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The Impact Analysis of Different Lipid-Lowering Regimens and Major Adverse Cardiovascular Events in ACS Patients after PCI

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Abstract: *Background and Objective*: Intensive lipid-lowering therapy serves as a core intervention to improve the long-term prognosis of patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI). Currently, evidence-based clarification is still required for the efficacy discrepancies and applicable populations of three first-line lipid-lowering regimens: high-intensity statin monotherapy, statin plus ezetimibe, and statin plus proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i). This study aimed to systematically evaluate the impacts of these three regimens on major adverse cardiovascular events (MACE) in patients with ACS after PCI. *Methods*: We collected relevant randomized controlled trials (RCTs) and high-quality cohort studies on the three first-line regimens published from 2016 to 2022 worldwide. A random-effects model was adopted to analyze the risk of MACE in post-PCI ACS patients, and the therapeutic effects and sources of heterogeneity across different regimens were assessed. *Results*: Thirty-four studies with a total of 50,537 patients were finally included. The baseline characteristics were generally comparable between groups, and minor inter-group differences did not affect the analysis. (1) High-intensity statin significantly reduced the risk of MACE (RR = 0.52, 95% CI [0.37, 0.72], $p < 0.0001$), with pronounced benefits in Asian populations but no significant benefit in Western populations. (2) Statin combined with ezetimibe lowered the MACE risk (RR = 0.59, 95% CI [0.40, 0.87], $p = 0.007$), and the benefit was more significant in Asian populations (3) Statin combined with PCSK9i reduced the MACE risk (RR = 0.80, 95% CI [0.72, 0.89], $p < 0.0001$) with low heterogeneity, and the benefit was more prominent in Asian populations and on the basis of moderate-intensity statin. Only the high-intensity statin group presented a positive Egger test, which was a false positive driven by heterogeneity, and the pooled results were stable. *Conclusion*: All three intensive lipid-lowering regimens can reduce the risk of MACE in post-PCI ACS patients, with more significant benefits observed in Asian populations. Statin combined with PCSK9i shows a stable risk-reduction effect.

Keywords: Acute coronary syndrome; Percutaneous coronary intervention; Lipid-lowering regimen; Major adverse cardiovascular events

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1. Introduction

Acute coronary syndrome (ACS) is an acute cardiovascular event caused by the rupture/erosion of unstable atherosclerotic plaques in the coronary arteries, leading to subsequent coronary thrombosis and myocardial ischemia [1,2]. With the widespread adoption of percutaneous coronary intervention (PCI) treatment, the mortality rate during the acute phase of ACS patients has significantly decreased. However, the high incidence of major adverse cardiovascular events (MACE) after surgery remains a core issue affecting long-term prognosis.

Multiple studies have confirmed a clear dose-response relationship between serum low-density lipoprotein cholesterol (LDL-C) and atherosclerotic events [3]. Therefore, early and sufficient reduction of LDL-C in ACS-PCI patients remains the cornerstone of secondary prevention [1,4]. Current guidelines recommend intensive lipid-lowering therapy based on statins, with common strategies including high-intensity statins, moderate-intensity statins combined with cholesterol absorption inhibitors, or combined with PCSK9 inhibitors (PCSK9i) [5]. However, differences in the effectiveness of various regimens in improving prognosis and differences in real-world adherence significantly impact regimen selection [3].

Therefore, this study focuses on three first-line initial intensive lipid-lowering regimens currently prioritized by clinical guidelines and supported by the most robust evidence (high-intensity statins, statins combined with cholesterol absorption inhibitors, and statins combined with PCSK9i). It systematically compares their effects on postoperative MACE in ACS-PCI patients through a meta-analysis. The determination of statin intensity and dosage strictly adheres to the definitions outlined in the Chinese Guidelines for Lipid Management (2023) [6].

2. Materials and methods

2.1. Inclusion criteria (All must be met for inclusion)

The inclusion criteria are as follows:

(1) Study population: ACS patients who have undergone PCI and meet the diagnostic criteria for ACS (referencing the 2023 ESC Guidelines for Acute Coronary Syndromes [2]);

(2) Interventions: High-intensity statins, statins combined with cholesterol absorption inhibitors, statins combined with PCSK9i;

(3) Language: Chinese or English;

(4) Outcome measures: Clear definition of MACE and the number of events reported;

(5) Study type: Randomized controlled trials (RCTs) or high-quality cohort studies;

(6) Follow-up duration: Not limited, but must be clearly reported for subgroup analysis.

2.2. Exclusion criteria (Exclusion if anyone is met)

The exclusion criteria are as follows:

(1) Study population does not meet requirements (including stable coronary artery disease patients with no separate ACS data extraction or patients not undergoing PCI);

(2) Failure to report clinical prognosis indicators such as MACE;
(3) Extremely low-quality literature (sample size < 50 cases, no control group, chaotic data reporting);
(4) Low-quality secondary research or reviews without original data;
(5) Non-clinical secondary research without original data.

2.3. Search strategy

Literature was searched on Wanfang Medical Network, PubMed, CNKI, and Web of Science from January 2016 to December 2022. Chinese search terms included: "acute coronary syndrome," "acute myocardial infarction," "acute ST-segment elevation myocardial infarction," "acute non-ST-segment elevation myocardial infarction," "unstable angina," "percutaneous coronary intervention," "statins," "ezetimibe," "hybutimibe," "PCSK9i," "cholesterol absorption inhibitors," etc.

English search terms included: "Acute Coronary Syndrome," "Acute Myocardial Infarction," "ST Elevation Myocardial Infarction," "Non-ST Elevated Myocardial Infarction," "Angina, Unstable," "Percutaneous Coronary Intervention," "Angioplasty, Balloon, Coronary," "Hydroxymethylglutaryl-CoA Reductase Inhibitors," "Ezetimibe," "Hybutimibe," "PCSK9 Inhibitors," "Prognosis," "Treatment Outcome," "Cardiovascular Diseases," "Patient Safety," "Cholesterol Absorption Inhibitor." Search terms were flexibly replaced and combined according to the characteristics of each database.

2.4. Literature screening and quality assessment

Two researchers independently screened the retrieved literature based on inclusion and exclusion criteria, initially reading titles and abstracts for preliminary screening, and then reading the full text of potentially eligible studies to decide on inclusion. Disagreements were resolved through discussion between the two researchers or by a third researcher. RCTs were assessed for bias risk using the RoB 2.0 tool recommended by the Cochrane Collaboration, while cohort studies were evaluated for methodological quality using the NOS [7,8].

2.5. Data extraction

The following data were extracted from the literature: study name, total sample size (intervention group/control group), intervention group/control group regimens, follow-up duration, definition of MACE events, baseline gender ratio, baseline age, and baseline LDL-C levels. For studies with multiple intervention groups or control groups (multi-arm studies), corresponding analysis cohorts were included separately according to different lipid-lowering regimens to avoid duplication.

2.6. Statistical analysis methods

Meta-analysis was performed using RevMan 5.3 software and Rstudio 2025. The outcome measure MACE, a binary variable, was analyzed using risk ratio (RR) and 95% confidence interval (CI) as effect analysis statistics. A Mantel-Haenszel (M-H) random-effects model was used for pooled analysis, with I^2 values < 25%, 25%–75%, and >75% indicating low, moderate, and high heterogeneity, respectively. Sensitivity analysis was conducted by excluding studies one by one, and subgroup analysis was performed based on background statin intensity, geographic population, and follow-up duration. Publication bias was assessed using funnel plots combined with Egger's linear regression test. For multi-arm studies sharing the

same control group, the control group sample size and event count were split proportionally according to the number of comparison groups, as recommended by Cochrane, to avoid duplicate inclusion of the same control group; this treatment did not alter the total sample size or event count and had a negligible impact on pooled effect estimates.

3. Results

3.1. Literature search results and basic information of included studies

A total of 2,345 articles were retrieved according to the search strategy, including 533 from Wanfang Medonline, 1,345 from CNKI, 355 from PubMed, and 112 from Web of Science. The detailed screening process is shown in **Figure 1**. A total of 34 studies were finally included [9-42], of which 31 were RCTs [9-16,18-23,25-28,30-42] and 3 were cohort studies [17,24,29]. Due to insufficient numbers of relevant studies and high data heterogeneity, regimens such as cholesterol absorption inhibitors combined with PCSK9i, statins combined with Hybutimibe, and statins combined with cholesterol absorption inhibitors plus PCSK9i (triple therapy) were not included. A total of 50,537 patients were enrolled, including 24,818 in the experimental groups and 25,719 in the control groups. The shared control groups from multi-arm studies (Ran_2017[13], Yuan_2018[16], Xinyu Feng_2019[34]) were split according to prespecified methods in all subsequent analyses [13,16,32]. The basic characteristics of the included studies are shown in **Table 1**.

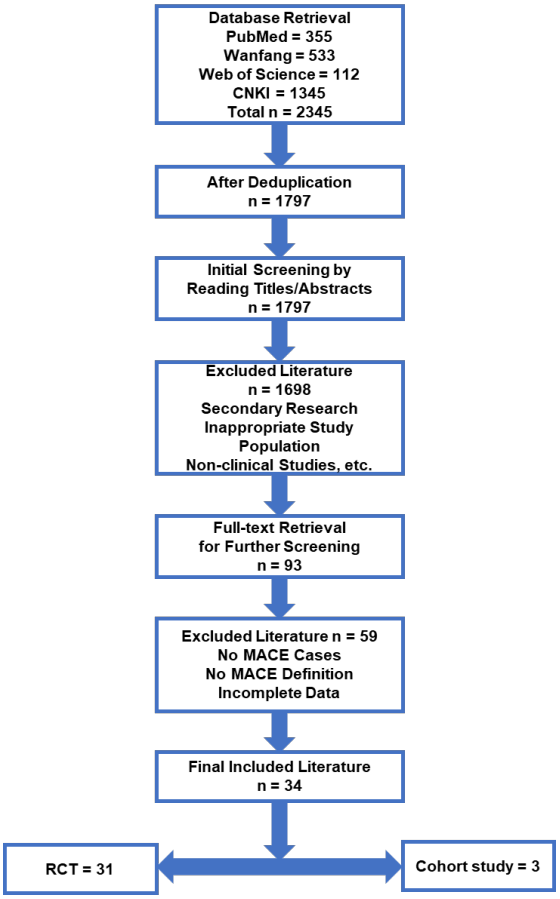

Figure 1. PRISMA flow diagram.

