Intensive versus non-intensive statin pretreatment before percutaneous coronary intervention in Chinese patients: a meta-analysis of randomized controlled trials

Xian Yang
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
Xi Lan
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
Xin-Lin Zhang
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
Zhong-Lin Han
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
Si-Min Yan
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
Wen-Xiao Wang
Affiliated Hospital of Medical College Qingdao University
Biao Xu
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
Wei-Hong Ge (WH.Ge.drumtower@outlook.com)
Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital https://orcid.org/0000-0002-6124-8742

Research

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Abstract

Background: The results of intensive statin pretreatment before percutaneous coronary intervention (PCI) is inconsistent between Chinese and Western populations and there are no corresponding meta-analyses involving hard clinical end-points in the available published literature. The aim of this study was to evaluate the efficacy and safety of high-dose statin loading before PCI in Chinese patients through a meta-analysis.

Method: Relevant studies were identified by searching the electronic databases of PubMed, Embase, and Cochrane's Library to December 2019. The outcomes included an assessment of major adverse cardiovascular event (MACE), non-fatal myocardial infarction (MI), cardiac death, target vessel revascularization (TVR), myalgia/myasthenia and abnormal alanine aminotransferase (ALT) in all enrolled patients.

Results: 12 studies involving 3,183 individuals were included The results showed statistically significant different in the incidence of MACE (RR=0.49, 95% CI: 0.30-0.80, P=0.004, I2=63%) and non-fatal MI (RR=0.54, 95% CI: 0.33-0.88, P= 0.01, I2=62%) on comparing the intensive statin and non-intensive statin treatment groups. Subgroup analysis further suggested the benefits of different treatments were inconsistent. Compared with preoperative intensive statin therapy, the incidence of MACE and non-fatal MI were significantly elevated in patients receiving placebo or no statin treatment before surgery (RR=0.47, 95% CI: 0.34-0.65, P<0.00001, I2=0%; RR=0.49, 95% CI: 0.35-0.70, P<0.0001, I2=0%). However, the incidence of MACE and non-fatal MI were not statistically significant when comparing preoperative high-intensity statin therapy with moderate-intensity statin therapy (RR=0.96, 95% CI: 0.44-2.08, P=0.91, I2=11%; RR=1.10, 95% CI: 0.86-1.39, P=0.44). The study also demonstrated that the Asian population could tolerate high-intensity atorvastatin during the perioperative period.

Conclusion: Compared with placebo or no statin pretreatment, Chinese patients receiving intensive statin therapy before PCI displayed reduced incidence of MACE and non-fatal MI. However, there was no significant benefit between high-intensity and moderate-intensity statin treatment. Further, the Chinese population tolerated well preoperative intensive statin pretretment.

Introduction

As the cornerstone of primary and secondary prevention of arteriosclerotic cardiovascular disease (ASCVD), statin have been widely used in clinical practice. In recent years, several studies have suggested that intensive statin before percutaneous coronary intervention (PCI) can significantly reduce the level of postoperative myocardial damage markers, the incidence of perioperative myocardial infarction and short-term cardiovascular events[1-3]. Current clinical practice guidelines recommend high-dose statin loading before PCI in Europe and the United States[4-5]. However, the research on this field was very limited in Chinese population and no corresponding meta-analysis involving hard clinical endpoints has been published so far. In addition, there were significant differences in statin metabolism between Chinese and Western people [6]. It was unknown whether this would affect the outcome of intensive statin treatment. This paper intended to

evaluate the efficacy and safety of intensive statin compared with non-intensive statin pretreatment before PCI in Chinese population through meta-analysis.

Methods

Search strategy

A comprehensive search of electronic databases including PubMed, EMBASE, and Cochrane Library was performed. The search was limited from the inception up to December 2019, and of English language. Search terms included “intensive”, “intensity”, “high”, “load”, “loading”, “statin”, “atorvastatin”, “rosuvastatin”, “percutaneous coronary intervention”, “PCI” and connected using the logical word “AND” or “OR”. It was worth mentioning that in order to avoid missing important literatures, retrieval type was not included some terms such as “China” or “Chinese”. We checked the location of the research center and the specific inclusion criteria in the article to comprehensively determine the patient was Chinese. The references of the identifed articles and relevant reviews were screened to include other potentially suitable trials.

Inclusion and exclusion criteria

Studies satisfying the following criteria were eligible: (1) randomized controlled trials (RCTs); (2) the patient was Chinese; (3) the patient with emergency or elective PCI; (4) preoperative interventions for intensive and non-intensive statin therapy which included moderate-intensity statin, placebo and no statin pretreatment; (5) high-intensity statin therapy referred to atorvastatin≥40mg/d or rosuvastatin≥20mg/d and moderate-intensity statin therapy referred to atorvastatin＜40mg/d or rosuvastatin＜20mg/d or equivalent dose statin; (6) outcome indicators included effectiveness and safety. The former referred to major adverse cardiovascular event (MACE) and the latter referred to myalgia/myasthenia and abnormal alanine aminotransferase (ALT). MACE is defined as cardiac death, nonfatal myocardial infarction and target vessel revascularization. Abnormal ALT is defined as ALT levels that rised more than 3 times the upper limit of normal; (7) follow-up lasted for 1~3 months after PCI; (8) literature language was English. Exclusion criteria included any of the following: chronic high-intensity statin therapy before PCI, abnormal liver enzymes (ALT or aspartate aminotransferase [AST] more than 40 U/L); blood creatinine >2 mg/dL, or history of muscle disease. The studies were reviewed by two independent investigators to determine whether they met the inclusion criteria and any disagreement was resolved by consensus.

