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Original Article

Compound Danshen Dripping Pills combined with isosorbide mononitrate for angina pectoris: A systematic review and a Meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy of Compound Danshen Dripping Pills (CDDP) combined with isosorbide mononitrate (ISMN) versus ISMN alone for treating angina pectoris in patients.

Methods: The PubMed, Web of Science, Cochrane Library, Embase China National Knowledge Infrastructure, China Biomedical Literature Service System, Chinese Medical Journal Database, and Wan Fang MED databases were searched from inception to November 2022. Randomized controlled trials (RCTs) and cohort studies were included. The primary outcomes were angina symptom and electrocardiography (ECG) efficacy, angina symptom efficacy, and ECG efficacy. The protocol was registered with PROSPERO No. CRD42022314774.

Results: Our study included 7 245 patients with angina (59 RCTs, 11 cohort studies). When ISMN was combined with CDDP, the efficacy of angina symptom and ECG [odds ratio (OR) = 4.824, 95% confidence interval (CI) = 3.636–6.401, P = 0.000], the efficacy of angina symptom (OR = 4.347, 95% CI = 3.635–5.198, P = 0.000), the efficacy of ECG (OR = 3.364, 95% CI = 2.767–4.089, P = 0.000) were better than that of patients treated with ISMN alone. CDDP combined with ISMN was superior to ISMN alone in reducing triglyceride (TG) [mean difference (MD) = −35.176, 95% CI = −37.439 to −32.912, P = 0.000], total cholesterol (TC) (MD = −24.296, 95% CI = −26.429 to −22.163, P = 0.000), the duration of angina attack (MD = −1.991, 95% CI = −2.349 to −1.633, P = 0.000), and the frequency of angina attack [standardized MD (SMD) = −2.840, 95% CI = −3.416 to −2.265, P = 0.000]. There was no increase in adverse events between CDDP combined with ISMN and ISMN alone (OR = 0.513, 95% CI = 0.421–0.626, P = 0.000).

Conclusion: CDDP combined with ISMN improved treatment efficacy and was well tolerated. Therefore, this combination could be used as an alternative treatment. However, clinical and patient conditions should be considered.

1. Introduction

Coronary heart disease (CHD), short for coronary atherosclerotic heart disease, is caused by myocardial ischemia, hypoxia, or necrosis attributed to coronary atherosclerosis, which narrows, spasms, or blocks the lumen of the coronary arteries. CHD is the most common clinical cardiovascular diseases (Zhu & Jia, 2005; Xiong, Wang, & Wang, 2015; Tobin, 2010). According to the 2020 China Cardiovascular Health and Disease Report, the prevalence of CHD in individuals aged ≥ 15 years was 12.3‰ (National Center for Cardiovascular Disease, 2021). Further, the 2021 China Cardiovascular Disease Medical Quality Report reported that the prevalence of CHD in hospitalized patients was 53.4% (5.31 million cases). The most common clinical manifestations of CHD were angina pectoris (37.8%) and myocardial infarction (14.9%); the mortality rate of angina pectoris (AP) was 0.1%; and the average hospital stay was 7.5 days with a total cost of 18 110.6 yuan (Ma et al., 2021). Based on the 2013–2016 NHANES data, it is estimated that 18.2 million Americans over the age of 20 had CHD. The overall prevalence of CHD, AP, and myocardial infarction was 6.7%, 3.6%, and 3.0%, respectively (Virani et al., 2020). These data suggest that CHD is common among cardiovascular diseases. Since AP is common in patients with CHD, it is essential to consider its clinical treatment.

Currently, the main drugs used to treat AP in patients with CHD are nitrates, beta-blockers, calcium antagonists, lipid-lowering drugs, and antiplatelet drugs. Nitrates can dilate blood vessels, reduce myocardial oxygen consumption, improve myocardial perfusion, and relieve symptoms (Chinese Society of Cardiology, 2010). Nitrates can be classified as short- or long-acting [e.g.,

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isosorbide mononitrate (ISMN)]. ISMN is not suitable for acute AP attack but is suitable for the long-term treatment of chronic AP (National Health and Family Planning Commission Expert Committee on Rational Drug Use, 2018). In China, AP of CHD belongs to the "chest and heart pain category" in traditional Chinese medicine (TCM) (Mao, Wu, & Shi, 2021). Treatment is primarily based on the promotion of blood circulation and the removal of blood stasis. With the development of integrative medicine, the treatment of AP combined with TCM has drawn increasing attention (Lin et al., 2017; Shi, Li, Wang, & Ding, 2020). Compound Danshen Dripping Pills (CDDP) is a representative TCM. Among its prescribed components, *Salviae Miltiorrhizae Radix* et *Rhizoma* (Danshen in Chinese) promotes blood circulation and removes blood stasis; *Notoginseng Radix* et *Rhizoma* (Sanqi in Chinese) disperses blood stasis and alleviates pain; and *Borneolum Syntheticum* (Bingpian in Chinese) has a diverging effect, which can promote the active components of *Salviae Miltiorrhizae Radix* et *Rhizoma* and *Notoginseng Radix* et *Rhizoma* into the body (Cheng et al., 2017). The preparation of CDDP involves a dropping pill. This formulation can help the drug dissolve and release quickly, giving it a quick effect. It is also suitable for sublingual ingestion and facilitates rapid relief for emergency patients. Expert consensus indicates that CDDP is safe and effective for the treatment of AP (Mao, Wu, & Shi, 2021; Cheng et al., 2017). All drugs were combined to remove blood stasis, clear arteries, promote blood circulation, and relieve pain (Wang, 2014a). CDDP has been widely used in the prevention, treatment, and first aid of CHD for myocardium protection, blood vessel protection, and microcirculation improvement (Ji, 2013, Liu et al., 2022; Wang et al., 2023a; Wang et al., 2022). Thus, CDDP can sufficiently compensate for the limitations of Western medicine. Currently, the TCM and Western medical guidelines recommend drug grades in their respective fields. However, there are very few recommended drug grades for integrated TCM and Western medicine. Therefore, this Meta-analysis compared the efficacy and safety of CDDP combined with ISMN *vs*. ISMN alone for the treatment of AP in CHD. A comprehensive understanding of the use of CDDP in combination with ISMN is expected to provide an additional clinical reference for the treatment of AP using a combination of TCM and Western medicine.

2. Materials and methods

2.1. Systematic review registration

This Meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) and was registered with PROSPERO (No. CRD42022314774) (Wang, Hu, Li, & Yin, 2022).

2.2. Search method and data extraction

We searched PubMed, Web of Science (SCI), the Cochrane Library, Embase, the China National Knowledge Infrastructure, the China Biomedical Literature Service System, Wan Fang MED Online, and the Chinese Medical Journal Database. The search period ranged from the establishment of the database to November 2022. The following search terms were used: CDDP, ISMN, coronary artery disease, angina, angina (unstable), angina (stable), AP (variant), microvascular angina, and chest pain. Two authors independently screened the abstracts and full texts.

All search records were imported into Endnote X8, where they were double-checked and filtered by two researchers. After reading the abstract, articles were excluded if they did not meet the inclusion criteria. All eligible materials were extracted after reading the full text. Disagreements were resolved through discussion. The data extraction table included the basic information, treatment measures, and evaluation metrics. The included studies had to have been published in the original literature to ensure the reliability and authenticity of the data extraction. Otherwise, the authors were contacted via e-mail for the raw data.

2.3. Inclusion and exclusion criteria

All randomized controlled trials (RCTs) and cohort studies were included in our study. Studies with the same data published later were excluded. Patients with typical symptoms of AP who met the diagnostic criteria of the Practice Guidelines for AP of CHD were included (Fihn et al., 2012). Studies comparing treatment with ISMN alone and CDDP combined with ISMN reported that angina symptom or electrocardiogram (ECG) efficacy was included. Patients treated with ISMN in combination with additional drugs for AP were excluded. Additional duplicate publications, review articles, and conference papers were excluded from the analysis.

2.4. Evaluation criteria

The primary outcomes were the efficacy of angina symptom and ECG. The efficacy of angina symptom was classified as marked response, moderate response, and no response (Evaluation criteria of curative effect on AP of CHD and electrocardiogram (Kan, 2016; Wang, 2005). A marked response indicated that the same amount of exertion did not trigger an angina attack or that the number of angina attack or nitroglycerin level was reduced by more than 80%. A moderate response was defined as a 50%−80% reduction in the frequency of angina attack or nitroglycerin consumption. No response was defined as a reduction of less than 50% in both the number of angina attack and the amount of nitroglycerin used.

The efficacy of ECG was also classified as a marked response, moderate response, and no response (Fan & Wang, 2014; Wang, 2005). A marked response indicated that the resting ECG had returned to normal. A moderate response refers to 1) the recovery of the ST segment by more than 0.05 mm after treatment and 2) the T-wave becoming shallow or straight on a flat surface. No response indicated that the ECG was essentially the same as before.

Secondary outcomes included lipid levels, the duration and frequency of angina attack, and adverse drug reactions (ADRs). Lipid levels included triglyceride (TG) (mg/dL) and total cholesterol (TC) (mg/dL). The duration of an angina attack was defined as the average duration of an angina attack over a specified period (min). The frequency of angina attack refers to the number of angina attack in a specified period (e.g., per day or week). The total number of ADRs that occurred during treatment was evaluated.

2.5. Quality assessment

The Cochrane risk-bias assessment tool was used to assess the methodological quality of the included studies (Higgins et al., 2011). The tool took into consideration whether the random method was appropriate, whether the allocation was hidden, whether researchers and subjects were double-blinded, whether the results of the study were evaluated using the blind method, whether the resulting data were complete, whether the study avoided selective result reporting, and whether the study avoided creating further problems. The risk of bias was assessed as low risk of bias, unclear risk of bias, or high risk of bias by individually scoring each item (Higgins et al., 2011). The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the methodological quality of the included studies (Luchini et al., 2021). The evaluation was conducted based on the aspects of selection (4 scores), comparability (2 scores), and outcome (3 scores). The higher the research evaluation score is, the better the quality is. Any differences were resolved by consensus.

2.6. Statistical analysis

Data analysis was performed using Review Manager 5.4 and Stata 14. The odds ratio (OR) or relative risk (RR) was used to assess binary variables. The continuous variables were the mean difference (MD) or standardized mean difference (SMD) as the effect quantity. The 95% confidence interval (CI) was used for analysis. We analyzed the heterogeneity of the included studies. If the results showed a P-value < 0.10 and I^2 > 50%, the study was considered to be highly heterogeneous, and a random effect model was selected. If the results showed a P-value > 0.10 and $I^2 \leq 50\%$, the heterogeneity among the studies was considered small, and a fixed-effect model was selected (Andrade, 2020). If heterogeneity was detected, a sensitivity analysis was performed. Sensitivity analysis was performed using one-to-one elimination. We also used subgroup analysis to analyze the factors influencing heterogeneity. Funnel plots and Egger's test were used to analyze the risk of publication bias. A P-value of < 0.05 indicated significant publication bias. The trim-and-fill method was used to analyze the publication bias. The age and disease course of patients were expressed as the combined mean and standard deviation (Yin, Zhou, & Chen, 2010) and the data were analyzed using Microsoft Excel 2019 and SPSS version 26.