Table 1. Basic characteristics of included studies

Included Study	Total Sample Size (Intervention/Control)	Intervention Group Regimen	Control Group Regimen	MACE Definition	Follow-up Duration
Berwanger_2018 [25]	4191 (2087/2104)	Atorvastatin 80 mg/d	Atorvastatin 40 mg/d	①②③④	12 months
Guo_2017 [14]	92 (47/45)	Rosuvastatin 20 mg/d	Rosuvastatin 10 mg/d	①②④	12 months
He_2020 [9]	192 (97/95)	Atorvastatin 80 mg/d, Rosuvastatin 20 mg/d, Simvastatin 40 mg/d	Atorvastatin 40 mg/d, Rosuvastatin 10 mg/d, Simvastatin 20 mg/d	①③④⑤⑩	6 months
Im_2018 [10]	2000 (1000/1000)	Atorvastatin 40 mg/d	Atorvastatin 20 mg/d	①②③④⑧⑨⑩	12 months
Li_2017 [15]	120 (60/60)	High-intensity Atorvastatin	Moderate-intensity Atorvastatin	①②⑤⑥	12 months
LiuQ_2019 [11]	265 (133/132)	Atorvastatin 40 mg/d	Atorvastatin 20 mg/d	①②④	12 months
LiuZ_2016 [12]	798 (400/398)	High-intensity Atorvastatin	Moderate-intensity Atorvastatin	①②④	12 months
Yuan_2018 [16] a	88 (41/47b)	High-intensity Statin	Moderate-intensity Statin	①②③④⑤	12 months
Ran_2017 [13] a	83 (41/42b)	High-intensity Rosuvastatin	Moderate-intensity Rosuvastatin	①②③④⑤	12 weeks
Furtado_2022 [18]	17073 (8510/8563)	Evolocumab + High-intensity Statin	High-intensity Statin	①②③④⑤	2.2 years
Koskinas_2019 [19]	308 (155/153)	Evolocumab + High-intensity Atorvastatin	High-intensity Atorvastatin	①②③④⑦⑩	8 weeks
Leucker_2020 [20]	57 (30/27)	Evolocumab + High-intensity Statin	High-intensity Statin	①②③⑤	30 days
Mehta_2022 [21]	68 (38/30)	Alirocumab + High-intensity Statin	High-intensity Statin	①②③⑦	6 weeks
Okada_2022 [22]	102 (52/50); final analysis 98 (49/49)	Evolocumab + Moderate-intensity Pitavastatin	Moderate-intensity Pitavastatin	①	4 weeks
Räber_2022 [23]	300 (148/152); final analysis 265 (130/135)	Alirocumab + High-intensity Rosuvastatin	High-intensity Rosuvastatin	④	52 weeks
Schwartz_2018 [30]	18924 (9462/9462)	Alirocumab + High-intensity Statin	High-intensity Statin	①②③⑤	Median 2.8 years
Xu_2021 [17]	334 (96/238)	Evolocumab + Moderate-intensity Statin	Moderate-intensity Statin	②④	12 weeks
Zhang_2022 [24]	1564 (414/1150)	Evolocumab + Moderate-intensity Statin	Moderate-intensity Statin	①②③④⑤	18 months
Yuan_2018 [16] a	85 (38/47b)	Moderate-intensity Statin + Ezetimibe	Moderate-intensity Statin	①②③④⑤	12 months
Sun_2021 [27]	171 (81/90)	Rosuvastatin 20 mg/d + Ezetimibe	Rosuvastatin 20 mg/d	①②③④⑤	3 months
Dai_2017 [29]	173 (55/115)	Moderate-intensity Statin + Ezetimibe	Moderate-intensity Statin	①②③④	6 months
Deng_2021 [26]	90 (42/48)	Moderate-intensity Atorvastatin + Ezetimibe	Moderate-intensity Atorvastatin	②④⑤	12 months
Hagiwara_2017 [31]	1734 (864/857)	Moderate-intensity Pitavastatin + Ezetimibe	Moderate-intensity Pitavastatin	①②③④⑤	Median 3.86 years
Hibi_2018 [28]	128 (50/53)	Moderate-intensity Pitavastatin + Ezetimibe	Moderate-intensity Pitavastatin	①②④	10 months

Jianhua Li_2022 [32]	76 (38/38)	Atorvastatin 40 mg/d	Atorvastatin 20 mg/d	②④	1 month
Jinghua Wei_2020 [33]	200 (100/100)	Atorvastatin 40 mg/d	Atorvastatin 20 mg/d	①②⑤⑦	1 month
Xinyu Feng_2019 [34] a	70 (35/35b)	Rosuvastatin 20 mg/d	Rosuvastatin 10 mg/d	①②③④⑤	6 months
Yi Jin_2019 [35]	100 (50/50)	Atorvastatin 40 mg/d	Atorvastatin 20 mg/d	①②⑦	1 month
Honghe Liu_2020 [36]	80 (40/40)	Atorvastatin 40 mg/d	Atorvastatin 20 mg/d	①②④⑩	1 month
Zhixian Chen_2020 [40]	120 (60/60)	Rosuvastatin 10 mg/d + Ezetimibe	Rosuvastatin 10 mg/d	②④⑤	12 months
Chuanxi Zhang_2022 [37]	70 (35/35)	Rosuvastatin 10 mg/d + Ezetimibe	Rosuvastatin 10 mg/d	②⑤⑥⑦	12 months
Xinyu Feng_2019 [34] a	69 (34/35b)	Rosuvastatin 10 mg/d + Ezetimibe	Rosuvastatin 10 mg/d	①②③④⑤	6 months
Jingjing Cai_2022 [38]	500 (250/250)	Evolocumab + Moderate-intensity Statin	Moderate-intensity Statin	①②④⑤⑦	12 weeks
Juan Zhao_2022 [41]	120 (60/60); final analysis 115 (57/58)	Alirocumab + Rosuvastatin 10 mg/d	Rosuvastatin 10 mg/d	①②④	6 months
Liuqing Yang_2022 [39]	207 (103/104); final analysis 198 (98/100)	Evolocumab + Atorvastatin 20 mg/d	Atorvastatin 20 mg/d	①②④	10 months
Hua Yang_2020 [42]	65 (32/33)	Evolocumab + Atorvastatin 20 mg/d	Atorvastatin 20 mg/d	①②④⑦	6 months
Ran_2017 [13] a	84 (42/42b)	Ezetimibe + Moderate-intensity Rosuvastatin	Moderate-intensity Rosuvastatin	①②③⑤⑦	12 weeks

Note: In the definition of MACE, ① cardiovascular death, ② non-fatal myocardial infarction, ③ non-fatal stroke/TIA, ④ unplanned coronary revascularization, ⑤ recurrent angina, ⑥ malignant arrhythmia, ⑦ heart failure, ⑧ renal function deterioration, ⑨ peripheral artery intervention, and ⑩ rehospitalization for cardiac events.

High-intensity statins: Atorvastatin 40-80 mg; Rosuvastatin 20 mg.

Moderate-intensity statins: Atorvastatin 10-20 mg; Rosuvastatin 5-10 mg; Pitavastatin 1-4 mg.

a indicates that the study is a multi-arm study, with different interventions compared separately as independent analysis units included in the meta-analysis, and the shared control group has been split according to the preset method; b indicates the sample size of the shared control group in the multi-arm study.

3.2. Quality assessment of included studies

Among the 34 included studies, there are 31 RCTs and 3 cohort studies [9–42]. Among the RCTs, a few studies have uncertain risks in terms of random sequence generation, outcome measurement, or completeness of reporting, but the overall risk of bias is low. The quality assessments of the cohort studies all scored above 7 points, indicating a generally high quality of the literature (**Table 2** and **Table 3**).

Table 2. Risk of bias in included RCTs

Study	Randomization process	Deviations from intended intervention	Missing outcome data	Outcome measurement	Reporting bias	Overall risk of bias
Berwanger_2018 [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Guo_2017 [14]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
He_2020 [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Im_2018 [10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li_2017 [15]	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
LiuQ_2019 [11]	Some concerns	Low risk	Low risk	Some concerns	Some concerns	Some concerns
LiuZ_2016 [12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Furtado_2022 [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Koskinas_2019 [19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Leucker_2020 [20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mehta_2022 [21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Okada_2022 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Räber_2022 [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schwartz_2018 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yuan_2018 [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sun_2021 [27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Deng_2021 [26]	Low risk	Low risk	Low risk	Some concerns	Some concerns	Some concerns
Hagiwara_2017 [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hibi_2018 [28]	Low risk	Low risk	Low risk	Some concerns	Some concerns	Some concerns
Jianhua Li_2022 [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jinghua Wei_2020 [33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xinyu Feng_2019 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yi Jin_2019 [35]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Honghe Liu_2020 [36]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Zhixian Chen_2020 [40]	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Chuanxi Zhang_2022 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jingjing Cai_2022 [38]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Juan Zhao_2022 [41]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Liuqing Yang_2022 [39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hua Yang_2020 [42]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Ran_2017 [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 3. Risk of bias in included cohort studies

Study ID	Study Population Selection (0-4 points)	Comparability (0-2 points)	Exposure/Outcome Measurement (0-3 points)	Total Score (0-9 points)	Quality Grade (≥ 7 = High Quality)
Xu_2021 [17]	4 points	2 points	2 points	8 points	High quality
Zhang_2022 [24]	3 points	2 points	2 points	7 points	High quality
Dai_2017 [29]	4 points	2 points	2 points	8 points	High quality

3.3. Meta-analysis

3.3.1. High-intensity statin therapy reduces the incidence of MACE in ACS patients after PCI

A total of 14 studies were included, with comparable baseline characteristics between groups (all $p > 0.05$), as detailed in **Table 4** [9–16,25,32–36]. Analysis using the Mantel-Haenszel (M-H) random-effects model (**Figure 2**) revealed that, compared to moderate-intensity statin therapy, high-intensity statin treatment significantly reduced the risk of MACE in ACS patients undergoing PCI (RR = 0.52, 95% CI [0.37, 0.72], $p < 0.0001$), although moderate heterogeneity was observed ($I^2 = 70\%$, $p < 0.0001$).

After excluding each study one by one, the pooled RR remained stable between 0.47 and 0.57 (all $p < 0.05$), indicating robust results (**Table 5**). After excluding the study by Berwanger_2018, the heterogeneity I^2 decreased to 42%, suggesting that this study may be the primary source of heterogeneity [25]. However, the pooled effect remained stable, supporting the conclusion of the benefits of high-intensity statin therapy in ACS patients undergoing PCI.

