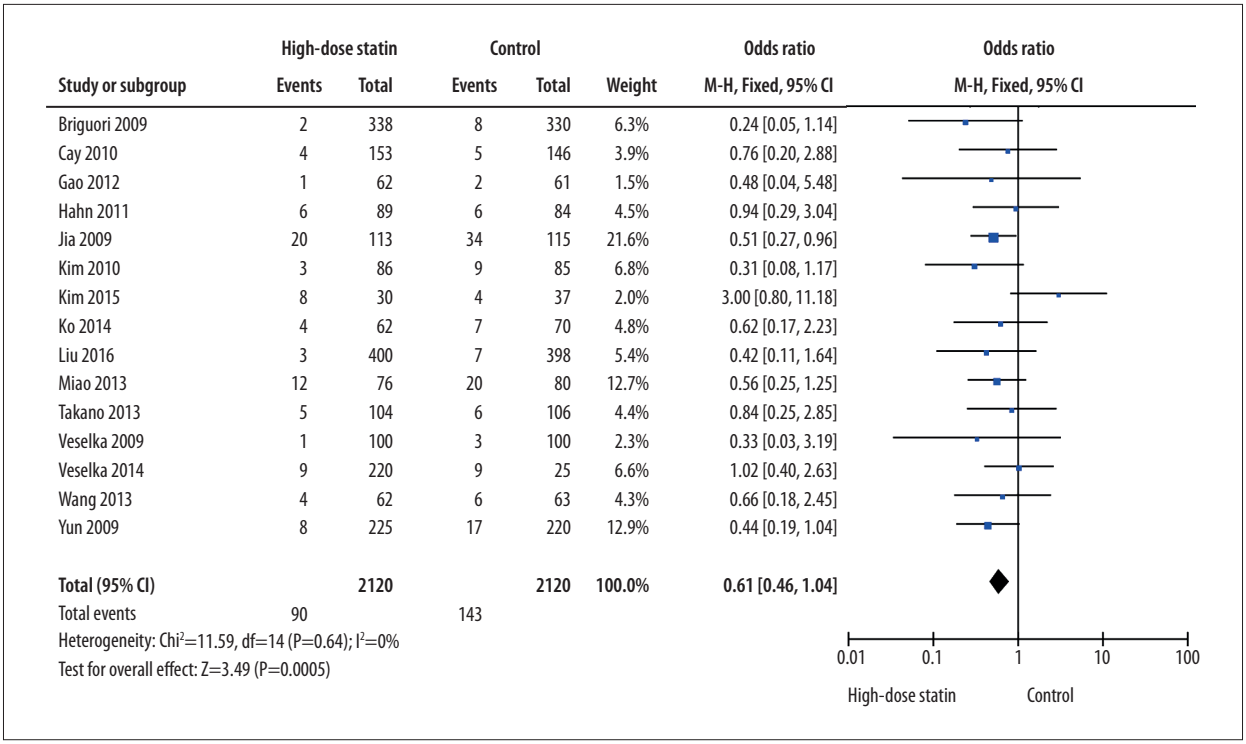

Figure 1. Study selection flow.

which defined as significant statistical heterogeneity as I2 >50%. The fixed-effects model was chosen if I2 was >50%, otherwise, a random-effects model was used. Publication bias was evaluated by visual funnel plots and Egger's regression test. P<0.05 was considered as statistically significant. Sensitivity analysis was used to investigate a single study's impact on our analysis and to assess the stability of our study model. RevMan 5.1 software (*http://www/cochrane.org*) was employed for statistical analysis. The Egger's regression test and sensitivity analysis were performed using Stata12.0 software.

Subgroup analysis

Subgroup analysis was determined by the type of statin, clinical presentation, statin therapy, and current status.

Sensitivity analysis

Sensitivity analysis was used to discover the remarkable single trail influencing the result in our analysis and enhance the reliability.

Results

Study selection

Our search strategy found 239 articles, but 118 articles were removed due to duplication. The randomized controlled studies were chosen and we also reviewed the full text of the remaining 46 articles and assessed them for eligibility. Finally, 15 RCTs [8,12–25] were selected for analyses. Figure 1 shows the process flow of selecting potentially eligible articles and the reasons for article exclusion.

Study characteristics and quality assessment

Study characteristics

The study characteristics, including clinical condition and drug assignment of the 15 eligible articles, are presented in Table 1. The selected studies were published between 2009 and 2016 and 4240 patients were included. The patients in each study were randomly allocated to 2 groups, 2120 of which were assigned to the high-dose statin group and the remaining patients were assigned to the control group receiving standard-dose or no statin pretreatment. Males accounted for 70% of all the enrolled patients, 64% of patients had hypertension, and about 30% of patients had diabetes. Nine studies [8,12,13,16–18,20,22,25] included patients with ACS and 5 studies [14,19,21,23,24] included patients with stable angina. Three types of statins (atorvastatin [8,12,15,16,21,24,25], rosuvastatin [13,14,18–20,22,23] or simvastatin [17]) were used, and the duration of pretreatment ranged from 1.5 hours to 7 days. In 11 studies, the patients had no history of statin use [8,12–16,18,21,22,24,25]. Patients took statins in 3 studies [19–21]. All patients received aspirin and clopidogrel

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Table 1. Characteristics of included studies.

