Check for updates

OPEN ACCESS

EDITED BY Xuezhong Zhou, Beijing Jiaotong University, China

REVIEWED BY Zhi Yong Du, Capital Medical University, China Xiao Li, Shandong Provincial Qianfoshan Hospital, China

*CORRESPONDENCE Dazhuo Shi, ⊠ shidazhuo@126.com Jianpeng Du, ⊠ 13811518062@163.com

[†]These authors have contributed equally to this work

RECEIVED 11 December 2023 ACCEPTED 16 February 2024 PUBLISHED 21 March 2024

CITATION

Chen P, Gao Z, Guo M, Pan D, Zhang H, Du J and Shi D (2024), Efficacy and safety of *Panax notoginseng* saponin injection in the treatment of acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Front. Pharmacol.* 15:1353662. doi: 10.3389/fphar.2024.1353662

COPYRIGHT

© 2024 Chen, Gao, Guo, Pan, Zhang, Du and Shi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Efficacy and safety of *Panax notoginseng* saponin injection in the treatment of acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials

Pengfei Chen^{1,2†}, Zhuye Gao^{1,2†}, Ming Guo^{1,2†}, Deng Pan^{1,2}, He Zhang^{1,2}, Jianpeng Du^{1,2*†} and Dazhuo Shi^{1,2*}

¹Xiyuan Hospital, Cohina Academy of Chinese Medical Sciences, Beijing, China, ²Cardiovascular Diseases Center, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Purpose: This study aimed to assess the efficacy and safety of *Panax notoginseng* saponin (PNS) injection, when combined with conventional treatment (CT), for acute myocardial infarction (AMI).

Methods: Comprehensive searches were conducted in seven databases from inception until 28 September 2023. The search aimed to identify relevant randomized controlled trials (RCTs) focusing on PNS injection in the context of AMI. This meta-analysis adhered to the PRISMA 2020 guidelines, and its protocol was registered with PROSPERO (number: CRD42023480131).

Result: Twenty RCTs involving 1,881 patients were included. The meta-analysis revealed that PNS injection, used adjunctively with CT, significantly improved treatment outcomes compared to CT alone, as evidenced by the following points: (1) enhanced total effective rate [OR = 3.09, p < 0.05]; (2) decreased incidence of major adverse cardiac events [OR = 0.32, p < 0.05]; (3) reduction in myocardial infarct size [MD = -6.53, p < 0.05]; (4) lower ST segment elevation amplitude [MD = -0.48, p < 0.05]; (5) mitigated myocardial injury as indicated by decreased levels of creatine kinase isoenzymes [MD = -11.19, p < 0.05], cardiac troponin T [MD = -3.01, p < 0.05], and cardiac troponin I [MD = -10.72, p < 0.05]; (6) enhanced cardiac function, reflected in improved brain natriuretic peptide [MD = -91.57, p < 0.05], left ventricular ejection fraction [MD = 5.91, p < 0.05], left ventricular end-diastolic dimension [MD = -3.08, p < 0.05], and cardiac output [MD = 0.53, p < 0.05]; (7) reduced inflammatory response, as shown by lower levels of C-reactive protein [MD = -2.99, p < 0.05], tumor necrosis factor- α [MD = -6.47, p < 0.05], interleukin-6 [MD = -24.46, p < 0.05], and pentraxin-3 [MD = -2.26, p < 0.05]; (8) improved vascular endothelial function, demonstrated by decreased endothelin-1 [MD = -20.56, p < 0.05] and increased nitric oxide [MD = 1.33, p < 0.05]; (9) alleviated oxidative stress, evidenced by increased superoxide dismutase levels [MD = 25.84, p < 0.05]; (10) no significant difference in adverse events [OR = 1.00, p = 1.00].

Conclusion: This study highlighted the efficacy and safety of adjunctive PNS injections in enhancing AMI patient outcomes beyond CT alone. Future RCTs need to solidify these findings through rigorous methods.

Systematic Review Registration: (https://www.crd.york.ac.uk/PROSPERO/), identifier (CRD42023480131)

KEYWORDS

Panax notoginseng saponins, acute myocardial infarction, meta-analysis, systematic review, randomized controlled trials

1 Introduction

Acute myocardial infarction (AMI) represents irreversible myocardial damage, typically precipitated by the rupture of coronary artery plaque (Byrne et al., 2023). Annually, it is responsible for over 2.4 million fatalities in the United States, 4 million in Europe and northern Asia, and affects more than 7 million individuals worldwide (Yeh et al., 2010; Nichols et al., 2014). As a significant contributor to global disability and mortality, AMI poses a critical challenge in contemporary medicine (Reed et al., 2017). Treatment strategies for AMI prioritize the restoration of coronary flow to enable myocardial tissue reperfusion, primarily through percutaneous coronary intervention (PCI) and pharmacological thrombolysis. This approach is complemented by the administration of several medications. These include antiplatelet agents, antianginal agents, anticoagulants, and vasodilators. Vasodilators are also used to enhance cardiomyocyte nutrition. Additionally, beta-blockers and calcium antagonists are administered to reduce myocardial oxygen consumption (Montecucco et al., 2016; Reed et al., 2017; Sanchis et al., 2023). Although reperfusion alleviates ischemic myocardial injury, it can also cause specific, irreversible damage to cardiomyocytes (Gong et al., 2021; Murphy and Goldberg, 2022). Furthermore, existing treatments fall short in restoring the cardiac structure and function during prolonged AMI therapy, resulting in persistently high morbidity and mortality rates despite conventional drug therapy (Heusch and Gersh, 2017).

Panax notoginseng (PN), known as the root of *Panax notoginseng* (Burk.) F. H. Chen, is a botanical drug with an extensive history of medicinal use in traditional Chinese medicine (TCM) in China (Wang et al., 2016). Over centuries, PN has demonstrated significant efficacy in managing internal and external bleeding and ameliorating blood stasis, leading to its widespread use in clinical practice for the treatment of cardiovascular diseases (CVDs) (Liu et al., 2020). *Panax notoginseng* saponins (PNS), the freeze-dried extract of PN, comprises metabolites

such as notoginsenoside R1 and ginsenosides Rb1, Rg1, Rd, and Re, as identified by high-performance liquid chromatography fingerprint analysis (Peng et al., 2018) (Figure 1) (Sun et al., 2020a). PNS formulations, including Xuesaitong, Xueshuantong , and Lulutong injections, have been clinically validated through trials and fundamental studies. These investigations substantiate PNS's efficacy in reducing cardiac damage, mitigating inflammation, and inhibiting platelet aggregation (Zhou et al., 2018a; Wang et al., 2021a; Li et al., 2022; Wang et al., 2022; Zeng et al., 2023).

In recent years, there have been an increasing amount of randomized controlled trials (RCTs) using PNS injection to treat AMI. However, no comprehensive literature review or meta-analysis has assessed the efficacy and safety of these interventions. Consequently, this study aims to elucidate the cardioprotective effects of PNS injection in AMI patients.

2 Methods

2.1 Search strategy

Comprehensive searches were conducted in PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, and VIP databases from inception until 28 September 2023. The search expression used in MEDLINE was ("acute myocardial infarction" OR "AMI" OR "st elevated myocardial infarction" OR "STEMI") AND ("*panax notoginseng saponins*" OR "PNS" OR "sanqi" OR "sanchi" OR "xuesaitong" OR "xueshuantong") AND ("randomized controlled trial" OR "RCT"). The detailed search strategies for all databases are presented in Supplementary Table S1. Titles, abstracts, and full texts were independently reviewed and cross-checked by two investigators (Pengfei Chen and Deng Pan), and any disagreement was decided by the senior reviewer (Dazhuo Shi).



2.2 Inclusion criteria

2.2.1 Type of study

The study type was RCT, with no restrictions on languages, publication date, or publication status.

2.2.2 Research object

All patients meeting any one of the current or previous diagnostic criteria for AMI were included. According to the Fourth Universal Definition of Myocardial Infarction (2018) standard (Thygesen et al., 2019), AMI is defined as acute myocardial injury [increased and/or decreased serum cardiac troponin (cTn), with at least once higher than the upper limit of the normal value (99 percentile of the upper limit of the reference value)], and there is at least one evidence of myocardial ischemia: (1) myocardial ischemic symptoms; (2) new ST-T changes or a new left bundle branch block (LBBB) observed in electrocardiogram (ECG); (3) a pathological Q-wave appeared in ECG; (4) imaging showed new loss of viable myocardium or new regional wall motion abnormalities; and (5) coronary angiography or autopsy confirmed thrombus in the coronary artery.

2.2.3 Intervention

The control group (CG) received conventional treatment (CT), which was the first-line therapy regimens recommended in the current guideline. The experimental group (EG) received PNS injection plus CT, and the courses and dosages of PNS injection were not limited.

2.2.4 Outcome indicators

The primary efficacy outcomes were total effective rates and major adverse cardiac events (MACEs). The secondary efficacy outcomes were (1) myocardial infarct size (MIS); (2) ST segment elevation amplitude; (3) myocardial injury markers: creatine kinase isoenzymes (CK-MB), cardiac troponin I (cTnI), and cardiac troponin T (cTnT); (4) cardiac function index: brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), and cardiac output (CO); (5) inflammatory response markers: C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and pentraxin-3 (PTX-3); (6) vascular endothelial function: endothelin-1 (ET-1) and nitric oxide (NO); and (7) oxidative stress: superoxide dismutase (SOD). The safety outcome was adverse events.

2.3 Exclusion criteria

The exclusion criteria are as follows: (1) the intervention included other TCM (oral PNS, other Chinese medicine injections, and oral Chinese patent medicines) other than PNS injection; (2) research data had obvious deficiencies or serious errors; (3) patients with severe comorbidities such as severe heart failure, severe arrhythmia, and severe liver and renal dysfunction; and (4) duplicate publication.

2.4 Data extraction

The document information extraction table was established by Excel software, including basic characteristics of trials (first author, publication year, journal, and country), characteristics of patients (sample size, gender, age, and medical history), PNS injection and CT treatments (initial time, dosage, frequency, duration, and mean follow-up time), and outcome indicators.

2.5 Bias assessment

Two investigators (Pengfei Chen and Deng Pan) independently evaluated the quality assessment and risk of bias using the Cochrane Risk of Bias Tool 2.0, according to the following six aspects: (1) random sequence generation; (2) allocation concealment; (3) blinding (patients, medical staff, outcome evaluations, and data analysis); (4) incompletion of the outcome report (important indicators and follow-up rate); (5) selective reporting; and (6) other biases (such as baseline imbalance and suspected fraud. The two investigators' answer of "yes" indicated a lower risk of bias, "no" indicated a higher risk of bias, and "unclear" indicated an uncertain risk of bias.

2.6 Statistical analysis

Statistical analysis was conducted using RevMan 5.4 software. Odds ratios (ORs) were used to represent categorical variables, and mean differences (MDs) were used for continuous variables while calculating 95% confidence intervals (CIs). The Cochrane's Q test and the I²-value were used to assess the statistical heterogeneity, where p > 0.1 or $I^2 \le 50\%$ suggested a favorable homogeneity among studies, and a fixed-effects model was used; $p \le 0.1$ or I²>50% suggested significant heterogeneity, so a random-effects model was used. When only two trials were included, although the heterogeneity was not significant, a random-effects model was selected to ensure the accuracy of the results. For sensitivity analysis, one study was omitted at a time to find the source of publication for heterogeneity, such as interventions, gender, age, and outcome indicators. When the number of trials was ≥ 10 , we used the funnel chart to test whether there was publication bias. Although planned, we did not check the publication bias using Egger's or Begg's test as these tests were unreliable when fewer than 10 trials were included.

3 Results

3.1 Study search

The process of the database search and study identification is presented in Figure 2. The initial database search identified 406 records. We excluded 245 duplicate records and 124 ineligible records by screening titles and abstracts. Of the remaining 37 articles that underwent full-text review, 17 were further excluded because of inaccurate data, ineligible interventions, and non-RCT study design. The exclusion studies and reasons are presented in Supplementary Table S2. Finally, 20 RCTs (Gan et al., 2010; Fu et al., 2014a; Fu et al., 2014b; Fan et al., 2015; Qiao et al., 2016; Feng et al., 2017; Xie, 2017; Liu et al., 2018; Wang, 2018; Xin and Qian, 2018; Zhou, 2018; Chen, 2019;



Guo, 2019; Zhang, 2019; Zhang and Du, 2019; Zhong and Zheng, 2019; Sun et al., 2020b; Sun, 2021; Ji and Liu, 2022; Yang et al., 2022) were included.

3.2 Basic information

All 20 RCTs were published in China from 2010 to 2023. The total sample size was 1,881 cases, with a maximum of 138 cases and a minimum of 39 cases. In total, there were 943 cases in the EG and 938 cases in the CG. According to the ConPhyMP guidelines (Heinrich et al., 2022), all included RCTs focused on "type A" extracts (documented in the national pharmacopeia with licensed applications). The composition, source, and chemical characteristics of PNS injection used in the included trials are presented in Supplementary Table S3. The other details are shown in Table 1.

3.3 Literature quality evaluation

Regarding randomization, 13 RCTs (Fu et al., 2014a; Fu et al., 2014b; Fan et al., 2015; Xie, 2017; Liu et al., 2018; Wang, 2018; Xin and Qian, 2018; Zhou, 2018; Chen, 2019; Zhang, 2019; Sun et al.,

2020b; Sun, 2021; Yang et al., 2022) generated random sequences using a random number table, which were rated as "low risk." The remaining trials did not report the specific randomized method, resulting in an "unknown risk." None of the RCTs reported the assignment hiding scheme, and the predictable future assignments could have led to the failure of randomization. Therefore, we rate the allocation concealment of all RCTs as "unknown risk." Whether or not outcomes were measured by a blinded assessor could not be established because of the lack of information. Therefore, we rate the blinding of all RCTs as "unknown risk". Two RCTs (Fu et al., 2014a; Feng et al., 2017) were rated as "high risk" due to incomplete data, which did not indicate the sample size and average age, while the others were rated as "low risk." The results of all study reports were rated as "low risk" without selective reporting. No other bias was reported in any RCTs and was rated as "unknown risk" (Figure 3).