3. Results

3.1. Screening results

A total of 9 011 articles were retrieved from the databases, and 6 696 duplicates were excluded. In the remaining articles, 2 245 did not meet the inclusion criteria; thus, they were excluded after reading the abstracts and full texts. Finally, 59 RCTs and 11 cohort studies were included (Chen, 2021; Cui, Zhang, & Zhu, 2013; Diao, 2016; Dong, 2019a; Dong, 2019b; Du & Song, 2019; Du, 2021; Fan & Wang, 2014; Gao, 2015; Gu, 2014; Guo, 2013; Huang & Cao, 2010; Jia & Zhu, 2005; Jiang, 2016; Jing, 2014; Kan, 2016; Kong, 2021; Li, 2017; Li & Xie, 2013; Li, 2021; Li, 2012; Li, 2010; Li, 2016; Liang, 2013; Lin & Wu, 2010; Lin, 2012; Liu, 2004; Liu, 2021a; Liu, 2022; Lu, 2017; Lv, 2021; Lv, Liang, & Liang, 2011; Peng, 2018; Qin, 2022; Qu, 2017; Ren, 2018; Ren, 2020; Shang, 2013; Shao, 2013; Shen, 2020; Sheng, 2015; Shi & Xu, 2013; Song, Li, & Lu, 2019; Sun, 2016; Wang, 2017; Wang, 2007; Wang, 2014b; Wang, 2012; Wang, 2005; Wu, 2021a; Wu & Wang, 2016; Wu, 2018; Wu, 2021b; Xu, 2020; Xu, 2018; Yan & Jiang, 2016; Yan, 2016; Zeng, 2014; Zhang & Wang, 2011; Zhang, 2021; Zhang, 2012; Zhang, 2016; Zhang, Zhang, & He, 2013; Zhang, 2022; Zhang, Wu, & Fang, 2017; Zhao & Guan, 2017; Zheng & Wei, 2006; Zhu, 2020; Ma, 2012; Wu, 2019). The screening process was illustrated in Fig. 1.

Seventy studies were written in Chinese, and 7 245 Chinese patients were enrolled. Sixty-one studies included detailed data on patient sex, with 1 654 men and 1 307 women in the experimental group and 1 650 men and 1 292 women in the control group. There was no significant sex difference between the two groups (χ^2 = 0.030 a, P = 0.862). Forty-five studies included detailed data on the age of the patients; the mean age ± standard deviation (years) was 63.2 ± 8.7 in the experimental group and 62.7 ± 8.7 in the control group. Twenty-six studies included detailed data on the patient's course of disease [experimental group, (6.8 ± 5.2) years; control group, (6.8 ± 5.3) years]. Forty-one articles mentioned routine care, including rest, smoking cessation, a light diet, anti-lipid medication, and antiplatelet therapy. Fifty studies involved the treatment of AP, and 20 studies involved

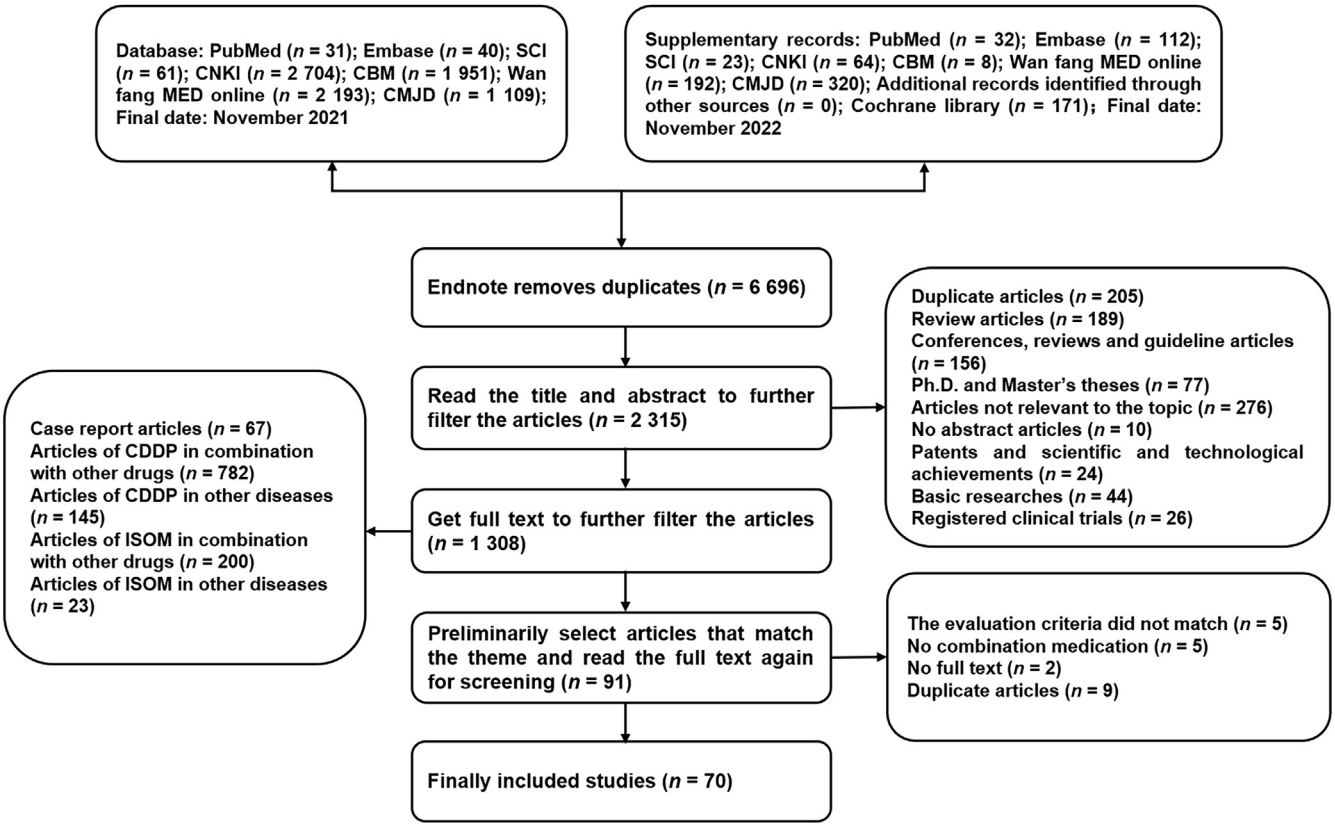

Fig. 1. Flow diagram of study selection.

Table 1
Basic characteristics of studies.

