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

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Research

Keywords: Intensive, Non-Intensive, Statin, Percutaneous Coronary Intervention, Meta-analysis

Posted Date: March 11th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-16709/v1>

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Abstract

Background: Studies of intensive statin pretreatment before percutaneous coronary intervention (PCI) was very limited in Chinese and there were no corresponding meta-analysis involving hard clinical endpoints has been published so far. Therefore, the guidelines did not give a positive recommendation, which was inconsistent with Western people. The aim of this study was to evaluate the efficacy and safety of high-dose statin loading before PCI in Chinese patients through meta-analysis.

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

Results: 12 studies involving 3183 individuals were included in this review. The results showed different from cardiac death and TVR, the incidence of MACE (RR = 0.49, 95% CI : 0.30 to 0.80, P = 0.004, I² = 63%) and nonfatal MI (RR = 0.54, 95% CI : 0.33~ 0.88, P = 0.01, I² = 62%) between intensive statin and non-intensive statin treatment group were statistically significant. The subgroup analysis further suggested the benefits of different treatment were not consistent. 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, I² = 0%; RR = 0.49, 95% CI : 0.35~0.70, P < 0.0001, I² = 0%). 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, I² = 11%; RR = 1.10, 95% CI : 0.86~1.39, P = 0.44). Besides, The study also demonstrated Asian population were able to tolerate high-intensity atorvastatin during the perioperative period.

Conclusion: Compared with placebo or no statin pretreatment, Chinese patients received intensive statin before PCI can further reduce the incidence of MACE and nonfatal myocardial infarction. 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 pretreatment.

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 identified 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 $\geq$ 40mg/d or rosuvastatin $\geq$ 20mg/d and moderate-intensity statin therapy referred to atorvastatin $\leq$ 40mg/d or rosuvastatin $\leq$ 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% confidence 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 significant when the value of *p*≤0.05.

Results

Study selection and quality assessment

As shown in Fig 1, 4020 potentially relevant articles were identified 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.

Table 1 Characteristics 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 2015 ^[10]	1202[573/629]	Stable Angina ,NSTEMI-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 <i>et al</i> ,2014 ^[11]	159[79/80]	NSTEMI-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 <i>et al</i> ,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 <i>et al</i> , 2013 ^[13]	67[31/36]	NSTEMI-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 <i>et al</i> ,2013 ^[14]	125[62/63]	NSTEMI-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 <i>et al</i> , 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 <i>et al</i> ,2012 ^[16]	117[59/58]	NSTEMI-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 <i>et al</i> , 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 <i>et al</i> , 2011 ^[18]	81[41/40]	NSTEMI-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

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

Variable	High-intensity statin n/population (%)	Moderate-intensity statin n/population (%)	Placebo or no statin pretreatment n/population (%)
Number of patients	1544/3183(48.5%)	758/3183(23.8%)	881/3183(27.7%)
Male	1070/1544(69.3%)	536/758(70.7%)	582/881(66.1%)
Hypertension	956/1544(61.9%)	501/758(66.1%)	544/881(61.7%)
Diabetes Mellitus	443/1449(30.6%)	234/758(30.9%)	251/778(32.3%)
Dyslipidaemia	201/771(26.1%)	152/649(23.4%)	78/201(38.8%)
Smokers	552/1544(35.8%)	293/758(38.7%)	297/881(33.7%)
Previous MI	99/630(15.7%)	9/20(45.0%)	96/632(%)
Previous PCI	159/1183(%)	51/629(%)	103/612(15.2%)
Previous CABG	6/500(1.2%)	0/0(0%)	6/496(1.2%)
Stable angina	230/506(45.5%)	109/109(100%)	118/398(29.6%)
NSTEMI-ACS	518/767(67.5%)	0/0(0%)	539/778(69.3%)
STEMI	223/498(44.8%)	20/20(100%)	224/501(44.7%)
Single vessel	84/266(31.6%)	6/20(30.0%)	80/279(28.7%)
Double vessel	106/266(39.8%)	4/20(20.0%)	111/279(39.8%)
More than three and triple vessel	81/266(30.5%)	10/20(50.0%)	95/279(34.1%)
Target vessel LM	36/877(4.1%)	25/629(4.0%)	7/320(2.2%)
Target vessel LAD	634/1038(61.1%)	427/649(65.8%)	261/483(54.0%)
Target vessel LCX	330/1038(31.8%)	201/649(31.0%)	159/483(32.9%)
Target vessel RCA	352/1038(33.9%)	243/649(37.4%)	168/483(34.8%)
Coronary lesions	346/609(56.8%)	0/0(0%)	333/615(54.1%)
Intervessel lesions	33/78(42.3%)	0/0(0%)	39/83(47.0%)
Intervessel intervention	244/773(31.6%)	215/629(34.2%)	62/201(30.8%)
Aspirin	1375/1491(92.2%)	622/738(84.3%)	802/822(97.6%)
P2Y12 inhibitor (Clopidogrel/Ticlopidine)	1300/1385(93.9%)	541/629(86.0%)	807/822(98.2%)
Beta-blockers	1104/1491(74.0%)	495/738(67.1%)	630/822(76.6%)
ACEI/ARB	1045/1491(70.1%)	404/738(54.7%)	667/822(81.1%)
Protein IIb/IIIa inhibitors	95/370(25.7%)	9/20(45.0%)	113/380(29.7%)
Stents	822/851(96.6%)	701/738(95.0%)	176/179(98.3%)

