Rosuvastatin plus ticagrelor decreases the risk of major adverse cardiovascular events and elevates cardiac function compared with ticagrelor alone in patients undergoing percutaneous coronary intervention: A meta-analysis

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Abstract. Several previous studies have reported that rosuvastatin plus ticagrelor is superior to ticagrelor monotherapy in patients receiving percutaneous coronary intervention (PCI); several others, however, dispute this. The present meta-analysis summarized relevant studies, aiming to comprehensively explore the efficacy of rosuvastatin plus ticagrelor vs. ticagrelor monotherapy in patients receiving PCI. Published studies comparing the efficacy between rosuvastatin plus ticagrelor and ticagrelor alone among patients receiving PCI were searched in the CNKI, Wanfang, CQVIP, EMBASE, Cochrane and PubMed databases until January 2023. The present meta-analysis included 3 cohort studies and 4 randomized controlled trials with 426 patients receiving rosuvastatin plus ticagrelor and 424 patients receiving ticagrelor monotherapy. Rosuvastatin plus ticagrelor decreased the occurrence of major adverse cardiovascular events (MACE) compared with ticagrelor [relative risk (RR), 0.29; 95% confidence interval (CI), 0.18-0.47]. Subgroup analysis revealed similar findings in studies with a follow-up of <6 months (RR, 0.24; 95% CI, 0.13-0.47) and ≥6 months (RR, 0.36; 95% CI, 0.18-0.70), as well as in studies using 10 mg rosuvastatin (RR, 0.27; 95% CI, 0.15-0.50) and 20 mg rosuvastatin (RR, 0.33; 95% CI, 0.16-0.69). In addition, rosuvastatin plus ticagrelor decreased the left ventricular (LV) end-systolic diameter [mean difference (MD), -0.71; 95% CI, -(1.36-0.07)], LV end-diastolic diameter [MD, -1.17; 95% CI, -(1.91-0.43)] and N-terminal pro-B-type natriuretic peptide [MD, -2.97; 95% CI, -(4.55-1.38)], and increased the LV ejection fraction (MD, 0.99; 95% CI, 0.74-1.25). In conclusion, rosuvastatin plus ticagrelor was shown to decrease the risk of MACE and elevate cardiac function compared with ticagrelor monotherapy in patients receiving PCI.

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Introduction

Percutaneous coronary intervention (PCI) is an interventional technology used for the treatment of acute coronary syndrome worldwide; it is able to quickly restore the patency of the occluded blood vessels and recover ischemic myocardial perfusion (1-3). Despite the fact that PCI has been shown to markedly decrease the mortality rate of patients with acute coronary syndrome, the incidence of major adverse cardiovascular events (MACE) and dysregulated cardiac function following the PCI procedure is a severe challenge affecting patient prognosis (4,5). Thus, it is crucial to explore strategies to reduce the incidence of these events after PCI (6).

Rosuvastatin is a representative statin mainly used for treating dyslipidemia, while ticagrelor is a platelet aggregation inhibitor (7,8). According to the guidelines of the American Heart Association (AHA), for most patients with acute coronary syndrome, only ticagrelor is recommended in the perioperative period of PCI (9). Although previous studies have reported the application of rosuvastatin in patients undergoing PCI, there is no consensus on the benefit of combining rosuvastatin and ticagrelor. For instance, it has been shown that ticagrelor decreases the rate of target vessel revascularization compared with prasugrel during the 1-year of follow-up in patients undergoing PCI (10). In addition, a previous study also reported that rosuvastatin enhances the left ventricular ejection fraction (LVEF) and reduces myocardial injury and inflammatory reaction caused by PCI (11). Of note, several studies have previously compared the efficacy between rosuvastatin plus ticagrelor and ticagrelor monotherapy among patients receiving PCI and the majority of these studies reported that rosuvastatin plus ticagrelor reduces the incidence of MACE and recovers myocardial function indices compared with ticagrelor alone (12-17); however, another study reported that rosuvastatin plus ticagrelor could not achieve these beneficial effects (18). Meanwhile, the sample sizes of these studies are relatively small, as most included <80 participants in each arm and may thus not lead to confident outcomes taken alone. Therefore, it is important to conduct a meta-analysis, which

may combine the data of these smaller studies and lead to a relatively more confident conclusion.

Therefore, the present meta-analysis intended to comprehensively compare the efficacy between rosuvastatin plus ticagrelor and ticagrelor monotherapy among patients receiving PCI, which may provide more solid evidence to facilitate the application of rosuvastatin plus ticagrelor in these patients in the future.