3.4 Main efficacy outcomes

3.4.1 Total effective rate

Four RCTs (Xie, 2017; Zhou, 2018; Sun et al., 2020b; Ji and Liu, 2022) were reported on the total effective rate of PNS injection plus CT *versus* CT. The heterogeneity was not

TABLE 1 Characteristics of included studies.

Author (publication	Sample size (T/C)		ile/ nale	Age (year)	Interver	ntion	Reperfusion strategy	Courses/ day	Follow- up/week	Outcomes
year)		т	С	T/C	т	С				
Yang et al. (2022)	55/55	35/ 20	31/ 24	62.45 ± 8.12/ 61.74 ± 7.69	Xueshuantong injection 300 mg + 5% G.S. 250 mL qd iv gtt	Aspirin, Plavix, low-molecular weight heparin, Tatin, ACEI, β- blockers, nitrates, and rhBNP	PCI	7 days	24w	800
Yang et al. (2015)	42/42	24/ 18	22/ 20	64.1 ± 9.2/ 62.7 ± 9.6	Xueshuantong injection 250 mg + 5% G.S. 250 mL qd iv gtt	Aspirin, Plavix, urokinase injection, and low-molecular weight heparin calcium	Thrombolysis	14 days	8w	456670
Zhong and Zheng. (2019)	69/69	38/ 31	36/ 33	51.7 ± 5.3/ 49.9 ± 6.1	Thrombolysis at the same time administering Xueshuantong injection 500 mg + 0.9% N.S. 250 mL qd iv gtt	Urokinase injection, aspirin, and alprostadil injection	Thrombolysis	7 days	1w	2866
Xie. (2017)	40/40	24/ 16	22/ 18	73.4 ± 6.3/ 72.6 ± 6.7	Xueshuantong injection 300 mg + 0.9% N.S. 250 mL qd iv gtt	СТ	PCI	7 days	4w	04689678
Guo. (2019)	44/44	27/ 17	25/ 19	55.28 ± 8.36/ 55.59 ± 8.14	Before PCI, Xuesaitong injection 400 mg iv drop. After PCI, Xuesaitong injection 400 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, low-molecular weight heparin, tirofiban hydrochloride, Tatin, ACEI, and β-blockers	PCI	14 days	4w	49789
Sun et al. (2020a)	50/50	34/ 16	35/ 15	55.83 ± 8.25/ 55.94 ± 8.39	Before PCI, Xuesaitong injection 100 mg iv drop. After PCI, Xuesaitong injection 100 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, low-molecular weight heparin, tirofiban hydrochloride, Tatin, ACEI, and β-blockers	PCI	14 days	2w	69009
Zhou et al. (2018a)	62/62	33/ 29	35/ 27	55.35 ± 7.24/ 54.79 ± 7.45	Xuesaitong injection 200 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, Tatin, ACEI, and β-blockers	PCI	14 days	4w	0460890089
Zhang. (2019)	60/60	38/ 22	41/ 19	51.13 ± 8.98/ 50.87 ± 7.94	Before PCI, Xuesaitong injection 100 mg iv drop. After PCI, Xuesaitong injection 100 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, and Tatin	PCI	14 days	2w	100
Chen. (2019)	54/54	33/ 21	30/ 24	59.87 ± 4.31/ 59.79 ± 4.28	Before PCI, Xuesaitong injection 400 mg iv drop. After PCI, Xuesaitong injection 400 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, low-molecular weight heparin, and tirofiban hydrochloride	PCI	14 d	2w	467890
Qiao et al. (2016)	40/40	22/ 18	24/ 16	62.1 ± 7.9/ 63.5 ± 7.8	Xuesaitong injection 400 mg + 5% G.S. 250 mL qd iv gtt	Aspirin, Plavix, and Tatin	PCI	14 days	2w	00
Sun et al. (2020b)	50/50	32/ 18	30/ 20	59.02 ± 6.15/ 59.14 ± 6.26	Xuesaitong injection 400 mg + 5% G.S. 250 mL qd iv gtt	Alteplase + CT	Thrombolysis	15 days	2w	0280

TABLE 1 (Continued) Characteristics of included studies.

Author (publication	Sample size (T/C)	Ma fem	ile/ nale	Age (year)	Interver	ntion	Reperfusion strategy	Courses/ day	Follow- up/week	Outcomes
year)		т	С	T/C	т	С				
Ji and Liu. (2022)	54/54	33/ 21	35/ 19	53.42 ± 9.65/ 53.79 ± 9.46	Xueshuantong injection 500 mg + 5% G.S. 250 mL qd iv gtt	Alteplase, Low-molecular weight heparin, ACEI, β- blockers, and nitrates	Thrombolysis	7 days	4w	04689®
Xin and Qian. (2018)	54/53	33/ 21	31/ 22	51.9 ± 8.4/ 52.3 ± 8.2	Before PCI, Xuesaitong injection 100 mg iv drop. After PCI, Xuesaitong injection 100 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, and Tatin	PCI	14 days	2w	1008
Zhang and Du, (2019)	40/40	28/ 12	26/ 14	67.23 ± 3.31/ 66.84 ± 3.53	Xuesaitong injection 400 mg + 0.9% G.S. 250 mL qd iv gtt	Edaravone + CT	_	14 days	2w	891
Fu et al. (2014a)	30/30	_		_	Thrombolysis at the same time administering Xueshuantong injection 250 mg + 5% G.S. 250 mL qd iv gtt	Urokinase + CT	Thrombolysis	7 days	1w	Ø
Fu et al. (2014b)	36/32	20/ 16	17/ 15	52.6/53.8	Thrombolysis at the same time administering Xueshuantong injection 250 mg + 5% G.S. 250 mL qd iv gtt	Urokinase + CT	Thrombolysis	14 days	24w	2690
Liu et al. (2018)	60/60	36/ 24	37/ 23	57.66 ± 10.12/ 57.55 ± 10.09	Before PCI, Xuesaitong injection 400 mg iv drop. After PCI, Xuesaitong injection 400 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, low molecular weight heparin, tirofiban hydrochloride, Tatin, ACEI, and β-blockers	PCI	14 days	4w	46789669
Wang. (2018)	52/52	31/ 21	28/ 24	56.71 ± 6.25/ 57.29 ± 6.61	Before PCI, Xuesaitong injection 400 mg iv drop. After PCI, Xuesaitong injection 400 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, low-molecular weight heparin, tirofiban hydrochloride, Tatin, and β- blockers	PCI	14 days	4w	809
Feng et al. (2017)	31/32	_	_	_	Xuesaitong injection 400 mg. Intracoronary injection via a guided catheter	Aspirin, Plavix, and low- molecular weight heparin	PCI	14 days	24w	0
Gan et al. (2010)	20/19	12/ 8	11/ 8	57.6 ± 10.2/ 55.4 ± 9.8	Xuesaitong injection 400 mg, intracoronary injection via a guided catheter. After PCI, Xuesaitong injection 400 mg + 0.9% N.S. 250 mL qd iv gtt	Aspirin, Plavix, and tirofiban hydrochloride	PCI	2 days	24w	30

T/C, treatment group/control group; PCI, percutaneous coronary intervention; CT, conventional treatment; qd, once a day; iv gtt, intravenous guttae; ① total effective rate, ② myocardial infarct size, ③ ST segment elevation amplitude, ④ CK-MB, ⑤ cTnT, ⑥ cTnI, ⑦ BNP, ⑧ LVEF, ⑨ LVEDD, ⑩ CO, ⑪ CRP, ⑫ TNF-a, ⑲ IL-6, ⑲ PTX-3, ⑲ ET-1, ⑲ NO, ⑰ SOD, ⑲ major adverse cardiac events, and ⑲adverse response.

Chen et al.



significant (p = 0.93, $I^2 = 0\%$), so a fixed-effects model was used. The results presented in Figure 4 show that the total effective rate in the EG is significantly higher than that in the CG, with statistically significant differences [OR = 3.09, 95% CI: 1.67 to 5.72, p < 0.05].

3.4.2 MACEs

Eight RCTs (Gan et al., 2010; Fu et al., 2014a; Fu et al., 2014b; Fan et al., 2015; Xie, 2017; Xin and Qian, 2018; Zhang, 2019; Ji and Liu, 2022; Yang et al., 2022) investigated the incidence of MACEs. As the heterogeneity was significant (p = 0.01, $I^2 = 60\%$), a random-

	Experim		Contr			Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl		
Ji Xiaohui2022	51	54	44	54	19.6%	3.86 [1.00, 14.93]			
Sun Xuelin2020	47	50	40	50	19.3%	3.92 [1.01, 15.22]			
Xie Qingping2017	32	40	25	40	40.1%	2.40 [0.88, 6.56]			
Zhou Shu2018	59	62	54	62	21.0%	2.91 [0.73, 11.55]			
Total (95% Cl)		206		206	100.0%	3.09 [1.67, 5.72]	•		
Total events	189		163						
Heterogeneity: Chi ² =	0.47, df = 1	3 (P = 0	.93); l ² = l	0%					
Test for overall effect:	Z = 3.59 (F	P = 0.00	03)				0.01 0.1 1 10 100 Favours [control] Favours [experimental]		



	Expe	riment	al	C	ontrol			Mean Difference	Mean Dif	ference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Rando	n, 95% Cl
Fu Xiaoxia2014(b)	-19.7	4.59	36	-12.2	3.46	32	29.9%	-7.50 [-9.42, -5.58]		
Sun Xuelin2020	-15.85	2.5	50	-11.3	2.59	50	35.4%	-4.55 [-5.55, -3.55]		
Zhong Hui2019	-17.7	3.25	69	-10	3.5	69	34.7%	-7.70 [-8.83, -6.57]	-	
Total (95% CI)			155			151	100.0%	-6.53 [-8.81, -4.24]	•	
Heterogeneity: Tau ² =	3.58; Ch	i ² = 19	.04, df	= 2 (P <	0.000	1); l² = 1	89%	-	-10 -5 0	
Test for overall effect:	Z= 5.60	(P < 0.	00001)						-10 -5 U Favours (experimental)	
GURE 6 prest plot of MIS.										

effects model was used. The results presented in Figure 5 show that the incidence of MACEs in the EG is significantly lower than that in the CG, and the differences were statistically significant [OR = 0.32, 95% CI: 0.16 to 0.64, p < 0.05].

3.5 Secondary efficacy outcomes

3.5.1 MIS

Three RCTs (Fu et al., 2014b; Zhong and Zheng, 2019; Sun et al., 2020b) examined the MIS. The statistical heterogeneity among them

was substantial (p < 0.01, $I^2 = 89\%$), so a random-effects model was used. As shown in the results, a statistical difference was found between the two groups, which meant that the MIS in the EG was significantly lower than that in the CG [MD = -6.53, 95% CI: -8.81 to -4.24, p < 0.05] (Figure 6).

3.5.2 ST segment elevation amplitude

Two RCTs (Gan et al., 2010; Feng et al., 2017) examined the ST segment elevation amplitude. Although the heterogeneity was not significant between the two studies (p = 0.92, $I^2 = 0\%$), the random-effects model was used. The results indicated that PNS injection plus



Experimental Control Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% CI IV, Random, 95% C -1.164.79 373.08 365.28 -1.088.07-76.72 [-215.98, 62.54] Chen Zhaodong2019 54 54 0.5% -1,078.76 -100.18 [-254.37, 54.01] Guo Quanbiao2019 -1,178.94 363.29 44 374.63 44 0.4% Ji Xiaohui2022 -278.85 15.23 54 -264.93 15.01 54 46.2% -13.92 [-19.62, -8.22] 0.5% 52.45 [-183.56, 78.66] Liu Huajin2018 -1,148.78 375.17 60 -1,096.33 357.38 60 Xie Qingping2017 -36.83 7.05 40 -31.46 8.36 40 51.5% -5.37 [-8.76, -1.98] Zhou Shu2018 -1,171.6 301.26 62 -1,063.5 281.83 62 0.9% -108.10 [-210.79, -5.41] Total (95% CI) 314 314 100.0% -11.19 [-20.88, -1.50] Heterogeneity: Tau² = 44.46; Chi² = 12.83, df = 5 (P = 0.03); l² = 61% -200 -100 100 200 Test for overall effect: Z = 2.26 (P = 0.02) Favours [experimental] Favours [control] в Experimental Control Mean Difference Mean Difference Total Weight Study or Subgroup Mean SD Total Mean SD IV, Random, 95% CI IV, Random, 95% Cl Chen Zhaodong2019 -91.57 25.41 54 -75.65 25.71 54 18.8% -15.92 [-25.56, -6.28] Guo Quanbiao2019 -96.85 22.84 44 -76.93 30.56 44 17.3% -19.92 [-31.19, -8.65] Liu Huajin2018 -91.53 24.94 60 -82.6 23.84 60 19.6% -8.93 [-17.66, -0.20] Yang Fan2015 0.15 42 24.5% -0.54 [-0.62, -0.46] 0.69 42 1.23 0.2 Zhou Shu2018 -90.68 -78.57 26.5 19.7% -12.11 [-20.76, -3.46] 22.5 62 62 Total (95% CI) 262 262 100.0% -10.72 [-19.37. -2.06] Heterogeneity: Tau² = 79.48; Chi² = 31.54, df = 4 (P < 0.00001); l² = 87% -100 -50 50 100 Test for overall effect: Z = 2.43 (P = 0.02) Favours [experimental] Favours [control] C Experimental Mean Difference Mean Difference Control Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 34.77 -205.5229.63 Ji Xiaohui2022 -206.68 54 54 4.8% -1.16 [-13.34, 11.02] Xie Qingping2017 -18.596.69 40 -15.495.81 40 95.2% -3.10 [-5.85, -0.35] Total (95% CI) 100.0% -3.01 [-5.68, -0.33] 94 94 Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); l² = 0% -20 10 20 -10 Test for overall effect: Z = 2.20 (P = 0.03) Favours [experimental] Favours [control] FIGURE 8 Forest plot of myocardial injury [(A) CK-MB; (B) cTnt; (C) cTnl].

CT significantly decreases the ST segment elevation amplitude compared with CT alone [MD = -0.48, 95% CI: -0.94 to -0.02, p < 0.05] (Figure 7).