Data extraction

The baseline data involving study characteristics(first author, year of publication, sample size, intervention, follow-up time), patient characteristics(clinical presentation, statin medication history) and outcome indicators were extracted directly from the articles. Differences in assessments were resolved by discussing with a third investigator.

Quality assessment

The RCTs were evaluated according to the following methodological criteria recommended by the Cochrane Collaboration: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

Statistical analysis

We used the RevMan (Version 5.3; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College Station, TX, USA) for the meta-analysis and statistical analysis. Dichotomous data were presented as risk ratios (RR) with 95% confdence intervals (CI).The heterogeneity was evaluated using I^2 and *p* value based on Chi-square test. $I^2 \leq 50\%$ or $p \geq 0.1$ did not demonstrate a signifcant heterogeneity and a fixed-effects model was used. I^2 50% or *p* 0.1 indicated a signifcant heterogeneity, and therefore, a random-effects model was applied. Subgroup analysis was carried out to explore the sources of heterogeneity. Sensitivity analyses were performed by excluding sequentially one study at a time to test the robustness of the results. Potential publication bias was assessed with a funnel plot and Egger's regression asymmetry test. All *p* values were two-sided, and results were considered statistically signifcant when the value of *p* 0.05.

Results

Study selection and quality assessment

As shown in Fig 1, 4020 potentially relevant articles were identifed in the initial analysis. Among them, a total of 3391 articles were identified after removal of duplicate studies. Only 27 articles were retained after screening the title and abstract. Finally, 12 studies involving 3183 patients were included in the present meta-analysis[7-18]. Among them, 1545 patients belonged to intensive statin treatment group and 1638 patients belonged to non-intensive statin treatment group. Further more, non-intensive statin treatment group involved moderate-intensity statin, placebo and no statin pretreatment group which included 738, 244 and 656 patients, respectively. All patients were female in one study[16]. The characteristics of the included studies were shown in Table 1. The baseline clinical, angiographic and procedural characteristics of patients are listed in Table 2. Quality assessment results were described in Table 3.

racteristics of the included studies

Study, years	Sample size(intensive/non-intensive statin)	Clinical Presentation	Statin medication history	Primary/Elective PCI	Statin Regimen Before PCI	Statin Regimen After PCI	Follow-up (days)	Outcome indicators	
								Effectiveness	Safety
Liu *et al*, 2016[7]	616（307/309）	Stable Angina, ACS	statin-naive or atorvastatin≤20 mg/day, or equivalent dose statin	Elective PCI	atorvastatin 80mg 12h before PCI **vs** no statin pretreatment	40mg/d **vs** 20mg/d	30	MACE, nonfatal MI	myalgia/myasthenia*
	182（93/89）	STEMI	statin-naive or atorvastatin≤20 mg/day, or equivalent dose statin	Primary PCI	atorvastatin 80mg just before primary PCI **vs** no statin pretreatment	40mg/d **vs** 20mg/d	90		ALT
Jiao *et al*, 2015[8]	72（33/39）	NSTE-ACS	Not mentioned	Elective PCI	rosuvastatin 20mg 12h before PCI + 20mg just before PCI **vs** no statin pretreatment	10mg/d	30	MACE, cardiac death, nonfatal MI, TVR	
Jiao *et al*, 2015[9]	126（62/64）	NSTE-ACS	Not mentioned	Elective PCI	rosuvastatin 20mg 12h before PCI + 20mg just before PCI **vs** no statin pretreatment	10mg/d	30		myalgia/myasthenia
Zheng *et al*, 2015[10]	1202（573/629）	Stable Angina ,NSTE-ACS	statin-naive or atorvastatin≤20 mg/day, or equivalent dose statin	Elective PCI	atorvastatin 80mg at night before PCI for 2-Day **vs** atorvastatin≤20mg or equivalent dose statin at night before PCI	40mg/d vs ≤20mg/d or equivalent dose statin	30	MACE, cardiac death, nonfatal MI, TVR	
Xie *et al*, 2014[11]	159（79/80）	NSTE-ACS	statin-naive	Elective PCI	rosuvastatin 20mg 12h before PCI + 20mg 2h before PCI **vs** no statin pretreatment	10mg/d	30	MACE, cardiac death, nonfatal MI, TVR	
Yong *et al*, 2014[12]	60（20/40）	STEMI	statin-naive	Primary PCI	atorvastatin 80mg 1.2h before PCI **vs** 20mg 1.2h before PCI atorvastatin 80mg 1.2h before PCI **vs** no statin pretreatment**	20mg/d	30	MACE, cardiac death, nonfatal MI, TVR	myalgia/myasthenia, ALT
Luo *et al*, 2013[13]	67（31/36）	NSTE-ACS	statin-naive	Elective PCI	rosuvastatin 20mg 12h before PCI + 20mg 2h before PCI **vs** no statin pretreatment	10mg/d	30	MACE, cardiac death, nonfatal MI, TVR	
Wang *et al*, 2013[14]	125（62/63）	NSTE-ACS	statin-naive	Elective PCI	rosuvastatin 20mg 2~4h before PCI **vs** placebo 2~4h before PCI	10mg/d	30	MACE, cardiac death, nonfatal MI, TVR	
Li *et al*, 2013[15]	215（106/109）	Stable Angina	regular statin for at least 3 months	Elective PCI	atorvastatin 80mg 12h before PCI **vs** 20mg 12h before PCI	20mg/d	30	MACE, cardiac death, nonfatal MI, TVR	
Gao *et al*, 2012[16]	117（59/58）	NSTE-ACS	statin-naive	Elective PCI	rosuvastatin 20mg 12h before PCI + 10mg 2h before PCI **vs** placebo 12h before PCI + 2h before PCI	10mg/d	90	MACE, cardiac death, nonfatal MI, TVR	