Materials and methods

Study search. The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (19). Studies that compared cardiac function or MACE occurrence in patients who received rosuvastatin plus ticagrelor or ticagrelor monotherapy following PCI were searched in the following databases: China National Knowledge Infrastructure (CNKI; https://www.cnki.net/), Wanfang (https://www.wanfangdata.com.cn/index.html), CQVIP (http://www.cqvip.com/), EMBASE (https://www.embase.com), Cochrane (https://www.cochrane.org/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) until January 2023. The following key words and the associated Medical Subject Heading terms were used: 'Ticagrelor', 'Tic', 'Brilique', 'Brilinta', 'rosuvastatin', 'Ros', 'Crestor', 'percutaneous coronary intervention', 'PCI' and 'percutaneous coronary revascularization'.

Eligibility criteria. The studies were eligible if: i) They compared rosuvastatin plus ticagrelor with ticagrelor monotherapy in patients receiving PCI; and ii) they reported at least one clinical outcome that was of interest to the present study, including MACE, LV end-systolic diameter (LVESD), LV end-diastolic diameter (LVEDD), LVEF and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as the endpoint through the follow-up period.

The studies were excluded if: i) They compared another treatment regimen with rosuvastatin plus ticagrelor, or a different dose of rosuvastatin plus ticagrelor; ii) they included the patients without PCI therapy; iii) they reported data that were not extractable and could not be analyzed in the present study; and iv) they were case reports, reviews, meta-analyses or animal studies.

Data extraction. Two investigators independently searched the studies, reviewed the data and evaluated the risk of bias. Consensus was reached between the two aforementioned investigators in case of disagreements. The investigators screened the titles and abstracts of studies that were considered relevant to the present study and eligible studies were then identified through full-text evaluation based on the aforementioned inclusion and exclusion criteria. Reference lists of eligible studies were also screened. Following study selection, the data were extracted, which included author, publication year, study type, patient type, follow-up duration, sample size, patient age, patient gender, treatment and outcomes. For risk of bias, the Cochrane Collaboration's tool and Newcastle-Ottawa Scale criteria were adopted for randomized controlled trials (RCTs) and cohort studies, respectively (20,21).

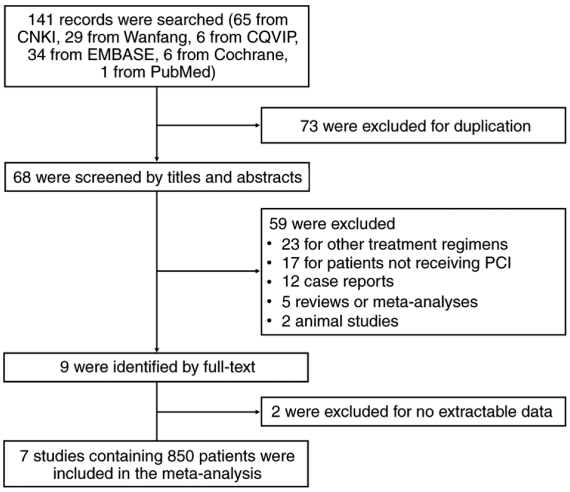

Figure 1. Study selection flow chart. CNKI, China National Knowledge Infrastructure; PCI, percutaneous coronary intervention.

Statistical analysis. Meta-analysis was carried out through the use of Stata (version 14.0; Stata Corp LP). Relative risk (RR) and mean difference (MD) with 95% confidence intervals (CI) were selected for binary variable assessment and continuous variable assessment, respectively. Random-effects models were utilized. Heterogeneity was assessed using I^2 statistics, with $I^2 \leq 50.0\%$ indicating low heterogeneity and $I^2 > 50.0\%$ indicating high heterogeneity. The sensitivity was assessed via a 'leave-one-out' method (omitting each study and repeating the analysis). Publication bias was examined through Begg's and Egger's tests. If publication bias existed, the trim-and-fill method was adopted for further assessment and adjustment (22). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Study selection procedure. A total of 141 records were retrieved in the initial search (including 65 from CNKI, 29 from Wanfang, 6 from CQVIP, 34 from EMBASE, 6 from Cochrane and 1 from PubMed) and 73 records were excluded due to duplication (Fig. 1). Next, the remaining 68 records were screened by titles and abstracts, of which 59 records were excluded (including 23 studies for other treatment regimens, 17 papers for patients not receiving PCI, 12 case reports, 5 reviews or meta-analyses and 2 animal studies). Subsequently, 9 studies were obtained as a full-text version, of which 2 were excluded for no extractable data. Finally, 7 studies containing 850 patients were included in the meta-analysis.

Features of the included studies. The included studies contained 3 cohort studies and 4 RCTs (Table I) (12-18). Briefly, 2 cohort studies were conducted in 2018 (12,13), while the remaining cohort study and 4 RCTs were conducted after 2019 (14-18). In total, 852 patients were included in the present meta-analysis, among which 426 received rosuvastatin plus ticagrelor and 424 patients received ticagrelor monotherapy.