3.5.3 Myocardial injury

Six RCTs (Xie, 2017; Liu et al., 2018; Zhou, 2018; Chen, 2019; Guo, 2019; Ji and Liu, 2022) reported on CK-MB. The metaanalysis revealed that the CK-MB levels in the EG were significantly lower than those in the CG [MD = -11.19, 95% CI: -20.88 to -1.50, p < 0.05; $I^2 = 61\%$]. Five RCTs (Fan et al., 2015; Liu et al., 2018; Zhou, 2018; Chen, 2019; Guo, 2019) addressed the cTnT, with the meta-analysis indicating that cTnT levels in the EG were significantly reduced compared to those in the CG [MD = -10.72, 95% CI: -19.37 to -2.06, p < 0.05; $I^2 = 87\%$]. Additionally, two RCTs (Xie, 2017; Ji and Liu, 2022) focused on cTnI, and the meta-analysis showed that cTnI levels in the EG were notably lower than those in the CG [MD = -3.01, 95% CI: -5.68 to -0.33, p < 0.05; $I^2 = 0\%$] (Figure 8).

3.5.4 Cardiac function

Five RCTs (Fu et al., 2014a; Liu et al., 2018; Zhou, 2018; Chen, 2019; Guo, 2019) reported on BNP. The meta-analysis showed that the BNP in the EG is significantly lower than that in the CG [MD = -91.57, 95% CI: -130.27 to -52.86, p < 0.05; $I^2 = 68\%$]. Thirteen RCTs (Fu et al., 2014b; Xie, 2017; Liu et al., 2018; Wang, 2018; Zhou, 2018; Chen, 2019; Guo, 2019; Zhang and Du, 2019; Zhong and Zheng, 2019; Sun et al., 2020b; Sun, 2021; Ji and Liu, 2022; Yang et al., 2022) focused on the LVEF, revealing that LVEF in

A	Expe	erimenta	1	C	ontrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl		
Chen Zhaodong2019	-243.78	112.19	54	-165.83	116.28	54	22.2%	-77.95 [-121.05, -34.85]			
u Xiaoxia2014(a)	-30	120.5	30	161	129.94	30	16.8%	-191.00 [-254.41, -127.59]			
Guo Quanbiao2019	-605.31	177.9	44	-554.77	178.87	44	14.3%	-50.54 [-125.08, 24.00]			
Liu Huajin2018	-237.55	113.84	60	-171.12	115.67	60	22.8%	-66.43 [-107.50, -25.36]			
Zhou Shu2018	-213.77	104.83	62	-130.95	107.89	62	23.8%	-82.82 [-120.26, -45.38]			
otal (95% CI)			250			250	100.0%	-91.57 [-130.27, -52.86]	•		
leterogeneity: Tau ² = 1	271.74; CH	ni² = 12.4	3, df = -	4 (P = 0.0)	1); l ² = 68	%					
est for overall effect: Z	= 4.64 (P <	< 0.00001	1)						-200 -100 0 100 200		
									Favours [experimental] Favours [control]		
3	Ext	eriment	al	Co	ntrol			Mean Difference	Mean Difference		
Church a see Carda are a sum						tel M		N/ Dandam 05% Cl	B/ Dandam OFW Cl		

	LAPO	innen	(Cal	0	ondor			mean Difference	Medil Dillelence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Chen Zhaodong2019	8.17	4.58	54	4.88	4.42	54	8.1%	3.29 [1.59, 4.99]	
Fu Xiaoxia2014(b)	20.4	4.61	36	9.7	4.07	32	7.8%	10.70 [8.64, 12.76]	
Guo Quanbiao2019	24.07	6.88	44	9.93	5.74	44	7.2%	14.14 [11.49, 16.79]	
Ji Xiaohui2022	16.29	6.59	54	8.78	6.27	54	7.4%	7.51 [5.08, 9.94]	
Liu Huajin2018	7.27	4.62	60	4.56	4.47	60	8.1%	2.71 [1.08, 4.34]	
Sun Aimin2021	8.6	3.66	50	4.73	3.75	50	8.3%	3.87 [2.42, 5.32]	
Sun Xuelin2020	18.46	5.73	50	12.13	5.67	50	7.6%	6.33 [4.10, 8.56]	
Wang Lianren2018	9.41	4.56	52	4.68	4.05	52	8.1%	4.73 [3.07, 6.39]	
Xie Qingping2017	31.2	5.73	40	25.9	5.24	40	7.5%	5.30 [2.89, 7.71]	
Yang Wei2022	9.29	4.79	55	5.76	4.62	55	8.0%	3.53 [1.77, 5.29]	
Zhang Zhennan2019	5.85	8.72	40	0.47	8.49	40	6.1%	5.38 [1.61, 9.15]	
Zhong Hui2019	11.9	3.57	69	4	3.56	69	8.4%	7.90 [6.71, 9.09]	
Zhou Shu2018	9.45	7.34	62	7.34	6.74	62	7.4%	2.11 [-0.37, 4.59]	+
Total (95% CI)			666			662	100.0%	5.91 [4.23, 7.59]	•
Heterogeneity: Tau ² = 8	.30; Chi ²	= 119	.31, df	= 12 (P	< 0.00	001); l ²	= 90%		
Test for overall effect: Z	= 6.91 (F	< 0.0	0001)						-10 -5 0 5 10
									Favours (control) Favours (experimental)

Favours [control] Favours [experimental]



the EG was significantly increased compared to that in the CG [MD = 5.91, 95% CI: 4.23 to 7.59, p < 0.05; $I^2 = 90\%$]. Nine RCTs (Xie, 2017; Liu et al., 2018; Wang, 2018; Zhou, 2018; Chen, 2019; Guo, 2019; Zhang and Du, 2019; Sun, 2021; Ji and Liu, 2022) focused on the LVEDD, revealing that LVEDD in the EG was significantly reduced compared to that in the CG [MD = -3.08, 95% CI: -4.34 to -1.82, p < 0.05; $I^2 = 84\%$]. Additionally, two RCTs (Sun et al., 2020b; Yang et al., 2022) reported on CO. Meta-analysis

showed that the CO in EG is significantly higher than that in the CG [MD = 0.53, 95% CI: 0.27 to 0.79, p < 0.05; $I^2 = 0\%$] (Figure 9).

3.5.5 Inflammatory response

Seven RCTs (Qiao et al., 2016; Liu et al., 2018; Xin and Qian, 2018; Zhou, 2018; Zhang, 2019; Zhang and Du, 2019; Sun, 2021) examined the CRP levels. The meta-analysis demonstrated that the CRP levels in the EG were significantly lower than those in the



CG [MD = -2.99, 95% CI: -5.36 to -0.61, p < 0.05; $l^2 = 98\%$]. Four RCTs (Xin and Qian, 2018; Zhou, 2018; Zhang, 2019; Sun, 2021) investigated TNF- α , revealing that TNF- α levels in the EG were significantly reduced compared to those in the CG [MD = -6.47, 95% CI: -8.76 to -4.18, p < 0.05; $l^2 = 62\%$]. Two RCTs (Qiao et al., 2016; Zhou, 2018) reported on IL-6, and the meta-analysis indicated that IL-6 levels in the EG were significantly lower than in the CG [MD = -24.46, 95% CI: -35.99 to -12.94, p < 0.05; $l^2 = 91\%$]. Similarly, two RCTs (Liu et al., 2018; Zhou, 2018) focused on PTX-3, and the meta-analysis showed that PTX-3 levels in the EG were significantly reduced compared to those in the CG [MD = -2.26, 95% CI: -3.21 to -1.31, p < 0.05; $l^2 = 0\%$] (Figure 10).

3.5.6 Vascular endothelial function

Three RCTs (Fan et al., 2015; Xie, 2017; Zhong and Zheng, 2019) investigated the ET-1, revealing that ET-1 levels in the EG were significantly reduced compared to those in the CG [MD = -20.56, 95% CI: -36.19 to -4.93, p < 0.05; $I^2 = 98\%$]. Similarly, Zhong and

Zheng (2019) reported on NO. The result showed that the NO level in the EG is higher than that in the CG [MD = 1.33, 95% CI: 0.92 to 1.74, p < 0.05] (Figure 11).

3.5.7 Oxidative stress

Two RCTs (Fan et al., 2015; Xie, 2017) reported on SOD. The results indicated that PNS injection plus CT significantly increases the SOD levels compared with CT alone. [MD = 25.84, 95% CI: 16.44 to 35.52, p < 0.05; $I^2 = 0\%$, random-effects model] (Figure 12).

3.6 Safety outcomes

Four RCTs (Liu et al., 2018; Wang, 2018; Chen, 2019; Sun, 2021) assess the adverse effects. Given the non-significant heterogeneity (p = 0.73, $I^2 = 0\%$), a fixed-effects model was employed for the analysis. Figure 13 illustrates that the incidence of adverse events did not significantly differ between the EG and CG [OR = 1.00, 95% CI:



Experimental Control Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% C 71.85 28.79 40 43.46 27.1 58.9% 28.39 [16.14, 40.64] Xie Qingping2017 40 Yang Fan2015 70.75 34.79 42 48.55 33.77 42 41.1% 22.20 [7.54, 36.86] Total (95% CI) 82 82 100.0% 25.84 [16.44. 35.25] Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); l² = 0% -100 -50 50 100 Test for overall effect: Z = 5.39 (P < 0.00001) Favours [control] Favours [experimental] FIGURE 12 Forest plot of SOD.

	Experime	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Chen Zhaodong2019	6	54	4	54	24.0%	1.56 [0.42, 5.88]	
Liu Huajin2018	3	60	5	60	32.1%	0.58 [0.13, 2.54]	
Sun Aimin2021	3	50	2	50	12.7%	1.53 [0.24, 9.59]	
Wang Lianren2018	4	52	5	52	31.2%	0.78 [0.20, 3.10]	
Total (95% CI)		216		216	100.0%	1.00 [0.49, 2.06]	+
Total events	16		16				
Heterogeneity: Chi ² = 1.	29, df = 3 (P = 0.73	3); I ² = 0%				
Test for overall effect: Z	= 0.00 (P =	1.00)					Favours [experimental] Favours [control]
GURE 13 orest plot of adverse eve	ents.						

0.49 to 2.06, p = 1.00]. Regarding bleeding events, Fan et al. (2015) observed three instances in the CG and one in the EG. Xie (2017) reported two severe bleeding events in the CG, while the EG recorded none. There was no significant difference in the incidence of bleeding events between the two groups (p = 0.16).

3.7 Subgroup analysis

Subgroup analysis stratified by the reperfusion strategies (PCI or thrombolysis) indicated that PNS injection could enhance the

total effective rate [OR = 2.57, 95% CI: 1.14 to 5.78, p < 0.05] and decrease MACEs [OR = 0.38, 95% CI: 0.21 to 0.67, p < 0.05] in patients undergoing PCI. Likewise, PNS injection was associated with an increased total effective rate [OR = 3.89, 95% CI: 1.49 to 10.14, p < 0.05] and a reduction in MACEs [OR = 0.24, 95% CI: 0.04 to 1.39, p < 0.05] in patients who underwent thrombolysis (Figure 14).

The subgroup analysis, stratified by the duration of PNS injection (7 days or 14 days), indicated that a 7-day PNS injection was associated with an increased total effective rate [OR = 2.84, 95% CI: 1.27 to 6.37, p < 0.05] and a