Author/Year	Study types	Samples (Number of cases)	Interventions		Dosage and frequency			Angina symptom and ECG efficacy		Angina symptom efficacy		ECG efficacy		Other effect indicators		Types
		C/T	C	T	C	T		C/S	T/S	C/S	T/S	C/S	T/S	C	T	
Chen, 2021	RCT	31/31	①,4 w	⑤; ①,4 w	40 mg,qd	10 P,tid	40 mg,qd			25/31	30/31	–	–	⑨;⑩;⑪	⑨;⑩;⑪	AP
Cui, Zhang, & Zhu, 2013	RCT	80/80	②,2 m	⑤; ②,2 m	20 mg,bid	10 P,tid	20 mg,bid	63/80	75/80	–	–	–	–	–	–	AP
Diao, 2016	cohort study	40/40	②,8 w	⑤; ②,8 w	20 mg,bid	10 P,tid	20 mg,bid	–	–	38/40	40/40	29/40	38/40	–	–	AP
Dong, 2019a	RCT	48/48	⑥,2 m	⑤; ⑥,2 m	20 mg,bid	10 P,tid	20 mg,tid	38/48	45/48	–	–	–	–	⑪	⑪	AP
Dong, 2019b	RCT	48/48	①,2 m	⑤; ①,2 m	40 mg,qd	10 P,tid	40 mg,qd	–	–	39/48	46/48	–	–	⑪	⑪	AP
Du & Song, 2019	cohort study	63/63	①,4 w	⑤; ①,4 w	40 mg,qd	10 P,tid	40 mg,qd	53/63	61/63	–	–	–	–	⑨;⑩;⑪	⑨;⑩;⑪	AP
Du, 2021	RCT	45/45	①,1 m	⑤; ①,1 m	20 mg,bid	10P,tid	20 mg,bid	37/45	44/45	–	–	–	–	⑦;⑧	⑦;⑧	AP
Fan & Wang, 2014	RCT	90/90	②,8 w	⑤; ②,8 w	20 mg,bid	10 P,tid	10 mg,bid	70/90	85/90	–	–	–	–	⑪	⑪	AP
Gao, 2015	RCT	42/42	①,1 m	⑤; ①,1 m	50 mg,qd	10 P,tid	50 mg,qd	–	–	30/42	39/42	28/42	40/42	⑪	⑪	AP
Huang & Cao, 2010	RCT	46/52	②,2 m	⑤; ②,2 m	20 mg,bid	10 P,tid	20 mg,bid	–	–	34/46	49/52	22/46	36/52	–	–	AP
Jia & Zhu, 2005	RCT	30/34	⑥,2 w	⑤; ⑥,2 w	20 mg,bid	10 P,tid	20 mg,bid	–	–	19/30	31/34	–	–	⑨;⑩	⑨;⑩	AP
Jiang, 2016	RCT	40/40	①,28 d	⑤; ①,28 d	40 mg,qd	10 P,tid	40 mg,qd	–	–	32/40	39/40	32/40	38/40	–	–	AP
Kan, 2016	RCT	60/60	①,4 w	⑤; ①,4 w	50 mg,qd	10 P,tid	50 mg,qd	–	–	41/60	56/60	–	–	⑪	⑪	AP
Kong, 2021	RCT	52/52	⑥,8 w	⑤; ⑥,8 w	10–20 mg, tid	10 P,tid	10–20 mg, tid	42/52	50/52	–	–	–	–	⑨;⑩	⑨;⑩	AP
Li, 2017	RCT	65/65	①,4 w	⑤; ①,4 w	40 mg,qd	10 P,tid	40 mg,qd	–	–	47/65	61/65	45/65	56/65	⑪	⑪	AP
Li & Xie, 2013	RCT	80/80	①,8 w	⑤; ①,8 w	40 mg,qd	10 P,tid	40 mg,qd	–	–	67/80	69/80	42/80	64/80	⑪	⑪	AP
Li, 2010	RCT	40/45	⑥,1 m	⑤; ⑥,1 m	10 mg,tid	10 P,tid	10 mg,tid	–	–	27/40	40/45	25/40	36/45	–	–	AP
Liang, 2013	RCT	54/53	①,4 w	⑤; ①,4 w	40 mg,qd	10 P,tid	40 mg,qd	–	–	29/54	44/53	26/54	41/53	–	–	AP
Lin & Wu, 2010	RCT	39/39	②,4 w	⑤; ②,4 w	–	10 P,tid	–	–	–	31/39	36/39	25/39	32/39	⑪	⑪	AP
Lin, 2012	RCT	41/41	②,8 w	⑤; ②,8 w	20 mg,bid	10 P,tid	20 mg,bid	–	–	31/41	39/41	29/41	38/41	–	–	AP
Liu, 2021a	RCT	43/43	②,6 w	⑤; ②,6 w	20 mg,bid	10 P,tid	20 mg,tid	–	–	–	–	34/43	41/43	⑦;⑧;⑨;⑩	⑦;⑧;⑨;⑩	AP
Lu, 2017	RCT	43/43	②,3 m	⑤; ②,3 m	half or one tablet,bid/tid	10 P,tid	half or one tablet,bid/tid	–	–	35/43	42/43	31/43	41/43	⑨	⑨	AP
Lv, 2021	RCT	18/18	⑥,4 w	⑤; ⑥,4 w	40 mg,qd	10 P,tid	40 mg,qd	–	–	13/18	17/18	–	–	⑨;⑩	⑨;⑩	AP
Lv, Liang, & Liang, 2011	RCT	80/84	⑥,2 m	⑥; ②,2 m	50 mg,qd	10 P,tid	50 mg,qd	–	–	63/80	79/84	50/80	71/84	–	–	AP
Peng, 2018	RCT	47/47	①,8 w	⑤; ①,8 w	30 mg,bid	10 P,tid	30 mg,bid	39/47	45/47	–	–	–	–	⑨;⑩;⑪	⑨;⑩;⑪	AP
Qin, 2022	RCT	60/60	①,3 m	⑤; ①,3 m	40–80 mg, qd	10 P,tid	40–80 mg, Qd	51/60	59/60	–	–	–	–	⑪	⑪	AP
Qu, 2017	cohort study	63/63	①,2 m	⑤; ①,2 m	40 mg,qd	10 P,tid	40 mg,qd	–	–	50/63	58/63	–	–	⑪	⑪	AP
Ren, 2018	RCT	44/44	②,14 d	⑤; ②,14 d	20 mg, tid	10 P,tid	20 mg,tid	–	–	33/44	40/44	–	–	⑦;⑧;⑨;⑩	⑦;⑧;⑨;⑩	AP
Ren, 2020	cohort study	60/60	②,1 m	⑤; ②,1 m	20 mg,bid	10 P,tid	20 mg,bid	–	–	46/60	58/60	–	–	⑨;⑩	⑨;⑩	AP
Shang, 2013	RCT	34/34	②,4 w	⑤; ②,4 w	–	10 P,tid	–	–	–	27/34	31/34	22/34	28/34	⑪	⑪	AP
Shen, 2020	RCT	31/32	①,4 w	⑤; ①,4 w	60 mg,qd	10 P,tid	60 mg,qd	–	–	20/31	28/32	22/31	30/32	–	–	AP
Song, Li, & Lu, 2019	cohort study	40/40	①,2 m	⑤; ①,2 m	30–60 mg,qd	10 P,tid	30–60 mg,qd	–	–	30/40	38/40	–	–	⑨;⑩	⑨;⑩	AP
Sun, 2016	RCT	68/68	③,4 w	⑤; ③,4 w	50 mg,qd	10 P,tid	50 mg,qd	–	–	49/68	64/68	51/68	65/68	⑪	⑪	AP
Wang, 2017	cohort study	55/55	④,30 d	⑤; ④,30 d	25 mg*,qd	10 P,tid	25 mg,qd	–	–	44/55	51/55	–	–	⑪	⑪	AP
Wang, 2007	RCT	46/52	②,2 m	⑤; ②,2 m	20 mg,bid	10 P,tid	20 mg,bid	–	–	36/46	48/52	20/46	33/52	–	–	AP
Wang, 2012	RCT	60/60	④,1 m	⑤; ④,1 m	20 mL*,bid	10 P,tid	20 mL*,bid	–	–	51/60	59/60	–	–	–	–	AP
Wang, 2005	RCT	30/30	②,8 w	⑤; ②,8 w	20 mg,bid	10 P,tid	20 mg,bid	20/30	28/30	21/30	29/30	14/30	23/30	–	–	AP
Wu & Wang, 2016	RCT	48/48	①,6 m	⑤; ①,6 m	10 mg,tid	10 P,tid	10 mg,tid	27/48	38/48	–	–	–	–	⑪	⑪	AP
Wu, 2018	cohort study	40/40	①,6 m	⑤; ①,6 m	10 mg,tid	10 P,tid	10 mg,tid	31/40	39/40	–	–	–	–	⑪	⑪	AP
Wu, 2021b	RCT	42/42	①,8 w	⑤; ①,8 w	20–40 mg, qd	10 P,tid	20–40 mg, qd	–	–	32/42	39/42	28/42	37/42	⑨;⑩;⑪	⑨;⑩;⑪	AP

(*continued on next page*)

Table 1 (*continued*)

Author/Year	Study types	Samples (Number of cases)	Interventions		Dosage and frequency			Angina symptom and ECG efficacy		Angina symptom efficacy		ECG efficacy		Other effect indicators		Types
		C/T	C	T	C	T		C/S	T/S	C/S	T/S	C/S	T/S	C	T	
Wu, 2019	RCT	51/51	①,8 w	⑤; ①,8 w	40 mg,qd	10 P,tid	40 mg,qd	36/51	48/51	–	–	–	–	⑦;⑧;⑨;⑩;⑪	⑦;⑧;⑨;⑩;⑪	AP
Xu, 2020	RCT	45/45	④,1 m	⑤; ④,1 m	20 mg*,qd	10 P,tid	20 mg*,qd	36/45	43/45	–	–	–	–	⑦;⑧;⑩	⑦;⑧;⑩	AP
Yan & Jiang, 2016	RCT	82/82	④,12 d	⑤; ④,12 d	20 mg*,qd	10 P,tid	20 mg*,qd	58/82	78/82	–	–	–	–	⑦;⑧;⑨;⑩;⑪	⑦;⑧;⑨;⑩;⑪	AP
Yan, 2016	RCT	36/37	①,4 w	⑤; ①,4 w	60 mg,qd	10 P,tid	60 mg,qd	–	–	27/36	34/37	27/36	33/37	–	–	AP
Zhang, 2021	RCT	50/50	①,4 w	⑤; ①,4 w	50 mg,qd	10 P,tid	50 mg,qd	40/50	47/50	–	–	–	–	⑦;⑧;⑩;⑪	⑦;⑧;⑩;⑪	AP
Zhang, 2012	RCT	20/20	⑥,4 w	⑤; ⑥,4 w	40 mg,qd	10 P,tid	40 mg,qd	–	–	16/20	18/20	13/20	17/20	–	–	AP
Zhang, 2022	cohort study	35/36	①,1 m	⑤; ①,1 m	40 mg,qd	10 P,tid	40 mg,qd	25/35	33/36	–	–	–	–	⑨;⑩;⑪	⑨;⑩;⑪	AP
Zhao & Guan, 2017	RCT	24/25	①,30 d	⑤; ①,30 d	10 mg,tid	8 P,tid	10 mg,tid	–	–	16/24	23/25	–	–	⑪	⑪	AP
Zheng & Wei, 2006	RCT	42/42	⑥,15 d	⑤; ⑥,15 d	20 mg,bid	10 P,tid	20 mg,bid	–	–	34/42	40/42	34/42	40/42	–	–	AP
Zhu, 2020	RCT	60/60	①,8 w	⑤; ①,8 w	30 mg, bid	10 P,tid	30 mg, bid	–	–	50/60	57/60	–	–	⑪	⑪	AP
Gu, 2014	RCT	74/76	⑥,10 d	⑤; ⑥,10 d	20 mg,bid	10 P,tid	20 mg,bid	–	–	62/74	71/76	58/74	69/76	–	–	UAP
Guo, 2013	RCT	107/129	④,4 w	⑤; ④,4 w	20 mg*,qd	10 P,tid	20 mg*,qd	–	–	81/107	117/129	94/107	118/129	–	–	UAP
Jing, 2014	RCT	84/84	①,4 w	⑤; ①,4 w	50 mg,qd	10 P,tid	50 mg,qd	61/84	75/84	–	–	–	–	⑪	⑪	UAP
Li, 2021	RCT	40/40	①,1 m	⑤; ①,1 m	20 mg,bid	10 P,tid	20 mg,bid	–	–	29/40	36/40	–	–	⑨;⑩	⑨;⑩	UAP
Li, 2012	RCT	52/60	④,4 w	⑤; ④,4 w	20 mg*,qd	10 P,tid	20 mg*,qd	–	–	38/52	54/60	–	–	–	–	UAP
Li, 2016	RCT	42/43	①,4 w	⑤; ①,4 w	50 mg,qd	10 P,tid	50 mg,qd	–	–	30/42	40/43	–	–	⑪	⑪	UAP
Liu, 2004	RCT	32/33	②,4 w	⑤; ②,4 w	20 mg,tid	10 P,tid	20 mg,tid	–	–	24/32	29/33	19/32	25/33	–	–	UAP
Liu, 2022	RCT	56/56	②,4 w	⑤; ②,4 w	30 mg,bid	10 P,tid	30 mg,bid	44/56	53/56	–	–	–	–	⑨;⑩;⑪	⑨;⑩;⑪	UAP
Ma, 2012	RCT	70/70	①,1 m	⑤; ①,1 m	30 mg,bid	10 P,tid	30 mg,bid	–	–	53/70	65/70	51/70	64/70	–	–	UAP
Shao, 2013	cohort study	40/40	①,4 w	⑤; ①,4 w	10 mg,tid	10 P,tid	10 mg,tid	–	–	32/40	38/40	–	–	⑪	⑪	UAP
Sheng, 2015	RCT	40/40	①,4 w	⑤; ①,4 w	10 mg,tid	10P,tid	10 mg,tid	–	–	30/40	37/40	–	–	–	–	UAP
Shi & Xu, 2013	cohort study	40/40	①,4 w	⑤; ①,4 w	50 mg,qd	10 P,tid	50 mg,qd	–	–	32/40	38/40	–	–	⑪	⑪	UAP
Wang, 2014b	RCT	75/75	①,4 w	⑤; ①,4 w	50 mg,qd	10 P,tid	50 mg,qd	–	–	59/75	72/75	–	–	⑪	⑪	UAP
Wu, 2021a	RCT	39/39	②,1 m	⑤; ②,1 m	30 mg,bid	10 P,tid	30 mg,bid	–	–	27/39	38/39	–	–	⑨;⑩;⑪	⑨;⑩;⑪	UAP
Xu, 2018	cohort study	40/40	①,1 m	⑤; ①,1 m	30 mg, bid	10 P,tid	30 mg, bid	–	–	30/40	37/40	–	–	⑨;⑩;⑪	⑨;⑩;⑪	UAP
Zeng, 2014	RCT	50/50	①,8 w	⑤; ①,8 w	20 mg,bid	10 P,tid	20 mg,bid	34/50	46/50	–	–	–	–	⑪	⑪	UAP
Zhang & Wang,2011	RCT	95/98	②,2 w	⑤; ②,2 w	20 mg,tid	10 P,tid	20 mg,tid	–	–	60/95	88/98	52/95	81/98	–	–	UAP
Zhang, 2016	RCT	45/45	①,1 m	⑤; ①,1 m	10 mg,tid	10 P,tid	10 mg,tid	–	–	27/45	42/45	–	–	⑪	⑪	UAP
Zhang, Zhang, & He, 2013	RCT	48/48	②,6 w	⑤; ②,6 w	20 mg,tid	10 P,tid	20 mg,tid	–	–	31/48	42/48	–	–	⑨;⑩	⑨;⑩	UAP
Zhang, Wu, & Fang, 2017	RCT	90/90	①,4 w	⑤; ①,4 w	40 mg,qd	10 P,tid	40 mg,qd	66/90	83/90	–	–	–	–	⑪	⑪	UAP