MACE occurrence. In total, 6 studies (2 cohort studies and 4 RCTs) compared MACE occurrence between rosuvastatin plus

Table I. Details of the included studies.

First author, year	Study type	Patient type	Follow-up duration, months	Sample size, n		Age, years (mean ± standard deviation)		Sex, n (male/female)		Treatment		Patient outcomes	(Refs.)
				Rosuvastatin plus ticagrelor	Ticagrelor	Rosuvastatin plus ticagrelor	Ticagrelor	Rosuvastatin plus ticagrelor	Ticagrelor	Rosuvastatin plus ticagrelor	Ticagrelor		
Li *et al*, 2018	Cohort study	ACS	1	47	47	57.5±5.3	57.6±5.1	26/21	25/22	Rosuvastatin 10 mg daily; ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	MACE, LVESD, LVEDD, LVEF, NT-proBNP	(12)
Wang, 2018	Cohort study	ACS	12	61	61	61.6±5.2	62.3±5.1	28/33	27/34	Rosuvastatin 20 mg daily, ticagrelor 180 mg for the first day, then 90 mg daily	Ticagrelor 180 mg for the first day, then 90 mg daily	MACE	(13)
Li, 2019	RCT	CHD	2	30	30	44.3±10.3	42.8±11.4	15/15	16/14	Rosuvastatin 20 mg daily, ticagrelor 180 mg for the first day, then 90 mg daily	Ticagrelor 180 mg for the first day, then 90 mg daily	MACE	(14)
Liu *et al*, 2020	Cohort study	AMI	12	132	130	72.7±4.2	72.6±4.2	76/56	68/62	Rosuvastatin 10 mg daily; ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	LVESD, LVEDD, LVEF, NT-proBNP	(15)
Zhang *et al*, 2020	RCT	AMI	3	75	75	63.1±8.4	62.4±8.3	43/32	41/34	Rosuvastatin 10 mg daily; ticagrelor 90 mg daily	Ticagrelor 90 mg daily	MACE, LVESD, LVEDD, NT-proBNP	(16)
Yong and Lei, 2021	RCT	CHD	6	51	51	60.3±4.5	60.3±4.6	28/23	27/24	Rosuvastatin 10 mg daily; ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	MACE	(17)
Hongjiang, 2021	RCT	AMI	1	30	30	57.1±4.2	56.9±4.5	16/14	17/13	Rosuvastatin 10 mg daily; ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	MACE, LVEDD, LVEFS	(18)

RCT, randomized controlled trial; ACS, acute coronary syndrome; CHD, coronary heart disease; AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

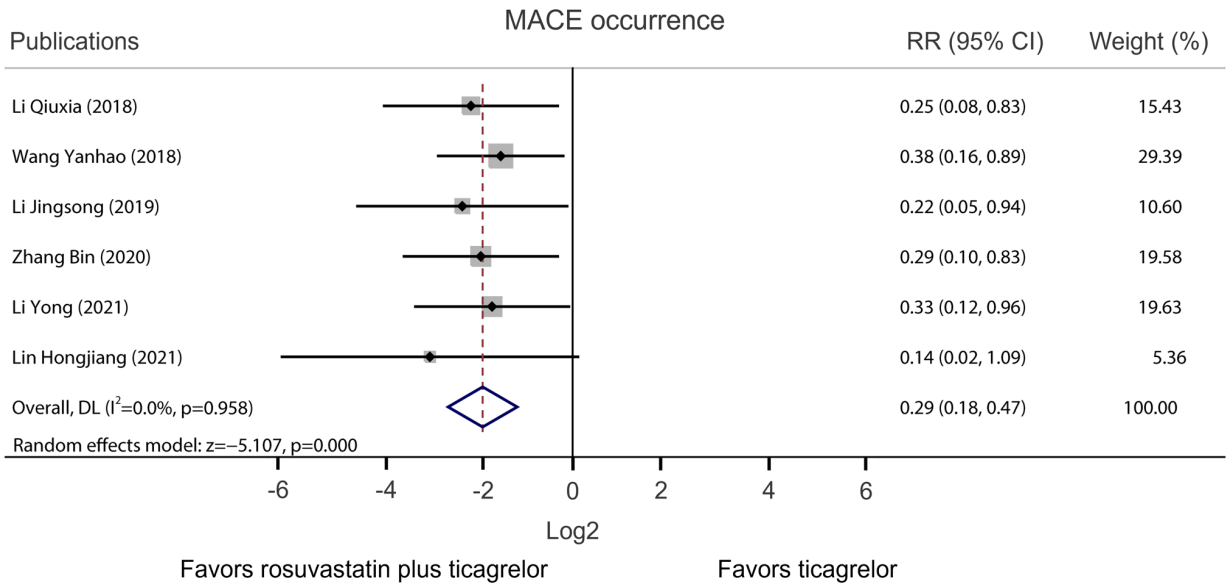

Figure 2. Forest plot of the comparison of MACE occurrence between rosuvastatin plus ticagrelor and ticagrelor monotherapy. Data are presented as RR with 95% CI. MACE, major adverse cardiovascular events; RR, relative risk; CI, confidence interval.