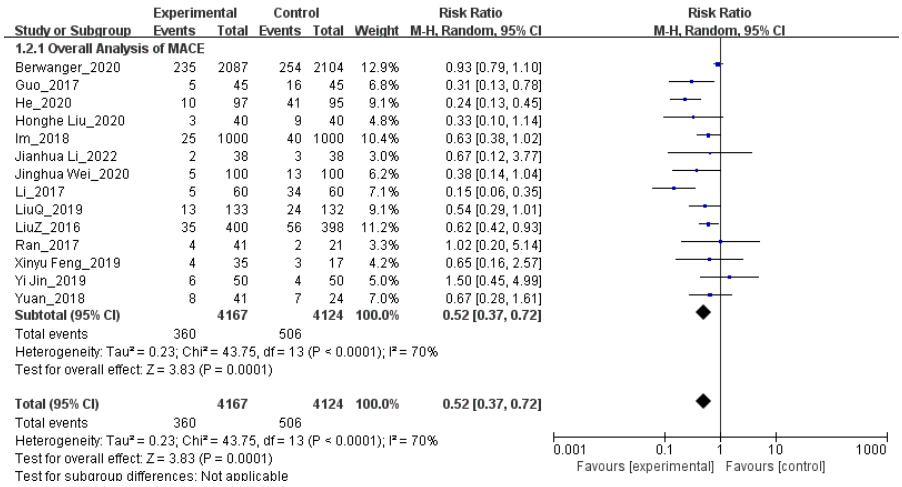

Figure 2. Forest plot of the impact of high-intensity statin therapy on major adverse cardiovascular events (MACE) in ACS patients after PCI. Note: The analysis was conducted using a random-effects model.

Table 4. Baseline characteristics table of the included studies

Included Study	Age (years)[1]		Male (%)				Inter-group Comparability
	Intervention	Control	Intervention	Control	Intervention	Control	
Berwanger_2018 [25]	61.7 (11.3)	61.9 (11.7)	1581/2031 (75.8)	1525/2104 (72.5)	2.87 (1.10)	2.84 (1.06)	All p >0.05
Guo_2017 [14]	57.8 (6.4)	62.3 (3.7)	20/47 (42.56)	26/45 (57.78)	Not reported	Not reported	LDL-C not reported; all other variables p > 0.05
He_2020 [9]	67.28 (7.51)	69.06 (7.81)	49/97 (50.52)	44/95 (46.32)	3.11 (1.4)	3.13 (1.4)	All p > 0.05

Honghe Liu_2020 [36]	Not reported	Not reported	21/40 (52.50)	22/40 (55.00)	4.11 (0.72)	4.07 (0.84)	Described in text: "No difference in age between groups"; all other variables p > 0.05
Im_2018 [10]	64 (12)	64 (12)	714/1000 (71.4)	701/1000 (70.1)	3.08 (1.16)	3.09 (1.12)	All $p > 0.05$
Jianhua Li_2022 [32]	48.75 (4.38)	48.57 (4.26)	20/38 (52.63)	19/38 (50)	4.66 (1.28)	4.65 (1.22)	All $p > 0.05$
Jinghua Wei_2020 [33]	60.03 (6.74)	58.76 (6.69)	58/100 (58)	55/100 (55)	3.50 (0.32)	3.49 (0.30)	All $p > 0.05$
Li_2017 [15]	61.65 (10.32)	61.68 (10.28)	32/60 (53.33)	33/60 (55)	2.74 (0.75)	2.75 (0.77)	All $p > 0.05$
LiuQ_2019 [11]	58.4 (15.7)	60.5 (16.1)	97/133 (72.9)	94/132 (71.2)	3.8 (1.1)	3.7 (0.9)	All $p > 0.05$
LiuZ_2016 [12]	61.8 (10.1)	62.5 (11.2)	293/400 (73.3)	284/398 (71.4)	3.4 (0.9)	3.4 (1.1)	All $p > 0.05$
Ran_2017 [13] *	60.5 (10.0)	60.6 (6.7)	30/41 (73.2)	31/42 (73.8)	3.65 (0.91)	3.65 (0.85)	All $p > 0.05$
Xinyu Feng_2019 [34] *	61 (8)	61 (8)	28/35 (80)	26/35 (74)	2.19 (0.78)	2.19 (0.78)	All $p > 0.05$
Yi Jin_2019 [35]	55.9 (9.1)	56.3 (8.7)	29/50 (58)	31/50 (62)	2.97 (0.46)	2.96 (0.48)	All $p > 0.05$
Yuan_2018 [16] *	Not reported	Not reported	Not reported	Not reported	3.30 (0.88)	3.08 (0.74)	Described in text: "No difference in age or gender" between groups

Note: 1. Age and LDL-C data are presented as "mean (standard deviation)" or "median (interquartile range)", depending on the original reporting format. 2. The study reports the median and interquartile range (or range). 3. Baseline LDL-C values were converted from mg/dL to mmol/L (conversion factor: 1 mg/dL = 0.0259 mmol/L).

This table only includes comparisons related to high-intensity statin therapy; * indicates that the study is a multi-arm trial, and its control group is shared with other comparisons.

Table 5. Summary of sensitivity analysis results for high-intensity statin therapy

Excluded Study	Pooled RR [95% CI]	*p*-value(Effect)	I^2	*p*-value (Heterogeneity)
Original pooled	0.52 [0.37, 0.72]	< 0.0001	70%	0.0001
Berwanger_2018 [25]	0.47 [0.35, 0.64]	< 0.00001	44%	0.05
Guo_2017 [14]	0.54 [0.38, 0.76]	0.0004	70%	< 0.0001
He_2020 [9]	0.56 [0.41, 0.78]	0.0004	61%	0.002
Honghe Liu_2020 [36]	0.53 [0.37, 0.75]	0.0003	72%	< 0.0001
Im_2018 [10]	0.50 [0.34, 0.74]	0.0004	72%	< 0.0001
Jianhua Li_2022 [32]	0.51 [0.36, 0.72]	0.0002	73%	< 0.0001
Jinghua Wei_2020 [33]	0.53 [0.37, 0.75]	0.0003	72%	< 0.0001
Li_2017 [15]	0.57 [0.42, 0.78]	0.0002	60%	0.003
LiuQ_2019 [11]	0.51 [0.35, 0.74]	0.0004	72%	< 0.0001
LiuZ_2016 [12]	0.50 [0.34, 0.74]	0.0006	72%	< 0.0001
Ran_2017 [13]	0.50 [0.35, 0.71]	0.0001	72%	< 0.0001
Xinyu Feng_2019 [34]	0.51 [0.36, 0.73]	0.0002	73%	< 0.0001
Yi Jin_2019 [35]	0.49 [0.34, 0.69]	< 0.0001	72%	< 0.0001
Yuan_2018 [16]	0.50 [0.35, 0.72]	0.0002	73%	< 0.0001

Subgroup analysis based on the geographical regions of the study populations revealed the following results (**Figure 3**):

(1) In the "Western" group (1.3.1 in **Figure 3**, comprising 2 studies [10,25]), no significant benefit of high-intensity statins in reducing MACE was observed (RR = 0.82, 95% CI [0.57, 1.18], $p = 0.29$), with moderate heterogeneity within the group;

(2) In the "Asian" group (1.3.2 in **Figure 3**, comprising 12 studies), high-intensity statins significantly reduced the risk of MACE in Asian patients with ACS undergoing PCI (RR = 0.45, 95% CI [0.32, 0.64], $p < 0.00001$), with moderate heterogeneity within the group [9,11–16,32–36]. There was a statistically significant difference between subgroups ($p = 0.02$, $I^2 = 80.9\%$), suggesting that geographical region is an important source of overall heterogeneity.

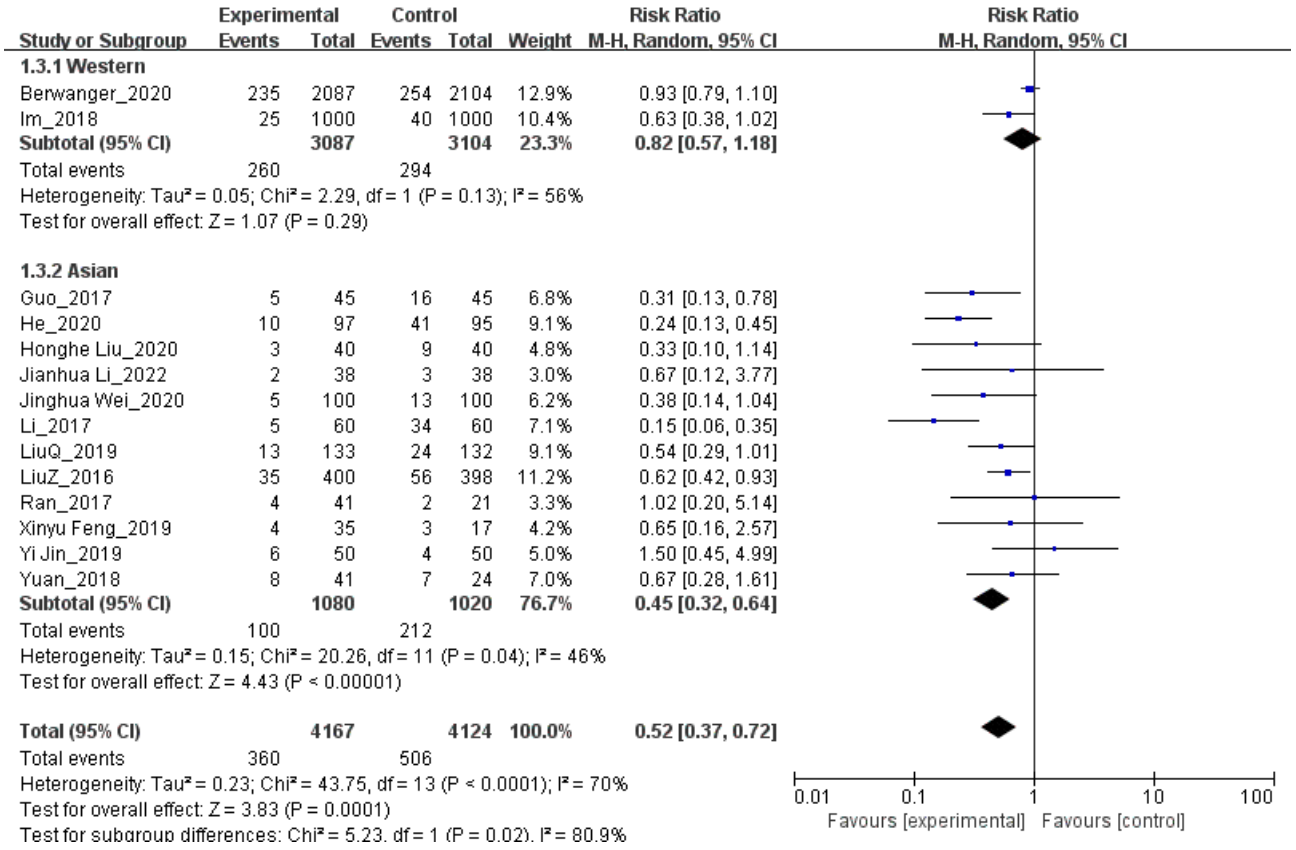

Figure 3. Subgroup analysis forest plot of the intervention effects of high-intensity statins among populations from different regions. Note: A random-effects model was used for the analysis.

