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Acupuncture therapy for stable angina pectoris: a systematic review and meta-analysis

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Abstract

Background Stable angina pectoris (SAP) is a common cardiovascular disease, which brings health burden to society. Acupuncture therapy is effective in improving SAP as adjunctive therapy, nevertheless, there were controversies on the effect of acupuncture on disease-affected meridian (DAM), sham acupoints and nonaffected meridian (NAM). This study evaluated the effect of acupuncture on DAM as adjunctive therapy, and the difference in acupuncture on DAM, sham acupoints, and nonaffected meridian NAM.

Methods Thirteen online databases were searched from inception to December 2, 2019. Risk of bias and quality of evidence for outcomes were respectively assessed by the Cochrane risk of bias assessment tool and the GRADE approach. RevMan 5.3 was adopted to conduct meta-analysis.

Results Thirteen RCTs including 1026 participants were included in this study. Acupuncture therapy could be effective in the improvement of angina severity, ECG results, 6-MWT, SAQ results (physical limitation, angina stability, angina frequency, treatment satisfaction, disease perception), anxiety, HRV (LF, LF/HF), ET, CRP, and reduction of nitroglycerin intake.

Acupuncture on DAM could be more beneficial than acupuncture on sham acupoints in aspects of angina severity, 6-MWT, SAQ results (angina stability, angina frequency, treatment satisfaction, disease perception). Compared to acupuncture in NAM, acupuncture on DAM could be more effective in SAQ results (angina stability, angina frequency, treatment satisfaction). Moreover, acupuncture on DAM did not increase the risk of dropout and adverse effect.

Conclusions Acupuncture on DAM could effectively improving SAP, and it could be more effective compared with acupuncture on sham acupoints or NAM. However, these conclusions were limited by low-quality of most of included studies.

Registration Open Science Framework registration (DOI: 10.17605/OSF.IO/F9DTW).

Keywords

Acupuncture therapy; stable angina pectoris; systematic review; meta-analysis

Background

Stable angina pectoris (SAP) is defined as a persistent and reproducible chest discomfort usually precipitated by a physical exertion that dissipates upon cessation of such an activity, and SAP is symptomatic manifestation of ischemia heart disease (IHD)[1, 2]. There is high prevalence rate of cardiovascular diseases in the United State, Central Europe, North Africa and the Middle East[3].

'The top 10 causes of death' indicated that IHD is the world's biggest killer, accounting for exceeded 9 million deaths in 2016[4], which brings burden of resource and economy to healthcare systems[5]. Previous studies indicated that around 9 million patients are diagnosed with angina in the United State[2], and in China, approximate 3.6 percent of population suffer from angina[6].

Patients with SAP have a high risk of major cardiovascular events[7].

The antianginal therapies of SAP are principally pharmacotherapy (β -blockers, calcium channel blockers, nitrates, etc.)[7, 8], besides, percutaneous coronary intervention (PCI)[9], coronary artery bypass grafting (CABG)[7, 10], acupuncture therapy[11, 12], change of lifestyle (smoking cessation, proper exercise, etc.)[8] are used to improve SAP. Acupuncture has long history for attenuating anginal symptom in China. With the advance of technology, type of acupuncture therapies become various, which includes manual acupuncture (MA), electroacupuncture (EA), acupoint application, laser acupuncture, and so on[13]. Thanks to safety and efficacy of acupuncture therapy, an increasing number of patients are willing to accept it. Previous clinical studies[14, 15] verified that acupuncture is effective in alleviating SAP, and animal experiments[16, 17] showed that acupuncture has the effect in protecting myocardium from ischemic injury. However, previous clinical trials[12, 18-20] came to different conclusions in the difference of effect in acupuncture on disease-affected meridian (DAM), sham acupoints and acupuncture on nonaffected meridian (NAM). The six published meta-analyses[21-26] discussed the effect of acupuncture on all acupoints, not acupuncture on DAM. Considering the importance of acupoint selection in treatment and growing number of randomized controlled trials (RCTs) of acupuncture therapy on DAM for SAP, we conducted this systematic review and meta-analysis. The purpose of this study was to assess (a) the effect and safety of various types of acupuncture therapies on DAM as adjunctive therapy in treating SAP, (b) the difference of therapeutic results in acupuncture therapies on DAM, sham acupoints and NAM.

Methods

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[27] and the findings were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[28]. Additionally, this study was registered in Open Science Framework (registration DOI: 10.17605/OSF.IO/F9DTW).

Literature search strategy

The following online databases were searched from their inception data to December 2, 2019: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Dissertations and Theses, Allied and Complementary Medicine Database (AMED), OpenGrey, Clinicaltrials.gov, who.int/trialsearch, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), WANFANG Data. The search terms included subject headings and free terms, such as “acupuncture”, “acupoint”, “point”, “angina, stable”, “angina*”, “angor pectoris”, etc. There were no language and publication data restrictions. Special search strategies for different online databases are shown in additional file 1.