Li *et al*, 2012[17]	161□78/83□	STEMI	statin-naive	Primary PCI	atorvastatin 80mg 1.5h before PCI **vs** placebo 1.5h before PCI	40mg/d	30		ALT
Yu *et al*, 2011[18]	81□41/40□	NSTE-ACS	statin-naive	Elective PCI	atorvastatin 80mg 12h before PCI + 40mg 2h before PCI **vs** placebo 12h before PCI + 2h before PCI	20mg/d	30	MACE, cardiac death, nonfatal MI, TVR	

. year; **Moderate-intensity group and no statin pretreatment group included 20 patients separately

ST segment elevation acute coronary syndrome, *STEMI* ST segment elevation myocardial infarction, *PCI* percutaneous coronary intervention, *MI* myocardial

:arget vessel revascularization

e 2 Baseline clinical, angiographic and procedural characteristics in the overall population

riable	High-intensity statin n/population (%)	Moderate-intensity statin n/population (%)	Placebo or no statin pretreatment n/population (%)
mber of patients	1544/3183(48.5%)	758/3183(23.8%)	881/3183(27.7%)
le	1070/1544(69.3%)	536/758(70.7%)	582/881(66.1%)
pertension	956/1544(61.9%)	501/758(66.1%)	544/881(61.7%)
ıbetes Mellitus	443/1449(30.6%)	234/758(30.9%)	251/778(32.3%)
slipidaemia	201/771(26.1%)	152/649(23.4%)	78/201(38.8%)
okers	552/1544(35.8%)	293/758(38.7%)	297/881(33.7%)
vious MI	99/630(15.7%)	9/20(45.0%)	96/632(%)
vious PCI	159/1183(%)	51/629(%)	103/612(15.2%)
vious CABG	6/500(1.2%)	0/0(0%)	6/496(1.2%)
ble angina	230/506(45.5%)	109/109(100%)	118/398(29.6%)
TE-ACS	518/767(67.5%)	0/0(0%)	539/778(69.3%)
EMI	223/498(44.8%)	20/20(100%)	224/501(44.7%)
ıgle vessel	84/266(31.6%)	6/20(30.0%)	80/279(28.7%)
uble vessel	106/266(39.8%)	4/20(20.0%)	111/279(39.8%)
re than three and triple vessel	81/266(30.5%)	10/20(50.0%)	95/279(34.1%)
rget vessel LM	36/877(4.1%)	25/629(4.0%)	7/320(2.2%)
rget vessel LAD	634/1038(61.1%)	427/649(65.8%)	261/483(54.0%)
rget vessel LCX	330/1038(31.8%)	201/649(31.0%)	159/483(32.9%)
rget vessel RCA	352/1038(33.9%)	243/649(37.4%)	168/483(34.8%)
/C lesions	346/609(56.8%)	0/0(0%)	333/615(54.1%)
ltivessel lesions	33/78(42.3%)	0/0(0%)	39/83(47.0%)
ltivessel intervention	244/773(31.6%)	215/629(34.2%)	62/201(30.8%)
pirin	1375/1491(92.2%)	622/738(84.3%)	802/822(97.6%)
pidogrel/Ticlopidine	1300/1385(93.9%)	541/629(86.0%)	807/822(98.2%)
lockers	1104/1491(74.0%)	495/738(67.1%)	630/822(76.6%)
EI/ARB	1045/1491(70.1%)	404/738(54.7%)	667/822(81.1%)
rcoprotein IIb/IIIa inhibitors	95/370(25.7%)	9/20(45.0%)	113/380(29.7%)
S	822/851(96.6%)	701/738(95.0%)	176/179(98.3%)

us MI previous myocardial infarction, *Previous PCI* previous percutaneous coronary intervention, *Previous CABG* Previous Coronary artery bypass ing, *NSTE-ACS* non-ST segment elevation acute coronary syndrome, *STEMI* ST segment elevation myocardial infarction, *LM* left main, *LAD* left anterior descending, eft circumflex, *RCA* right coronary artery, *DES* drug-eluting stent