Author	Year	Clinical condition	Type of statin	Statin regimen before PCI	Statin regimen after PCI	Control	Follow- up	Outcome
JIA	2009	ACS	Simvastatin	80 mg at least 7 d	20 mg	20 mg at least 7d	NA	TIMI
Miao	2013	STEMI	Atorvastatin	80 mg at a mean of 1.5 h	NA	Placebo	NA	TIMI
Hahn	2011	STEMI	Atorvastatin	80 mg in the ER	80 mg for 5 days + 10 mg after	No statin	6 months	TIMI/MACE
KIM	2010	STEMI	Atorvastatin	80 mg in the ER	10 mg	10 mg/day	1 month	TIMI/MACE
Veselka	2014	Stable angina	Rosuvastatin	20 mg 12 h	NA	No statin	NA	TIMI
Ko	2014	STEMI	Rosuvastatin	40 mg in ER	40 mg for 7 d + 10 mg for 3 w	10 mg	NA	TIMI
Kim	2015	STEMI	Atorvastatin	80 mg in ER	80 mg for 5d + 10 mg after	No statin	6 months	TIMI/MACE
Briguori	2009	CAD	Atorvastatin	80 mg within 24 h	20 mg	No statin	NA	TIMI
Yun	2009	NSTE-ACS	Rosuvastatin	40 mg 16±5 h (range 7–25 h)	20 mg	No statin	1 month	TIMI/MACE
Takano	2013	Stable angina	Rosuvastatin	20 mg from 5 to 7 days before	20mg	2.5mg	<1 year	TIMI/MACE
Wang	2013	NSTE-ACS	Rosuvastatin	20 mg 2–4 h	10 mg	Placebo	NA	TIMI/MACE
Cay	2010	Stable angina	Rosuvastatin	40 mg 24 h	NA	No statin	NA	TIMI
Veselka	2009	Stable angina	Atorvastatin	80 mg 2 d	NA	No statin	NA	TIMI
Liu	2016	CAD	Atorvastatin	80 mg 12 h	40 mg up to 1 year and 20 mg thereafter	No statin	1 year	TIMI/MACE
Gao	2012	NSTE-ACS	Rosuvastatin	20 mg 12 h before angioplasty procedure, 10 mg 2 h before procedure	10 mg	No statin	3 months and 6 months	TIMI/MACE

therapy before the procedure. Some patients also received glycoprotein IIb/IIIa inhibitors according to surgeon's judgment.

Quality assessment

The details of quality assessment are depicted in Figure 2. Eight of 15 studies [8,12,15,20–23,25] described the specific methods of the random selection, while other studies were not clear about that. Four studies [8,15,21,25] had low risk of bias of allocation concealment, while the remaining studies did not mention this. Two studies [8,17] used the blinded approach both for participants and outcome assessment, 4 studies [12,13,16,20] only used blinding for outcome assessment, while 5 studies [18,19,22–24] had high risk of bias of double-blinding. All the enrolled studies had low risk of bias of incomplete outcome data and selective reporting, none of which had reported other bias in detail.

Data for the post-PCI TIMI flow grade were presented in all included studies. Data for the incidence of MACEs during a period of time from 1 month to 1 year were presented in 7 studies [8,12,13,15,16,22,23]. Approximately two-thirds [8,12,15,22,23] of those had low risk of bias of random sequence generation and blinding of outcome assessment. Only one-third of those [8,15] provided detail about allocation concealment. However, 2 studies [22,23] had high risk of