ticagrelor and ticagrelor alone, while no significant heterogeneity was found among them (I^2=0.0%; P=0.958; Fig. 2). Meta-analysis with the random-effects model demonstrated that rosuvastatin plus ticagrelor significantly decreased MACE occurrence compared with ticagrelor monotherapy (RR, 0.29; 95% CI, 0.18-0.47; P<0.001).

Subgroup analyses were carried out based on follow-up duration and rosuvastatin dose. Among studies with a follow-up duration of <6 months, pooled analysis demonstrated that rosuvastatin plus ticagrelor significantly decreased MACE occurrence compared with ticagrelor monotherapy (RR, 0.24; 95% CI, 0.13-0.47; P<0.001), while no significant heterogeneity was discovered (I^2=0.0%; P=0.947). In studies with a follow-up duration of ≥6 months, pooled analysis revealed that rosuvastatin plus ticagrelor significantly decreased MACE occurrence compared with ticagrelor monotherapy (RR, 0.36; 95% CI, 0.18-0.70; P=0.003), while no significant heterogeneity was identified (I^2=0.0%; P=0.866; Fig. 3A). Furthermore, in the study with a rosuvastatin dose of 10 mg, rosuvastatin plus ticagrelor significantly decreased MACE occurrence compared with ticagrelor monotherapy (RR, 0.27; 95% CI, 0.15-0.50; P<0.001), while no significant heterogeneity was identified (I^2=0.0%; P=0.907). Regarding the studies with a rosuvastatin dose of 20 mg, rosuvastatin plus ticagrelor significantly decreased MACE occurrence compared with ticagrelor monotherapy (RR, 0.33; 95% CI, 0.16-0.69; P=0.003) without significant heterogeneity between the two studies (I^2=0.0%; P=0.543; Fig. 3B).

Cardiac function. A total of 3 studies compared LVESD following rosuvastatin plus ticagrelor vs. ticagrelor alone. Pooled analysis demonstrated that rosuvastatin plus ticagrelor decreased the LVESD compared with ticagrelor monotherapy [MD, -0.71; 95% CI, -(1.36-0.07); P=0.030] with heterogeneity observed among studies (I^2=91.2%; P<0.001; Fig. 4A). Furthermore, 4 studies reported the LVEDD and pooled analysis demonstrated that, compared with ticagrelor monotherapy, rosuvastatin plus ticagrelor decreased the LVEDD [MD, -1.17; 95% CI, -(1.91-0.43); P=0.002]. Meanwhile, heterogeneity was observed among studies (I^2=93.2%; P<0.001; Fig. 4B). In addition, pooled analysis demonstrated that LVEF rosuvastatin plus ticagrelor increased the LVEF compared with ticagrelor monotherapy (MD, 0.99; 95% CI, 0.74-1.25; P<0.001) without any heterogeneity observed among the three studies (I^2=25.7%; P=0.260; Fig. 4C). Furthermore, pooled analysis demonstrated that rosuvastatin plus ticagrelor decreased NT-proBNP compared with ticagrelor monotherapy [MD, -2.97; 95% CI, -(4.55-1.38); P<0.001], with heterogeneity observed among the three studies (I^2=97.2%; P<0.001; Fig. 4D).

Quality assessment of included studies. The risk of bias in RCTs was assessed with the Cochrane Collaboration's tool, which demonstrated that the overall risk of bias was low (low risk of sequence generation, completeness of outcome data and free from selective reporting), while concealment of allocation and blinded adjudication were unclear among four RCTs; meanwhile, free from other bias of Zhang *et al* (16) was unclear (Table II). Furthermore, the risk of bias of cohort studies was assessed using the Newcastle-Ottawa Scale criteria, which demonstrated that the total score of these studies ranged from 8-9, suggesting low risk of bias (Table III).

Sensitivity analysis and publication bias. Sensitivity analysis demonstrated that omitting the study by Zhang *et al* (16) changed the statistical significance of LVESD and NT-proBNP, while MACE occurrence, LVEDD and LVEF were not significantly changed by omitting any single study, which suggested that the results of the present meta-analysis were stable (Table IV).