Note: –: Not mentioned in studies. [1]: C: control group; T: treatment group; S: sample; P: pills; T: tablets; d: day; m: month; w: week; *: Injection. [2]: ① ISMN release tablets; ② ISMN tablets; ③ ISMN dispersible tablets; ④ ISMN injection; ⑤ CDDP; ⑥ unclear; ⑦ Triglyceride (mg/dL); ⑧ Total cholesterol (mg/dL); ⑨ The duration of angina attack (min); ⑩ The frequency of angina attack (one day or one week); ⑪ Adverse drug reactions. [3]: tid: three times a day; bid: twice a day; qd: once a day. [4]: AP: angina pectoris; UAP: unstable angina pectoris; RCT: randomized controlled trial; ECG, electrocardiogram.

the treatment of unstable angina pectoris (UAP). The median daily ISMN dose was 40 mg [Q1 (first quartile): 40 mg, Q3 (third quartile): 50 mg]. The CDDP dose was 270 mg (10 pills), three times a day. The median duration of medication use was 30 d (Q1, 28 d; Q3, 56 d). Table 1 summarized the basic characteristics of the included studies.

3.2. Risk of bias

The risk of bias for the RCTs was shown in Figs. 2 and 3. Thirty-five studies referred to "randomization into two groups", and the risk of selection bias was unknown. Twenty-four studies referred to a "random number table", which was assessed as low-risk. One study was double-blinded; thus, it was considered to have a low risk of performance bias. One study that used a single-blind was evaluated as high-risk. Fifty-seven studies did not specify whether the investigators and participants were double-blinded, and 59 studies did not specify whether the outcomes were assessed in a blinded manner, whether selective reporting of results was avoided, or whether additional issues were avoided. A quality assessment table for the cohort studies was provided in Table 2. The scores in these two studies were 7 (Ren, 2020; Wu, 2018). The mean score for the eight studies was 6 (Diao, 2016; Du & Song, 2019; Qu, 2017; Song, Li, & Lu, 2019; Shao, 2013; Shi & Xu, 2013; Wang, 2017; Zhang, 2022;). The score in one study was 5 (Xu, 2018). Seven studies did not describe the duration or adequacy of follow-up.

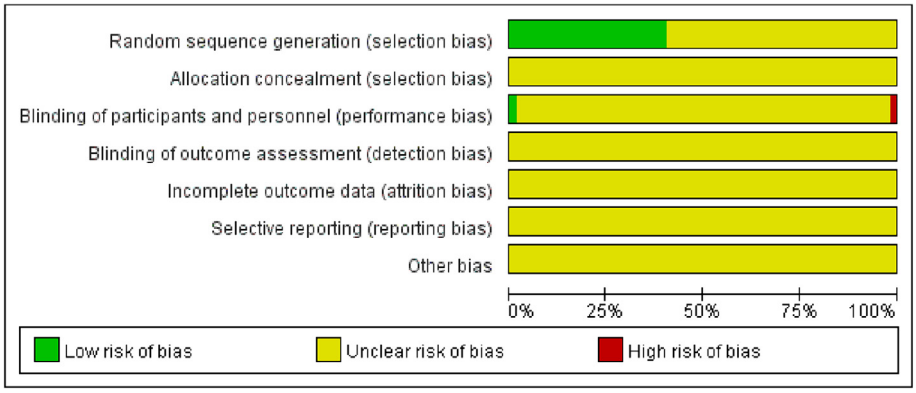

Fig. 2. Risk of bias.

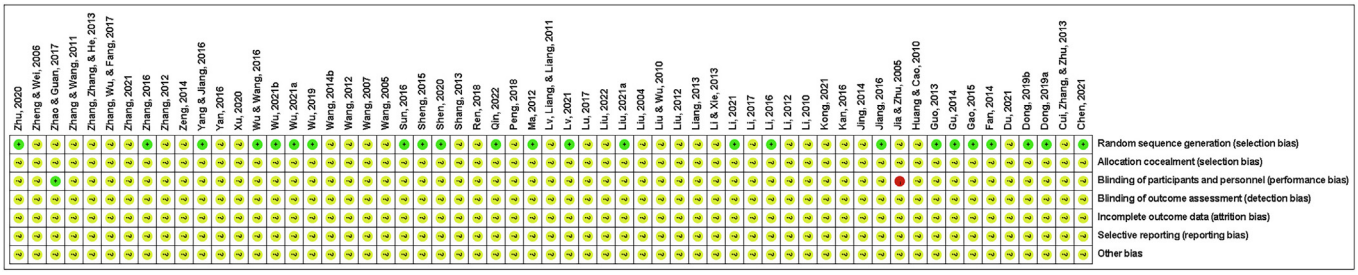

Fig. 3. Summary of risk of bias.

Table 2
A quality assessment table for cohort studies.

Studies	Selection				Comparability	Outcome			Scores
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on basis of design or analysis controlled for confounders	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Diao, 2016	1	1	1	1	1	1	/	/	6
Du & Song, 2019	1	1	1	1	1	1	/	/	6
Qu, 2017	1	1	1	1	1	1	/	/	6
Ren, 2020	1	1	1	1	1	1	1	/	7
Song, Li, & Lu, 2019	1	1	1	1	1	1	/	/	6
Wang, 2017	1	1	1	1	1	1	/	/	6
Wu, 2018	1	1	1	1	2	1	/	/	7
Zhang, 2022	1	1	1	1	1	1	/	/	6
Shao, 2013	/	1	1	1	2	1	/	/	6
Shi & Xu, 2013	/	1	1	1	2	1	/	/	6
Xu, 2018	/	1	1	1	1	1	/	/	5

3.3. Primary outcomes

Nineteen studies reported the efficacy of angina symptom combined with ECG. The efficacy of angina symptom combined with ECG was assessed in 2 233 patients. The curative effect on angina symptom combined with ECG in 1 117 patients in the treatment group was better than that in 1 116 patients in the control group. (OR = 4.824, 95% CI = 3.636–6.401, P = 0.000, Fig. 4A). The heterogeneity test result was low (I^2 = 0.0%, P = 0.998), and a fixed-effect model was selected. Sensitivity analysis showed that the combined results were stable after excluding each study (Fig. 5A). The funnel plot (Fig. 6A) and Egger's test (t = 4.08, P = 0.001) showed significant publication bias. The trim-and-filling method was used to analyze the stability of the combined results of the effect indices. After five iterations with the linear method, the number of missing studies in software evaluation was 7. Finally, data from seven virtual studies were included. All the studies were re-analyzed. Compared with the results before trim (OR = 1.542, 95% CI = 1.257–1.828, P = 0.000), the results after filling showed that the curative effect of the treatment group was better than that of the control group (OR = 4.041, 95% CI = 3.125–5.226, P = 0.000). It further indicated that the results of the analysis were stable, as shown in Fig. 7A.

The efficacy of the ECG was reported in 27 studies. The efficacy of ECG was assessed in 2 810 patients; 1 430 patients in the treatment group exhibited better ECG efficacy than 1 380 patients in the control group in the treatment of angina pectoris (OR = 3.364, 95% CI = 2.767–4.089, P = 0.000, Fig. 4B). The heterogeneity test result was low (I^2 = 0.0%, P = 0.964), and a fixed-effect model was selected. Sensitivity analysis showed that the final results were significantly different after excluding each study (Fig. 5B). The funnel plot (Fig. 6B) and Egger's test (t = 2.88, P = 0.008) showed that there was significant publication bias. The trim-and-filling method was used to analyze the stability of the combined results of the effect indices. After five iterations of the linear method, the number of missing studies in software was seven. Finally, data from seven virtual studies were included. All the studies were re-analyzed. Compared with the results before trim (OR = 1.187, 95% CI = 0.989–1.385, P = 0.000), The results after filling showed that the curative effect of the treatment group was better than that of