Muche on Culture our	Experime		Contro		Mainha	Odds Ratio	Odds Ratio
<u>Study or Subgroup</u> 1.21.1 PCI	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
(ie Qingping2017	32	40	25	40	38.0%	2 40 00 00 6 561	
Thou Shu2018	59	40 62	20 54	62	20.2%	2.40 [0.88, 6.56] 2.91 [0.73, 11.55]	
Subtotal (95% CI)	39	102	34	102	58.2%	2.57 [1.14, 5.78]	
	91	102	79	102	30.270	2.57 [1.14, 5.76]	-
otal events		0.05		0.000	17 - 001		
leterogeneity: Tau ² =			11 = 1 (P =	= 0.82)	; in = 0%		
est for overall effect:	Z = 2.28 (P	= 0.02)					
.21.2 Thrombolysis							
li Xiaohui2022	51	54	44	54	21.0%	3.86 [1.00, 14.93]	
Sun Xuelin2020	47	50	40	50	20.8%	3.92 [1.01, 15.22]	
Subtotal (95% CI)		104		104	41.8%	3.89 [1.49, 10.14]	
otal events	98		84				
leterogeneity: Tau ² =		= 0.00 c		= 0.99)	$ ^{2} = 0\%$		
est for overall effect:				,			
otal (95% CI)		206		206	100.0%	3.05 [1.64, 5.67]	-
Total events	189	200	163	200	100.070	5.05[1.04, 5.07]	-
		- 0.47		- 0.02	12 - 00		
Heterogeneity: Tau² = Fest for overall effect:				- 0.93)	, 17 = 0%		0.01 0.1 1 10 100
'est for subaroup diff				~ ~ ~		~	Favours [control] Favours [experimental]
	Experime	ental	Contr	01		Odds Ratio	Odds Ratio
tudy or Subgroup	Experime				Weight	M-H, Random, 95% Cl	
itudy or Subgroup .22.1 PCI	Events	Total	Events	Total		M-H, Random, 95% Cl	
<mark>Study or Subgroup</mark> 1.22.1 PCI San Lijun2010	Events 6	Total 20	Events 8	<u>Total</u> 19	11.9%	M-H, Random, 95% Cl 0.59 [0.16, 2.21]	
Study or Subgroup 1.22.1 PCI San Lijun2010 Gie Qingping2017	Events 6 6	<u>Total</u> 20 40	Events 8 16	<u>Total</u> 19 40	11.9% 13.9%	M-H, Random, 95% Cl 0.59 [0.16, 2.21] 0.26 [0.09, 0.77]	
Study or Subgroup 1.22.1 PCI San Lijun2010 Kie Qingping2017 Kin Danzhen2018	Events 6 6 2	<u>Total</u> 20 40 54	Events 8 16 10	Total 19 40 53	11.9% 13.9% 10.1%	M-H, Random, 95% Cl 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80]	
Study or Subgroup I.22.1 PCI San Lijun2010 (ie Qingping2017 (in Danzhen2018 (ang Wei2022	Events 6 6 2 3	Total 20 40 54 55	Events 8 16 10 10	Total 19 40 53 55	11.9% 13.9% 10.1% 11.7%	M-H, Random, 95% Cl 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00]	
tudy or Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Gang Wei2022 Chang Zhigang2019	Events 6 6 2	Total 20 40 54 55 60	Events 8 16 10	Total 19 40 53 55 60	11.9% 13.9% 10.1% 11.7% 13.3%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67]	
tudy or Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Gang Wei2022 Gang Zhigang2019 Gubtotal (95% CI)	Events 6 2 3 6	Total 20 40 54 55	Events 8 16 10 10 7	Total 19 40 53 55	11.9% 13.9% 10.1% 11.7% 13.3%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67]	
tudy or Subgroup .22.1 PCI an Lijun2010 de Qingping2017 din Danzhen2018 dang Wei2022 dhang Zhigang2019 dubtotal (95% CI) fotal events	Events 6 2 3 6 23	Total 20 40 54 55 60 229	Events 8 16 10 10 7 51	19 40 53 55 60 227	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67]	
.22.1 PCI can Lijun2010 ie Qingping2017 in Danzhen2018 ang Wei2022 hang Zhigang2019 ubtotal (95% CI) iotal events leterogeneity: Tau ² =	Events 6 2 3 6 23 0.01; Chi ^a =	Total 20 40 54 55 60 229 = 4.08, c	Events 8 16 10 10 7 51 If = 4 (P =	19 40 53 55 60 227	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67]	
.22.1 PCI can Lijun2010 ie Qingping2017 in Danzhen2018 ang Wei2022 hang Zhigang2019 ubtotal (95% CI) iotal events leterogeneity: Tau ² =	Events 6 2 3 6 23 0.01; Chi ^a =	Total 20 40 54 55 60 229 = 4.08, c	Events 8 16 10 10 7 51 If = 4 (P =	19 40 53 55 60 227	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67]	
.22.1 PCI can Lijun2010 ie Qingping2017 in Danzhen2018 iang Wei2022 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect:	Events 6 2 3 6 23 0.01; Chi ^a =	Total 20 40 54 55 60 229 = 4.08, c	Events 8 16 10 10 7 51 If = 4 (P =	19 40 53 55 60 227	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67]	
Audy or Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Gang Wei2022 Chang Zhigang2019 Gubtotal (95% CI) Total events Heterogeneity: Tau ² = Text for overall effect: .22.2 Thrombolysis	Events 6 2 3 6 23 0.01; Chi ^a =	Total 20 40 54 55 60 229 = 4.08, c	Events 8 16 10 10 7 51 If = 4 (P =	19 40 53 55 60 227	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67]	
tudy or Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Gang Wei2022 Chang Zhigang2019 Gubtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: .22.2 Thrombolysis Tu Xiaoxia2014(b)	Events 6 2 3 6 23 0.01; Chi [≇] = Z = 3.34 (P	Total 20 40 54 55 60 229 = 4.08, c = 0.000	Events 8 16 10 10 7 51 ff = 4 (P = 8)	Total 19 40 53 55 60 227 : 0.40);	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 % ; i² = 2%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46]	M-H, Random, 95% Cl
Autor of Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Gang Wei2022 Chang Zhigang2019 Gubtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: .22.2 Thrombolysis Tu Xiaoxia2014(b) i Xiaohui2022	Events 6 6 2 3 6 23 0.01; Chi [≥] = Z= 3.34 (P 23	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36	Events 8 16 10 10 7 51 1f = 4 (P = 8) 25	Total 19 40 53 55 60 227 0.40); 32	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 % ; ² = 2% 13.9% 13.4% 11.7%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13]	M-H, Random, 95% Cl
tudy or Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Gang Wei2022 Chang Zhigang2019 Gubtotal (95% CI) Gotal events Heterogeneity: Tau ² = Fest for overall effect: .22.2 Thrombolysis U Xiaoxia2014(b) i Xiaohui2022 Gang Fan2015	Events 6 6 2 3 6 23 0.01; Chi [≥] = Z = 3.34 (P 23 6	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54	Events 8 16 10 10 7 51 ff = 4 (P = 8) 25 8	Total 19 40 53 55 60 227 : 0.40); 32 54	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 % ; ² = 2% 13.9% 13.4% 11.7%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13]	M-H, Random, 95% Cl
.22.1 PCI can Lijun2010 ie Qingping2017 in Danzhen2018 ang Wei2022 hang Zhigang2019 ubtotal (95% CI) iotal events leterogeneity: Tau ² = est for overall effect: .22.2 Thrombolysis u Xiaoxia2014(b) i Xiaohui2022 ang Fan2015 ubtotal (95% CI)	Events 6 6 2 3 6 23 0.01; Chi [≥] = Z = 3.34 (P 23 6	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42	Events 8 16 10 10 7 51 ff = 4 (P = 8) 25 8	Total 19 40 53 55 60 227 : 0.40); 32 54 42	11.9% 13.9% 10.1% 11.7% 13.3% 60.9 % ; ² = 2% 13.9% 13.4% 11.7%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13]	M-H, Random, 95% Cl
.22.1 PCI can Lijun2010 ie Qingping2017 in Danzhen2018 ang Wei2022 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: .22.2 Thrombolysis u Xiaoxia2014(b) i Xiaohui2022 ang Fan2015 ubtotal (95% CI) otal events leterogeneity: Tau ² =	Events 6 6 2 3 6 23 0.01; Chi [#] = Z = 3.34 (P 23 6 13 42 2.04; Chi [#] =	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25,	Events 8 16 10 10 7 51 (f = 4 (P = 8) 25 8 39 72	Total 19 40 53 55 60 227 : 0.40); 32 54 42 128	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% ; ² = 2% 13.9% 13.4% 11.7% 39.1 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39]	M-H, Random, 95% Cl
Audy or Subgroup .22.1 PCI San Lijun2010 Ge Qingping2017 Gin Danzhen2018 Sang Wei2022 Chang Zhigang2019 Subtotal (95% CI) Total events Heterogeneity: Tau² = Fest for overall effect: .22.2 Thrombolysis 'u Xiaoxia2014(b) i Xiaohui2022 'ang Fan2015 Subtotal (95% CI) 'otal events Heterogeneity: Tau² = 'est for overall effect:	Events 6 6 2 3 6 23 0.01; Chi [#] = Z = 3.34 (P 23 6 13 42 2.04; Chi [#] =	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25,	Events 8 16 10 10 7 51 (f = 4 (P = 8) 25 8 39 72	Total 19 40 53 55 60 227 0.40); 32 54 42 128 = 0.000	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% ; ² = 2% 13.9% 13.4% 11.7% 39.1 %	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.38 [0.21, 0.67] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39]	M-H, Random, 95% Cl
Study or Subgroup 1.22.1 PCI San Lijun2010 Kie Qingping2017 Kin Danzhen2018	Events 6 6 2 3 6 23 0.01; Chi [#] = Z = 3.34 (P 23 6 13 42 2.04; Chi [#] =	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25, = 0.11)	Events 8 16 10 10 7 51 (f = 4 (P = 8) 25 8 39 72	Total 19 40 53 55 60 227 0.40); 32 54 42 128 = 0.000	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% ; r = 2% 13.9% 13.4% 11.7% 39.1% (1); r = 8{	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.38 [0.21, 0.67] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39]	M-H, Random, 95% Cl
Study or Subgroup I.22.1 PCI San Lijun2010 Gie Qingping2017 Gin Danzhen2018 /ang Wei2022 Chang Zhigang2019 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = Fest for overall effect: I.22.2 Thrombolysis Fu Xiaoxia2014(b) Ii Xiaohui2022 /ang Fan2015 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = Fest for overall effect:	Events 6 6 2 3 6 23 0.01; Chi [≇] = Z = 3.34 (P 23 6 13 42 2.04; Chi [≇] = Z = 1.60 (P 65	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25, = 0.11) 361	Events 8 16 10 10 7 51 1f = 4 (P = 8) 25 8 39 72 df = 2 (P 123	Total 19 40 53 55 60 227 6.0.40); 32 54 42 128 = 0.000 355	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% ()" = 2% 13.9% 13.4% 11.7% 39.1% (1); " = 8! 100.0%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39] 5%	M-H, Random, 95% Cl
tudy or Subgroup .22.1 PCI San Lijun2010 tie Qingping2017 tin Danzhen2018 'ang Wei2022 hang Zhigang2019 subtotal (95% CI) 'otal events Heterogeneity: Tau ² = est for overall effect: .22.2 Thrombolysis u Xiaoxia2014(b) i Xiaohui2022 'ang Fan2015 subtotal (95% CI) 'otal events Heterogeneity: Tau ² = est for overall effect: otal (95% CI) 'otal events	Events 6 6 2 3 6 23 0.01; Chi ² = Z= 3.34 (P 23 6 13 42 2.04; Chi ² = Z= 1.60 (P 65 0.60; Chi ² =	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25, = 0.11) 361 = 17.68,	Events 8 16 10 10 7 51 17 = 4 (P = 8) 25 8 39 72 df = 2 (P 123 df = 7 (P	Total 19 40 53 55 60 227 6.0.40); 32 54 42 128 = 0.000 355	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% ()" = 2% 13.9% 13.4% 11.7% 39.1% (1); " = 8! 100.0%	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39] 5%	M.H, Random, 95% Cl
.22.1 PCI can Lijun2010 ie Qingping2017 in Danzhen2018 ang Wei2022 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: .22.2 Thrombolysis u Xiaoxia2014(b) i Xiaohui2022 ang Fan2015 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: otal events leterogeneity: Tau ² = est for overall effect:	Events 6 6 2 3 6 23 0.01; Chi [#] = Z = 3.34 (P 23 6 13 42 2.04; Chi [#] = Z = 1.60 (P 65 0.60; Chi [#] = Z = 3.24 (P	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25, = 0.11) 361 = 17.68, = 0.001	Events 8 16 10 10 7 51 1f = 4 (P = 8) 25 8 39 25 8 39 df = 2 (P 123 df = 7 (P)	Total 19 40 53 55 60 227 : 0.40); : 0.40); 32 54 42 128 = 0.000 355 = 0.01	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% 13.9% 13.4% 11.7% 39.1% 1); I ² = 85 100.0%); I ² = 60°	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39] 5% 0.32 [0.16, 0.64]	M-H, Random, 95% Cl
Audy or Subgroup .22.1 PCI San Lijun2010 San Lijun2010 San Lijun2010 San Lijun2010 San Danzhen2018 Sang Wei2022 Sang Zhigang2019 Subtotal (95% CI) Sotal events Reterogeneity: Tau ² = set for overall effect: .22.2 Thrombolysis u Xiaoxia2014(b) i Xiaohui2022 Sang Fan2015 Subtotal (95% CI) Sotal events Reterogeneity: Tau ² = set for overall effect: Sotal events Ideterogeneity: Tau ² = set for overall effect: Sotal events Ideterogeneity: Tau ² =	Events 6 6 2 3 6 23 0.01; Chi [#] = Z = 3.34 (P 23 6 13 42 2.04; Chi [#] = Z = 1.60 (P 65 0.60; Chi [#] = Z = 3.24 (P	Total 20 40 54 55 60 229 = 4.08, c = 0.000 36 54 42 132 = 13.25, = 0.11) 361 = 17.68, = 0.001	Events 8 16 10 10 7 51 1f = 4 (P = 8) 25 8 39 25 8 39 df = 2 (P 123 df = 7 (P)	Total 19 40 53 55 60 227 : 0.40); : 0.40); 32 54 42 128 = 0.000 355 = 0.01	11.9% 13.9% 10.1% 11.7% 13.3% 60.9% 13.9% 13.4% 11.7% 39.1% 1); I ² = 85 100.0%); I ² = 60°	M-H, Random, 95% CI 0.59 [0.16, 2.21] 0.26 [0.09, 0.77] 0.17 [0.03, 0.80] 0.26 [0.07, 1.00] 0.84 [0.27, 2.67] 0.38 [0.21, 0.67] 0.38 [0.21, 0.67] 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.03 [0.01, 0.13] 0.24 [0.04, 1.39] 5% 0.32 [0.16, 0.64]	M.H, Random, 95% Cl

reduction in MACEs [OR = 0.41, 95% CI: 0.23 to 0.72, p < 0.05]. Similarly, a 14-day PNS injection enhanced the total effective rate [OR = 3.39, 95% CI: 1.29 to 8.90, p < 0.05] and decreased MACEs [OR = 0.17, 95% CI: 0.02 to 1.22, p < 0.05] (Figure 15).

Further subgroup analysis, stratified by the initial time of the injection (before reperfusion or after reperfusion), revealed that administering PNS prior to reperfusion was linked to a decrease in MACEs [OR = 0.51, 95% CI: 0.27 to 0.94, p < 0.05] and an increase in LVEF [MD = 6.65, 95% CI: 4.06 to 9.25, p < 0.05]. Conversely, administering PNS

post-reperfusion was also correlated with a reduction in MACEs [OR = 0.21, 95% CI: 0.06 to 0.70, p < 0.05] and an elevation in LVEF [MD = 4.97, 95% CI: 3.36 to 6.58, p < 0.05] (Figure 16).