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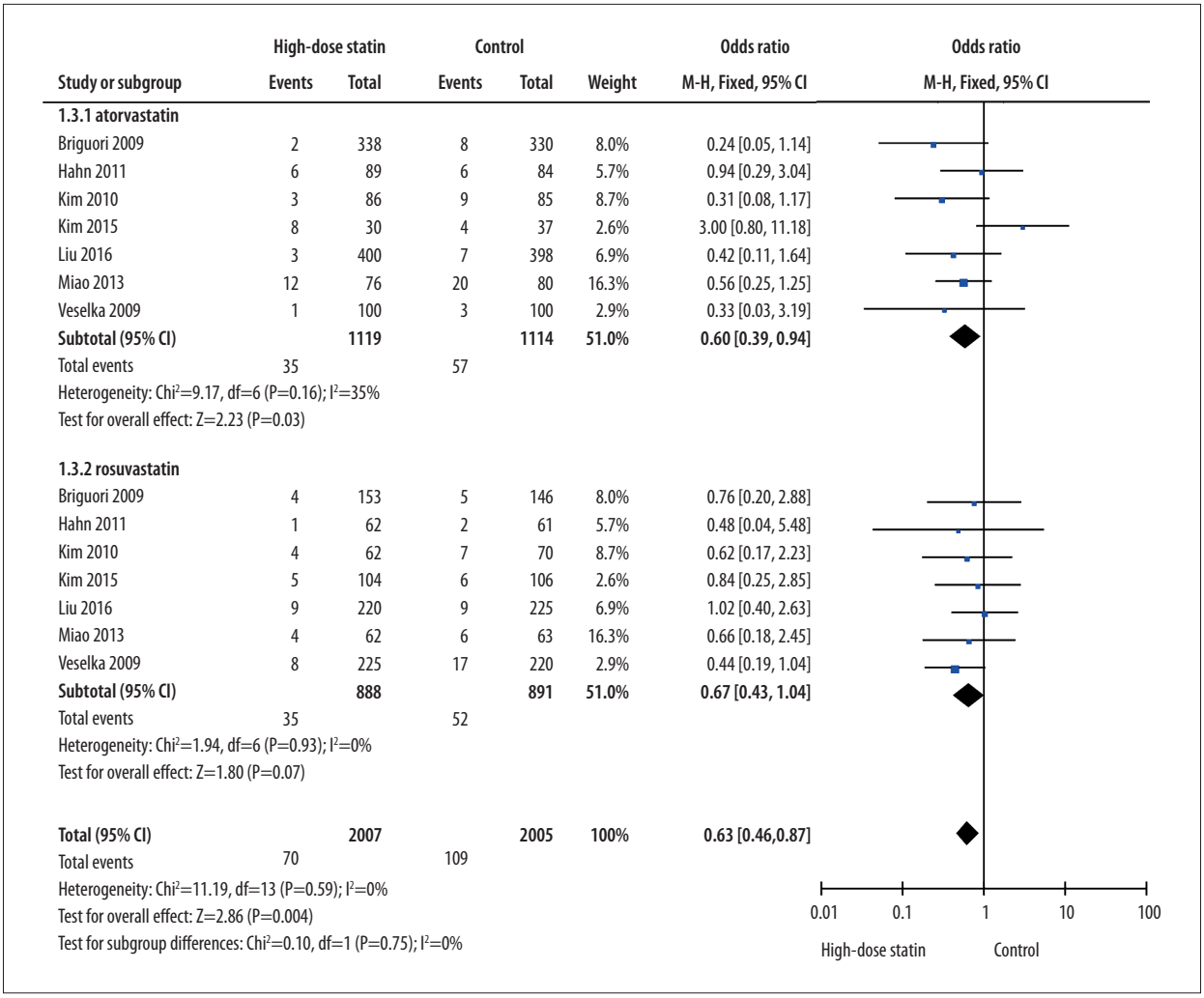

Figure 2. Quality assessment, risk of bias graph and risk of bias summary.

bias of double-blinding. Attrition bias and reporting bias were low risk in 7 studies.

Primary outcomes

TIMI flow grade

The available data of patients with TIMI flow grade <3 after undergoing PCI were analyzed. The analysis showed no significant heterogeneity between the 2 groups (I2=0%, p=0.64). Therefore, the fixed-effects model was chosen for further analysis. The overall event rate was 4.2% (90 of 2120) in the statin group and 6.7% (143 of 2120) in the control group, suggesting that high-dose statin pretreatment before PCI significantly improved the final TIMI flow grade compared with the control group (OR=0.61, 95% CI: 0.46 to 0.80, p=0.0005) (Figure 3). The funnel plot analysis did not show obvious asymmetry, indicating there was publication bias and this was consistent with the results of Egger's test (P=0.589) (Figure 4).

MACE

The available data of MACE, including death, myocardial infarction, target vessel revascularization, or left ventricular dysfunction, were analyzed with the fixed-effects model, which were based on the low heterogeneity (I2=0%, P=0.65). The incidence was 7.9% (79 of 994) in statin group and 14% (140 of 992) in control group, demonstrating that high-dose statin therapy preloading before PCI had a favorable trend toward the following outcome and reduced the incidence of MACE (OR=0.53, 95% CI: 0.39 to 0.71, p<0.0001) (Figure 5).

Subgroup analysis

Subgroup analysis according to prior statin therapy

In order to determine whether chronic statin or no statin treatment prior to high-dose statin therapy before PCI affects post-PCI myocardial perfusion, patients were grouped based