The funnel plot is generally symmetrical, with studies primarily distributed around the pooled effect size (RR = 0.52). The vast majority of studies fall within the funnel boundaries of the 95% confidence interval. However, the results of the Egger test suggest the presence of publication bias ($t = -2.55$, $p < 0.05$) (**Figure 4**).

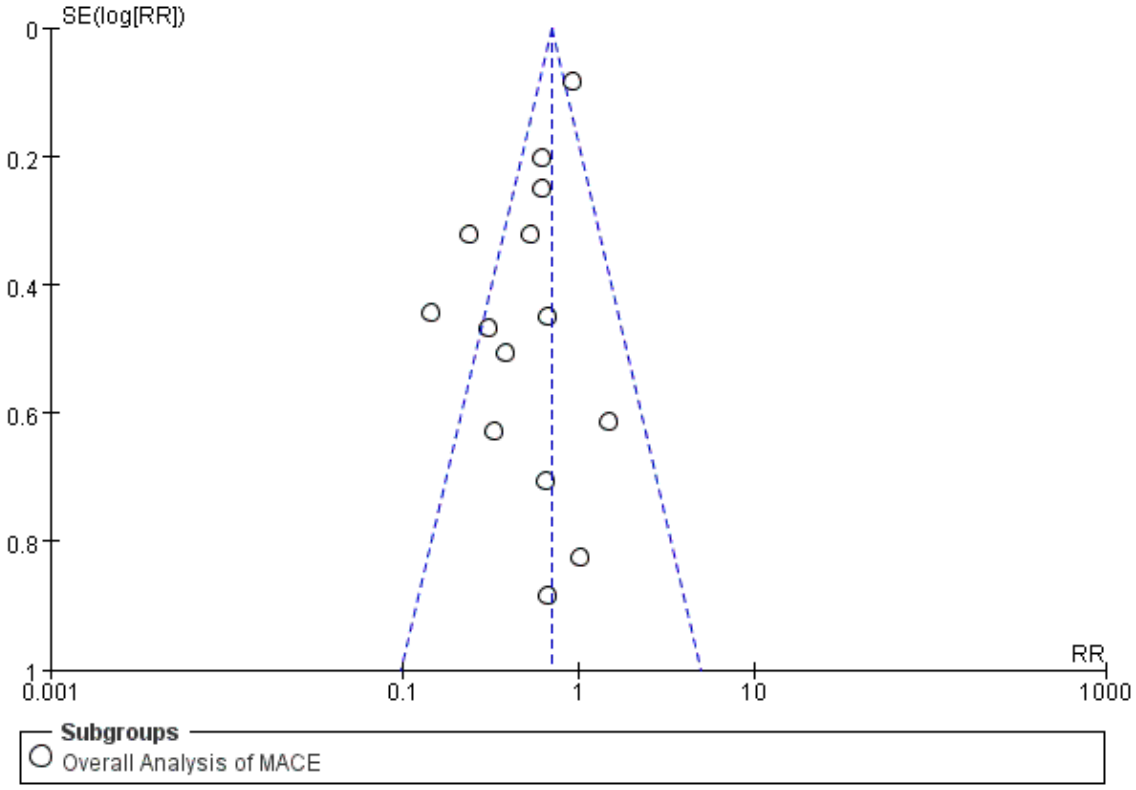

Figure 4. Funnel plot for the high-intensity statin group.Note: This funnel plot was drawn based on a fixed-effects model, while a random-effects model was used for the actual pooled analysis.

3.3.2. Statin combined with ezetimibe reduces the incidence of major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI)

Ten studies were included, with specific baseline characteristics detailed in **Table 6** [13,16,26–29,31,34,37,40]. Apart from the statistically significant differences in baseline LDL-C levels between groups in the studies by Dai_2017 and Yuan_2018 (both $p < 0.001$), the overall comparability among the other studies was notable [16,29]. Considering that these differences were only present in a minority of studies and that the overall sample size of the included studies was large, it was deemed that these differences did not significantly impact the overall pooled effect. Therefore, overall comparability between groups was maintained. The analysis using the Mantel-Haenszel (M-H) random-effects model (**Figure 5**) revealed that compared to statin monotherapy, the combination of statin and ezetimibe significantly reduced the risk of MACE in patients with ACS undergoing PCI (RR = 0.59, 95% CI [0.40, 0.87], $p = 0.007$), with moderate heterogeneity among studies ($I^2 = 57\%$, $p = 0.01$).

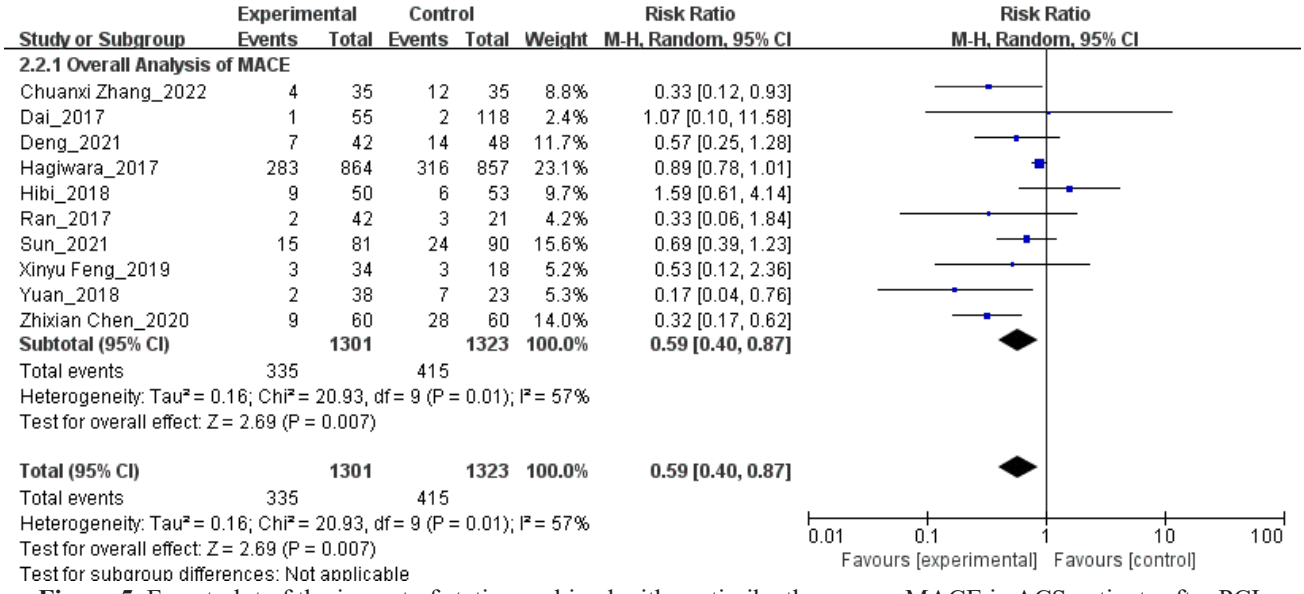

Figure 5. Forest plot of the impact of statin combined with ezetimibe therapy on MACE in ACS patients after PCI.
Note: A random-effects model was used for the analysis.

Table 6. Baseline characteristics of the included studies

Included Study	Age (years)[1]		Male(%)		Baseline[1,3] LDL-C (mmol/L)		Comparability Between Groups
	Intervention	Control	Intervention	Control	Intervention	Control	
Chuanxi Zhang_2022 [37]	56.28 (9.39)	57.52 (10.03)	21/35 (60.00)	25/35 (71.43)	3.20 (0.51)	3.15 (0.48)	All $p > 0.05$
Dai_2017 [29]	60.02 (9.81)	60.58 (9.04)	41/55 (74.5)	94/118 (79.7)	3.21 (0.95)	2.60 (0.85)	Baseline LDL-C $p < 0.001$; all other variables $p > 0.05$
Deng_2021 [26]	Not reported	Not reported	Not reported	Not reported	2.55 (0.79)	2.70 (1.41)	Baseline LDL-C $p > 0.05$; age and sex not reported
Hagiwara_2017 [31]	65.7 (11.7)	65.5 (11.9)	661/857 (77.1)	639/864 (74.0)	3.49 (0.76)	3.51 (0.78)	All $p > 0.05$
Hibi_2018 [28]	63 (10)	63 (12)	41/82 (50.0)	41/77 (53.2)	3.18 (0.83)	3.26 (0.85)	All $p > 0.05$
Ran_2017 [13] *	60.4 (8.2)	60.6 (6.7)	32/42 (76.2)	31/42 (73.8)	3.65 (0.70)	3.65 (0.80)	All $p > 0.05$
Sun_2021 [27]	61.74 (8.78)	64.08 (10.45)	55/81 (67.9)	63/90 (70.0)	2.95 (0.85)	2.94 (1.06)	All $p > 0.05$
Xinyu Feng_2019 [34]*	59 (9)	61 (8)	24/34 (70.59)	26/35 (74.29)	2.61 (0.84)	2.59 (0.88)	All $p > 0.05$
Yuan_2018 [16] *	Not reported	Not reported	Not reported	Not reported	3.92 (1.05)	3.08 (0.74)	Baseline LDL-C $p < 0.001$; authors stated "no differences in age and sex"
Zhixian Chen_2020 [40]	66.35 (13.42)	68.12 (16.27)	49/60 (81.67)	52/60 (86.67)	2.76 (0.63)	2.75 (0.56)	All $p > 0.05$

Note: 1. Age and LDL-C data are presented as "mean (standard deviation)" or "median (interquartile range)" depending on the original reporting format. 2. The study reports median and interquartile range. 3. Baseline LDL-C was converted from mg/dL to mmol/L (conversion factor: 1 mg/dL = 0.0259 mmol/L). This table includes only comparisons related to statin combined with ezetimibe; * indicates that the study is a multi-arm

trial, and its control group is shared with other comparisons.

After excluding studies one by one, the combined relative risk (RR) fluctuated between 0.52 and 0.68 (all $p < 0.05$), indicating robust results (**Table 7**). After excluding the study Hagiwara_2017, the overall heterogeneity decreased from 57% to 32% ($p = 0.16$); similarly, excluding the study Zhixian Chen_2020 resulted in a significant reduction in overall heterogeneity to 37% ($p = 0.12$), suggesting that these two studies are the primary sources of heterogeneity [31,40]. However, the combined effect size remained statistically significant after their exclusion.