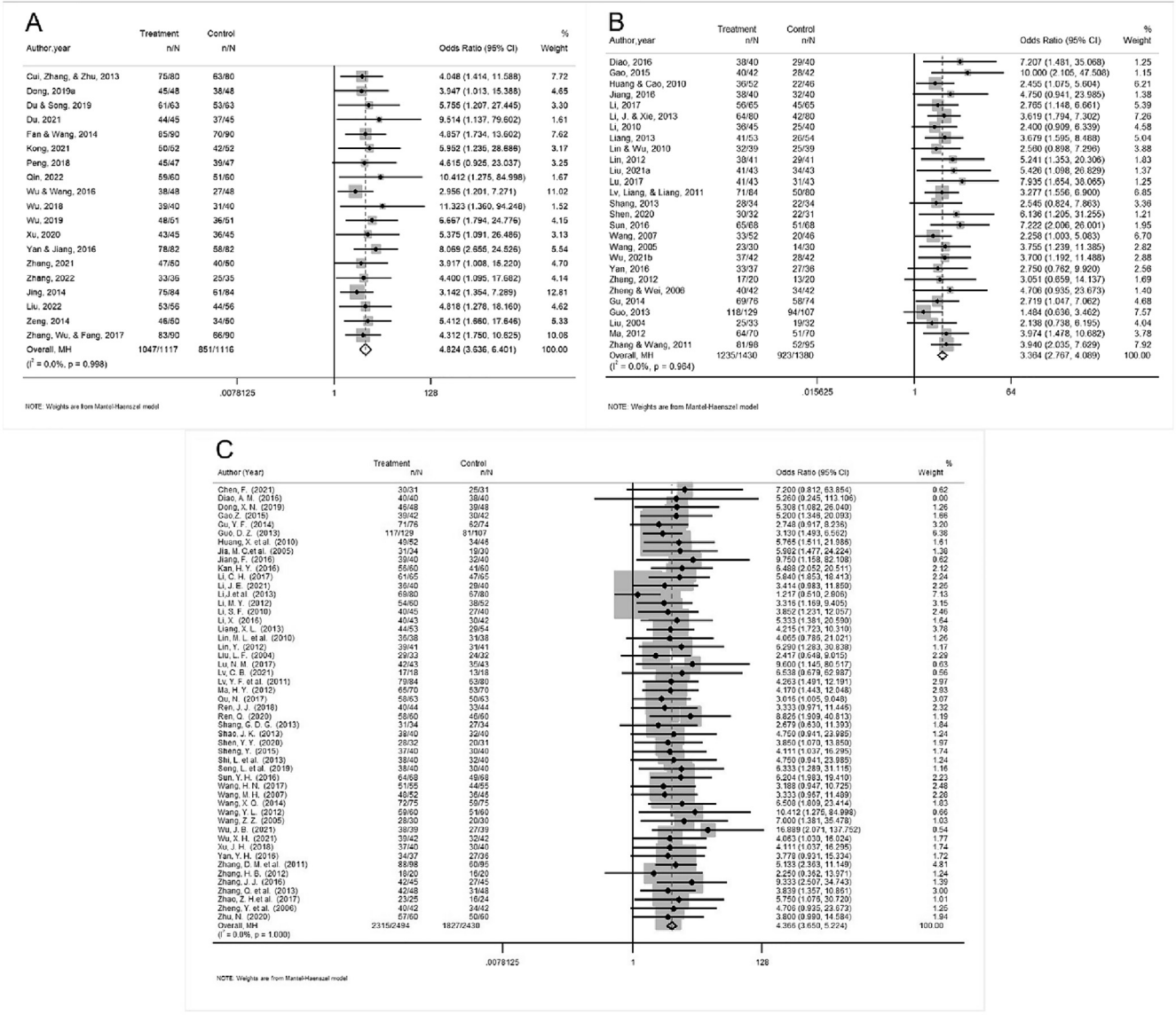

Fig. 4. Forest plots of angina symptom and ECG efficacy (A), ECG efficacy (B) and angina symptom efficacy (C).

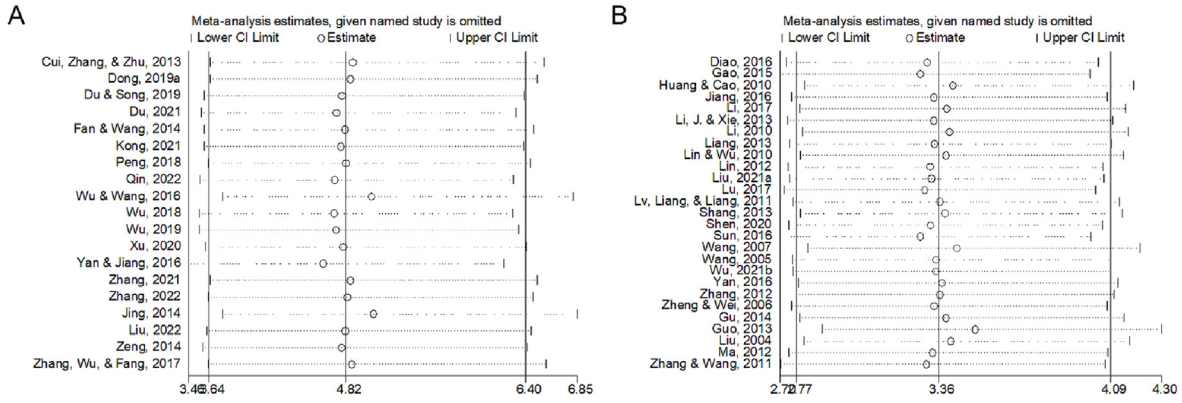

Fig. 5. Sensitivity analysis of angina symptom and ECG efficacy (A) and ECG efficacy (B).

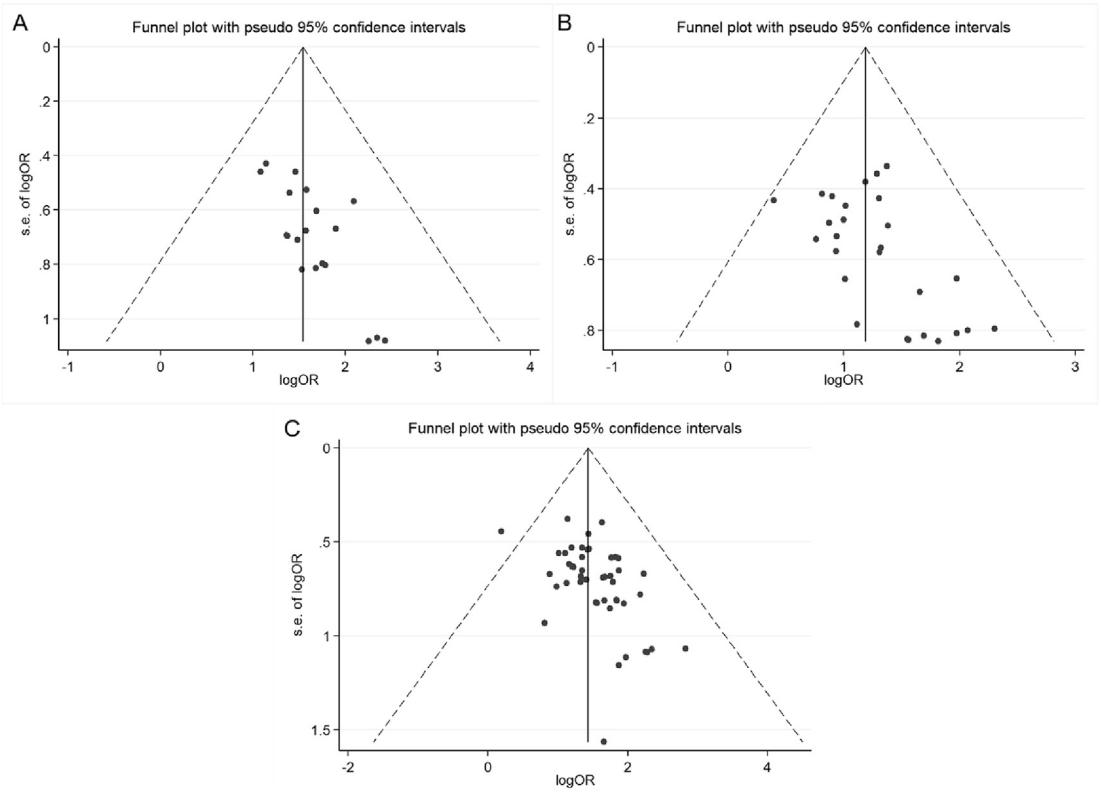

Fig. 6. Funnel plots of angina symptom and ECG efficacy (A), ECG efficacy (B) and angina symptom efficacy (C).

the control group (OR = 2.955, 95% CI = 2.453–3.562, P = 0.000). It further indicated that the results of the analysis are stable, as shown in Fig. 7B.

Fifty studies had reported the efficacy of angina symptom. The treatment efficacy of angina symptom was assessed in 4 926 patients. The curative effect on AP in 2 495 patients in the treatment group was better than that in 2 431 patients in the control group (OR = 4.347, 95% CI = 3.635–5.198, P = 0.000, Fig. 4C). The heterogeneity test result was low (I^2 = 0.0%, P = 1.000), and a fixed-effect model was selected. Sensitivity analysis revealed that the final results were significantly different after excluding each study (Table 3). The funnel plot (Fig. 6C) and Egger's test (t = 3.73, P = 0.001) showed that there was significant publication bias. The trim-and-filling method was used to analyze the stability of the combined results of the effect indices. After six iterations with the linear method, the number of missing studies in software was 16. Finally, data from 16 virtual studies were included. All the studies were re-analyzed. Compared with the results before trim (OR = 1.434, 95% CI = 1.253–1.616, P = 0.000), the results after filling showed that the curative effect of the treatment group was better than that of the control group (OR = 3.639, 95% CI = 3.084–4.294, P = 0.000). It further indicated that the results of the analysis were stable, as shown in Fig. 7C.

3.4. Secondary outcomes

Seven studies had reported the determination of TG levels. In total, 720 patients were enrolled, half of whom belonged to the experimental group. The results showed that CDDP combined with

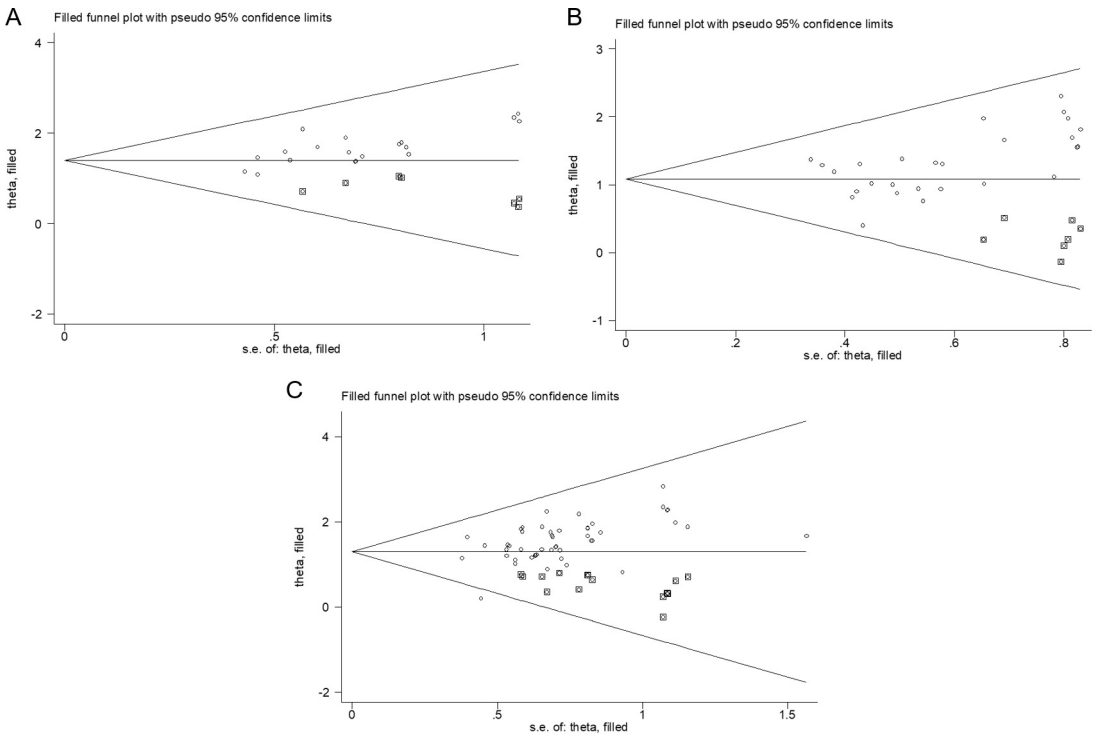

Fig. 7. Trim-and-filling method of angina symptom and ECG efficacy (A), ECG efficacy (B) and angina symptom efficacy (C).