In addition, Begg's and Egger's tests were conducted to estimate the potential publication bias and it was demonstrated that publication bias existed with regard to MACE (P<0.05). Meanwhile, according to the trim-and-fill method, there was no difference between the combined and the original results (no

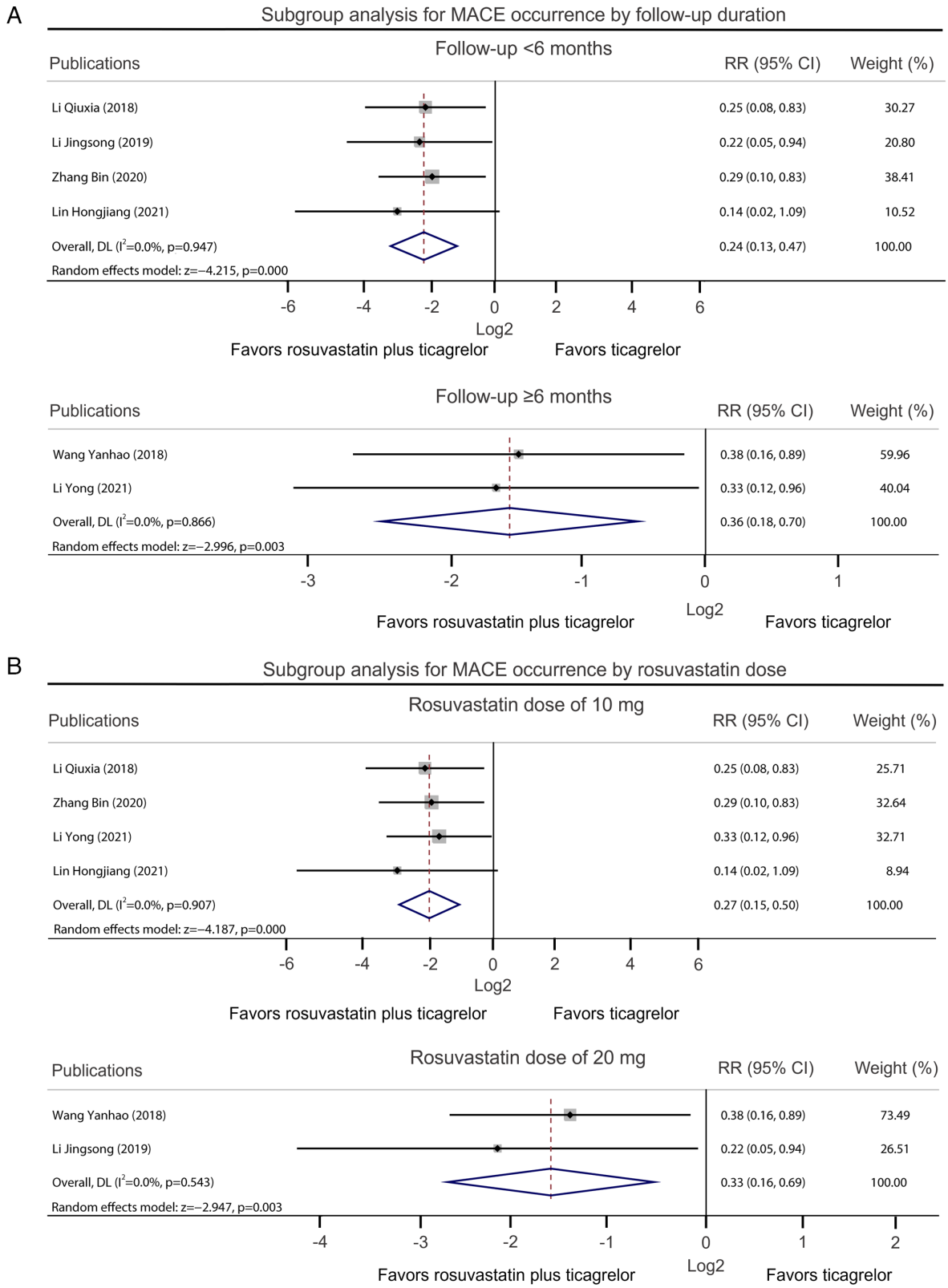

Figure 3. Forest plot of subgroup analysis of MACE occurrence based on follow-up duration and rosuvastatin dose. Pooled analysis of MACE occurrence in studies with different (A) follow-up duration and (B) rosuvastatin dose. Data are presented as RR with 95% CI. MACE, major adverse cardiovascular events; RR, relative risk; CI, confidence interval.

new studies added). Regarding LVESD, LVEDD, LVEF and NT-proBNP, no obvious publication bias was found (P>0.05; Table V). The funnel plots of MACE, LVESD, LVEDD, LVEF and NT-proBNP are shown in Fig. S1.