Table 7. Summary of sensitivity analysis results for statin combined with ezetimibe therapy

Excluded Study	Pooled RR [95% CI]	*p*-value (Overall Effect)	I^2	*p*-value for Heterogeneity
Original pooled	0.59 [0.40, 0.87]	0.007	57%	0.01
Chuanxi Zhang_2022 [37]	0.62 [0.42, 0.93]	0.02	55%	0.02
Dai_2017 [29]	0.58 [0.39, 0.86]	0.007	62%	0.007
Deng_2021 [26]	0.58 [0.38, 0.90]	0.01	60%	0.01
Hagiwara_2017 [31]	0.52 [0.35, 0.79]	0.002	32%	0.16
Hibi_2018 [28]	0.53 [0.35, 0.79]	0.002	58%	0.01
Ran_2017 [13]	0.60 [0.40, 0.90]	0.01	60%	0.01
Sun_2021 [27]	0.56 [0.35, 0.89]	0.01	61%	0.008
Xinyu Feng_2019 [34]	0.59 [0.39, 0.88]	0.01	61%	0.008
Yuan_2018 [16]	0.64 [0.45, 0.92]	0.02	52%	0.03
Zhixian Chen_2020 [40]	0.68 [0.48, 0.97]	0.03	37%	0.12

Subgroup analyses were conducted based on background statin intensity, geographic region of the study population, and follow-up duration, with the results shown in detail in **Figures 6**, **7**, and **8** as follows:

(1) In the "moderate-intensity background statin" group (2.3.1 in **Figure 6**, encompassing 9 studies), the combination of ezetimibe with moderate-intensity statins significantly reduced the risk of major adverse cardiovascular events (MACE) in patients with ACS undergoing PCI (RR = 0.56, 95%CI [0.35, 0.89], $p = 0.01$), with moderate heterogeneity within the group [13,16,26,28,29,31,34,37,40];

(2) In the "high-intensity background statin" group (2.3.2 in **Figure 6**, involving 1 study), no significant benefit was observed with the addition of ezetimibe (RR = 0.69, 95%CI [0.39, 1.23], $p = 0.21$) [27]. The p-value for the test of differences between subgroups was 0.56 (I^2=0%), indicating no statistically significant impact of background statin intensity on treatment efficacy; however, the limited number of studies in the high-intensity statin subgroup and the consequent limited statistical power necessitate cautious interpretation of the results.

(3) In the "Western" subgroup (2.3.3 in **Figure 7**, involving 1 study), the addition of ezetimibe did not significantly reduce the risk of MACE in Western patients with ACS undergoing PCI (RR = 1.59, 95 %CI [0.61, 4.14], $p = 0.34$) [28];

(4) In the "Asian" subgroup (2.3.4 in **Figure 7**, including 9 studies), the combination of ezetimibe reduced the risk of MACE by 47% in Asian patients with ACS undergoing PCI (RR = 0.53, 95%CI [0.35, 0.79], $p = 0.002$), with moderate heterogeneity within the subgroup [13,16,26,27,29,31,34,37,40]. The p-value for the test of differences between subgroups was 0.04, with $I^2 = 76.8\%$, suggesting that geographic region is the primary source of overall heterogeneity, and that Asian patients with ACS undergoing PCI derive significantly greater clinical benefit from statin-ezetimibe combination therapy than their Western counterparts; however, the limited number of studies in the Western group means that these results should be considered as reference only.

(5) In the " ≥ 12 months follow-up period" group (2.3.5 in **Figure 8**, involving 4 studies), the addition of ezetimibe significantly reduced the risk of MACE in patients with ACS undergoing PCI when the follow-up duration was ≥ 12 months (RR = 0.48, 95% CI [0.24, 0.98], $p = 0.04$), with high heterogeneity within the subgroup [16,26,31,40];

(6) In the "<12 months follow-up period" group (2.3.6 in **Figure 8**, including 6 studies), the addition of ezetimibe did not significantly reduce the risk of MACE when the follow-up duration was < 12 months (RR = 0.68, 95% CI [0.42, 1.08], $p = 0.10$), with low heterogeneity within the subgroup [13,27–29,34,37]. The difference between subgroups was not significant ($p = 0.44$, $I^2 = 0\%$), and follow-up duration is not currently considered the primary source of heterogeneity.

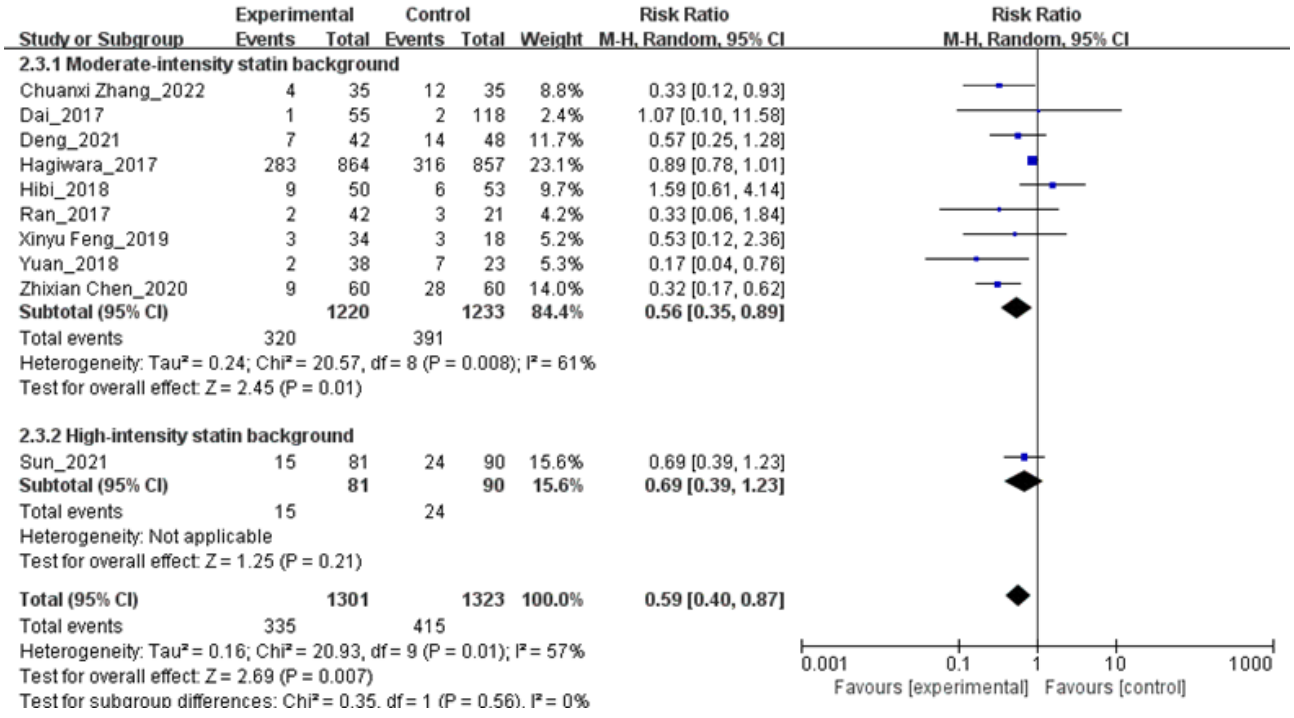

Figure 6. Forest plot of subgroup analysis on the intervention effects of statin combined with ezetimibe across different background statin intensities.Note: A random-effects model was used for the analysis.

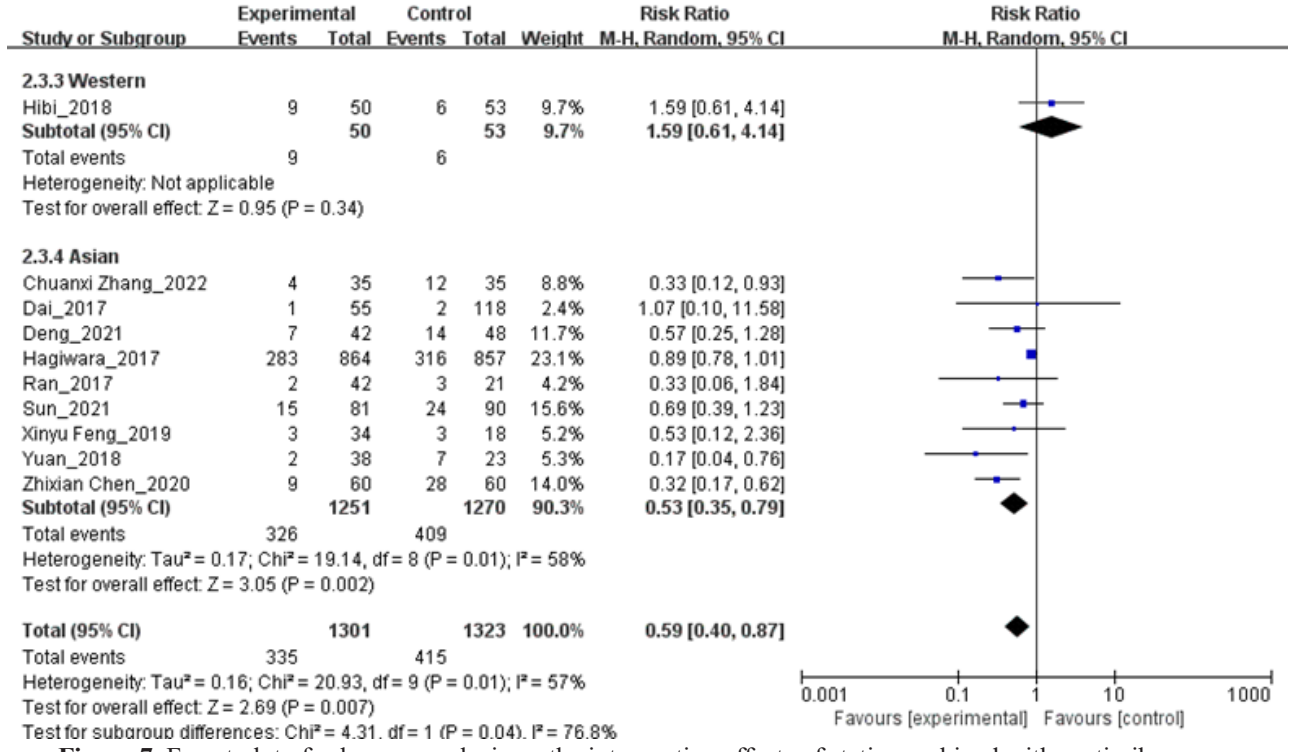

Figure 7. Forest plot of subgroup analysis on the intervention effects of statin combined with ezetimibe across populations from different geographical regions. Note: A random-effects model was employed for the analysis.