ISMN for the treatment of AP was superior to ISMN alone in reducing TG levels (MD = −35.176, 95% CI = −37.439 to −32.912, P = 0.000, Fig. 8A). The heterogeneity was low (I^2 = 0.0%, P = 0.567) and a fixed-effect model was chosen. Sensitivity analysis showed that the final combined results were significantly different after excluding each study (Fig. 9A). Egger's test (t = −0.37, P = 0.726) showed no significant publication bias.

Seven studies reported TC levels. In total, 720 patients were enrolled, half of whom belonged to the experimental group. The results showed that CDDP combined with ISMN for the treatment of AP was superior to ISMN alone in reducing TC levels (MD = −24.296, 95% CI = −26.429 to −22.163, P = 0.000, Fig. 8B). The heterogeneity was high (I^2 = 64.3%, P = 0.010) and a random-effect model was chosen. Sensitivity analysis showed that the study by Liu et al was the source of heterogeneity (MD = −23.268, 95% CI = −24.582 to −21.954, P = 0.000, I^2 = 0.0%). The combined results after excluding this study were consistent with the original results (Fig. 9B). No differences were found in sample size, patient age, sex, evaluation criteria, and outcome indicators. Therefore, the relevant literature (Liu, 2021a) was not excluded. Egger's test (t = −2.35, P = 0.065) showed no significant publication bias.

Twenty studies reported the duration of an angina attack (min). A total of 1 813 patients were enrolled, with 909 patients in the experimental group. The results showed that CDDP combined with ISMN for the treatment of AP was superior to ISMN alone in reducing the duration of angina attack (MD = −1.991, 95% CI = −2.349 to −1.633, P = 0.000, Fig. 8C). The funnel plot (Fig. 10A) and Egger's test (t = 0.09, P = 0.930) showed no significant publication bias. The heterogeneity was high (I^2 = 97.6%, P = 0.000) and a random-effect model was chosen. To examine which factors influenced the heterogeneity, we conducted subgroup analysis according to the disease type (AP or UAP), different drug dosages (≤ 40 mg or > 40 mg), different courses of treatment (≤ 4 weeks or > 4 weeks), and whether conventional treatment was used or not (Fig. S1). The results of the subgroup analysis showed that these factors did not cause the high heterogeneity. Additional sensitivity analyses were also performed. The results showed that the result was consistent with the original results after excluding individual studies (Fig. 9C).

Twenty-one studies reported the frequency of angina attack (1 day or 1 week). A total of 1 921 patients were enrolled, with 961 patients in the experimental group. The results showed that CDDP combined with ISMN for the treatment of AP was superior to ISMN alone in reducing the frequency of angina attack (SMD = −2.840, 95 % CI = −3.416 to −2.265, P = 0.000, Fig. 8D). The funnel plot (Fig. 10B) and Egger's test (t = −8.30, P = 0.000) indicated significant publication bias. The trim-and-filling method was used to analyze the stability of the combined results of the effect indices. The results showed that there was no need to fill in the virtual study, as consistent with the original merge results (Fig. 11). A subgroup analysis was conducted to explore the factors influencing the heterogeneity. The subgroup analysis showed that different disease types, different drug dosages (≤ 40 mg or > 40 mg), different courses of treatment (≤ 4 weeks or > 4 weeks), and different outcome evaluation criteria (1 d or 1 week) were not the sources of heterogeneity (Fig. S2). Sensitivity analysis confirmed that the combined results were stable (Fig. 9D).

Thirty-six studies reported ADRs. A total of 3 855 patients were enrolled. Compared to ISMN alone, the results showed no increase in ADRs with CDDP combined with ISMN (OR = 0.513, 95% CI = 0.421–0.626, P = 0.000, Fig. 8E). The combination drug was well-tolerated by the patients. The heterogeneity was low (I^2 = 0.0%, P = 0.807), and a fixed effect model was chosen. Sensitivity analysis showed that the results were stable after excluding the studies one by one (Fig. 9E). The funnel plot (Fig. 10C) and Egger's test (t = −0.21, P = 0.832) showed that there was no significant publication bias. ADRs in the experimental and control groups were mainly caused by nervous system damage (headache and dizziness), circulatory system damage (facial flushing), and gastrointestinal system damage (nausea and gastrointestinal discomfort) (Table 4). No serious ADRs were observed.

Table 3
Sensitivity analysis for AP efficacy.

Study omitted	Estimate	95 % CI
Chen, 2021	4.3 291 306	3.6 177 325–5.1 804 199
Diao, 2016	4.3 315 573	3.6 218 257–5.1 803 679
Dong, 2019b	4.3 347 831	3.6 205 833–5.1 898 661
Gao, 2015	4.3 326 454	3.617 193–5.1 896 095
Huang & Cao, 2010	4.3 238 649	3.6 097 152–5.1 793 027
Jia & Zhu, 2005	4.3 242 154	3.6 105 504–5.1 789 446
Jiang, 2016	4.3 134 732	3.6 043 501–5.1 621 103
Kan, 2016	4.3 009 396	3.5 883 563–5.1 550 298
Li, 2017	4.3 129 444	3.5 984 087–5.1 693 654
Li & Xie, 2013	4.5 858 517	3.8 157 866–5.5 113 244
Li, 2010	4.3 593 626	3.6 371 241–5.225 019
Liang, 2013	4.3 52 119	3.6 259 079–5.2 237 778
Lin & Wu, 2010	4.3 703 308	3.64 908–5.2 341 385
Lin, 2012	4.3 240 647	3.6 115 539–5.1 771 441
Lu, 2017	4.3 138 318	3.60 465–5.1 625 381
Lv, 2021	4.3 347 011	3.6 225 963–5.1 867 862
Lv, Liang, & Liang, 2011	4.3 494 964	3.6 274 302–5.2 152 944
Qu, 2017	4.3 888 903	3.6 609 557–5.2 615 657
Ren, 2018	4.370 914	3.6 479 061–5.2372 212
Ren, 2020	4.2 934 527	3.5 853 322–5.1 414 309
Shang, 2013	4.3 781 123	3.6 557 534–5.2 432 065
Shen, 2020	4.3 568 621	3.6 367 407–5.2 195 768
Song, Li, & Lu, 2019	4.3 237 486	3.611 299–5.176 753
Sun, 2016	4.3 048 124	3.5 914 569–5.1 598 582
Wang, 2017	4.3 76 235	3.6 520 975–5.2 439 542
Wang, 2007	4.3 704 138	3.6 475 167–5.2 365 813
Wang, 2012	4.3 070 087	3.5 988 126–5.1 545 677
Wang, 2005	4.3 194 404	3.6 078 334–5.1 714 044
Wu, 2021b	4.3 520 474	3.6 335 893–5.2 125 645
Yan, 2016	4.3 568 449	3.6 378 064–5.2 180 071
Zhang, 2012	4.3 731 022	3.6 534 278–5.2 345 424
Zhao & Guan, 2017	4.3 327 031	3.6 192 646–5.1 867 762
Zheng & Wei, 2006	4.342 423	3.6 271 231–5.1 987 867
Zhu, 2020	4.3 576 851	3.638 072–5.2 196 388
Gu, 2014	4.399 487	3.6 696 892–5.2 744 212
Guo, 2013	4.429 368	3.6 831 563–5.3 267 636
Li, 2021	4.3 682 599	3.6 458 206–5.2 338 548
Li, 2012	4.3 803 163	3.6 528 108–5.2 527 142
Li, 2016	4.3 306 074	3.6 154 773–5.1 871 877
Liu, 2004	4.3 918 653	3.6 659 727–5.2 614 903
Ma, 2012	4.3 522 701	3.6 299 331–5.218 348
Shao, 2013	4.3 419 271	3.626 725–5.1 981 688
Sheng, 2015	4.3 511 095	3.6 328 459–5.2 113 843
Shi & Xu, 2013	4.3 419 271	3.626 725–5.1 981 688
Wang, 2014b	4.3 069 582	3.5 949 044–5.1 600 509
Wu, 2021a	4.2 797 556	3.5 754 974–5.1 227 303
Xu, 2018	4.3 511 095	3.6 328 459–5.2 113 843
Zhang & Wang, 2011	4.3 074 231	3.5 841 024–5.1 767 201
Zhang, 2016	4.2 768 908	3.5 698 328–5.1 239 915
Zhang, Zhang, & He, 2013	4.3 625 793	3.6 380 978–5.2 313 328
Combined	4.3 469 529	3.6 349 295–5.1 984 501

3.5. Subgroup analysis

Our study included 59 RCTs and 11 cohort studies. Seventy studies were analyzed in subgroups according to the study type (RCTs or cohort studies). Both the TC and TG levels were included in the RCT analysis. Therefore, we did not perform subgroup analyses. Subgroup analyses were performed for other outcomes (Primary outcomes and Secondary outcomes). All subgroup analysis results were consistent with those of the main analyses. (Fig. S3).

4. Discussion

AP is an episode of myocardial ischemia caused by an imbalance between myocardial oxygen supply and demand (Manfredi et al., 2022). Myocardial oxygen is delivered through the coronary arteries. The coronary artery is divided into several small arteries. When myocardial oxygen consumption increases, the arterioles dilate in response to nitric oxide, prostaglandins, carbon dioxide, hydrogen ions, adenosine, and other nucleotides. With this modulation, blood flow to the normal heart muscle can be increased four- to five-fold. Coronary artery stenosis, which leads to insufficient blood supply to the myocardium and can cause myocardial ischemia or angina (Jain et al., 2017). Organic nitrates are one of the most commonly used drugs for the treatment of AP. Organic nitrates release nitric acid via cellular metabolism. Nitric oxide activates guanylate cyclase, leading to the conversion of guanosine triphosphate to cyclic guanosine monophosphate, which causes vasodilation (Parker & Parker, 1998). Organic nitrates can relax the veins and arteries, reduce the pre- and post-load on the heart, and reduce oxygen consumption in the heart muscle. Short-acting organic nitrates can also be used to treat acute AP. Long-acting organic nitrates are used for the long-term prophylactic treatment of AP (Chinese Society of Cardiovascular Diseases & Chinese Medical Association, 2007). Most organic nitrates are tolerant of nitrate. ISMN does not induce vascular tolerance and can lead to endothelial dysfunction and increase cardiovascular risk (Münzel, Steven, & Daiber, 2014). Therefore, the development of new treatment options is essential.