Table 3 Assessment of randomized controlled trials

Study, year	Randomization sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
Liu *et al*, 2016[7]	Low risk	Low risk	High risk	Unclear risk	Unclear risk	Unclear risk
Jiao *et al*, 2015[8]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Jiao *et al*, 2015[9]	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Zheng *et al*, 2015[10]	Unclear risk	Unclear risk	High risk	Low risk	Low risk	Unclear risk
Xie *et al*, 2014[11]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Yong *et al*, 2014[12]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Luo *et al*, 2013[13]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Wang *et al*, 2013[14]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Li *et al*, 2013[15]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Gao *et al*, 2012[16]	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk
Li *et al*, 2012[17]	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Yu *et al*, 2011[18]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

Effectiveness analysis

There were 10 studies that compared the effects of preoperative intensive statin therapy and non-intensive statin therapy on the incidence of MACE and nonfatal MI respectively[7-8,10-16,18]. Due to the heterogeneity between different results, a random effects model was used. The results showed the incidence of MACE (*RR*=0.49, 95%*CI*: 0.30~0.80, *p*=0.004, I^2=63%, Fig. 2a) and nonfatal MI (*RR*=0.54, 95%*CI*: 0.33~0.88, *p*=0.01, I^2=62%, Fig. 2b) between two groups were statistically significant. There were 9 studies that compared the effects of preoperative intensive statin therapy and non-intensive statin therapy on the incidence of cardiac death and target vessel revascularization[8,10-16,18]. Considering the homogeneity between the results, a fixed effect model was used and both indicators were not statistically significant（*RR*=0.37, 95%*CI*:0.01~8.96, *p*=0.54, Fig. 2c; *RR*=0.43, 95%*CI*:0.18~1.02, *p* =0.06, I^2=0%, Fig. 2d）.

Safety analysis

There were 3 studies that compared the effects of preoperative intensive statin therapy and non-intensive statin therapy on the incidence of myalgia/myasthenia[7,9,12] and abnormal ALT[7,12,17] respectively. No significant difference was observed between two groups（*RR*=1.35, 95%*CI*:0.30~5.95, *p*=0.69, I^2=0%, Fig. 3a; *RR*=1.47, 95%*CI*:0.54~4.02, *p*=0.45, I^2=0%, Fig. 3b）.

Subgroup analysis according to intensive statin therapy

Due to the heterogeneity in MACE and nonfatal MI for the overall results, a subgroup analysis was attempted to find a source of heterogeneity. It was performed by dividing the non-intensive statin treatment group into moderate-intensity[10,12,15] and placebo/no statin treatment group[7,8,11-14,16,18] involving 10 studies. The results showed that the heterogeneity has disappeared in both two subgroup. Compared with the preoperative intensive statin therapy, the incidence of MACE and nonfatal MI were significantly elevated in patients receiving placebo or no statin treatment before surgery（*RR*=0.47, 95%*CI*: 0.34~0.65, *p*<0.00001, I^2=0%, Fig. 2a; *RR*=0.49, 95%*CI*: 0.35~0.70, *p*<0.0001, I^2=0%, Fig. 2b）. These findings were consistent with the general population. However, the incidence of MACE and nonfatal MI were not statistically significant compared preoperative high-intensity statin therapy with moderate-intensity statin therapy（*RR*=0.96, 95%*CI*: 0.44~2.08, *p*=0.91, I^2=11%, Fig. 2a; *RR*=1.10, 95%*CI*: 0.86~1.39, *p*=0.44, Fig. 2b）. The results for this subgroup were inconsistent with overall results and could explain the cause of heterogeneity.

Sensitivity analysis

Considering the results of the subgroup were inconsistent with overall population, sensitivity analysis conducted further through the removal of any single trial. The heterogeneity of general population in MACE and nonfatal MI no longer existed when excluding the study by Zheng *et al*（*RR*=0.46, 95%*CI*: 0.33~0.65, *p*<0.00001, I^2=0%, Additional file 1: Figure S1a; *RR*=0.49, 95%*CI*: 0.35~0.70, *p*<0.0001, I^2=0%, Additional file 1: Figure S1b）and it did not essentially affect the results of pooled general population and subgroup[10].

Publication bias

The plots were symmetrical on visual inspection, indicating risk of publication bias (Fig.4). Egger’s regression test also demonstrated risk of publication bias (*p*=0.001, Fig.5). The small number of studies included in the overall population and subgroup may be one of the reasons for publication bias [19].