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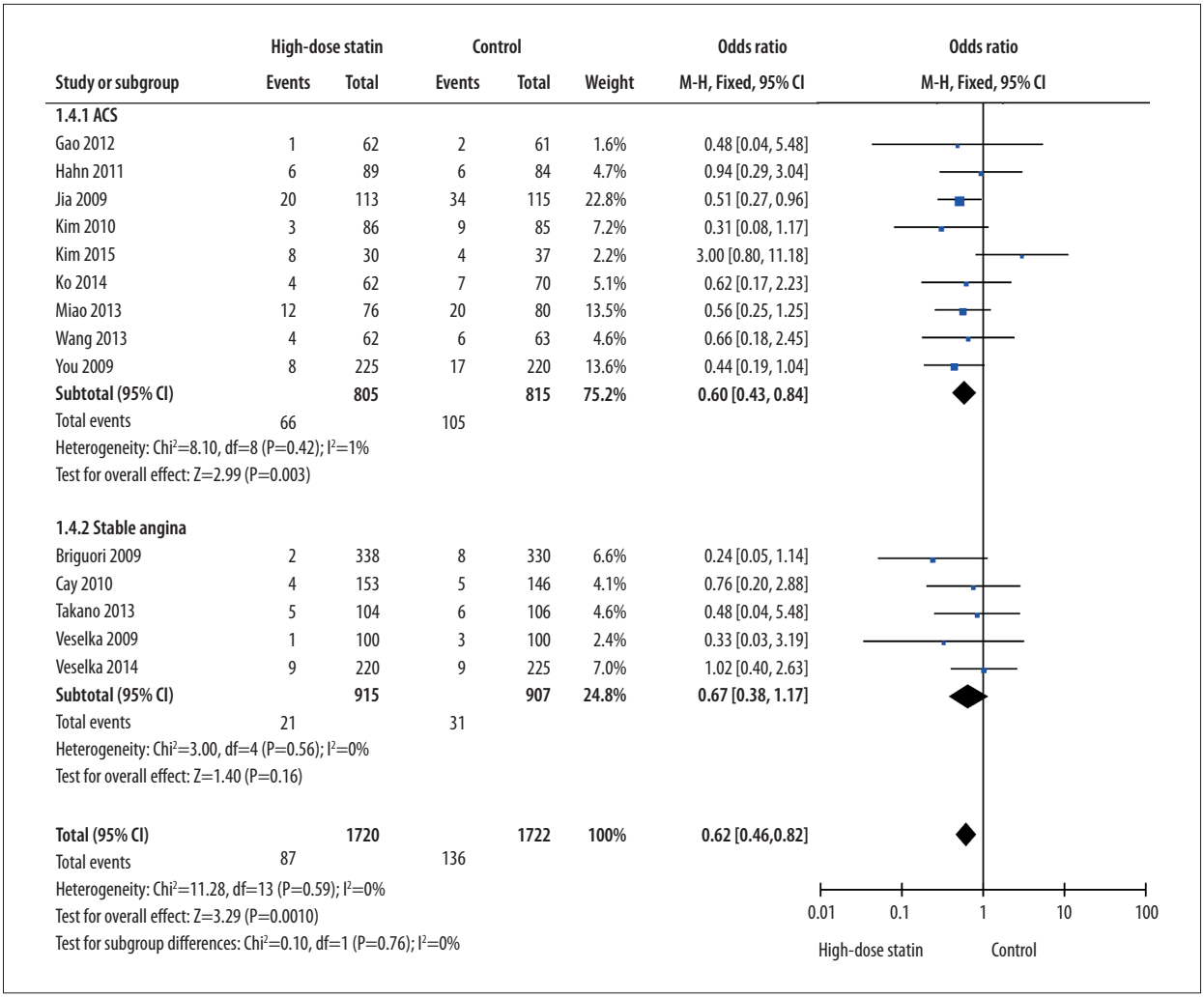

Figure 3. Forest plots for TIMI flow grade.

on their history of statin treatment before PCI. The subgroup analysis [8,12–16,18–25] showed no significant heterogeneity for all studies (I2=0%, P=0.59). Therefore, we also used the fixed-effects model. For the previous statin therapy subgroup, the overall event rate was 4.6% (18 of 386) in the statin group and 5.5% (22 of 401) in the control group. There was no difference in final TIMI flow grade between the statin group and control group (OR=0.85, 95% CI: 0.45 to 1.62, p=0.62, I2=0%), suggesting that high-dose statin pretreatment had no beneficial effect on post-PCI myocardial perfusion. For the statin-naive subgroup, the rate was 3.2% (52 of 1621) in the statin group and 5.4% (87 of 1604) in the control group. The final TIMI flow grade was improved in the statin group compared with the control group (OR 0.58, 95% CI: 0.40 to 0.83, p=0.003, I2=0%), revealing that high-dose statin therapy prior to PCI was significantly superior to low-dose or no statin therapy in statin-naive patients (Figure 6).

Subgroup analysis according to the type of statin therapy

Atorvastatin and rosuvastatin were the main types of statin in this analysis. There was no significant heterogeneity for the atorvastatin subgroup (I2=35%, P=0.16) and rosuvastatin subgroup (I2=0%, P=0.93). We also used the fixed-effects model for the subgroup analysis. The atorvastatin subgroup analysis showed that high-dose atorvastatin before PCI had significant effect on the post-PCI TIMI flow grade (OR 0.6, 95% CI: 0.39 to 0.94, p=0.03, I2=35%), but there was no significant effect in the rosuvastatin subgroup analysis (OR 0.64, 95% CI: 0.43 to 1.04, p=0.07, I2=0%). Furthermore, the total effect for these statins revealed a significant impact on the flow grade (OR 0.63, 95% CI: 0.46 to 0.87, p=0.004, I2=0%) (Figure 7).