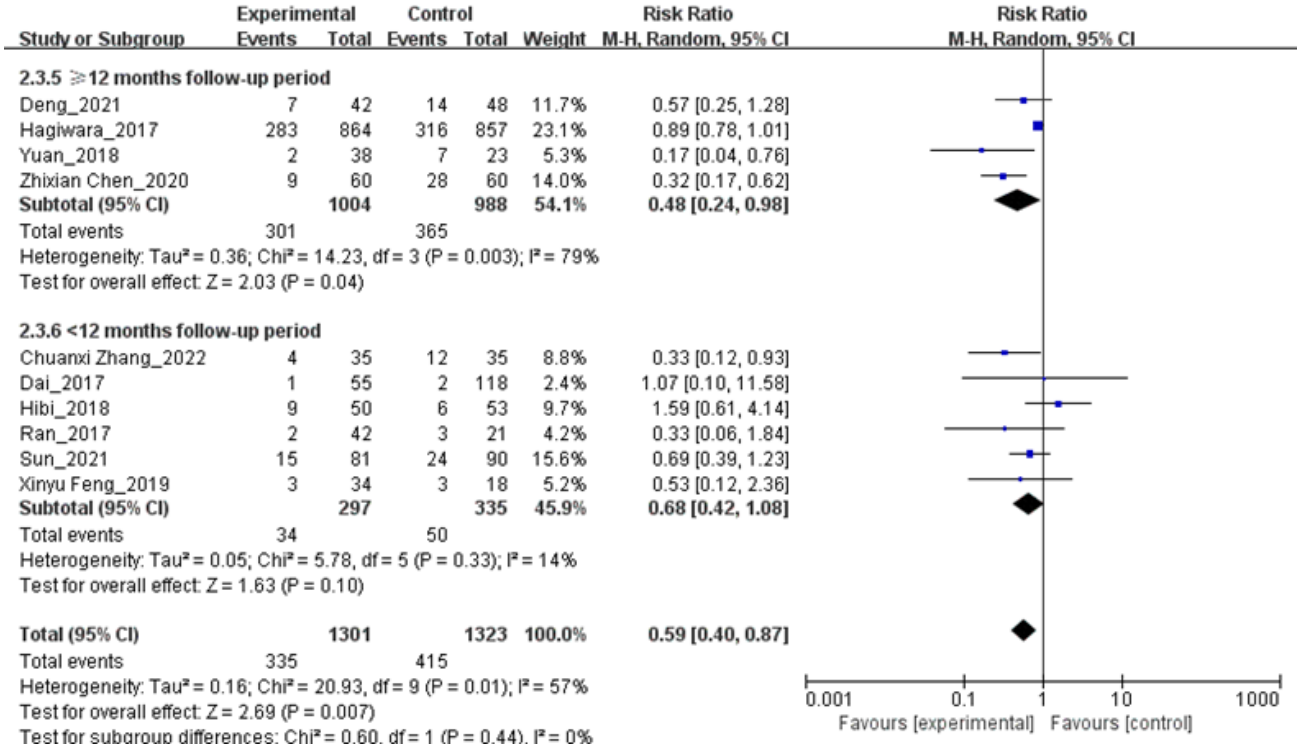

Figure 8. Forest plot of subgroup analysis on the intervention effects of statin combined with ezetimibe across different follow-up durations.Note: A random-effects model was used for the analysis.

In the funnel plot, the studies are roughly symmetrically distributed around the pooled effect size (RR = 0.59), with only a very small number (2 studies) falling outside the 95% confidence interval. Egger's test indicates no significant publication bias among the included studies (t = -2.23, p = 0.06) (**Figure 9**).

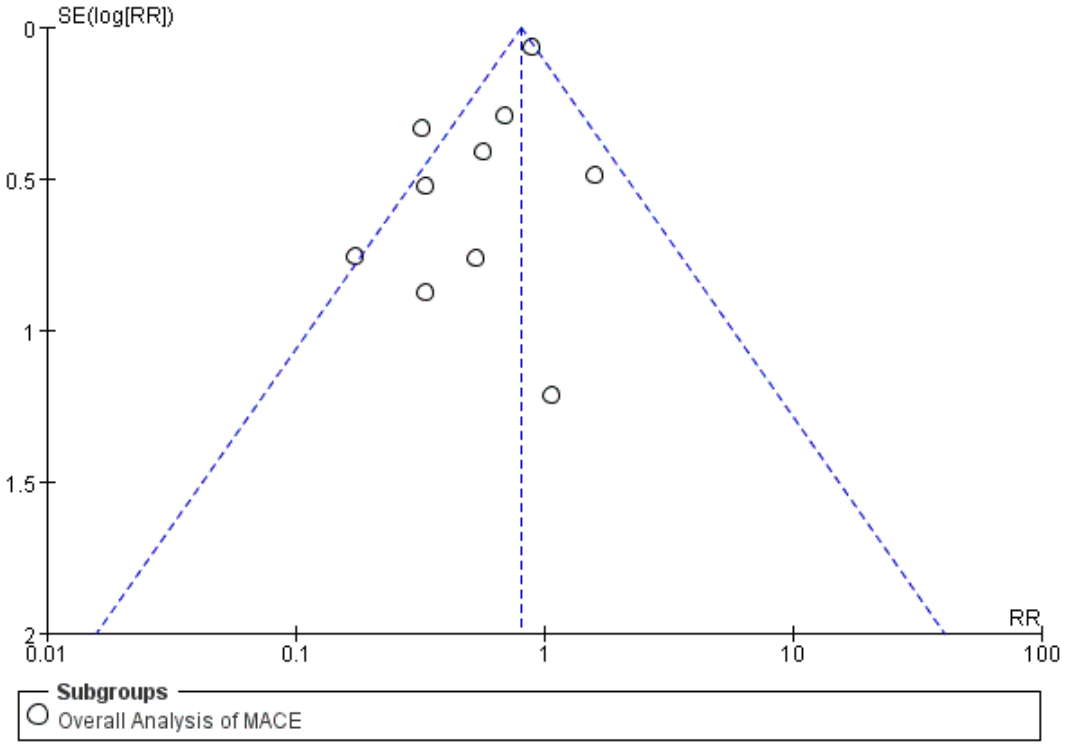

Figure 9. Funnel plot of the statin combined with ezetimibe groupNote: This funnel plot was drawn based on a fixed-effects model, while a random-effects model was employed for the actual pooled analysis.

3.3.3. Statin combined with PCSK9i can significantly reduce the incidence of MACE in ACS patients after PCI

A total of 13 studies were included [17–24,33,38,39,41,42]. In 9 studies, there were no statistically significant differences in core baseline characteristics such as age, gender, and baseline LDL-C between the two groups (p > 0.05) [18,19,22,24,33,38,39,41,42]. Only in the studies by Leucker 2020 and Mehta 2022 were there statistically significant differences in gender proportions (p = 0.03) [20,21]. In the studies by Räber 2022 and Xu 2021, there were statistically significant differences in baseline LDL-C levels (p < 0.05), as detailed in **Table 8** [17,23]. These differences were limited to single indicators, and there was no imbalance in multiple core indicators, indicating good overall comparability between groups. The analysis using a random-effects model revealed (**Figure 10**) that compared to statin monotherapy, statin combined with PCSK9i significantly reduced the risk of MACE in ACS-PCI patients (RR = 0.80, 95% CI [0.72, 0.89], p < 0.0001), with low heterogeneity (I^2 = 25%, p = 0.19).

Table 8. Baseline characteristics of included studies

Study	Age (years)		Male (%)		Baseline LDL-C (mmol/L)		Baseline LDL-C (mmol/L)
	Intervention	Control	Intervention	Control	Intervention	Control	
Furtado 2022 [18]	622 (55, 68)	622 (55, 68)	Not reported	Not reported	2.37 (2.06, 2.80)	2.37 (2.06, 2.80)	The original text described "no differences in age, sex, and baseline LDL-C between the two groups"
Hua Yang_2020 [42]	61.00 (10.00)	58.00 (9.00)	23/32 (71.88)	21/33 (63.64)	2.80 (1.20)	2.80 (1.10)	All $p > 0.05$
Jingjing Cai_2022 [38]	59.08 (11.67)	61.00 (10.77)	198/250 (79.20)	212/250 (84.80)	3.77 (0.91)	3.07 (0.80)	All $p > 0.05$
Juan Zhao_2022 [41]	59.12 (10.74)	60.39 (11.23)	34/57 (59.65)	31/58 (53.45)	2.88 (0.71)	2.83 (0.71)	All $p > 0.05$
Koskinas_2019 [19]	60.5 (12.00)	61.0 (10.70)	128/155 (83.00)	123/153 (80.00)	3.61 (1.00)	3.42 (0.94)	All $p > 0.05$
Leucker 2020 [20]	55 (13.00)	55 (13.00)	22/30 (73.00)	11/27 (41.00)	2.37 (0.91)	2.32 (1.06)	$p = 0.03$ for sex; all other variables $p > 0.05$
Liuqing Yang_2022 [39]	59.65 (3.05)	59.30 (4.46)	60/98 (61.20)	68/100 (68.00)	3.73 (0.96)	3.78 (0.65)	All $p > 0.05$
Mehta_2022 [21]	61.37 (11.04)	63.63 (10.38)	27/38 (71.05)	28/30 (93.33)	2.97 (1.09)	2.87 (0.90)	$p = 0.03$ for sex; all other variables $p > 0.05$
Okada 2022 [22]	66.4 (13.1)	63.4 (14.0)	43/52 (82)	47/50 (94)	3.12 (0.79)	3.22 (0.87)	All $p > 0.05$
Räber_2022 [23]	58.4 (10.0)	58.6 (9.4)	124/148 (83.8)	119/152 (78.3)	4.01 (0.80)	3.91 (0.94)	All $p > 0.05$ except baseline LDL-C
Schwartz 2018 [30]	58.5 (9.3)	58.6 (9.4)	7072/9462 (74.7)	7090/9462 (74.9)	2.38 (0.8)	2.38 (0.8)	All $p > 0.05$
Xu_2021 [17]	56.53 (10.84)	58.91 (10.350)	73/96 (76.04)	175/238 (73.53)	3.67 (0.59)	3.34 (0.82)	All $p > 0.05$ except baseline LDL-C
Zhang_2022 [24]	62.1 (10.9)	62.2 (10.0)	258/414 (62.3)	681/1150 (59.2)	3.34 (0.73)	3.26 (0.77)	All $p > 0.05$

Note: 1. Age and LDL-C data are presented as "mean (standard deviation)" or "median (interquartile range)," depending on the format of the original report. 2. The study report provides the median and interquartile range. 3. Baseline LDL-C values were converted from mg/dL to mmol/L (conversion factor: 1 mg/dL = 0.0259 mmol/L).