Discussion

Some studies have been completed on intensive statin therapy before PCI. In 2013, the ALPACS study took the lead in exploration in Asia[20]. It was a prospective, multicenter, randomized, open-label study involving 499 patients with NSTE-ACS(26 clinical centers in China and South Kore). None of the enrolled patients had previously received statin. The intensive treatment group received additional atorvastatin loading doses of 80 mg at 12 h and 40 mg at 2 h pre-PCI. The conventional treatment group was only treated with atorvastatin 40 mg/d after PCI. The results suggested the intensive treatment group failed to significantly reduce the occurrence of MACE at 30 days after PCI compared with the conventional treatment group (15.7% vs 14.7%, *p*=0.80). The study also demonstrated Asian population were able to tolerate high-intensity atorvastatin during the perioperative period. Unfortunately, the ALPACS were not included in this meta-analysis because of the mixed data from the Korean population. The ISCAP study subsequently published in 2015 was a large-scale, multicenter, randomized, prospective, open-label, blinded, parallel controlled clinical study with Chinese patients[10]. Follow-up results showed no significant difference in the incidence of MACE at 30 days between the intensive statin treatment group and the conventional treatment group (19.4% vs 18.3%, *P*=0.43). Followed up for 6 months, there was still no difference between the two groups (20.1% vs 18.3%, *P*=0.63). In terms of safety, no significant differences were found in liver enzymes, creatine kinase and other indicators.

In addition to multi-center clinical studies, many scholars tried to find further answers with meta-analysis. In 2013, Guo *et al.*conducted a meta-analysis on the impact of sequential statin therapy on the prognosis of Chinese patients with PCI[21]. 10 studies involving 1015 patients were included in this article. The results suggested a significant reduction in the incidence of MACE within 6 months. Since some patients in experimental group just received intensive statin treatment after PCI, the subjects were not entirely consistent with the characteristics discussed in this paper. In 2017, a systematic review and meta-analysis involving 11 RCTs with 802 patients was performed by Ye *et al*[22]. Compared with preoperative rosuvastatin 10mg/d, using loading dose of 20 mg/d before PCI could significantly reduce cTnT and hs-CRP levels 24 hours and LDL-C, TC, and TG levels 30 days after PCI. However, the clinical indicators analyzed and evaluated in this article were surrogate indicators, which did not involve cardiovascular end point events, nor did they examine the safety. In 2018, Cao *et al.* discussed the effectiveness of high-dose statin before PCI in reducing cardiovascular events in Asian populations[23]. The systematic review included 7 RCTs involving 1381 patients, all of whom were Chinese or Korean. The analysis results indicated that the incidence of MACE and perioperative myocardial infarction in the intensive statin group were significantly lower than those in the control group. This article did not discuss the benefits of the Chinese population through subgroup analysis.

Compared with the previously published meta-analysis, this article was improved in the following aspects. First of all, four new studies published after 2014 were included in this paper[7-10]. The full paper included 12 RCTs with 3183 patients. It meant the total number of studies as well as patients exceeded any previously published meta-analysis. Secondly, the population involved in this paper was all Chinese, so the interference of other Asian populations such as Korean population was removed. Thirdly, new outcome indicators such as cardiac death and target vessel revascularization were established to make the data more complete.

An important finding of this study was that the subgroup analysis could eliminate the heterogeneity of the overall population, which suggested the benefits of different treatment were not consistent. On the one hand,

people received high-intensity statin could benefit from patients received placebo or no statin treatment before PCI. This conclusion was consistent with the results of previous studies involving Western populations. On the other hand, there were no statistically differences in MACE and other outcome indicators between patients received high-intensity and patients received moderate-intensity statin preoperatively, which suggested two regimens had a consistent effect on short-term outcomes. We further searched the database and found the lack of RCTs of two regimens in Western populations at present. In fact, there have been reports of racial differences in the pharmacokinetics of statin. With a single dose of 20 mg or 40 mg rosuvastatin, the area under the curve and peak blood concentration of Chinese were 1.79, 1.89, 2.31, and 2.36 times that of Caucasians, respectively[24-25]. Differences in race sensitivity to statin may be related to genetic factors. Genetic differences in metabolic enzymes and drug transporters between Chinese and white may partially explain this phenomenon[6]. However, based on the results of this paper and previous studies, we did not find any racial differences on the efficacy and safety of preoperative intensive statin therapy.

The sensitivity analysis of this study suggested that the results of the ISCAP was the source of heterogeneity which was the largest clinical study to date targeting Chinese patients. Although negative results were obtained, we also noticed there might be some confounding factors that affected the final conclusions. Firstly, about 60% patients enrolled had previously taken low-intensity even moderate-intensity statin and only 40% were statin-naive patients. It was unclear whether statin history could reduce the benefits from intensive treatment in Chinese patients. Secondly, the time of drug administration in the ISCAP was at night before the operation and it was not exactly fixed. Different from it, the time were 2~4 hours or 12 hours before elective PCI and relatively fixed in other trials[7-9,11,13-16,18]. On the one hand, the regimen in the ISCAP was more consistent with clinical practice. On the other hand, it was uncertain whether the time of administration could affect the benefits of intensive statin. Finally, characteristics of patients enrolled in the ISCAP with higher proportion of multiple lesions, higher average number of stents, longer average length of stents and higher incidence of MACE at 30 days after PCI indicated that the complexity of coronary lesion might reduce the effectiveness of high-dose statin treatment.