Discussion

Previous studies have reported that the incidence of MACE is 10.9-30.5% if there is no related treatment among patients

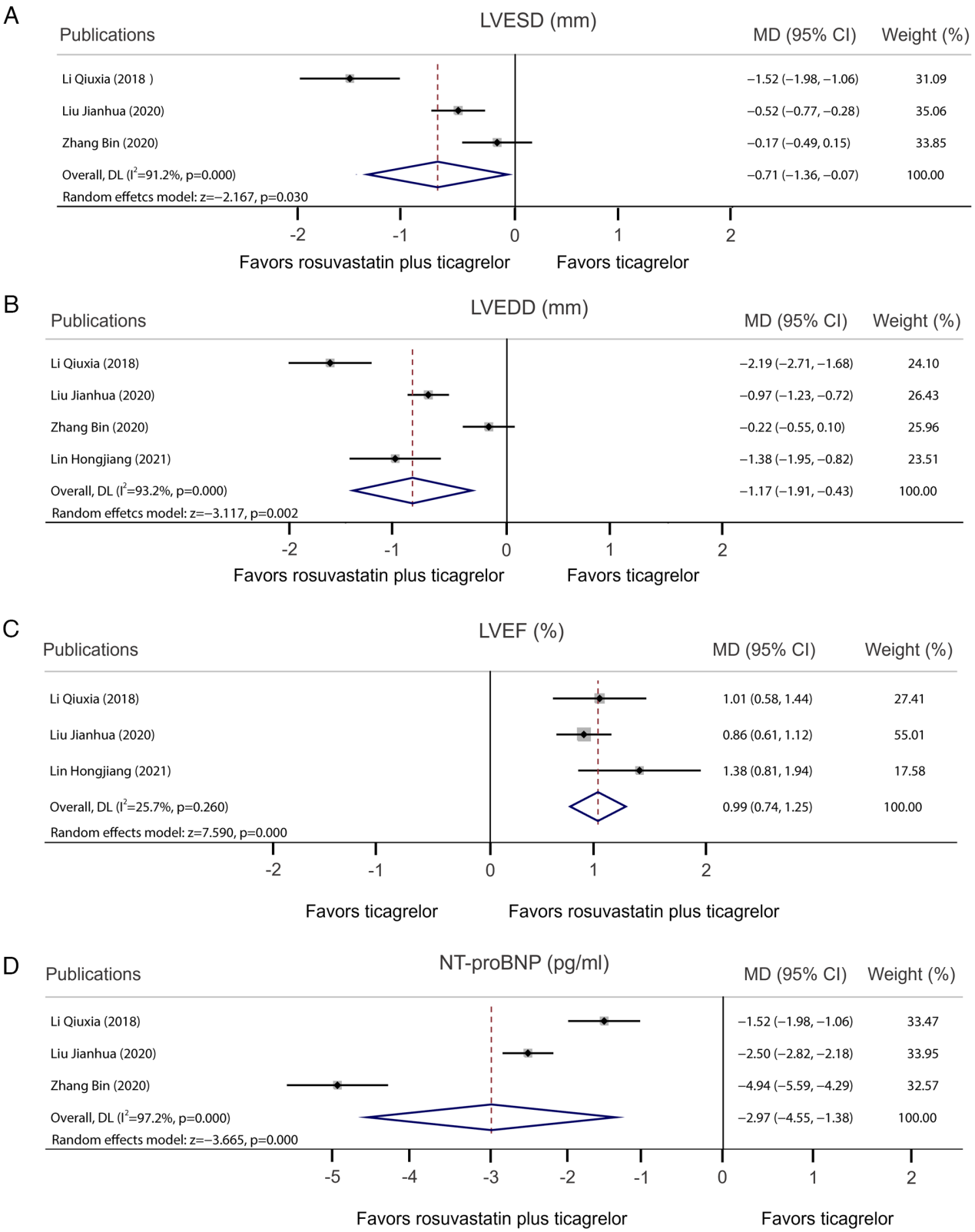

Figure 4. Forest plot of the comparison of cardiac function between rosuvastatin plus ticagrelor and ticagrelor monotherapy. Pooled analysis of (A) LVESD, (B) LVEDD, (C) LVEF and (D) NT-proBNP. Data are presented as MD with 95% CI. LVESD, LV end-systolic diameter; LVEDD, LV end-diastolic diameter; LVEF, left ventricular ejection; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MD, mean difference; CI, confidence interval.

receiving PCI (23-25). Several therapies are recommended to prevent the incidence of MACE during the perioperative period of PCI according to the American College of Cardiology/AHA guidelines, among which statins serve a crucial role (26,27). Currently, a number of clinical trials reported that atorvastatin, simvastatin and rosuvastatin administered prior to PCI reduced the incidence of MACE (28-31). Among these drugs, rosuvastatin is able to regulate blood lipid levels by inhibiting

Table II. Assessment of the risk of bias in randomized controlled trials by Cochrane Collaboration's tool.