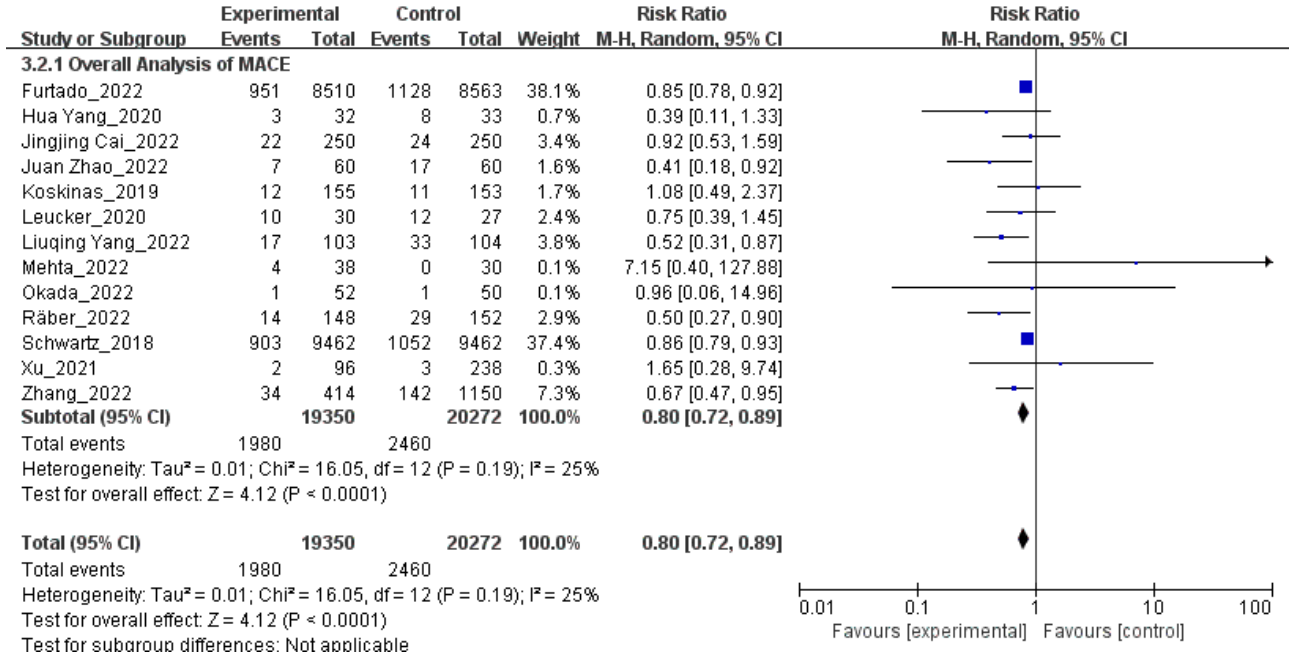

Figure 10. Forest plot depicting the impact of statin combined with PCSK9i therapy on major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI).Note: A random-effects model was employed for the analysis.

Following sensitivity analysis, where studies were excluded one by one (**Table 9**), the pooled relative risk (RR) remained stable between 0.72 and 0.83, with heterogeneity maintained at a low level, indicating robust results.

Table 9. Summary of sensitivity analysis results for statin combined with PCSK9i therapy.

Excluded Study	Pooled RR [95% CI]	p-value (Overall Effect)	I^2	Heterogeneity p-value
Original pooled	0.80 [0.72, 0.89]	< 0.0001	25%	0.19
Furtado 2022 [18]	0.72 [0.60, 0.88]	0.001	31%	0.15
Hua Yang_2020 [42]	0.81 [0.73, 0.90]	< 0.0001	24%	0.20
Jingjing Cai_2022 [38]	0.79 [0.71, 0.89]	< 0.0001	31%	0.14
Juan Zhao_2022 [41]	0.82 [0.75, 0.90]	< 0.0001	16%	0.29
Koskinas_2019 [19]	0.79 [0.71, 0.89]	< 0.0001	30%	0.15
Leucker 2020 [20]	0.80 [0.71, 0.89]	< 0.0001	31%	0.14
Liuqing Yang_2022 [39]	0.83 [0.76, 0.90]	< 0.0001	14%	0.31
Mehta_2022 [21]	0.81 [0.73, 0.89]	< 0.0001	21%	0.24
Okada 2022 [22]	0.80 [0.71, 0.89]	< 0.0001	31%	0.14
Räber_2022 [23]	0.82 [0.76, 0.90]	< 0.0001	16%	0.29
Schwartz 2018 [30]	0.72 [0.60, 0.88]	0.001	29%	0.16
Xu_2021 [17]	0.80 [0.72, 0.89]	< 0.0001	29%	0.16
Zhang_2022 [24]	0.82 [0.73, 0.91]	0.0002	24%	0.21

Subgroup analyses were conducted based on background statin intensity and geographical population, and the results were as follows:

(1) In the group with “moderate-intensity statin background” (Section 3.3.1 in **Figure 11**, comprising 7

studies), combination therapy significantly reduced the risk of major adverse cardiovascular events (MACE) (RR = 0.64, 95% CI [0.51, 0.82], $p = 0.0003$), with no significant heterogeneity observed among the studies [17,22,24,38,39,41,42];

(2) In the group with "high-intensity statin background" (Section 3.3.2 in **Figure 11**, comprising 6 studies), combination therapy also significantly reduced the risk of MACE (RR = 0.85, 95% CI [0.79, 0.91], $p < 0.0001$), with low heterogeneity [18-21,23,33]. The test for subgroup differences yielded a p-value of 0.03 and an I^2 of 78.8%, suggesting that background statin intensity is associated with the overall heterogeneity in this study;

(3) In the "Western" population group (Section 3.3.3 in **Figure 12**, comprising 7 studies), statin combined with PCSK9i significantly reduced the risk of MACE in patients with ACS undergoing PCI (RR = 0.85, 95% CI [0.80, 0.90], $p < 0.00001$), with minimal heterogeneity within the group [18–23,33];

(4) In the "Asian" group (Section 3.3.4 in **Figure 12**, comprising 6 studies), statin combined with PCSK9i also significantly reduced the risk of MACE (RR = 0.64, 95% CI [0.50, 0.82], $p = 0.0004$), with no heterogeneity observed within the group [17,24,38,39,41,42]. The test for subgroup differences was significant ($p = 0.03$, $I^2 = 79.1\%$), indicating that geographical region is also an important source of heterogeneity in the efficacy of this treatment regimen.

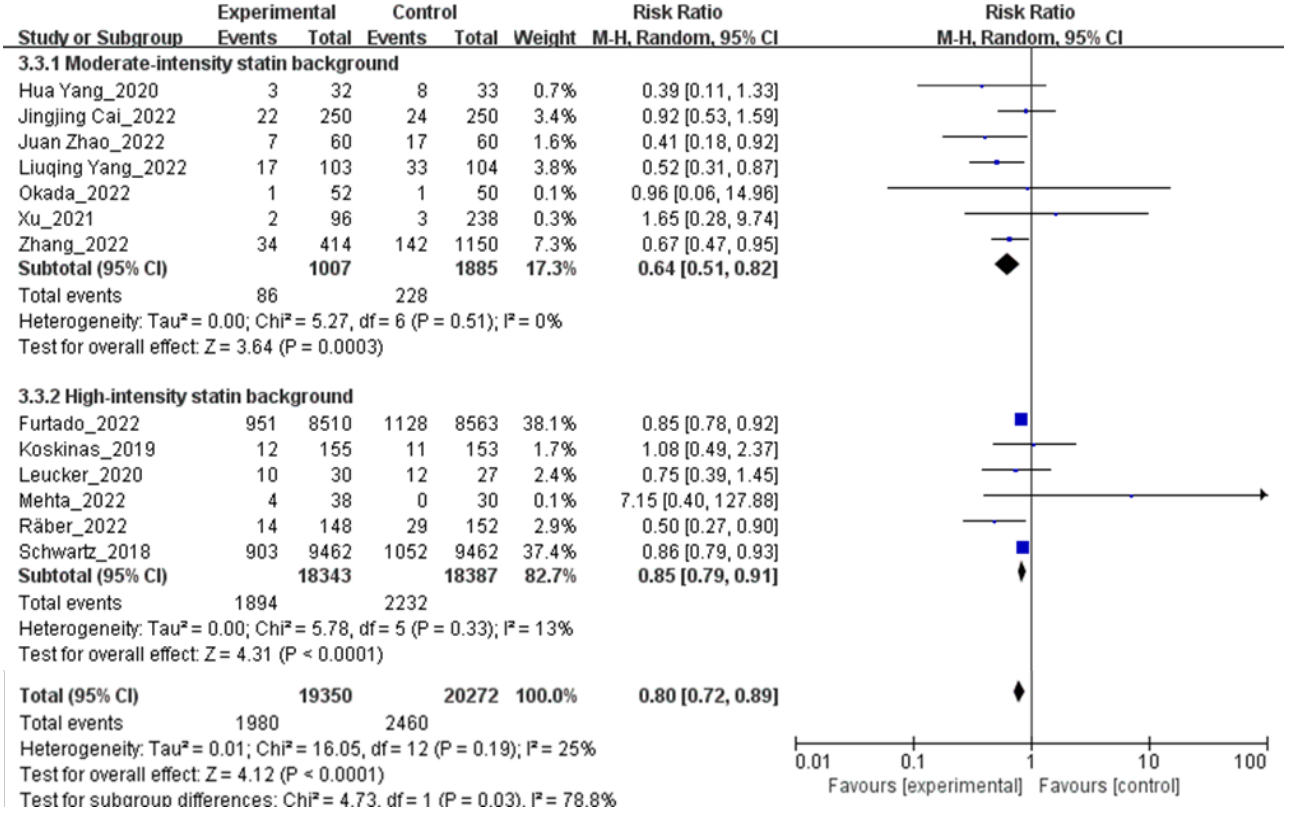

Figure 11. Subgroup analysis forest plot of the intervention effects of statins combined with PCSK9i with varying background statin intensities. Note: A random-effects model was used for the analysis.