The guidelines and consensuses underwent a process of deepening understanding on whether the patients should receive preoperative intensive statin therapy in Chinese. Based on evidence for Western populations, expert consensus released in 2014 recommended all patients with acute coronary syndrome (ACS) undergoing PCI, including emergency and elective PCI, should initiate high-dose statin treatment immediately before PCI, such as atorvastatin 80mg/d[26]. As ALPACS and ISCAP published in succession, guidelines issued in 2016 concluded that in the absence of more evidence of high-quality RCTs with hard endpoints, it was not recommended patients with ACS received intensive statin therapy before PCI[27-28]. The results of this meta-analysis were consistent with the recommendations of the guidelines and further strengthen the foundation of evidence-based medicine.

Study limitations

This article has the following limitations and deficiencies: (1) The quality of included studies were generally not high. The remaining 11 RCTs were single-center and lacked rigorous trial design except ISCAP. The randomization, blinding and data analysis of these trials were not described in detail. We also need to noticed that ISCAP was an open-label trial. Although it had all outcome events adjudicated by a blind CEC group and all laboratory tests have been done by blind laboratory staff, the investigators and subjects were not blinded to the treatment arms of this trial, and as such, both might tend to report more adverse events in the experiment arm and this might lead to more withdrawal from study in this group. This trend could still have some affects on the results of the study. (2) Subgroup analysis was not comprehensive. Limited by the included literatures, this meta-analysis only performed a subgroup analysis based on the intensity of statin without involving other factors, such as statin medication history (patients with chronic statin therapy or statin-naive patients), categories of statin (atorvastatin or rosuvastatin), timing of statin administration (12 hours before surgery or other time), timing of revascularization (emergency PCI or elective PCI). (3) Due to the lack of RCTs received moderate and high-intensity statin before PCI in Western populations, the effects of race differences on statin pretreatment could not be further analyzed.

Conclusions

Available evidence suggested, compared with placebo or no statin pretreatment, Chinese patients received intensive statin before PCI can further reduce the incidence of MACE and nonfatal MI. However there was no significant benefit between high-intensity and moderate-intensity statin. In addition, the Chinese population was well tolerated by preoperative intensive statin pretretment.

Additional File

Figure S1. Forest plot of MACE and nonfatal MI with preoperative intensive statin therapy and non-intensive statin therapy in patients when excluding the study by Zheng *et al*.

Abbreviations

PCI: Percutaneous coronary intervention; MACE: Major adverse cardiac events; MI: Myocardial infarction; TVR: Target vessel revascularization; ALT: Alanine aminotransferase; ASCVD: Arteriosclerotic cardiovascular disease; RCTs: Randomizedcontrolled trials; AST: Aspartate aminotransferase; RR: Risk ratios; CI: Confidence intervals; NSTE-ACS: Non-ST segment elevation acute coronary syndrome; STEMI: ST segment elevation myocardial infarction; CABG: Coronary artery bypass grafting; LM: Left main; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery; DES: Drug-eluting stent; ACS: Acute coronary syndrome.

Declarations

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Not applicable.

Authors' contributions

WHG and XY conceived of the study, participated in the design, and drafted the manuscript. XL and XLZ carried out the study searches, XL, ZLH and SMY collected the data. WXW and BX performed the statistical analyses. All authors reviewed and revised the manuscript, and approved the manuscript for submission.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Pharmacy, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjin 210008, China. [2]Department of Cardiology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjin 210008, China. [3]Department of Pharmacy, The Affiliated Hospital of Qingdao University, Qingdao 266000, China.