Previous MI previous myocardial infarction, Previous PCI previous percutaneous coronary intervention, Previous CABG Previous Coronary artery bypass grafting, NSTEMI-ACS non-ST segment elevation acute coronary syndrome, STEMI ST segment elevation myocardial infarction, LM left main, LAD left anterior descending, LCX left 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 <i>et al</i> , 2016 ^[7]	Low risk	Low risk	High risk	Unclear risk	Unclear risk	Unclear risk
Jiao <i>et al</i> , 2015 ^[8]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Jiao <i>et al</i> , 2015 ^[9]	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Zheng <i>et al</i> , 2015 ^[10]	Unclear risk	Unclear risk	High risk	Low risk	Low risk	Unclear risk
Xie <i>et al</i> , 2014 ^[11]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Yong <i>et al</i> , 2014 ^[12]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Luo <i>et al</i> , 2013 ^[13]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Wang <i>et al</i> , 2013 ^[14]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Li <i>et al</i> , 2013 ^[15]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Gao <i>et al</i> , 2012 ^[16]	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk
Li <i>et al</i> , 2012 ^[17]	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Yu <i>et al</i> , 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 NSTEMI-ACS (26 clinical centers in China and South Korea). 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-naïve 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 consensus 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-naïve 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 pretreatment.

Additional File

Additional file 1

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: Randomized controlled trials; AST: Aspartate aminotransferase; RR: Risk ratios; CI: Confidence intervals; NSTEMI: 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

Acknowledgements

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.

Funding

No funding was received for this study.

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.

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References

1. Di SG 1, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. *J Am Coll Cardiol*. 2009;54:558-65.
2. Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation*. 2011;123:1622-32.
3. Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, et al. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol*. 2009;54:2157-63.
4. Catapano AL, Graham I, De BG, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias: The task force for the management of dyslipidaemias of the European society of cardiology (ESC) and European atherosclerosis society (EAS). *Eur Heart J*. 2016;37:2999-3058.
5. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44-e122.
6. Naito R, Miyauchi K, Daida H. Racial Differences in the Cholesterol-Lowering Effect of Statin. *J Atheroscler Thromb*. 2017;24:19-25.
7. Liu Z, Herrmann J, Hao HJ, Xu J, Hu SD, Li BY, et al. Efficacy of High-Intensity Atorvastatin for Asian Patients Undergoing Percutaneous Coronary Intervention. *Ann Pharmacother*. 2016;50:725-33.
8. Jiao YG, Hu F, Zhang ZG, Gong KZ, Sun XN, Li AH, et al. Effect of rosuvastatin dose-loading on serum sLox-1, hs-CRP, and postoperative prognosis in diabetic patients with acute coronary syndromes undergoing selected percutaneous coronary intervention (PCI). *Int J Clin Exp Med*. 2015;8:21565-71.
9. Jiao YG, Hu F, Zhang ZG, Gong KZ, Sun XN, Li AH, et al. Efficacy and Safety of Loading-Dose Rosuvastatin Therapy in Elderly Patients with Acute Coronary Syndromes Undergoing Elective Percutaneous Coronary Intervention. *Clin Drug Investig*. 2015;35:777-84.
10. Zheng B, Jiang J, Liu HL, Zhang J, Li H, Su L, Wang HC, et al. Efficacy and safety of serial atorvastatin load in Chinese patients undergoing elective percutaneous coronary intervention: results of the ISCAP (Intensive Statin Therapy for Chinese Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention) randomized controlled trial. *Eur Heart J Suppl*. 2015;17 (Supplement B) :B47-B56.
11. Xie WC, Li P, Wang ZD, Chen J, Lin ZH, Liang XW, et al. 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*. 2014;32:276-82.
12. Yong HJ, Wang X, Mi L, Guo LJ, Gao W, Zhang YZ, et al. Effects of atorvastatin loading prior to primary percutaneous coronary intervention on endothelial function and inflammatory factors in patients with ST-segment elevation myocardial infarction. *Exp Ther Med*. 2014;7:316-22.
13. Luo J, Li J, Shen XQ, Hu XQ, Fang ZF, Lv XL, et al. The effects and mechanisms of high loading dose rosuvastatin therapy before percutaneous coronary intervention in patients with acute coronary syndrome. *Int J Cardiol*. 2013;167:2350-3.
14. Wang ZZ, Dai HY, Xing MQ, Yu ZX, Lin XR, Wang SD, et al. Effect of a single high loading dose of rosuvastatin on percutaneous coronary intervention for acute coronary syndromes. *J Cardiovasc Pharmacol Ther*.