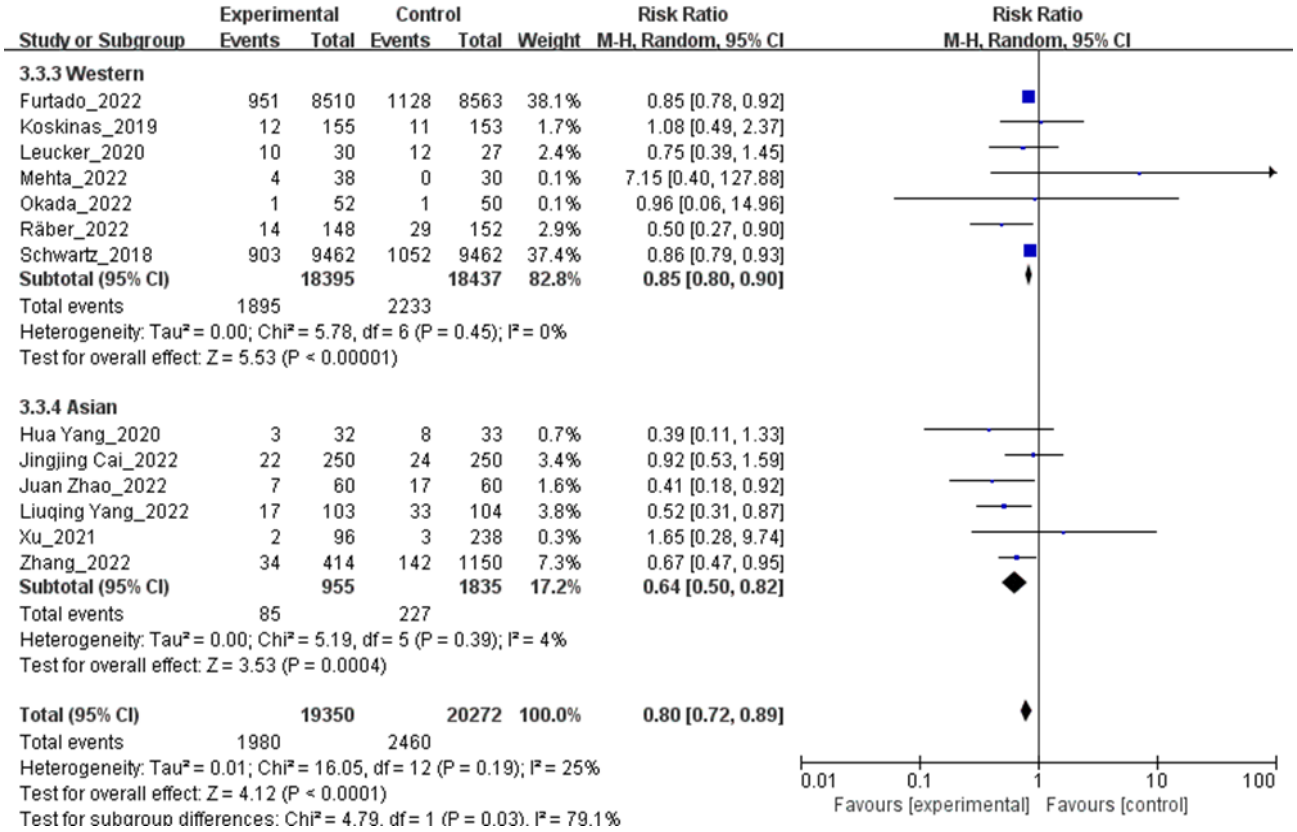

Figure 12. Forest plot of subgroup analysis on the intervention effect of statins combined with PCSK9i in populations from different regions. Note: A random-effects model was used for the analysis.

The funnel plot (**Figure 13**) in this case shows that the study points are roughly symmetrically distributed on both sides of the combined effect size. The Egger test did not reveal significant publication bias (t = -1.18, p = 0.26).

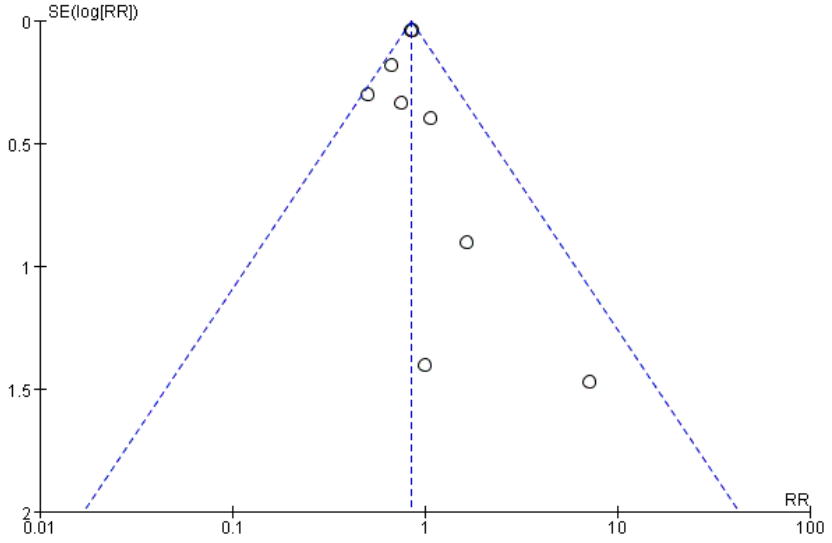

Figure 13. Funnel plot of the statin combined with PCSK9i group.Note: This funnel plot was drawn based on a fixed-effects model, while a random-effects model was used for the actual pooled analysis.

4. Discussion

This study included 34 clinical studies (31 RCTs [9-16,18-23,25-28,30-42] and 3 high-quality cohort studies [17,24,29]), comprising a total of 50,537 patients with ACS-PCI, to systematically evaluate the effects of three types of lipid-lowering regimens on the occurrence of MACE. Subgroup analyses and sensitivity analyses were conducted to explore the sources of heterogeneity.

4.1. High-intensity statin therapy

Compared with moderate-intensity statin therapy, this study suggests that high-intensity statin therapy can reduce the risk of MACE in patients with ACS-PCI by approximately 48%, confirming the core value of intensive lipid-lowering in secondary prevention of ACS. However, there was moderate heterogeneity, and subgroup analysis revealed that region was a key source of heterogeneity: Asian populations showed significant benefits, while no statistical difference was observed in Western populations. It is speculated that this difference is related to population genetic background, statin metabolic enzyme phenotype, baseline lipid profile, and body mass index distribution.

Sensitivity analysis indicated a substantial reduction in heterogeneity after excluding Berwanger_2018, suggesting that this large-sample Western study was the primary source of overall heterogeneity [25]. The pooled effect remained stable after exclusion, further supporting the reliability of the conclusion regarding the benefits of intensive lipid-lowering in Asian populations. Although the Egger linear test in this subgroup suggested statistically significant publication bias, this result was not considered to be due to true publication bias based on study characteristics for the following reasons:

(1) The funnel plot showed a roughly symmetrical distribution of studies, with the vast majority falling within the 95% confidence interval and no obvious signs of missing negative-result studies;

(2) The included studies had a wide range of sample sizes, and extreme differences in sample size can directly interfere with the statistical power of the Egger test;

(3) Varying follow-up times among studies and clinical heterogeneity in region, statin type, and baseline risk can inherently lead to dispersion of effect sizes, resulting in false-positive test results.

In summary, this study suggests that the positive Egger test result is more likely related to methodological and clinical heterogeneity.

4.2. Statin combined with ezetimibe therapy

Statin combined with ezetimibe significantly reduced the risk of MACE in patients with ACS-PCI, and sensitivity analysis supported the robustness of the results, consistent with conclusions from classic studies such as IMPROVE-IT [43]. Hagiwara_2017 and Zhixian Chen_2020 were the main sources of heterogeneity; the former was a large-sample cohort study with long-term follow-up, while the latter was a single-center RCT in Asia. Differences in follow-up duration and baseline risk between the two studies directly led to dispersion of effect sizes [31,40]. After exclusion, heterogeneity decreased, suggesting stable benefits of the combination regimen.

Subgroup studies were analyzed from three dimensions: background statin intensity, region, and follow-up time as follows:

(1) Adding ezetimibe on the basis of moderate-intensity statin therapy provided significant benefits, while the high-intensity statin group included only one study with insufficient statistical power, so the clinical

value of this combination cannot be denied;

(2) Regional differences were also a core influencing factor, with Asian populations showing significantly better benefits than Western populations, suggesting that East Asian populations are more sensitive to additional benefits from non-statin lipid-lowering drug combination therapy. However, the Western population subgroup included only one study, so the analysis results should be interpreted with caution;

(3) In the two subgroups with different follow-up durations, the difference test showed no statistical significance. Although numerically the benefit of the combination regimen appeared more pronounced in the subgroup with follow-up duration ≥12 months,it cannot be concluded that follow-up duration is the key factor for the benefit.

The funnel plot in this section was symmetrical, and the Egger test showed no statistical difference, indicating high credibility of the conclusions.

4.3. Statin combined with PCSK9i therapy

The pooled results of the statin combined with PCSK9i regimen were the most stable with the lowest heterogeneity, significantly reducing the risk of MACE, highly consistent with large clinical trials such as FOURIER and ODYSSEY OUTCOMES [30,44]. Subgroup analysis suggested that background statin intensity and region were the main sources of heterogeneity: the benefit magnitude of adding PCSK9i on the basis of moderate-intensity statin therapy was significantly higher than that of the high-intensity statin combination group, and there was no heterogeneity among studies in the former group; the benefit magnitude in Asian populations was significantly better than that in Western populations, with statistically significant differences between subgroups.

This difference may be related to differences in the treatment gradient of background lipid-lowering intensity: moderate-intensity statin therapy has limited inhibitory effects on cardiovascular events, and adding PCSK9i can bring more obvious prognostic improvements; while on the basis of high-intensity statin therapy, the intervention is close to the intensive upper limit, and the relative benefit space is compressed. In addition, the mechanism of action of PCSK9i was uniform, the dosing regimen was standardized, and most of the included studies were high-quality international multicenter RCTs with low risk of methodological bias, which also contributed to the low heterogeneity in this section. Neither the funnel plot nor the Egger test suggested publication bias, indicating reliable conclusions regarding the efficacy of this regimen.

4.4. Clinical implications

Based on the “Chinese Guideline for Lipid Management (2023)”, high-intensity statin therapy can be used as the basic regimen for Asian patients with ACS-PCI; for those intolerant to high-intensity statin therapy or requiring further intensification, moderate-intensity statin combined with ezetimibe can be preferred; for extremely high-risk patients, statin combined with PCSK9i provides more stable and potent benefits [6].

4.5. Limitations

Limitations and shortcomings of this study are as outlined:

(1) Inconsistencies in MACE definitions, follow-up durations, and baseline characteristics among

studies;

(2) Failure to further stratify comparisons by specific types of statins or PCSK9i;

(3) Lack of systematic analysis of safety and adherence;

(4) Inherent biases still present in some RCTs and cohort studies;

(5) Cholesterol absorption inhibitor combined with PCSK9i, statin combined with bococizumab, and triple regimens were not included in the analysis due to insufficient studies.

5. Conclusion

In conclusion, all three first-line intensive lipid-lowering regimens can effectively reduce the postoperative risk of MACE in patients with ACS-PCI. Region is a key factor in efficacy heterogeneity, with Asian patients with ACS-PCI showing more significant benefits. Furthermore, statin combined with PCSK9i showed a relatively stable risk-reducing effect in this study, and the benefit was more obvious when combined with moderate-intensity statin therapy.

Disclosure statement

The authors declare no conflict of interest.

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