Previous studies have confirmed the positive effects of ISMN in combination with TCMs on angina pectoris (Jia et al., 2020). Thus, the combination of TCM and Western medicine provides a new approach for the treatment of angina. CDDP is widely used to treat AP in patients with CHD. CDDP consists of *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Notoginseng Radix* et *Rhizoma*, and *Borneolum Syntheticum*. *Salviae Miltiorrhizae Radix* et *Rhizoma*, the main prescribed drug, has antimyocardial ischemic effects, increasing cardiac output and coronary blood volume. *Salviae Miltiorrhizae Radix* et *Rhizoma* is more effective at dilating the coronary arteries than *Notoginseng Radix* et *Rhizoma*. However, *Notoginseng Radix* et *Rhizoma* has a stronger protective effect on heart muscle than *Salviae Miltiorrhizae Radix* et *Rhizom*. Their combination has both synergistic and complementary effects (Zhang et al., 2003). Network pharmacology studies have shown that CDDP has 65 core targets and 61 active components for the treatment of AP. Quercetin, luteolin, salvianone, and asiatic acid are key chemical components of CDDP used in the treatment of AP. These components regulate lipoproteins and atherosclerosis, as well as the tumor necrosis factor signaling pathway, HIF-1 signaling pathway, and PI3K-Akt signaling pathway through related targets. They play a role in anti-inflammation, the regulation of oxidative stress and lipid metabolism disorders, and the repair of vascular damage. CDDP contains different active ingredients that act on the same target, indicating that CDDP has a multi-component and multi-target mechanism of action in the treatment of AP (Ai, 2022; Li et al., 2023). In summary, the mechanism of CDDP in the treatment of AP is different from that of ISMN, which provides an essential theoretical basis for the treatment of CHD with TCM. Chinese guidelines recommend CDDP during an episode of AP (Society of Cardiovascular Disease and Chinese Association of Traditional Chinese Medicine, 2019); however, there is little evidence supporting the use of CDDP combined with ISMN for the treatment of AP.

The ECG of patients with AP may show ST-segment depression or T-wave inversion. The Chinese criteria for efficacy assessment are angina symptom and ECG efficacy (Wang, 2005; Chinese Society of Cardiovascular Diseases and Chinese Medical Association, 2007). ECG combined with clinical symptom features can improve the accuracy of angina diagnosis and evaluation (Liu, 2021b). Dyslipidemia is a risk factor for atherosclerotic cardiovascular disease (ASCVD) and CHD, and low-density lipoprotein cholesterol (LDL-C) are pathogenic risk factors for ASCVD (Wang et al., 2023b; Xu et al., 2023). The monitoring and management of blood lipids are essential for assessing and preventing ASCVD and CHD. Therefore, TG and TC levels were used as secondary out-

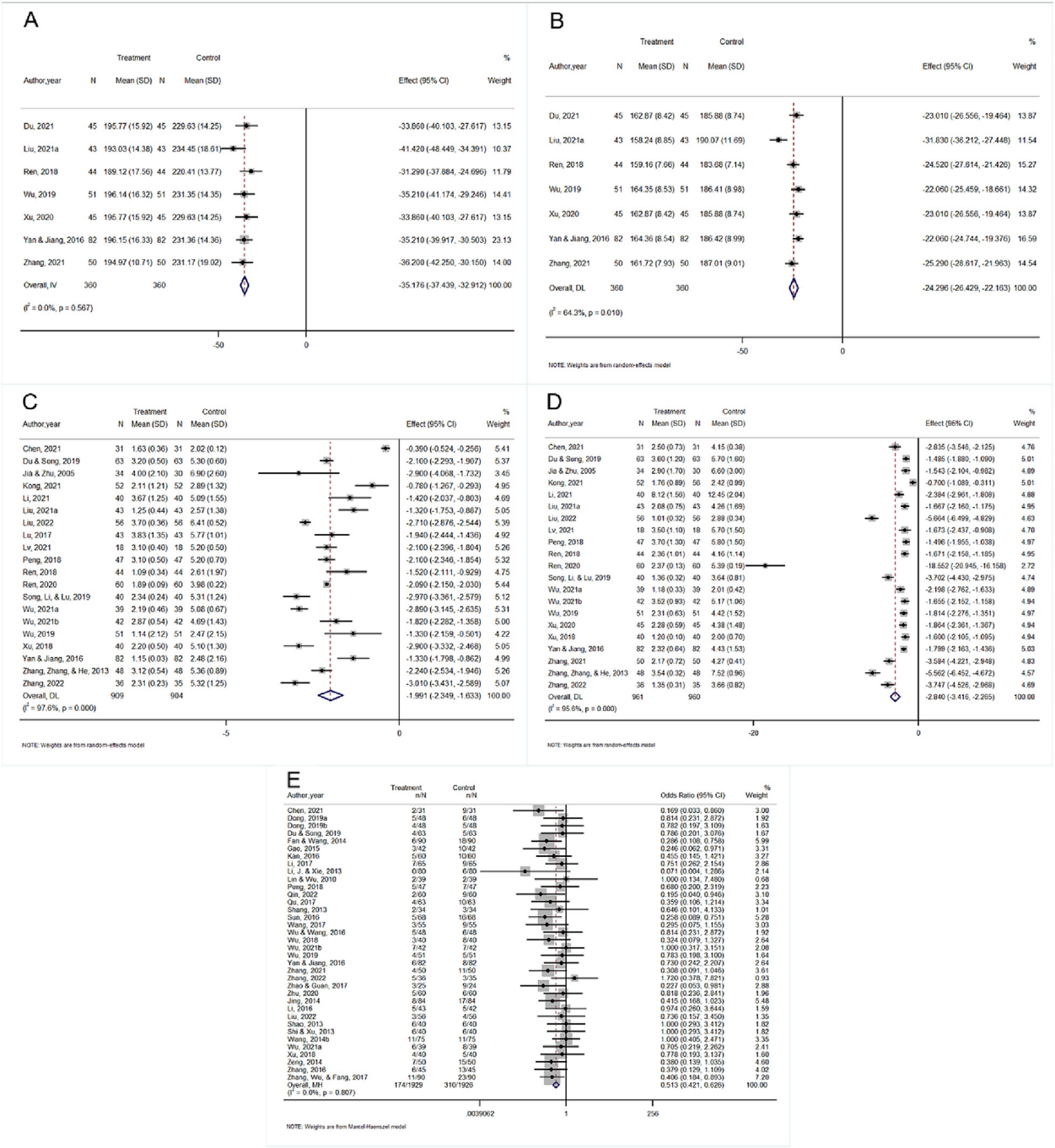

Fig. 8. Forest plots of TG levels (A), TC levels (B), duration of angina attack (min) (C), frequency of angina attack (in 1 d or 1 week) (D) and ADRs (E).

comes of angina in our study. Compared with previous Meta-analyses (Xue et al., 2013; Zhang et al., 2018), our study included not only angina symptom and ECG efficacy but also lipid levels, angina attack frequency, and angina attack duration. Thus, our study was more comprehensive than previous studies.

This systematic review included 7 245 angina patients from 70 studies (59 RCTs, 11 cohort studies). The results showed that CDDP combined with ISMN was superior to ISMN alone in treating AP symptoms and improving ECG findings. The combined medication was also beneficial for lowering TG and TC levels. In terms of reducing the frequency and duration of angina attack, drug combinations were more effective than single drugs. For example, a Meta-analysis showed that the clinical efficacy of CDDP plus aspirin was superior to that of aspirin alone in the treatment of AP (Wang et al., 2021). Moreover, a study of CDDP combined with trimetazidine indicated that this treatment could significantly improve clinical efficacy in patients with AP (Zhu & Deng, 2019). Together, these findings suggest that the combination of TCM and Western medicine is beneficial for the treatment of AP. TCM can also be used as a vital supplement to Western medicine for the treatment of cardiovascular diseases.

In terms of safety, there was no significant difference in the ADRs between CDDP combined with ISMN and ISMN alone for AP. The main ADRs were headaches, dizziness, facial flushing, gastrointestinal reactions, palpitations, and other common reactions. Headache and dizziness may also be associated with ISMN. Head-