An additional subgroup analysis, stratified by the duration of the follow-up, established that the incidence of MACEs in the EG was significantly lower than that in the CG at a 6-month checkpoint [OR = 0.44, 95% CI: 0.21 to 0.89, p < 0.05]. However, no significant differences were observed at the 14-day [OR = 0.41, 95% CI: 0.08 to 2.01, p = 0.27] and 1-month intervals [OR = 0.43, 95% CI: 0.16 to 1.14, p = 0.09] (Figure 17).

tudy or Subgroup	Experime Events		Contr		Moight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
.24.1 7d	LVCIIIS	Total	LVCIIIS	Total	weight	M-H, Kandolli, 55% Cl	m-n, Kandoni, 95 % Ci
i Xiaohui2022	51	54	44	54	21.0%	3.86 [1.00, 14.93]	
ie Qingping2017	32	40	25	40	38.0%	2.40 [0.88, 6.56]	
ubtotal (95% CI)		94		94	59.0%	2.84 [1.27, 6.37]	
otal events	83		69			• • •	
leterogeneity: Tau ² =	0.00; Chi ²	= 0.31.	df = 1 (P	= 0.58)	; I ² = 0%		
est for overall effect:							
.24.2 14d							
un Xuelin2020	47	50	40	50	20.8%	3.92 [1.01, 15.22]	
hou Shu2018	59	62	54	62	20.2%	2.91 [0.73, 11.55]	
ubtotal (95% CI)		112		112	41.0%	3.39 [1.29, 8.90]	-
otal events	106		94				
leterogeneity: Tau ² =	0.00; Chi ²	= 0.09,	df = 1 (P	= 0.76)	; l² = 0%		
est for overall effect:	Z= 2.47 (P	= 0.01)					
otal (95% CI)		206		206	100.0%	3.05 [1.64, 5.67]	•
otal events	189		163				
leterogeneity: Tau ² =	0.00; Chi ²	= 0.47,	df = 3 (P	= 0.93)	; l² = 0%		
est for overall effect:							0.01 0.1 1 10 100
est for subaroup diff	erences: C	hi ² = 0.0	07. df = 1	(P = 0.	79), I² = 0	1%	Favours [control] Favours [experimental]
	-		6				
	Experim		Cont		Weight	Odds Ratio	Odds Ratio
tudy or Subgroup	Experim Events				Weight	Odds Ratio M-H, Random, 95% CI	
tudy or Subgroup .25.1 7d	Events	Total	Events	Total		M-H, Random, 95% Cl	
itudy or Subgroup .25.1 7d u Xiaoxia2014(b)	Events 23	Total 36	Events 25	Total 32	15.6%	M-H, Random, 95% Cl 0.50 [0.17, 1.46]	
itudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022	Events 23 6	<u>Total</u> 36 54	Events 25 8	Total 32 54	15.6% 15.2%	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017	Events 23 6 6	Total 36 54 40	Events 25 8 16	Total 32 54 40	15.6% 15.2% 15.7%	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77]	
tudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 'ang Wei2022	Events 23 6	<u>Total</u> 36 54	Events 25 8	Total 32 54	15.6% 15.2% 15.7% 13.4%	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00]	
tudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 'ang Wei2022 iubtotal (95% CI)	Events 23 6 6	Total 36 54 40 55	Events 25 8 16	Total 32 54 40 55	15.6% 15.2% 15.7% 13.4%	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77]	
tudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 ubtotal (95% CI) iotal events	Events 23 6 6 3 3	Total 36 54 40 55 185	Events 25 8 16 10 59	32 54 40 55 181	15.6% 15.2% 15.7% 13.4% 59.9 %	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00]	
tudy or Subgroup .25.1 7d 'u Xiaoxia2014(b) i Xiaohui2022 Ge Qingping2017 'ang Wei2022 Gubtotal (95% CI) Total events Heterogeneity: Tau ² =	Events 23 6 3 3 0.00; Chi ² :	Total 36 54 40 55 185 = 2.14, 1	Events 25 8 16 10 59 df = 3 (P =	32 54 40 55 181	15.6% 15.2% 15.7% 13.4% 59.9 %	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00]	
tudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 subtotal (95% CI) fotal events leterogeneity: Tau ² = fest for overall effect: .	Events 23 6 3 3 0.00; Chi ² :	Total 36 54 40 55 185 = 2.14, 1	Events 25 8 16 10 59 df = 3 (P =	32 54 40 55 181	15.6% 15.2% 15.7% 13.4% 59.9 %	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 subtotal (95% CI) fotal events leterogeneity: Tau ² = fest for overall effect: .	Events 23 6 3 3 0.00; Chi ² :	Total 36 54 40 55 185 = 2.14, 1	Events 25 8 16 10 59 df = 3 (P =	32 54 40 55 181	15.6% 15.2% 15.7% 13.4% 59.9 %	M-H, Random, 95% Cl 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00]	
Study or Subgroup .25.1 7d u Xiaoxia2014(b) ii Xiaohui2022 Ge Qingping2017 'ang Wei2022 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . .25.2 14d Gin Danzhen2018 'ang Fan2015	Events 23 6 3 3 38 0.00; Chi [≇] : Z = 3.09 (P	<u>Total</u> 36 54 40 55 185 = 2.14, 1 = 0.002	Events 25 8 16 10 59 df = 3 (P = 2) 10	Total 32 54 40 55 181 = 0.54);	15.6% 15.2% 15.7% 13.4% 59.9 % ; ² = 0%	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 'ang Wei2022 ubtotal (95% Cl) 'otal events leterogeneity: Tau ² = 'est for overall effect: . .25.2 14d in Danzhen2018 'ang Fan2015	Events 23 6 6 3 3 38 0.00; Chi [≇] : Z = 3.09 (P 2	<u>Total</u> 36 54 40 55 185 = 2.14, - = 0.002 54	Events 25 8 16 10 59 df = 3 (P = 2) 10	Total 32 54 40 55 181 = 0.54); 53	15.6% 15.2% 15.7% 13.4% 59.9 % ; ² = 0%	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 'ang Wei2022 ubtotal (95% Cl) otal events leterogeneity: Tau ² = 'est for overall effect: . .25.2 14d in Danzhen2018 'ang Fan2015 'hang Zhigang2019	Events 23 6 3 3 0.00; Chi [#] : Z = 3.09 (P 2 13	Total 36 54 40 55 185 = 2.14, - = 0.002 54 42	Events 25 8 16 10 59 df = 3 (P = 2) 10 39	Total 32 54 40 55 181 = 0.54); 53 42	15.6% 15.2% 15.7% 13.4% 59.9% ; ² = 0% 11.7% 13.4% 15.0%	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13]	
tudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 subtotal (95% CI) fotal events leterogeneity: Tau ² = fest for overall effect: . .25.2 14d in Danzhen2018	Events 23 6 3 3 0.00; Chi [#] : Z = 3.09 (P 2 13	Total 36 54 40 55 185 = 2.14, 1 = 0.002 54 42 60	Events 25 8 16 10 59 df = 3 (P = 2) 10 39	Total 32 54 40 55 181 = 0.54); 53 42 60	15.6% 15.2% 15.7% 13.4% 59.9% ; ² = 0% 11.7% 13.4% 15.0%	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13] 0.84 [0.27, 2.67]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: . .25.2 14d in Danzhen2018 ang Fan2015 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² =	Events 23 6 3 38 0.00; Chi ² : Z = 3.09 (P 2 13 6 21 2.51; Chi ² :	Total 36 54 40 55 185 = 2.14, = 0.002 54 42 60 156 = 12.65	Events 25 8 16 10 59 df = 3 (P = 2) 10 39 7 56 , df = 2 (P	Total 32 54 40 55 181 = 0.54); 53 42 60 155	15.6% 15.2% 15.7% 13.4% 59.9 % ; ² = 0% 11.7% 13.4% 15.0% 40.1 %	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13] 0.84 [0.27, 2.67] 0.17 [0.02, 1.22]	
tudy or Subgroup .25.17d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: . .25.2 14d in Danzhen2018 ang Fan2015 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: .	Events 23 6 3 38 0.00; Chi ² : Z = 3.09 (P 2 13 6 21 2.51; Chi ² :	Total 36 54 40 55 185 = 2.14, - = 0.002 54 42 60 156 = 12.65 = 0.08)	Events 25 8 16 10 59 df = 3 (P = 2) 10 39 7 56 , df = 2 (P	Total 32 54 40 55 181 = 0.54); 53 42 60 155 = 0.000	15.6% 15.2% 15.7% 13.4% 59.9% (I ² = 0% 11.7% 13.4% 15.0% 40.1% (2); I ² = 84	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13] 0.84 [0.27, 2.67] 0.17 [0.02, 1.22]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: . .25.2 14d in Danzhen2018 ang Fan2015 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: . otal (95% CI)	Events 23 6 3 38 0.00; Chi≆: Z = 3.09 (P 2 13 6 21 2.51; Chi≅: Z = 1.76 (P	Total 36 54 40 55 185 = 2.14, = 0.002 54 42 60 156 = 12.65	Events 25 8 16 10 59 ctf = 3 (P = 2) 10 39 7 56 , df = 2 (P	Total 32 54 40 55 181 = 0.54); 53 42 60 155 = 0.000	15.6% 15.2% 15.7% 13.4% 59.9 % ; ² = 0% 11.7% 13.4% 15.0% 40.1 %	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13] 0.84 [0.27, 2.67] 0.17 [0.02, 1.22]	
tudy or Subgroup .25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: . .25.2 14d in Danzhen2018 ang Fan2015 hang Zhigang2019 ubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: . otal (95% CI) otal events	Events 23 6 3 38 0.00; Chi [≇] : Z = 3.09 (P 2 13 6 21 2.51; Chi [≇] : Z = 1.76 (P 59	Total 36 54 40 55 185 = 2.14, 1 = 0.002 54 42 60 156 = 12.65 = 0.08) 341	Events 25 8 16 10 59 df = 3 (P = 2) 10 39 7 56 , df = 2 (P 115	Total 32 54 40 55 181 = 0.54); 60 155 = 0.000 336	15.6% 15.2% 15.7% 13.4% 59.9% (* = 0% 11.7% 13.4% 15.0% 40.1% (2); * = 84 100.0%	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13] 0.84 [0.27, 2.67] 0.17 [0.02, 1.22]	M-H, Random, 95% Cl
.25.1 7d u Xiaoxia2014(b) i Xiaohui2022 ie Qingping2017 ang Wei2022 ubtotal (95% Cl) otal events leterogeneity: Tau ² = est for overall effect: . .25.2 14d in Danzhen2018 ang Fan2015 hang Zhigang2019 ubtotal (95% Cl) otal events leterogeneity: Tau ² = est for overall effect: . otal (95% Cl)	Events 23 6 6 3 38 0.00; Chi [≇] : Z = 3.09 (P 2 13 6 21 2.51; Chi [≇] : Z = 1.76 (P 59 0.70; Chi [≇] :	Total 36 54 40 55 185 = 2.14, 1 = 0.002 54 42 60 156 = 12.65 = 0.08) 341 = 16.90	Events 25 8 16 10 59 df = 3 (P = 2) 10 39 7 56 , df = 2 (P 115 , df = 6 (P	Total 32 54 40 55 181 = 0.54); 60 155 = 0.000 336	15.6% 15.2% 15.7% 13.4% 59.9% (* = 0% 11.7% 13.4% 15.0% 40.1% (2); * = 84 100.0%	M-H, Random, 95% CI 0.50 [0.17, 1.46] 0.72 [0.23, 2.23] 0.26 [0.09, 0.77] 0.26 [0.07, 1.00] 0.41 [0.23, 0.72] 0.41 [0.23, 0.72] 0.17 [0.03, 0.80] 0.03 [0.01, 0.13] 0.84 [0.27, 2.67] 0.17 [0.02, 1.22]	

Subgroup analysis stratified by the courses of PNS injection [(A) total effective rate; (B) MACEs].

3.8 Sensitivity analysis

When the heterogeneity was significant, we performed a sensitivity analysis, including MACEs, MIS, CK-MB, cTnT, BNP, LVEF, LVEDD, CRP, TNF- α , and ET-1. Sensitivity analysis found that the reasons may lie in the heterogeneity of trials with respect to the sample size, the age range of participants, PNS dosing protocols, duration of the intervention, and the outcome measures used. After excluding these studies, the heterogeneity significantly reduced, and the results showed a limited impact

(Supplementary Table S4). Therefore, these results of metaanalysis were stable and reliable.

3.9 Publication bias

We performed the publication bias for LVEF. As the number of trials was ≥ 10 , we used the funnel chart to determine whether there was publication bias. The results showed that the points of the effects of each trial show a symmetrical inverted funnel distribution, suggesting that the possibility of publication bias was small (Figure 18).

4	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.29.1 Before reperfu	sion						
Fu Xiaoxia2014(b)	23	36	25	32	13.9%	0.50 [0.17, 1.46]	
Gan Lijun2010	6	20	8	19	11.9%	0.59 [0.16, 2.21]	
Xin Danzhen2018	2	54	10	53	10.1%	0.17 [0.03, 0.80]	
Zhang Zhigang2019	6	60	7	60	13.3%	0.84 [0.27, 2.67]	
Subtotal (95% CI)		170		164	49.2%	0.51 [0.27, 0.94]	◆
Total events	37		50				
Heterogeneity: Tau ² =	0.00; Chi ² =	= 2.77, 0	df = 3 (P =	0.43);	I ² = 0%		
Test for overall effect: .	Z = 2.15 (P	= 0.03)					
1.29.2 After reperfusi			222		10 1017 (11-1-0-14)		
Ji Xiaohui2022	6	54	8	54	13.4%	0.72 [0.23, 2.23]	
Xie Qingping2017	6	40	16	40		0.26 [0.09, 0.77]	
Yang Fan2015	13	42	39	42	11.7%	0.03 [0.01, 0.13]	
Yang Wei2022	3	55	10	55	11.7%	0.26 [0.07, 1.00]	
Subtotal (95% CI)		191		191	50.8%	0.21 [0.06, 0.70]	
Total events	28		73				
Heterogeneity: Tau ² =				= 0.00	8); I² = 74	%	
Test for overall effect: .	Z = 2.54 (P	= 0.01)					
Total (95% CI)		361		355	100.0%	0.32 [0.16, 0.64]	◆
Total events	65		123				
Heterogeneity: Tau ² =	0.60; Chi ² =	= 17.68.	df = 7 (P	= 0.01); I ² = 609	6	
Test for overall effect: .							0.01 0.1 1 10 10
							Favours [experimental] Favours [control]