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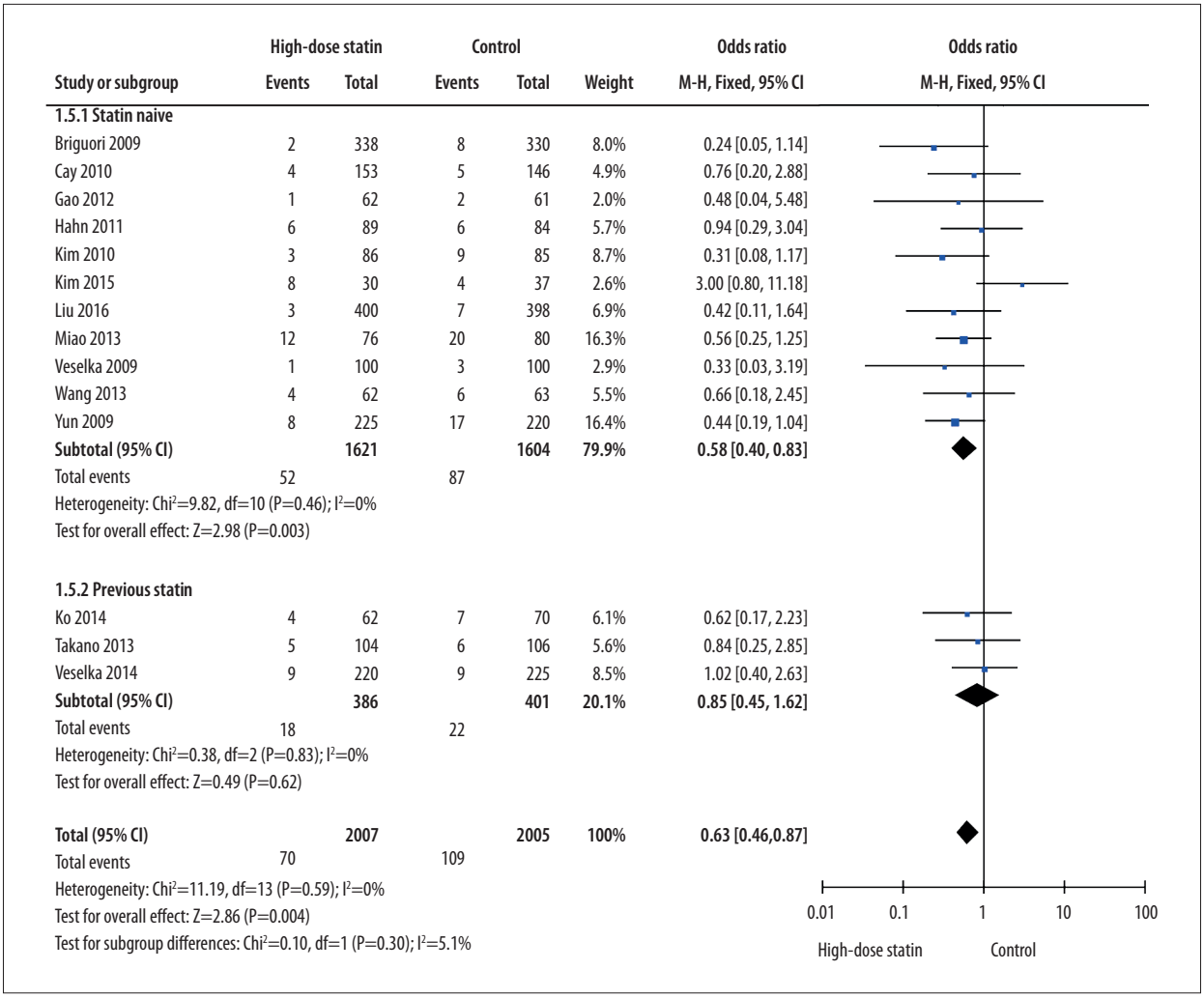

Figure 4. Funnel plots for TIMI flow grade to eliminate the publication bias.

Subgroup analysis according to the difference clinical presentation

In the ACS and stable angina subgroup, fixed-effects model was also chosen due to lack of significant heterogeneity (I2=1%, P=0.42 and I2=0%, P=0.56). The results showed that high-dose statin preloading improved the post-PCI TIMI flow, particularly in patients with ACS (OR 0.60, 95% CI: 0.43 to 0.84, p=0.003, I2=1%), but there was no significant effect in patients with stable angina (OR 0.67, 95% CI: 0.38 to 1.17, p=0.16, I =0%) (Figure 8).

Sensitivity analysis

The sensitivity analysis for TIMI flow grade in all studies showed that no single trail affected the pooled results, which shows our analysis was reliable (Figure 9).