First author, year	Sequence generation	Concealment of allocation	Blinded adjudication	Completeness of outcome data	Free from selective reporting	Free from other bias	(Refs.)
Li, 2019	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	(14)
Zhang *et al*, 2020	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(16)
Yong and Lei, 2021	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	(17)
Hongjiang, 2021	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	(18)

Table III. Assessment of the risk of bias in cohort studies by Newcastle-Ottawa Scale criteria.

First author, year	Selection	Comparability	Outcome	Total score	(Refs.)
Li *et al*, 2018	4	2	2	8	(12)
Wang, 2018	4	2	2	8	(13)
Liu, 2020	4	2	3	9	(15)

cholesterol synthesis and consequently suppressing the formation of atherosclerosis; furthermore, its half-life period is relatively longer and its lipid-lowering effect is relatively better compared with other statins (32). According to the guidelines of the AHA for patients with acute coronary syndromes, ticagrelor is recommended for the perioperative period of PCI, while the application of rosuvastatin is rarely reported (9). Rosuvastatin and ticagrelor, when used together, may exert different effects in managing cardiovascular conditions. Rosuvastatin inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase and consequently reduces cholesterol production (7). Ticagrelor, a P2Y12 receptor antagonist, prevents blood clot formation by inhibiting platelet activation and aggregation (8). Several clinical studies reported that rosuvastatin plus ticagrelor reduces the incidence of MACE and recovers myocardial function indices compared with ticagrelor alone (12-17); however, another previous study suggested that rosuvastatin plus ticagrelor could not achieve these benefits (18). Thus, a future study with a comprehensive assessment to confirm the effect of rosuvastatin plus ticagrelor in patients receiving PCI is needed.

In the present study, 7 studies (including 3 cohort studies and 4 RCTs) including 852 patients receiving rosuvastatin plus ticagrelor or ticagrelor monotherapy were reviewed. The subsequent meta-analysis demonstrated that rosuvastatin plus ticagrelor decreased the incidence of MACE compared with ticagrelor in patients undergoing PCI. Possible explanations for this may be the following: i) Rosuvastatin may modify vascular endothelial function, enhance immune function, accelerate plaque stability and prevent thrombosis formation, which consequently decreases MACE and protect the cardiovascular system (7,32); or ii) rosuvastatin may suppress T-cell-activated inflammation by inhibiting miRNA (miR)-155 and proinflammatory cytokines, such as IFN-γ, TNF-α and IL-6, while increasing Src homology 2-containing inositol phosphatase-1 (SHIP-1) and consequently decreasing MACE (33). Of note, the subgroup analysis further confirmed that the effect of rosuvastatin plus ticagrelor in decreasing the incidence of MACE in patients undergoing PCI was independent of follow-up duration and rosuvastatin dose. To the best of our knowledge, this is the first meta-analysis to explore the efficacy of rosuvastatin plus ticagrelor vs. ticagrelor monotherapy in patients undergoing PCI, which may provide solid evidence for the application of rosuvastatin plus ticagrelor in such patients. Of note, a previous study reported that rosuvastatin plus ticagrelor increases myocardial adenosine, reduces infarct size and inhibits inflammation in rats, which may also explain the findings of the current meta-analysis (34).

Dysregulated cardiac function is also a severe complication of PCI (35). Of note, it has been reported that rosuvastatin treatment may restore ventricular remodeling and enhance LV systolic function in patients undergoing PCI (36). The present meta-analysis compared the effects of rosuvastatin plus ticagrelor and ticagrelor monotherapy on cardiac function in patients receiving PCI. The pooled analysis demonstrated that rosuvastatin plus ticagrelor decreased LVESD, LVEDD and NT-proBNP, but increased LEVF compared with ticagrelor monotherapy in patients receiving PCI. It may be suggested that rosuvastatin is able to relieve cardiac damage by decreasing inflammation and downregulating blood lipids through several pathways, such as the nod-like receptor protein 3/toll-like receptor and miR-155/SHIP-1 pathways, which may attenuate cardiac injury (33,37,38). However, heterogeneity existed among the analyzed studies reporting LVESD, NT-proBNP and LVEDD. Meanwhile, the sensitivity analysis demonstrated that omitting the study by Liu *et al* (15) changed the significance of LVESD and NT-proBNP, indicating that further investigation is required.