E	Experi	iment	tal	C	ontrol			Mean Difference	Mean Difference
r Subgroup Me	ean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Before reperfusion									
haodong2019 8	8.17	4.58	54	4.88	4.42	54	8.1%	3.29 [1.59, 4.99]	
xia2014(b) 2	20.4 4	4.61	36	9.7	4.07	32	7.8%	10.70 [8.64, 12.76]	
anbiao2019 24	4.07 6	6.88	44	9.93	5.74	44	7.2%	14.14 [11.49, 16.79]	
ajin2018 7.	7.27	4.62	60	4.56	4.47	60	8.1%	2.71 [1.08, 4.34]	
nin2021	8.6 3	3.66	50	4.73	3.75	50	8.3%	3.87 [2.42, 5.32]	
ianren2018 9.	9.41 4	4.56	52	4.68	4.05	52	8.1%	4.73 [3.07, 6.39]	
Hui2019 1	11.9 3	3.57	69	4	3.56	69	8.4%	7.90 [6.71, 9.09]	-
al (95% Cl)			365			361	56.0%	6.65 [4.06, 9.25]	
geneity: Tau ² = 11.39;	9; Chi²	² = 102	2.07, di	f=6(P	< 0.00	001); l²	= 94%		
overall effect: Z = 5.0	.03 (P	< 0.00	0001)						
After reperfusion									
nui2022 16.	6.29 6	6.59	54	8.78	6.27	54	7.4%	7.51 [5.08, 9.94]	
elin2020 18.	8.46 5	5.73	50	12.13	5.67	50	7.6%	6.33 [4.10, 8.56]	
gping2017 3	31.2 5	5.73	40	25.9	5.24	40	7.5%	5.30 [2.89, 7.71]	
/ei2022 9.	9.29	4.79	55	5.76	4.62	55	8.0%	3.53 [1.77, 5.29]	
Zhennan2019 5.	5.85 8	8.72	40	0.47	8.49	40	6.1%	5.38 [1.61, 9.15]	
hu2018 9.	9.45 7	7.34	62	7.34	6.74	62	7.4%	2.11 [-0.37, 4.59]	
al (95% CI)			301			301	44.0%	4.97 [3.36, 6.58]	•
geneity: Tau ² = 2.46; (Chi ² =	= 13.3	6, df =	5 (P = 0).02); P	² = 63%			
overall effect: Z = 6.0	.06 (P	< 0.00	0001)						
5% CI)			666			662	100.0%	5.91 [4.23, 7.59]	•
geneity: Tau² = 8.30; r overall effect: Z = 6.9 r suboroup difference	91 (P	< 0.00	0001)						-10 -5 0 5 10 Favours [control] Favours [experimental]
15% CI) geneity: Tau² = 8.30; « r overall effect: Z = 6.9	Chi² = .91 (P es: Ch	= 119. < 0.00 hi ² = 1.	666 31, df: 0001) .17. df	= 1 (P =	: 0.28)	001); l² . l² = 14	= 90% .5%	5.91 [4.23, 7.59]	

4 Discussion

4.1 Summary of findings

To the best of our knowledge, this is the first meta-analysis that systematically assesses the efficacy and safety of PNS injection in the treatment of AMI. The findings indicate a significant enhancement in the total effective rate and a reduction in MACEs at 6 months, ST segment elevation, and MIS in AMI patients treated with PNS injection. Additionally, PNS injections were found to improve cardiac and vascular endothelial functions and mitigate myocardial injury, inflammatory responses, and oxidative stress, likely attributing to the protective mechanism of PNS in AMI. Safety assessments suggest that PNS does not increase the incidence of adverse events, particularly bleeding. These results demonstrate the efficacy and safety of PNS injection, offering improved functional outcomes in AMI patients compared to CT alone

1.35.1 14d Xin Darchen2018 2 54 10 53 8.5% 0.17 [0.03, 0.80] Zhang Zhigag2019 6 60 7 60 15.7% 0.84 [0.27, 2.67] Subtotal (95% CI) 114 113 24.2% 0.41 [0.08, 2.01] Total events 8 1 7 Heterogeneity: Tau ² = 0.85; Ch ² = 2.72, df = 1 (P = 0.10); P = 63% Test for overall effect Z = 1.10 (P = 0.27) 1.35.2 1m Ji Xiaohui2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xike Qingping2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% CI) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Ch ² = 1.57, df = 1 (P = 0.21); P = 36% Test for overall effect Z = 1.70 (P = 0.09) 1.35.4 6m Fu Xiaoxia2014 (b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.86); P = 0% Test for overall effect Z = 2.29 (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); P = 0% Test for overall effect Z = 3.51 (P = 0.0005)	Charles Calanda	Experime		Contr		104-1-1-1	Odds Ratio	Odds Ratio
Xin Darzhen2018 2 54 10 53 8.5% 0.17 [0.03, 0.80] Zhang Zhigang2019 6 60 7 60 15.7% 0.84 [0.27, 2.67] Subtotal (95% CI) 114 113 24.2% 0.41 [0.08, 2.01] Total events 8 17 Heterogeneity: Tau ² = 0.85; Chi ² = 2.72, df = 1 (P = 0.10); P = 63% Test for overall effect: $Z = 1.10$ (P = 0.27) 1.35.2 1m Ji Xiaohui2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xiu Galingping2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% CI) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); P = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); P = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); P = 0% Test for overall effect: $Z = 2.29$ (P = 0.005)	Study or Subgroup	Events	Total	Events	Total	weight	м-н, капаот, 95% СГ	м-н, капаот, 95% СГ
Zhang Zhigang 2019 6 60 7 60 15.7% 0.84 [0.27, 2.67] Subtotal (95% CI) 114 113 24.2% 0.41 [0.08, 2.01] Total events 8 17 Heterogeneifty: Tau ² = 0.85; Ch ² = 2.72, df = 1 ($P = 0.10$); $P = 63\%$ Test for overall effect: $Z = 1.10$ ($P = 0.27$) 1.35.2 1m Ji Xiaohui 2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xie Qingping 2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% CI) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneifty: Tau ² = 0.18; Chi ² = 1.57, df = 1 ($P = 0.21$); $P = 36\%$ Test for overall effect: $Z = 1.70$ ($P = 0.09$) 1.35.4 6m Fu Xiaoxia 2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun 2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei 2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneifty: Tau ² = 0.00; Chi ² = 0.82, df = 2 ($P = 0.66$); $P = 0\%$ Test for overall effect: $Z = 2.29$ ($P = 0.02$) Total events 52 84 Heterogeneifty: Tau ² = 0.00; Chi ² = 512, df = 6 ($P = 0.53$); $P = 0\%$ Test for overall effect: $Z = 3.51$ ($P = 0.0005$) Total events 52 84 Heterogeneifty: Tau ² = 0.00; Chi ² = 512, df = 6 ($P = 0.53$); $P = 0\%$ Test for overall effect: $Z = 3.51$ ($P = 0.0005$)								
Subtotal (95% CI) 114 113 24.2% 0.41 [0.08, 2.01] Total events 8 17 Heterogeneity: Tau ² = 0.85; Chi ² = 2.72, df = 1 ($P = 0.10$); $P = 63\%$ Test for overall effect: Z = 1.10 ($P = 0.27$) 1.35.2 Im Ji Xiaohui2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xiaohui2022 6 54 8 54 16.3% 0.26 [0.09, 0.77] Subtotal (95% CI) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 ($P = 0.21$); $P = 36\%$ Test for overall effect: Z = 1.70 ($P = 0.09$) 1.35.4 6m Fu Xiaoxia2014 (b) 23 36 25 32 18.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 ($P = 0.66$); $P = 0\%$ Test for overall effect: Z = 3.51 ($P = 0.005$) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 ($P = 0.53$); $P = 0\%$ Test for overall effect: Z = 3.51 ($P = 0.005$)								
Total events 8 17 Heterogeneity: Tau ² = 0.85; Chi ² = 2.72, df = 1 (P = 0.10); P = 63% Test for overall effect: $Z = 1.10$ (P = 0.27) 1.35.2 1m Ji Xiaohui2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xie Qingping2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% Cl) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); P = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia2014 (b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); P = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); P = 0% Test for overall effect: $Z = 3.51$ (P = 0.005)		6		ſ				
Heterogeneity: Tau ² = 0.86; Chi ² = 2.72, df = 1 (P = 0.10); P = 63% Test for overall effect: $Z = 1.10$ (P = 0.27) 1.35.2 1m Ji Xiaohui2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xie Qingping2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% Cl) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 2 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); P = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia2014 (b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); P = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); P = 0% Test for overall effect: $Z = 3.51$ (P = 0.0005)			114		113	24.2%	0.41 [0.08, 2.01]	
Test for overall effect: $Z = 1.10$ (P = 0.27) 1.35.2 1m Ji Xiaohui 2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xie Qingping 2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% Cl) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); P = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia 2014 (b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun 2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei 2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); P = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); P = 0% Test for overall effect: $Z = 3.51$ (P = 0.0005)		-			_			
1.35.2 Im 1.35.2 Im 1.36.2 Im 1.36.2 Im 1.36.4 CM 1.36.4 Second Secon	- /			if = 1 (P =	: 0.10);	I² = 63%		
Ji Xiaohui 2022 6 54 8 54 16.3% 0.72 [0.23, 2.23] Xie Qingping 2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% CI) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); l ² = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia 2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun 2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei 2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); l ² = 0% Test for overall effect: $Z = 3.51$ (P = 0.0005)	Test for overall effect: Z	.= 1.10 (P :	= 0.27)					
Xie Qingping2017 6 40 16 40 18.1% 0.26 [0.09, 0.77] Subtotal (95% CI) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); l ² = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total (95% CI) 319 313 100.0% 0.44 [0.28, 0.70] Total (95% CI) 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); l ² = 0% Test for overall effect: $Z = 3.51$ (P = 0.0005) Total effect: $Z = 3.51$ (P = 0.0005)	1.35.2 1m							
Subtotal (95% Cl) 94 94 34.4% 0.43 [0.16, 1.14] Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); P = 36% Test for overall effect: Z = 1.70 (P = 0.09) 1.35.4 6m Fu Xiaoxia2014(b) 23 Gan Lijun2010 6 20 6 20 8 19 Yang Wei2022 3 55 10 55 Yang Wei2022 3 55 10 55 11.5% Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); P = 0% 0.44 [0.28, 0.70] Image: Control 1 Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Image: Control 1 Total events 52 84 Eavours [avnerimental] Eavours [control] Favours [control] Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); I ² = 0% Image: Control] Image: Control] Image: Control]	Ji Xiaohui2022	6	54	8	54	16.3%	0.72 [0.23, 2.23]	
Total events 12 24 Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); l ² = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); l ² = 0% Test for overall effect: $Z = 3.51$ (P = 0.0005) Favours [avnerimental]. Favours [avnerimental]. Favours [avnerimental]. Favours [avnerimental]. Favours [avnerimental].	Xie Qingping2017	6	40	16	40	18.1%	0.26 [0.09, 0.77]	
Heterogeneity: Tau ² = 0.18; Chi ² = 1.57, df = 1 (P = 0.21); l ² = 36% Test for overall effect: $Z = 1.70$ (P = 0.09) 1.35.4 6m Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% Test for overall effect: $Z = 2.29$ (P = 0.02) Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); l ² = 0% Test for overall effect: $Z = 3.51$ (P = 0.0005) Favours for overall effect: $Z = 3.51$ (P = 0.0005)	Subtotal (95% CI)		94		94	34.4%	0.43 [0.16, 1.14]	
Test for overall effect: $Z = 1.70 (P = 0.09)$ 1.35.4 6m Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); I ² = 0% Test for overall effect: $Z = 2.29 (P = 0.02)$ Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); I ² = 0% Test for overall effect: $Z = 3.51 (P = 0.0005)$	Total events	12		24				
1.35.4 6m Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 [0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); I ² = 0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); I ² = 0% 0.01 0.1 10 100 Total events 52 84 0.01 0.1 100 100 Total events 52 84 0.01 0.1 100 100 Test for overall effect: Z = 3.51 (P = 0.0005) 52 84 52 53 54 55 55 56 56 56 56 56 56 56 56 56 56 56 56 56 56 56 56 56 <	Heterogeneity: Tau ² = 0	.18; Chi ² =	1.57, 0	if = 1 (P =	0.21);	I ² = 36%		
Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% 0.44 [0.28, 0.70] Total (95% CI) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 10.01 0.1 10 100 Test for overall effect: Z = 3.51 (P = 0.0005) 52 84 10.01 0.1 100 100 Favours formertall	Test for overall effect: Z	= 1.70 (P	= 0.09)					
Fu Xiaoxia2014(b) 23 36 25 32 18.0% 0.50 0.17, 1.46] Gan Lijun2010 6 20 8 19 12.0% 0.59 [0.16, 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% CI) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% 0.44 [0.28, 0.70] Total (95% CI) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 10.01 0.1 10 100 Test for overall effect: Z = 3.51 (P = 0.0005) 52 84 10.01 0.1 100 100 Favours formertall	4 25 4 Gm							
Gan Lijun2010 6 20 8 19 12.0% 0.59 0.16 2.21] Yang Wei2022 3 55 10 55 11.5% 0.26 [0.07, 1.00] Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); I ² = 0% 0.44 [0.28, 0.70] Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); I ² = 0% 0.01 0.1 10 100 Test for overall effect: Z = 3.51 (P = 0.0005) 52 84		22	20	25	22	40.00	0 50 10 47 4 461	
Yang Wei2022 3 55 10 55 11.5% $0.26 [0.07, 1.00]$ Subtotal (95% Cl) 111 106 41.4% $0.44 [0.21, 0.89]$ Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82; df = 2 (P = 0.66); l ² = 0% 0.44 [0.28, 0.70] Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12; df = 6 (P = 0.53); l ² = 0% 0.01 0.1 10 100 Test for overall effect: Z = 3.51 (P = 0.0005) Eavours [avnerimental] Eavours [control]								
Subtotal (95% Cl) 111 106 41.4% 0.44 [0.21, 0.89] Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% Test for overall effect: Z = 2.29 (P = 0.02) Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); l ² = 0% 0.01 0.1 10 100 Test for overall effect: Z = 3.51 (P = 0.0005) Eavours [eventremental] Favours [eventremental] Favours [eventremental]		-		-				
Total events 32 43 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); l ² = 0% Test for overall effect: Z = 2.29 (P = 0.02) Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); l ² = 0% 0.01 0.1 1 100 100 Test for overall effect: Z = 3.51 (P = 0.0005) Eavours [avnerimental] Favours [avnerimental] Favours [control]		3		10				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 2 (P = 0.66); i ² = 0% Test for overall effect: Z = 2.29 (P = 0.02) Total (95% Cl) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); i ² = 0% Test for overall effect: Z = 3.51 (P = 0.0005) Favours [avnerimental] Favours [control]			111	10	100	41.4%	0.44 [0.21, 0.89]	
Test for overall effect: Z = 2.29 (P = 0.02) Total (95% CI) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); i ² = 0% 0.01 0.1 1 100 100 Test for overall effect: Z = 3.51 (P = 0.0005) Eavours [evnerimental] Favours [control]					0.000			
Total (95% CI) 319 313 100.0% 0.44 [0.28, 0.70] Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); i ² = 0% 0.01 0.1 1 100 100 Test for overall effect: Z = 3.51 (P = 0.0005) Eavours [evnerimental] Favours [evnerimental] Favours [evnerimental]	Heterogeneity: Tau* = U			if = 2 (P =	0.66);	1~= 0%		
Total events 52 84 Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); i ² = 0% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.51 (P = 0.0005) Eavours [evnerimental] Eavours [evnerimental] Eavours [evnerimental]	T	= 2.29 (P =	= 0.02)					
Heterogeneity: Tau ² = 0.00; Chi ² = 5.12, df = 6 (P = 0.53); i ² = 0% Test for overall effect: Z = 3.51 (P = 0.0005) Favours [experimental] Favours [control]	Test for overall effect: Z				343	100.0%	0.44 [0.28, 0.70]	◆
Test for overall effect: Z = 3.51 (P = 0.0005)			319		315			
Test for overall effect: Z = 3.51 (P = 0.0005)	Total (95% CI)	52	319	84	515			
Test for subgroup differences: Chi ² = 0.01. df = 2 (P = 1.00). I ² = 0%	Total (95% Cl) Total events							
	Total (95% CI) Total events Heterogeneity: Tau² = 0).00; Chi² =	= 5.12, 0	if = 6 (P =				
RE 17	Total (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z).00; Chi² = := 3.51 (P :	= 5.12, d = 0.000	if = 6 (P = 5)	0.53);	I² = 0%	6	