2013;18:327-33.

15. Li Q, Deng SB, Xia S, Du JL, She Q. Impact of intensive statin use on the level of inflammation and platelet activation in stable angina after percutaneous coronary intervention: a clinical study . *Med Clin (Barc)*. 2013;140:532-6.
16. Gao Y, Jia ZM, Sun YJ, Zhang ZH, Ren LN, Qi GX, et al. Effect of high-dose rosuvastatin loading before percutaneous coronary intervention in female patients with non-ST-segment elevation acute coronary syndrome. *Chin Med J (Engl)*. 2012;125:2250-4.
17. Li W, Fu XH, Wang YB, Li XN, Yang ZX, Wang XC, et al. Beneficial effects of high-dose atorvastatin pretreatment on renal function in patients with acute ST-segment elevation myocardial infarction undergoing emergency percutaneous coronary intervention. *Cardiology*. 2012;122:195-202.
18. Yu XL, Zhang HJ, Ren SD, Geng J, Wu TT, Chen XQ, et al. Effects of loading dose of atorvastatin before percutaneous coronary intervention on periprocedural myocardial injury. *Coron Artery Dis*. 2011;22:87-91.
19. Jang YS, Zhu JR, Ge JB, Kim YJ, Ji C, Lam W. Preloading with atorvastatin before percutaneous coronary intervention in statin-naïve Asian patients with non-ST elevation acute coronary syndromes: A randomized study. *Coron Artery Dis*. 2011;22:87-91.
20. Guo XY. A meta-analysis of sequential therapy of statins on PCI patients in china. CNKI. 2019. <https://www.cnki.net/>.
21. Ye ZL, Lu HL, Su Q, Guo WQ, Dai WR, Li HQ, et al. Effect of high-dose rosuvastatin loading before percutaneous coronary intervention in Chinese patients with acute coronary syndrome: A systematic review and meta-analysis. *Plos One*. 2017;12:e0171682.
22. Cao AL, Qian J, Wang Z. Efficacy of high-dose statin administration before surgery on the reduction of cardiovascular events: a meta analysis. *Pharm Care Res*. 2018;18:282-7.
23. 2 Birmingham BK, Bujac SR, Elsby R, Azumaya CT, Zalikowski J, Chen YS, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. *Eur J Clin Pharmacol*. 2015;71:329-40.
24. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther*. 2005;78:330-41.
25. Huo Y, Ge JB, Han YL, Wang JA, Wan Z, Li JP, et al. Expert consensus on intensive statin therapy for patients with acute coronary syndrome. *Chin J Intervent Cardiol*. 2014;22:4-6.
26. Joint committee issued Chinese guideline for the management of dyslipidemia in adults. Chinese guideline for the management of dyslipidemia in adults. *Chin Circ J*. 2016;32:937-53.
27. Chinese Medical Association in cardiovascular disease branch interventional cardiology group, Chinese Medical Doctor Association cardiovascular physician branch thrombus prevention and control Specialized Committee, Chinese Journal of cardiovascular disease editorial board. Guidelines for percutaneous coronary intervention in China (2016). *Chin J Cardiol*. 2016;44:382-400.

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

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