Discussion

In this study, we selected 15 randomized controlled trials with 4240 individuals and performed one meta-analysis. We found that that high-dose statin preloading therapy before PCI improved postprocedure myocardial perfusion and greatly reduced the incidence of MACE in patients undergoing PCI.

Although PCI is the preferred therapy and reduces the incidence of reperfusion injury, including myocardial necrosis, myocardial stunning, and reperfusion arrhythmias, microvascular dysfunction results in the failure of recovering postprocedural levels of myocardial perfusion [26]. Studies showed that statins exert many protective effects, known as pleiotropic effects, beyond the lipid-lowering properties, such as improving endothelial function, decreasing oxidative stress and biomarkers of inflammation, inhibiting prothrombotic mechanisms, adjusting the molecular signal, and stabilizing atherosclerotic plaque [6]. These effects are expected to become an efficient treatment

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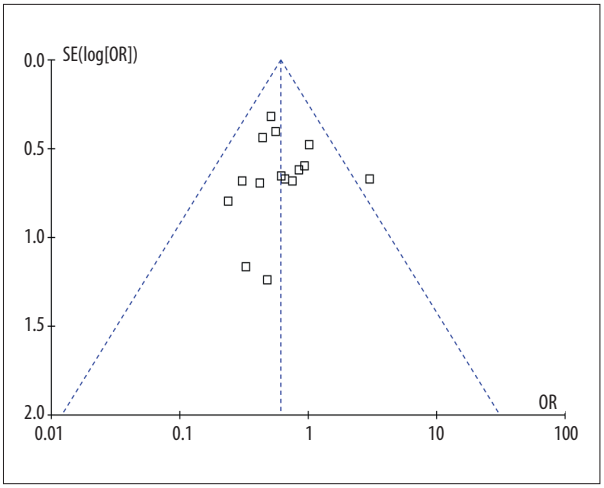

Figure 5. Forest plots for the incidence of MACE.

to improve postprocedural coronary blood flow and attenuate the MACE rate. Statin therapy improves clinical outcome and effectively prevents cardiac events [27,28]. Current guidelines unequivocally recommend statin therapy in secondary prevention for ACS and PCI, and demonstrate that high-dose statin should be started before PCI unless there is a history of tolerance and contraindication [29]. However, the effect of high-dose statin pretreatment before PCI for myocardial perfusion and MACE were not specified in these guidelines.

Celik et al. reported that prior statin therapy improved post-PCI coronary blood flow [30]. Fuernau et al. did not find a positive effect of statin pretreatment on myocardial perfusion or reduced incidence of MACE [31]. Ting Lyu et al. demonstrated that statin pretreatment in STEMI patients undergoing PCI improved epicardial coronary blood flow [32]. Pan et al. reported that high-dose RSV preloading can significantly improve myocardial perfusion and reduce both MACE and PMI in patients undergoing PCI [33]. However, the supporting evidence for this is still controversial. In our study, we included more RCTs and patients with different statins to analyze the effect of statins on myocardial perfusion and clinical outcome. We found that high-dose statin preloading therapy significantly improved TIMI flow, especially in ACS patients. Studies showed that the reduction of periprocedural myocardial injury in patients receiving high-dose statins preloading mostly resulted from the anti-inflammation effect, which is more obvious in ACS patients [25,34]. A meta-analysis also confirmed that patients with high levels of inflammation had a more protective effect of statin pretreatment before PCI [7]. Therefore, high-dose statin appears to be sensitive in patients with ACS other than patients with stable angina.

In view of the history of statin therapy, high-dose statin pretreatment significantly improves TIMI flow grade in statin-naive patients, but this effect was not as obvious in patients who previously received statins. Similar to the study by Yilong Pan, high-dose statin treatment in statin-naive patients protected against spontaneous MI and TVR, while no effects were found in patients with previous statin treatment [35]. However, another study showed that high-dose statin pretreatment had similar positive effects on PMI in statin-naive patients and in patients previously treated with statins, and confirmed that high-dose statins use in patients with long-term statin therapy improved the clinical outcome [36]. At present, there are limited trails to compare the long-term and statin-naive patients with high-dose statin reloading before PCI. In our analysis, there was no effect in previous statin treatment, which was possibly related to the limited number of patients. Further studies are needed to explore the mechanism underlying the action of short-term high-dose statin therapy.