and potentially presenting a promising treatment modality for AMI. Subgroup analysis further revealed that regardless of the variation in reperfusion strategies (PCI or thrombolysis), initiation timing (pre or post-reperfusion), and duration of treatment (7 or 14 days), PNS exhibited significant therapeutic benefits and favorable long-term prognoses in AMI management. Consequently, PNS is advocated as a secondary treatment in reperfusion AMI patients. The decision to initiate PNS immediately post-reperfusion should consider the risk of bleeding, with a recommended treatment duration of 1–2 weeks.

4.2 Mechanism of PNS in AMI

Apoptosis, occurring within hours after the occurrence of AMI, is a primary factor contributing to myocardial injury (Zhou et al., 2018b). This process is intricately linked to the Bcl-2 gene (Bcl-2) and Bcl-2-associated X protein (Bax). PNS is shown to mitigate ultrastructural damage in cardiomyocytes, suppress Bax expression, and enhance the Bcl-2/Bax ratio, thereby reducing cardiomyocyte apoptosis induced by myocardial injury (Zhang et al., 2022). Liu et al. (2019) reported that PNS promotes cardiomyocyte autophagy via the phosphorylation of AMPK and CaMKII, conferring cardioprotection in AMI. Furthermore, PNS has been observed to prevent the decline in mitochondrial membrane potential triggered by hypoxia and serum glucose starvation (SGOD) in vitro, inhibiting apoptosis in H9c2 cells. The anti-apoptotic property of PNS may be associated with the upregulation of miR-21 and the inhibition of the PI3K/Akt signaling pathway (Chen et al., 2011; Chen et al., 2019).

Frequent inflammatory reactions aggravate ischemia-reperfusion injury post-AMI, leading to an elevation in MIS (Toldo and Abbate, 2018). TNF-α and IL-6 are the primary inflammatory mediators (Neumann et al., 1995; Frangogiannis, 2014). Fundamental research has demonstrated that PNS can decrease the levels of inflammatory mediators such as nuclear factor kappa B (NF- κ B), TNF-α, and IL-6 in rat models of AMI. This reduction mitigates the extent of inflammatory infiltration and myocardial cell edema (Pan et al., 2015; Ning et al., 2020). Sun et al. (2013) and Zhong et al. (2015) corroborated that notoginsenoside R1, a significant phytoestrogen, mitigates H9c2 cell injury by diminishing inflammatory responses and apoptosis in both *in vivo* and *in vitro* experiments.

Oxidative stress injury critically contributes to irreversible and severe damage to cardiomyocytes in AMI (Neri et al., 2015). Experimental findings (Yamada et al., 2019; Wang et al., 2020) confirm that PNS curtails the generation of oxygen-free radicals in cardiomyocytes post-AMI. This modulation alleviates the imbalance between oxidative and antioxidative mechanisms, ameliorating oxidative stress injury and safeguarding the damaged myocardium. Yu et al. (2016) verified through *in vivo* and *in vitro* studies that PNS scavenges oxygen-free radicals, augments the activity of antioxidant enzymes, decreases the expression of endoplasmic reticulum stress-associated proteins, and suppresses the expression of proteins linked to pro-apoptosis.

Alterations in the structure and function of vascular endothelial cells are intimately associated with AMI onset. PNS inhibits the apoptosis of rat vascular endothelial cells by downregulating caspase-3 expression and upregulating the Bcl-2 gene. It enhances endothelium-dependent vasodilation function by

elevating NO levels and reducing ET-1 levels (Kwan and Kwan, 2000; Qiao et al., 2015; Zhang et al., 2021). Certain studies (Yang et al., 2016; Zhou et al., 2019) have suggested that angiogenesis induced by PNS post-AMI might correlate with the upregulation of vascular endothelial growth factor A (VEGFA) gene expression. PNS notably promotes the VEGF-stimulated migration of human umbilical vein endothelial cells (HUVECs) and induces approximately a three-fold increase in VEGF mRNA expression.

Platelet activation is a direct precursor to platelet aggregation, potentially leading to AMI. PNS exerts a notable inhibitory effect on platelet-activating factor CD62P and platelet membrane glycoprotein IIb/IIIa. This effect significantly counteracts platelet aggregation and adhesion, enhances fibrinolytic activity, and decelerates thrombosis (Lau et al., 2009). Studies indicate that PNS not only reduces platelet aggregation but also, when used with aspirin, enhances its antiplatelet effect and protects the gastric mucosa. This effect is likely due to PNS's impact on the metabolic pathways of cyclooxygenase-1 and cytochrome enzymes in the platelet arachidonic acid (AA) pathway (Wang et al., 2021b; Wang et al., 2021c; Dai et al., 2022). Zhong and Zheng (2019) observed that the platelet aggregation rate in the PNS plus CT group was significantly lower than that in the CT group 2 h post-thrombolysis, although no significant difference was noted at 10 h. Although our study did not include indicators related to platelet function and coagulation, future research may address this gap.

4.3 Advantages and limitations

The advantages of this meta-analysis included the following. First, a comprehensive search was conducted in a variety of databases without language and time restrictions. Second, independent study selection, data extraction, and bias assessment by two investigators minimized errors. Third, sensitivity analyses did not significantly affect the results, indicating the results were credible. Fourth, multiple subgroup analyses were conducted to assess potential influencing factors and reduce heterogeneity.

There were some limitations in this study. First, the quality of included RCTs was generally low, according to the collaboration tool. None of the 20 RCTs clearly described the method of allocation concealment and blinding, resulting in methodological deficiencies. Therefore, we assessed and reviewed the eligible RCTs by applying considerably high standards. Our meta-analysis attempted to secure methodological rigor and therefore draw unbiased conclusions. Second, all of 20 RCTs were written in Chinese and no English article was involved, and the publication biases could probably affect the results. Third, there were differences in CT of the 20 RCTs, which may increase heterogeneity between the included trials and influence the results. In addition, the heterogeneity in meta-analysis was significant. We used sensitivity and subgroup analyses to explore the source of heterogeneity.

5 Conclusion

This study highlighted the efficacy and safety of adjunctive PNS injection in enhancing AMI patient outcomes beyond CT alone. Future RCTs need to solidify these findings through rigorous methods, including double-blinding, enlarged sample sizes, the incorporation of multiple centers, and prolonged follow-up durations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Author contributions

PC: data curation, software, and writing-original draft. ZG: writing-review. MG: formal analysis, software, and writing-original draft. DP: data curation and writing-original draft. HZ: software. JD: conceptualization and writing-review and editing. DS: conceptualization and writing-review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the project of Major New Drug Creation (No. 2018ZX09301-011-001).

References

Byrne, R. A., Rossello, X., Coughlan, J. J., Barbato, E., Berry, C., Chieffo, A., et al. (2023). 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur. Heart J.* 44 (38), 3720–3826. doi:10.1093/eurheartj/ehad191

Chen, J., Xue, R., Li, L., Xiao, L. L., Shangguan, J., Zhang, W., et al. (2019). Panax notoginseng saponins protect cardiac myocytes against endoplasmic reticulum stress and associated apoptosis through mediation of intracellular calcium homeostasis. *Front. Pharmacol.* 10, 1013. doi:10.3389/fphar.2019.01013

Chen, S., Liu, J., Liu, X., Fu, Y., Zhang, M., Lin, Q., et al. (2011). Panax notoginseng saponins inhibit ischemia-induced apoptosis by activating PI3K/ Akt pathway in cardiomyocytes. *J. Ethnopharmacol.* 137 (1), 263–270. doi:10. 1016/j.jep.2011.05.011

Chen, Z. (2019). Effect of Xuesaitong injection on myocardial injury and cardiac function in patients with acute ST segment elevation myocardial infarction. *Xizang Med.* (01), 145–147.

Dai, L., Zhang, Y., Jiang, Y., and Chen, K. (2022). Panax notoginseng preparation plus aspirin versus aspirin alone on platelet aggregation and coagulation in patients with coronary heart disease or ischemic stroke: a meta-analysis of randomized controlled trials. *Front. Pharmacol.* 13, 1015048. doi:10.3389/fphar.2022.1015048

Fan, Y., Fu, X., and Li, Y. (2015). Application of Xueshuantong injection in the treatment of acute ST segment elevation myocardial infarction. *China Med. Her.* (04), 111–114.

Feng, G., Wei, Y., Bai, Y., Zhao, D., et al. (2017). Clinical effect of coronary injection of Panax notoginseng saponins during PCI in STEMI patients. J. Pract. Med. (02), 143–145. doi:10.14172/j.issn1671-4008.2017.02.016

Frangogiannis, N. G. (2014). The inflammatory response in myocardial injury, repair, and remodelling. *Nat. Rev. Cardiol.* 11 (5), 255–265. doi:10.1038/nrcardio.2014.28

Fu, X., Lu, J., Yang, F., and Xiao, W. (2014a). Preventive and therapeutic effect of Xueshuantong injection on reperfusion injury in acute myocardial infarction. *Propr. Chin. Med.* (05), 933–936.

Fu, X., Xiao, W., and Yang, F. (2014b). Effect of Xueshuantong injection on BNP level in patients with acute myocardial infarction. *Today's Pharm.* (4), 273–275.

Gan, L., Zhang, C., Zhang, M., Cheng, Y., Liao, Y., et al. (2010). Effect of intracoronary injection with xuesaitong in treating post-PCI slow-reflow phenomenon in patients with ST-segment elevation myocardial infarction. *Chin. J. Integr. traditional Chin. West. Med.* 30 (04), 348–351.

Gong, F. F., Vaitenas, I., Malaisrie, S. C., and Maganti, K. (2021). Mechanical complications of acute myocardial infarction: a review. *JAMA Cardiol.* 6 (3), 341–349. doi:10.1001/jamacardio.2020.3690

Guo, Q. (2019). To explore the clinical efficacy of Xuesaitong combined with PCI in the treatment of acute ST segment elevation myocardial infarction. *Pract. Clin. integration traditional Chin. West. Med.* (3), 62–63. doi:10.13638/j.issn.1671-4040. 2019.03.030

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1353662/ full#supplementary-material

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L. J., et al. (2022). Best Practice in the chemical characterisation of extracts used in pharmacological and toxicological research-The ConPhyMP-Guidelines. *Front. Pharmacol.* 13, 953205. doi:10.3389/fphar.2022.953205

Heusch, G., and Gersh, B. J. (2017). The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. *Eur. Heart J.* 38 (11), 774–784. doi:10.1093/eurheartj/ehw224

Ji, X., and Liu, Z. (2022). Effect of alteplase combined with Xueshuantong on thrombolysis and myocardial injury in STEMI patients. *Inn. Mong. Med. J.* (06), 680–682. doi:10.16096/j.cnki.nmzyxzz.2022.54.06.011

Kwan, C. Y., and Kwan, T. K. (2000). Effects of Panax notoginseng saponins on vascular endothelial cells *in vitro*. Acta Pharmacol. Sin. 21 (12), 1101–1105.