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Figures

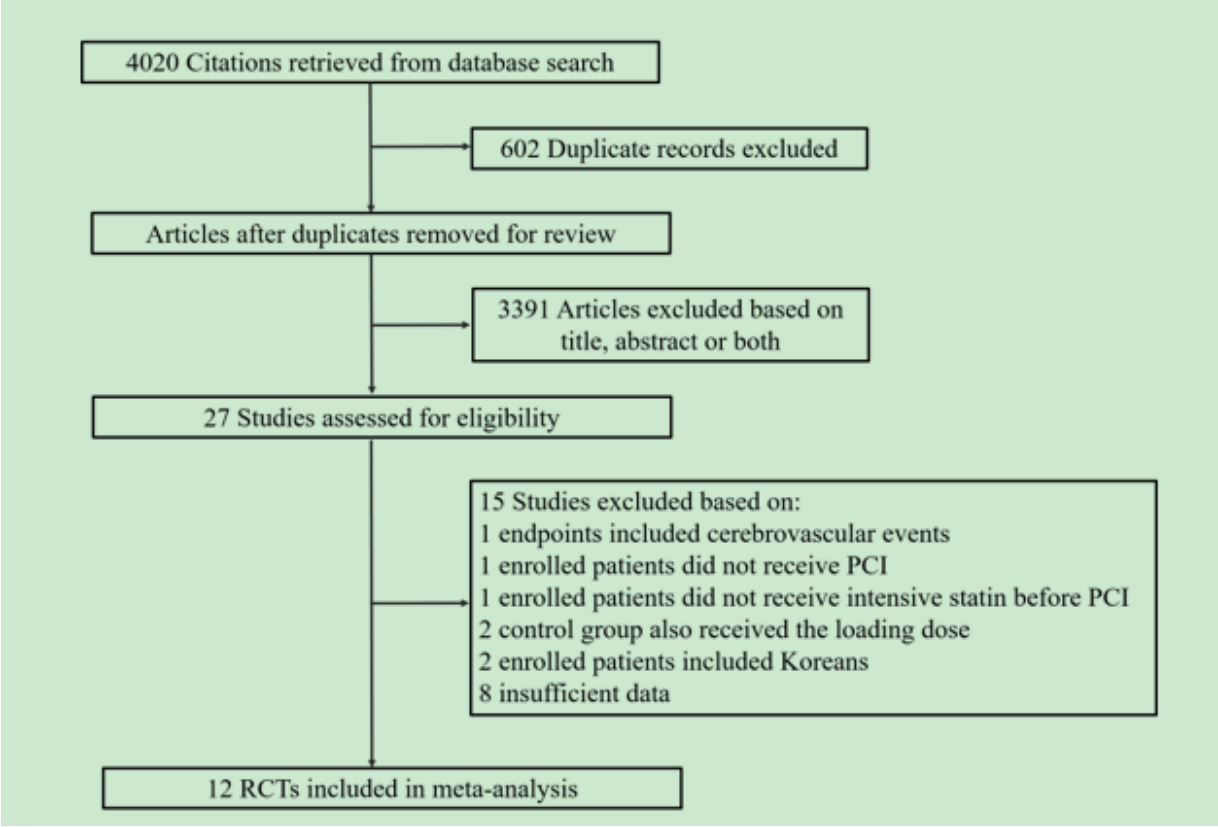

Figure 1

Flowchart of literature search for this meta-analysis. PCI: Percutaneous coronary intervention.