For different statins, there was no difference in postprocedural TIMI flow in high-dose rosuvastatin; however, atorvastatin preloading had significant benefits. Chitose et al. demonstrated

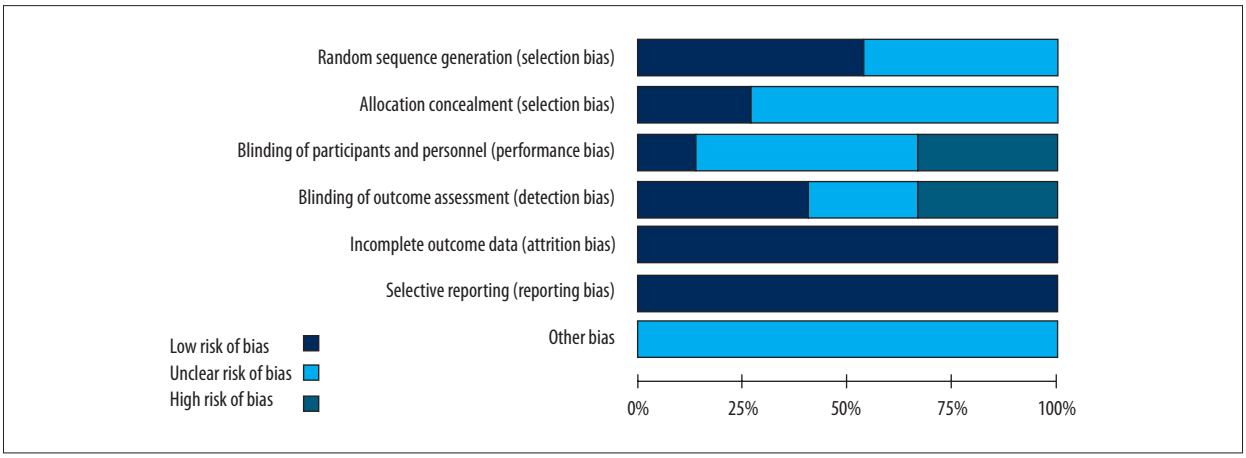

Figure 6. Forest plots for TIMI flow grade for the statin-naive and previous statin patients.

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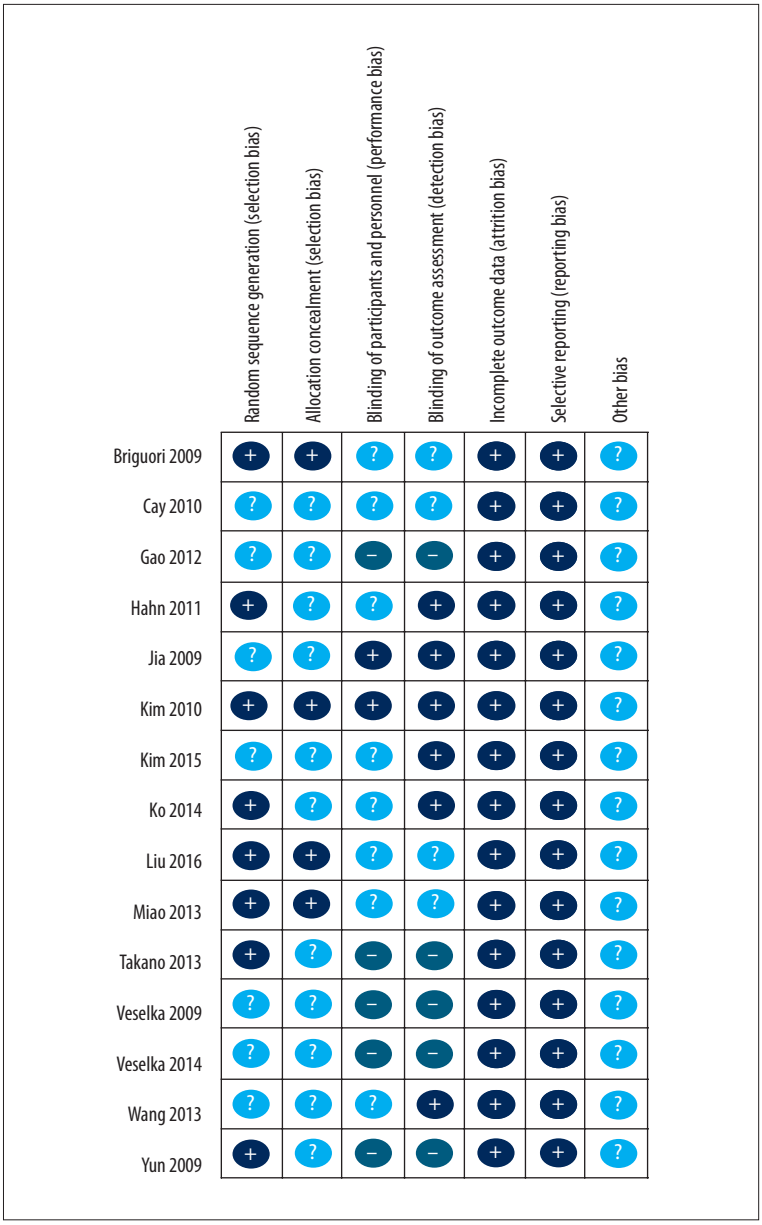

Figure 7. Forest plots for TIMI flow grade for the different types of statins.

that only rosuvastatin reduced BNP levels and improved LVEF and myocardial salvage compared with atorvastatin therapy in STEMI patients [37]. However, the ROMA-II trial showed no difference between 80 mg atorvastatin and 40 mg rosuvastatin in terms of the incidence of MACE and cerebrovascular events [38]. Our data revealed that high-dose statin therapy resulted in a 48% reduction in incidence of MACE from 1 month to 1 year after PCI. Although high-dose statin pretreatment had a lower rate of MACE compared with moderate-dose statins (8.8% *vs.* 14.1%, P=0.018), it did not make a difference in the rate of MACE in patients with stable angina [39]. Similarly, in the PROVE-IT TIMI 22 study, early high-dose statin pretreatment reduced the composite outcome, including cardiovascular death, myocardial infarction, ischemic stroke, or rehospitalization in patients with unstable angina (HR: 0.73; 95% CI: 0.61 to 0.87; P=0.001) [40].