Lau, A. J., Toh, D. F., Chua, T. K., Pang, Y. K., Woo, S. O., and Koh, H. L. (2009). Antiplatelet and anticoagulant effects of Panax notoginseng: comparison of raw and steamed Panax notoginseng with Panax ginseng and Panax quinquefolium. *J. Ethnopharmacol.* 125 (3), 380–386. doi:10.1016/j.jep.2009.07.038

Li, H., Zhu, J., Xu, Y. W., Mou, F. F., Shan, X. L., Wang, Q. L., et al. (2022). Notoginsenoside R1-loaded mesoporous silica nanoparticles targeting the site of injury through inflammatory cells improves heart repair after myocardial infarction. *Redox Biol.* 54, 102384. doi:10.1016/j.redox.2022.102384

Liu, H., Lu, X., Hu, Y., and Fan, X. (2020). Chemical constituents of Panax ginseng and Panax notoginseng explain why they differ in therapeutic efficacy. *Pharmacol. Res.* 161, 105263. doi:10.1016/j.phrs.2020.105263

Liu, H., Qiao, Z., Ma, J., Zhang, L., Cao, H., Wang, H., et al. (2018). Clinical study of Xuesaitong combined with percutaneous coronary intervention in the treatment of acute ST segment elevation myocardial infarction. *Study Cardiovasc. Dis. China* 16 (8). doi:10.3969/j.issn.1672-5301.2018.08.021

Liu, Z., Wang, H., Hou, G., Cao, H., Zhao, Y., and Yang, B. (2019). Notoginsenoside R1 protects oxygen and glucose deprivation-induced injury by upregulation of miR-21 in cardiomyocytes. *J. Cell Biochem.* 120 (6), 9181–9192. doi:10.1002/jcb.28194

Montecucco, F., Carbone, F., and Schindler, T. H. (2016). Pathophysiology of STsegment elevation myocardial infarction: novel mechanisms and treatments. *Eur. Heart J.* 37 (16), 1268–1283. doi:10.1093/eurheartj/ehv592

Murphy, A., and Goldberg, S. (2022). Mechanical complications of myocardial infarction. Am. J. Med. 135 (12), 1401–1409. doi:10.1016/j.amjmed.2022.08.017

Neri, M., Fineschi, V., Di Paolo, M., Pomara, C., Riezzo, I., Turillazzi, E., et al. (2015). Cardiac oxidative stress and inflammatory cytokines response after myocardial infarction. *Curr. Vasc. Pharmacol.* 13 (1), 26–36. doi:10.2174/15701611113119990003

Neumann, F. J., Ott, I., Gawaz, M., Richardt, G., Holzapfel, H., Jochum, M., et al. (1995). Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. *Circulation* 92 (4), 748–755. doi:10.1161/01.cir.92.4.748

Nichols, M., Townsend, N., Scarborough, P., and Rayner, M. (2014). Cardiovascular disease in Europe 2014: epidemiological update. *Eur. Heart J.* 35 (42), 2929–2959. doi:10.1093/eurheartj/ehu378

Ning, K., Jiang, L., Hu, T., Wang, X., Liu, A., and Bao, Y. (2020). ATP-sensitive potassium channels mediate the cardioprotective effect of panax notoginseng saponins against myocardial ischaemia-reperfusion injury and inflammatory reaction. *Biomed. Res. Int.* 2020, 3039184. doi:10.1155/2020/3039184

Pan, L., Zhang, Y., Lu, J., Geng, Z., Jia, L., Rong, X., et al. (2015). Panax notoginseng saponins ameliorates coxsackievirus B3-induced myocarditis by activating the cystathionine-γ-lyase/hydrogen sulfide pathway. *J. Cardiovasc Transl. Res.* 8 (9), 536–544. doi:10.1007/s12265-015-9659-8

Peng, M., Yi, Y. X., Zhang, T., Ding, Y., and Le, J. (2018). Stereoisomers of saponins in panax notoginseng (sanqi): a review. *Front. Pharmacol.* 9, 188. doi:10.3389/fphar.2018. 00188

Qiao, Y., Zhang, P. J., Lu, X. T., Sun, W. w., Liu, G. I., Ren, M., et al. (2015). Panax notoginseng saponins inhibits atherosclerotic plaque angiogenesis by down-regulating vascular endothelial growth factor and nicotinamide adenine dinucleotide phosphate oxidase subunit 4 expression. *Chin. J. Integr. Med.* 21 (4), 259–265. doi:10.1007/s11655-014-1832-4

Qiao, Z., Gao, F., Xu, B., and Yang, J. (2016). Effect of Xuesaitong injection on inflammatory factors and matrix metalloproteinases in patients with acute myocardial infarction after PCI. *J. Cardiovasc. Cerebrovasc. Dis. Integr. traditional Chin. West. Med.* (20), 2394–2396. doi:10.3969/j.issn.1672.1349.2016.20.017

Reed, G. W., Rossi, J. E., and Cannon, C. P. (2017). Acute myocardial infarction. Lancet 389 (10065), 197–210. doi:10.1016/S0140-6736(16)30677-8

Sanchis, J., Bueno, H., Miñana, G., Guerrero, C., Martí, D., Martínez-Sellés, M., et al. (2023). Effect of routine invasive vs conservative strategy in older adults with frailty and non-ST-segment elevation acute myocardial infarction: a randomized clinical trial. *JAMA Intern Med.* 183 (5), 407–415. doi:10.1001/jamainternmed.2023.0047

Sun, A. (2021). Effect of Xuesaitong on inflammatory factors and cardiac function after PCI in patients with acute ST segment elevation myocardial infarction. *J. chronic Venereol.* (09), 1425–1427. doi:10.16440/J.CNKI.1674-8166.2021.09.40

Sun, B., Xiao, J., Sun, X. B., and Wu, Y. (2013). Notoginsenoside R1 attenuates cardiac dysfunction in endotoxemic mice: an insight into oestrogen receptor activation and PI3K/ Akt signalling, Br. J. Pharmacol. 168 (7), 1758–1770. doi:10.1111/bph.12063

Sun, T., Wang, P., Deng, T., Tao, X., and Xu, Y. (2020a). Effect of panax notoginseng saponins on focal cerebral ischemia-reperfusion in rat models: a meta-analysis. *Front. Pharmacol.* 11, 572304. doi:10.3389/fphar.2020.572304

Sun, X., Cao, H., Kou, L., and Di, P. (2020b). Effect of Xuesaitong injection combined with Ateplase on Hcy, TM, PIC and thrombus load in patients with acute myocardial infarction. *Study drug Eval.* (7), 1363–1366. doi:10.7501/j.issn.1674-6376.2020.07.030

Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., Morrow, D. A., et al. (2019). Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* 40 (3), 237–269. doi:10.1093/eurheartj/ehy462

Toldo, S., and Abbate, A. (2018). The NLRP3 inflammasome in acute myocardial infarction. *Nat. Rev. Cardiol.* 15 (4), 203–214. doi:10.1038/nrcardio.2017.161

Wang, A., Li, Y., Wang, Z., Xin, G., You, Y., Sun, M., et al. (2022). Proteomic analysis revealed the pharmacological mechanism of Xueshuantong injection in preventing early acute myocardial infarction injury. *Front. Pharmacol.* 13, 1010079. doi:10.3389/fphar. 2022.1010079

Wang, D., Lv, L., Xu, Y., Jiang, K., Chen, F., Qian, J., et al. (2021a). Cardioprotection of Panax Notoginseng saponins against acute myocardial infarction and heart failure through inducing autophagy. *Biomed. Pharmacother*. 136, 111287. doi:10.1016/j. biopha.2021.111287

Wang, L. (2018). Application value of Xuesaitong injection in interventional therapy of acute ST segment elevation myocardial infarction. *Int. Med. Health Bull.* (11), 1679–1682. doi:10.3760/cma.j.issn.1007-1245.2018.11.025

Wang, L., Chen, X., Wang, Y., Zhao, L., and Zhao, X. (2020). MiR-30c-5p mediates the effects of panax notoginseng saponins in myocardial ischemia reperfusion injury by inhibiting oxidative stress-induced cell damage. *Biomed. Pharmacother.* 125, 109963. doi:10.1016/j.biopha.2020.109963

Wang, M. M., Xue, M., Xin, Z. H., Wang, Y. H., Li, R. J., Jiang, H. Y., et al. (2021c). Panax notoginseng saponin attenuates gastric mucosal epithelial cell injury induced by dual antiplatelet drugs through COX and PI3K/akt/VEGF-GSK- 3β -RhoA network pathway. *Chin. J. Integr. Med.* 27 (11), 819–824. doi:10.1007/s11655-021-2854-3

Wang, T., Guo, R., Zhou, G., Zhou, X., Kou, Z., Sui, F., et al. (2016). Traditional uses, botany, phytochemistry, pharmacology and toxicology of Panax notoginseng (Burk.) F.H. Chen: a review. J. Ethnopharmacol. 188, 234–258. doi:10.1016/j.jep.2016.05.005

Wang, W., Yang, L., Song, L., Guo, M., Li, C., Yang, B., et al. (2021b). Combination of Panax notoginseng saponins and aspirin potentiates platelet inhibition with alleviated

gastric injury via modulating arachidonic acid metabolism. *Biomed. Pharmacother.* 134, 111165. doi:10.1016/j.biopha.2020.111165

Xie, Q. (2017). Clinical effect of Xueshuantong injection on acute myocardial infarction and its effect on cardiac function. *Pract. J. Cardiac, Cerebropulmonary Vasc. Dis.* (03), 73–76. doi:10.3969/j.issn.1008-5971.2017.03.018

Xin, D., and Qian, L. (2018). Effect of Atto vastatin combined with Xuesaitong injection on inflammatory factors after PCI in patients with myocardial infarction. *Chin. Rural. Med.* (12), 39–40. doi:10.19542/j.cnki.1006-5180.001756

Yamada, Y., Minatoguchi, S., Endo, N., Kanamori, H., Kawasaki, M., Nishigaki, K., et al. (2019). Post-MI treatment with G-CSF and EPO-liposome with SLX repairs infarcted myocardium through EPCs mobilization and activation of prosurvival signals in rabbits. *Pharmacol. Res. Perspect.* 7 (1), e00451. doi:10.1002/prp2.451

Yang, B. R., Cheung, K. K., Zhou, X., Xie, R. F., Cheng, P. P., Wu, S., et al. (2016). Amelioration of acute myocardial infarction by saponins from flower buds of Panax notoginseng via pro-angiogenesis and anti-apoptosis. *J. Ethnopharmacol.* 181, 50–58. doi:10.1016/j.jep.2016.01.022

Yang, W., Liu, H., Chen, J., and Huang, Y. (2022). Clinical observation of Xueshuantong injection combined with recombinant human brain natriuretic peptide after emergency PCI in patients with acute ST segment elevation myocardial infarction. *Tianjin Tradit. Chin. Med.* (11), 1373–1378. doi:10.11656/j. issn.1672-1519.2022.11.03

Yeh, R. W., Sidney, S., Chandra, M., Sorel, M., Selby, J. V., and Go, A. S. (2010). Population trends in the incidence and outcomes of acute myocardial infarction. *N. Engl. J. Med.* 362 (23), 2155–2165. doi:10.1056/NEJMoa0908610

Yu, Y., Sun, G., Luo, Y., Wang, M., Chen, R., Zhang, J., et al. (2016). Cardioprotective effects of Notoginsenoside R1 against ischemia/reperfusion injuries by regulating oxidative stress- and endoplasmic reticulum stress-related signaling pathways. *Sci. Rep.* 6, 21730. doi:10.1038/srep21730

Zeng, J. J., Shi, H. Q., Ren, F. F., Zhao, X. S., Chen, Q. Y., Wang, D. J., et al. (2023). Notoginsenoside R1 protects against myocardial ischemia/reperfusion injury in mice via suppressing TAK1-JNK/p38 signaling. *Acta Pharmacol. Sin.* 44 (7), 1366–1379. doi:10.1038/s41401-023-01057-y

Zhang, T., Liu, W., Yang, J., Xu, H., Cao, Y., Guo, L., et al. (2022). Components of salvia miltiorrhiza and panax notoginseng protect pericytes against OGD/ R-Induced injury via regulating the PI3K/AKT/mTOR and JNK/ERK/ P38 signaling pathways. J. Mol. Neurosci. 72 (12), 2377-2388. doi:10.1007/ s12031-022-02082-y

Zhang, X., Zhou, C., Miao, L., Tan, Y., Zhou, Y., Cheong, M. S., et al. (2021). Panax notoginseng protects against diabetes-associated endothelial dysfunction: comparison between ethanolic extract and total saponin. *Oxid. Med. Cell Longev.* 2021, 4722797. doi:10.1155/2021/4722797

Zhang, Z. (2019). Effect of Xuesaitong combined with western medicine on cardiac function and inflammatory factors after emergency PCI in patients with acute myocardial infarction. *New tradit. Chin. Med.* (6), 121–124. doi:10.13457/j.cnki. jncm.2019.06.036

Zhang, Z., and Du, P. (2019). Effects of Edaravone combined with Xuesaitong on hemorheology and inflammation in elderly patients with acute myocardial infarction. *Guizhou Med.* (12), 1921–1922.

Zhong, H., and Zheng, W. (2019). Effects of Xueshuantong injection combined with intravenous thrombolysis on platelet aggregation, vascular endothelial function and cardiac function in patients with acute myocardial infarction. J. Cardiovasc. Cerebrovasc. Dis. Integr. traditional Chin. West. Med. (22), 3561–3562. doi:10.12102/jssn.1672-1349.2019.22.028

Zhong, L., Zhou, X. L., Liu, Y. S., Wang, Y. M., Ma, F., Guo, B. L., et al. (2015). Estrogen receptor α mediates the effects of notoginsenoside R1 on endotoxin-induced inflammatory and apoptotic responses in H9c2 cardiomyocytes. *Mol. Med. Rep.* 12 (1), 119–126. doi:10.3892/mmr.2015.3394

Zhou, M. N., Delaveris, C. S., Kramer, J. R., Kenkel, J. A., Engleman, E. G., and Bertozzi, C. R. (2018b). N-carboxyanhydride polymerization of glycopolypeptides that activate antigen-presenting cells through dectin-1 and dectin-2. *Angew. Chem. Int. Ed. Engl.* 57 (12), 3137–3142. doi:10.1002/anie.201713075

Zhou, S. (2018). Study on the efficacy of Xuesaitong combined with western medicine in the treatment of AMI emergency PCI and its effect on cardiac function and inflammatory factors. *Shaanxi Tradit. Chin. Med.* (12), 1687–1690. doi:10.3969/j. issn.1000-7369.2018.12.009

Zhou, X., Li, Z. C., Chen, P. P., and Xie, R. F. (2019). Primary mechanism study of panax notoginseng flower (herb) on myocardial infarction in rats. *Cardiol. Res. Pract.* 2019, 8723076. doi:10.1155/2019/8723076

Zhou, Z., Wang, J., Song, Y., He, Y., Zhang, C., Liu, C., et al. (2018a). Panax notoginseng saponins attenuate cardiomyocyte apoptosis through mitochondrial pathway in natural aging rats. *Phytother. Res.* 32 (2), 243–250. doi:10.1002/ptr.5961