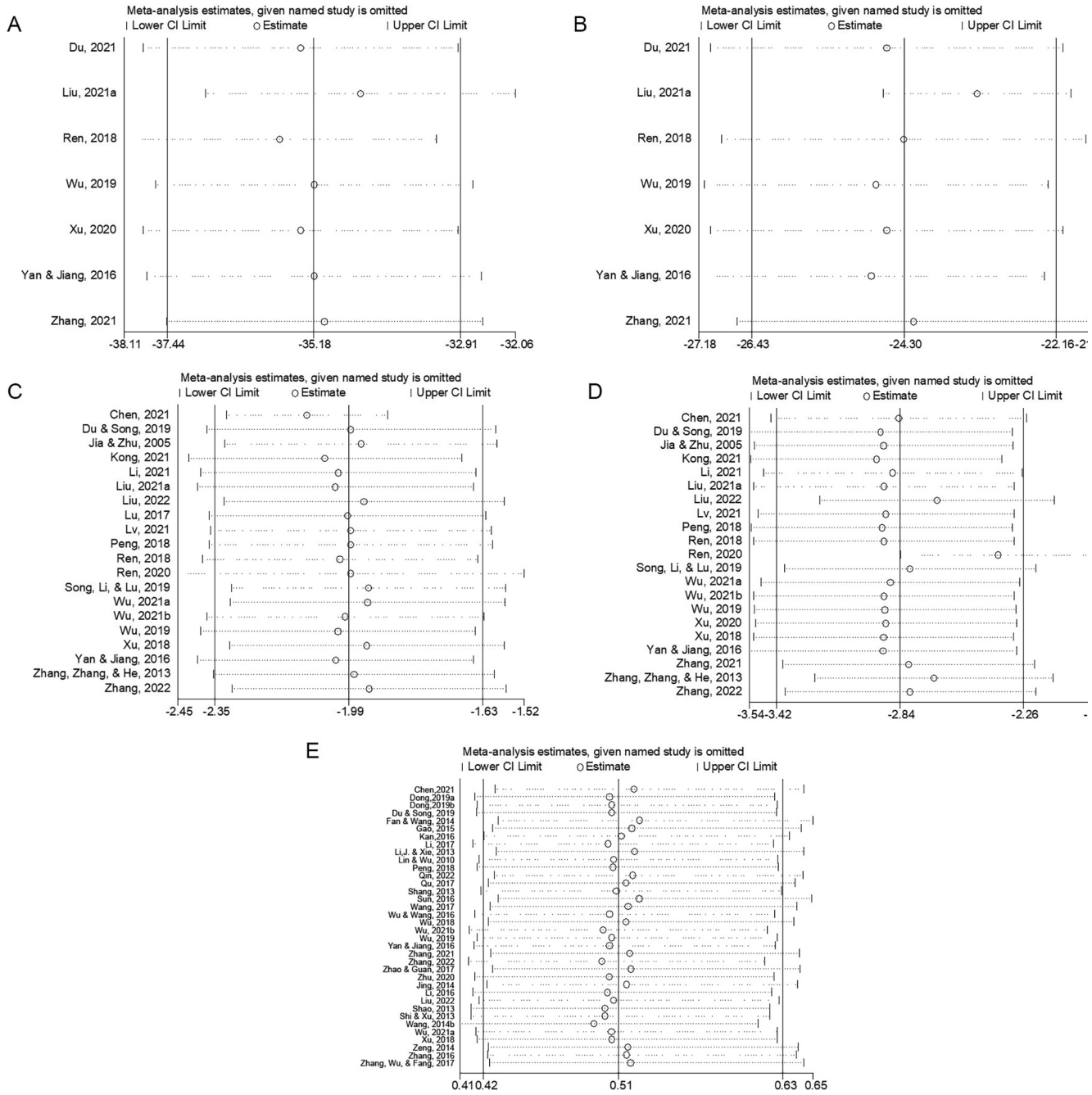

Fig. 9. Sensitivity analysis of TG levels (A), TC levels (B), duration of angina attack (min) (C), frequency of angina attack (in 1 d or 1 week) (D) and ADRs (E).

ache rates decreased with treatment duration (Boettcher et al., 2022). No serious ADRs were observed in the trial group, suggesting there was superior tolerability of AP in patients treated with ISMN in combination with CDDP.

CDDP combined with ISMN was superior to ISMN alone for the treatment of AP, with better efficacy for angina combined with ECG, angina alone, and ECG alone. However, all three evaluated metrics exhibited significant publication bias. The trim-and-filling method showed that the combined results of the three effect indicators did not change, indicating that the results were robust. The stability of the results was confirmed by sensitivity analysis. Meanwhile, quality control in data retrieval and extraction and selection of evaluation criteria were also performed in this study, although there was still publication bias. Although the common databases of the retrieved literature contained both Chinese and English, the search results showed that CDDP mainly focused on China, which could lead to regional publication bias. All studies had positive and no negative results, which could have resulted in publication bias. The low overall quality of the included studies was also responsible for the publication bias.

CDDP combined with ISMN was superior to ISMN alone in reducing the duration and frequency of angina attack. However, the combined results for both metrics showed high heterogeneity. Subgroup analysis was carried out according to the different disease types (AP or UAP), different drug doses ($\leq$ 40 mg or > 40 mg), different courses of treatment ($\leq$ 4 weeks

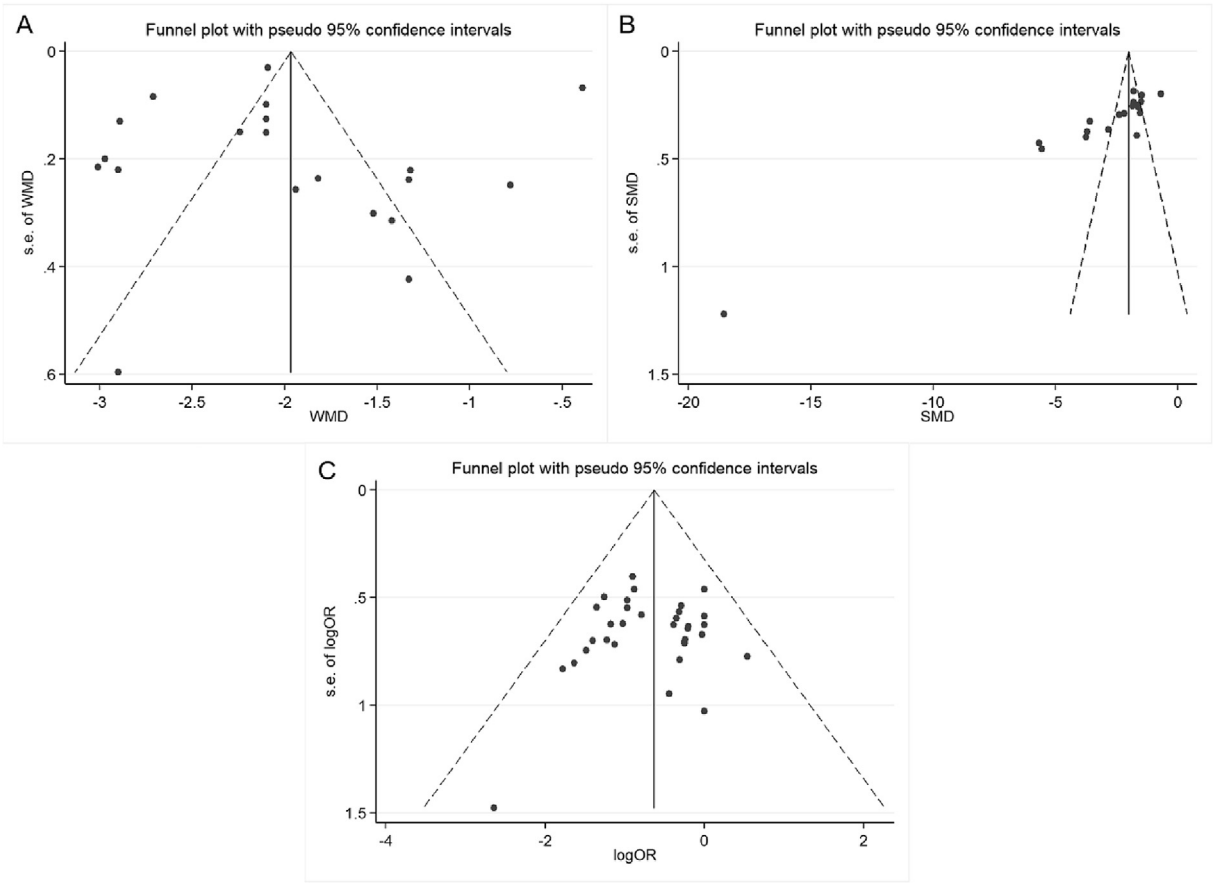

Fig. 10. Funnel plots of duration of angina attack (min) (A), frequency of angina attack (in 1 d or 1 week) (B) and ADRs (C).

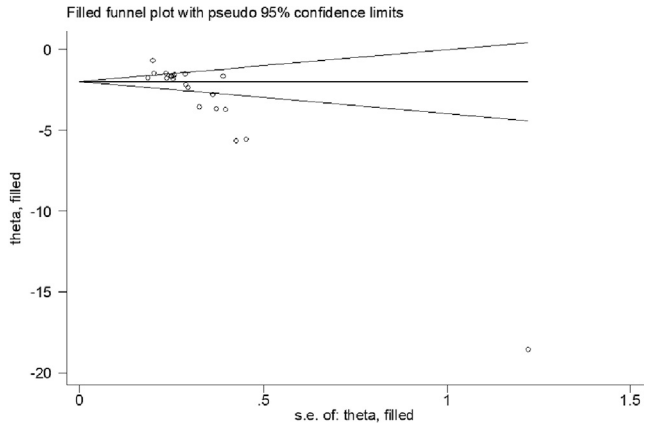

Fig. 11. Trim-and-filling method of frequency of angina attack (in 1 d or 1 week).

or > 4 weeks), and whether conventional treatment was performed. No source of heterogeneity was found in the subgroup analysis. Of the 70 included studies, 20 reported detailed data on the angina onset time and frequency, with a low data reporting rate. These metrics should be used with caution in combination with specific clinical references.

This study has some limitations. First, the overall quality of the original studies was low. There was a significant publication bias in the primary outcome measures. Significant heterogeneity was observed in the secondary outcome measures. No source of heterogeneity was found based on the available data from the various institutes. The Cochrane Library database was screened simultaneously. Most Chinese literature was not registered, and the experimental design was not published, which reduced the quality of the experiment. Researchers should use standardized test designs to improve the quality of the literature and data reliability (Shi et al., 2015). Secondly, there were insufficient observations of ADRs in the included studies. Chinese patent medicines may cause some known adverse reactions; however, they have not attracted sufficient general attention. The observation and evaluation of ADRs in TCMs require further exploration (Jiang, Xu, & Sun, 2018).

5. Conclusion

CDDP combined with ISMN was superior to ISMN alone in the treatment of AP, with patients showing good tolerance. This combination of TCM and Western medicine can be used as an alternative treatment option for patients. Although the results were positive, publication bias and heterogeneity need to be considered. The results of this study suggested that clinical therapy should be tailored based on the clinical presentation of patients; however, caution should be taken. In future studies, rigorous clinical trial design processes should be considered to improve the quality of studies. More scholars will pay attention to the clinical treatment of TCM to provide additional evidence for TCM diagnosis and treatment.

Table 4
Comparison of adverse drug reactions between treatment group and control group.

Systems and organs involved	Clinical manifestations (frequency)	
	Control group	Treatment group
Central and peripheral nervous system disorders	Headache (115), dizziness (99), vertigo (7), headache or dizziness (5), syncope (1).	Headache (62), dizziness (52), vertigo (3), tongue paralysis (3).
Cardiovascular system damage	Facial flushing (88), palpitation (8), hypotension (1).	Facial flushing (52), palpitation (1), hypotension (2).
Gastro-intestinal system disorders	Nausea (33), gastrointestinal discomfort (26), vomiting (10), loss of appetite (4), constipation (2).	Gastrointestinal discomfort (28), nausea (6), vomiting (1), loss of appetite (1).
Body as a whole-general disorder	Fatigue (18), shortness of breath (2), chest distress (2), chest pain (1), collapse (1).	Fatigue (10), shortness of breath (1), chest pain (1).
Others	No detailed clinical presentation (11).	No detailed clinical presentation (7).
Skin and appendages disorders	Rash (1).	
Total	435	230

CRediT authorship contribution statement

Ru Wang: Conceptualization, Validation, Methodology, Formal analysis, Data curation, Resources, Writing – original draft, Writing – review & editing. **Jing Hu:** Methodology, Formal analysis, Data curation. **Yuanyuan Li:** Conceptualization, Validation, Methodology, Formal analysis, Writing – review & editing. **Hong Yin:** Conceptualization, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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