There were several limitations to the present study. First, the results were considered robust despite the existence of publication bias and bias may be due to the small number of included studies. Furthermore, the type of patient varied among studies. For instance, some studies only included patients with AMI (15,16,18), while other studies included

Table IV. Sensitivity analysis.

A, MACE occurrence[a]

First author, year	Relative risk or mean difference	95% CI		(Refs.)
		Lower	Upper	
Li *et al*, 2018	0.29	0.18	0.49	(12)
Wang, 2018	0.26	0.15	0.45	(13)
Li, 2019	0.30	0.18	0.48	(14)
Zhang *et al*, 2020	0.29	0.17	0.48	(16)
Yong and Lei, 2021	0.28	0.16	0.47	(17)
Hongjiang, 2021	0.30	0.19	0.49	(18)

B, LVESD, mm[b]

First author, year	Relative risk or mean difference	95% CI		(Refs.)
		Lower	Upper	
Li *et al*, 2018	-0.36	-0.71	-0.01	(12)
Liu *et al*, 2020	-0.83	-2.16	0.50	(15)
Zhang *et al*, 2020	-1.00	-1.98	-0.03	(16)

C, LVEDD, mm[b]

First author, year	Relative risk or mean difference	95% CI		(Refs.)
		Lower	Upper	
Li *et al*, 2018	-0.83	-1.45	-0.21	(12)
Liu *et al*, 2020	-1.25	-2.50	-0.01	(15)
Zhang *et al*, 2020	-1.50	-2.24	-0.75	(16)
Hongjiang, 2021	-1.11	-2.02	-0.20	(18)

D, LVEF, %[b]

First author, year	Relative risk or mean difference	95% CI		(Refs.)
		Lower	Upper	
Li *et al*, 2018	0.95	0.72	1.18	(12)
Liu *et al*, 2020	1.14	0.80	1.49	(15)
Hongjiang, 2021	0.90	0.68	1.12	(18)

E, NT-proBNP, pg/ml[b]

First author, year	Relative risk or mean difference	95% CI		(Refs.)
		Lower	Upper	
Li *et al*, 2018	-3.70	-6.09	-1.31	(12)
Liu *et al*, 2020	-3.22	-6.57	0.12	(15)
Zhang *et al*, 2020	-2.03	-2.98	-1.07	(16)

[a]Relative risk was used for estimation; [b]mean difference was used for estimation. CI, confidence interval; MACE, major adverse cardiovascular events; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table V. Publication bias.

Item	Begg's test	Egger's test
MACE occurrence	0.009	0.002
LVESD, mm	1.000	0.529
LVEDD, mm	0.734	0.418
LVEF, %	0.296	0.206
NT-proBNP, pg/ml	1.000	0.612

MACE, major adverse cardiovascular events; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

patients with ACS or CHD (12-14,17), which may lead to bias in the findings. In addition, all included studies were conducted in China, which may result in regional bias. The possible reasons for this phenomenon were as follows: i) The clinicians' prescription preference and decisions may lead to the prevalent application of rosuvastatin plus ticagrelor; ii) both rosuvastatin and ticagrelor are covered by the medical insurance of all patients in China, which may influence the high accessibility of these drugs to patients; and iii) the efficacy of rosuvastatin plus ticagrelor may vary among different patient populations; however, there are currently no studies that have investigated this. Therefore, the efficacy of rosuvastatin plus ticagrelor should be verified in patients undergoing PCI from different populations. As another limitation, the original studies did not provide the time-line of the clinical course. Hence, it was difficult to obtain related data for further analysis of the relationship between the time-points of the clinical course and concurrent medications. Furthermore, the clinical studies included in the present meta-analysis were mostly small studies and the follow-up duration varied among studies, which may limit the possibility to conclude with confident outcomes. In addition, the included studies did not present the data of the low-density lipoprotein-cholesterol (LDL-C) level in both treatment groups, which is an important individual risk factor of outcome in patients receiving PCI (39). Therefore, further studies should verify the impact of LDL-C levels on the outcomes for patients undergoing PCI who receive rosuvastatin plus ticagrelor or ticagrelor monotherapy.

In conclusion, the present meta-analysis demonstrated that rosuvastatin plus ticagrelor decreased the occurrence of MACE and elevated cardiac function compared with ticagrelor monotherapy among Chinese patients receiving PCI, indicating rosuvastatin plus ticagrelor may be a superior treatment choice for these patients, while its application in other patient populations requires further exploration.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HY supervised the study. JS and XJ designed and conceived the study. JS, XJ and HS participated in the literature search/selection and data collection. JS and XJ performed the data analysis and wrote the manuscript. JS, HS, LZ and HY contributed to the analysis of the results and revised the manuscript. JS and LZ contributed critically to the intellectual content during the revision stage. HS and HY confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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