The evidence on optimal time at which to administer high-dose statin pretreatment in patients undergoing PCI was inconclusive. In the present study, the initiation of statin treatment was within 1.5 h before PCI in STEMI patients, 2 h to 25 h in NSTEMI patients, and 12 h to 7 days in stable angina patients. As mentioned above, high-dose statins were sensitive in ACS patients, which was possibly related to the short preloading time. A previous study showed a meta-regression analysis for statin time-dependent benefits and revealed a significant linear correlation between early initiation of statins and better clinical outcome [40]. It is logical that patients experience small

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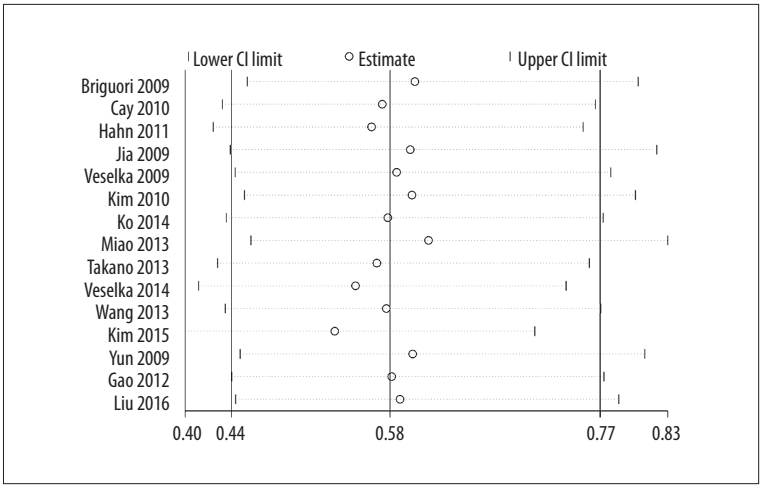

Figure 8. Forest plots for TIMI flow grade for the different clinical presentations.

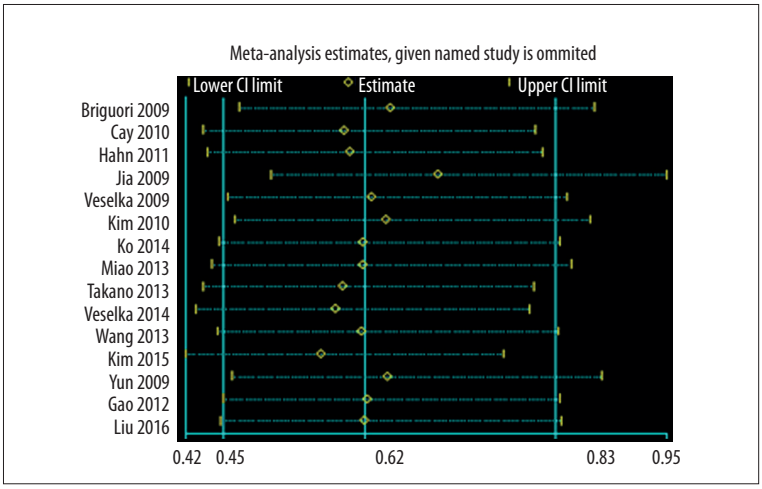

Figure 9. Sensitivity analysis for all the included studies.

myocardial infarcts with short ischemic times, particularly after 2 h [2]. Therefore, a narrow therapeutic window may exist for reducing reperfusion injury and improving clinical outcome.

There were several limitations to the present meta-analysis. First, some factors may have influenced the analysis, such as individual genetic heterogeneity. Second, the degree of severity of concomitant comorbidities, such as diabetes, hyperlipidemia, and kidney failure, also may have influenced the response to statin therapy. Third, the postprocedure statin therapy and the following anti-thrombus methods were not totally reported in detail in some trails, which may also have influenced the clinical outcome. In addition, the control groups were not unified with a mixture of moderate- or low-dose statin, no statins, or placebo.

Conclusions

In conclusion, we performed a meta-analysis and found that high-dose statin pretreatment has an important effect on post-procedure myocardial perfusion by improving TIMI flow in patients undergoing PCI, particularly in statin-naive patients and those with STEMI. High-dose statin preloading also reduces the incidence of MACE.

Conflict of interest

None.

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