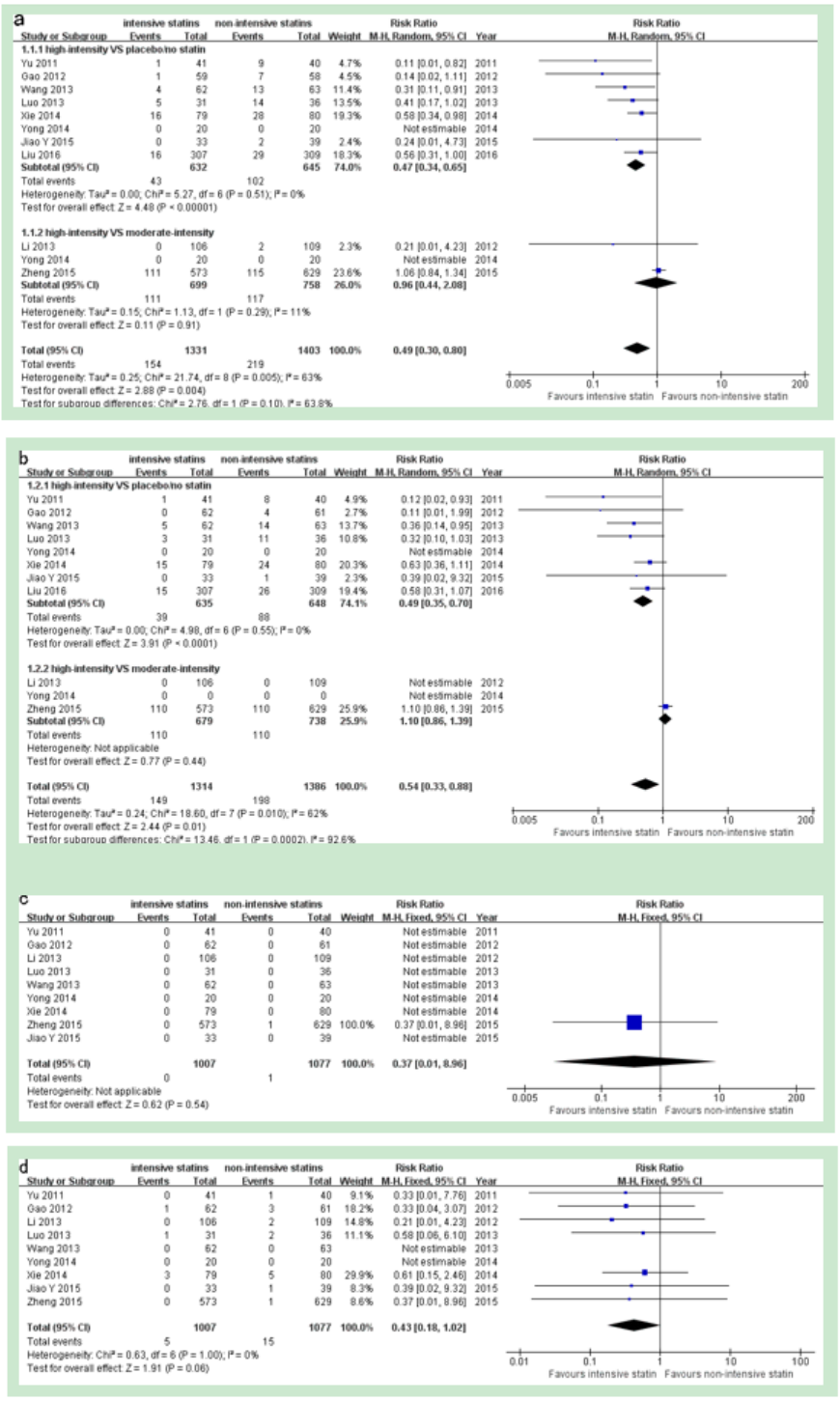

Figure 2

Forest plot of MACE (a), nonfatal MI (b), cardiac death (c), and TVR (d) with preoperative intensive statin therapy and non-intensive statin therapy in ACS patients.

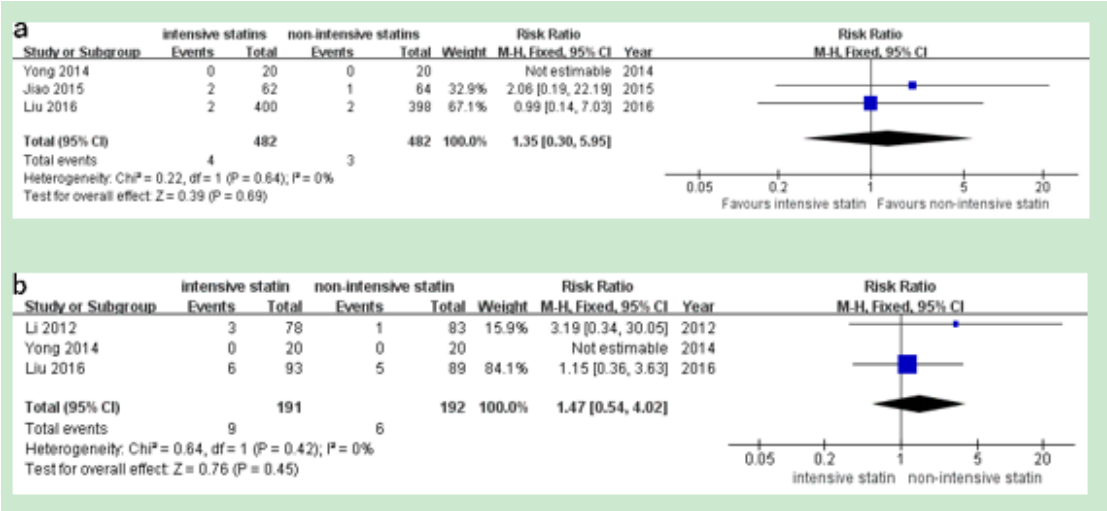

Figure 3

Forest plot of myalgia/myasthenia (a), and abnormal ALT (b) with preoperative intensive statin therapy and non-intensive statin therapy in ACS patients.

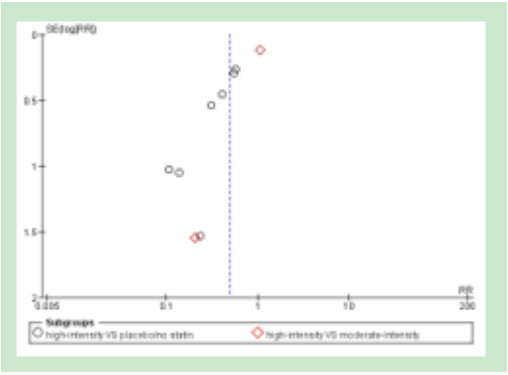

Figure 4

Funnel plot of MACE with preoperative intensive statin therapy and non-intensive statin therapy in ACS patients

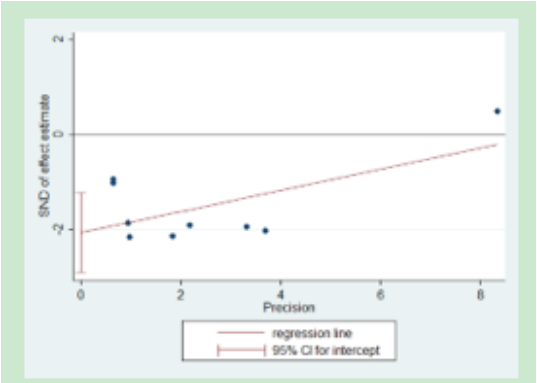

Figure 5

Egger plot of MACE with preoperative intensive statin therapy and non-intensive statin therapy in ACS patients

Supplementary Files

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