Inclusion and exclusion criteria

Types of studies: clinical RCTs and quasi-RCTs were included in this study; crossover trials, cluster RCTs, cohort studies, case control studies, case series, case reports were excluded.

Types of participants: male and female participants (aged 18 years or over) who diagnosed with SAP by validated criteria. There were no restrictions on race, country of setting, previous antianginal medications and severity of symptoms. Participants with unstable angina pectoris (UAP) were excluded.

Types of interventions: experimental interventions included all types of acupuncture therapies on DAM combined with basic therapies, such as antianginal medications, health education. Control interventions included simple basic therapies, acupuncture therapies on sham acupuncture combined with basic therapies, acupuncture therapies on NAM combined with basic therapies. Thus, eligible studies must include at least one of the following comparators: (1) DAM group versus wait list group (participants only treated by basic therapies); (2) DAM group versus sham acupuncture group; (3) DAM group versus NAM group.

Type of outcomes measures: the primary outcome was frequency of angina attacks, and the secondary outcomes included severity of angina, the number of participants with changes in electrocardiogram (ECG), 6-minute walk test (6-MWT), nitroglycerin intake, Seattle Angina Questionnaire (SAQ), intensity of anxiety, intensity of depression, heart rate variability (HRV), endothelin (ET), C-reactive protein (CRP), brain natriuretic peptide (BNP), retention of treatment, adverse events.

Data extraction and quality assessment

After removed duplicates to trash, two reviewers (ZC and YW) independently screened the search results from online databases by titles and abstracts according to the inclusion and exclusion criteria in EndNote X9. Then, the two reviewers independently screened the search results by full-text. Any disagreements were resolved by the third reviewer (YR). The two reviewers (ZC and YW) independently extracted data from included articles to a self-designed data extraction form, which included title, authors, publication year, type of study, country of setting, sample size, diagnosis criteria, characteristics of participants, details of intervention, duration of SAP, previous antianginal medications, outcome measures, and so on. The two reviewers cross-checked completed data extraction forms. If there were any diversities, the third reviewer (YR) was consulted.

The two reviewers (ZC and YW) independently assessed the risk of bias (selection bias, performance bias, detection bias, attrition bias and reporting bias) by the Cochrane risk of bias assessment tool[27]. All included studies were graded as low risk of bias, high risk of bias, or unclear risk of bias. Any diversities were resolved by the third reviewer (YR). For quality of evidence for outcomes, the two reviewers (ZC and YW) independently assessed it through the GRADE approach[29]. The quality of evidence was rated as high, moderate, low, or very low quality in GRADEprofiler (GRADEpro) 3.6.1. Any controversies were handled by the third reviewer (YR).

Data synthesis and analysis

RevMan 5.3 was adopted to conduct meta-analysis of efficacy data. Dichotomous data were analyzed via risk ratios (RRs) with 95% confidence intervals (CIs), and continuous data were analyzed by standardized mean differences (SMDs) or mean differences (MDs) with 95% CIs. When there were no events in all arms, this study was excluded from meta-analysis of RR[27].

When outcomes were measured by different tools, data were summarized as SMDs; when outcomes were measured by same tool, data were summarized as MDs. Heterogeneity was tested by I^2 statistic. If I^2 statistic $> 50\%$, data analyses were conducted using random-effects model; if I^2 statistic $\leq 50\%$, fixed-effect model was adopted to perform data analyses[27]. Sensitivity analyses, which were conducted to explore the potential sources of heterogeneity, were performed by excluding studies with high risk of bias from meta-analysis. On account of the difference in therapeutic effect caused by different types of acupuncture therapies, subgroup analysis was carried out when the number of studies was sufficient. Reporting bias was assessed by funnel plots, if the number of included studies was more than 10[27].

Results

Selected Studies

A total of 14660 articles were initially identified by online database searches, from which 6455 were duplicates, 7366 were excluded through reading titles and abstracts, 839 were reserved for further assessment. After screening by full-texts, 15 articles were included in this study, of which 4 articles[30-33] belonged to 2 studies. Flow diagram for study selection was showed in Figure 1.

Characteristics of included studies

A total thirteen studies with 1026 participants were included in this study, which were published between 2004 to 2019. All studies were conducted in different provinces of China, from which one study[12] was reported in English and the others[18-20, 30-40] were reported in Chinese. The sample size of included studies varied from 20 to 398, all participants were diagnosed by validated criteria. Nine studies[12, 20, 32-38, 40] adopted EA as intervention to improve SAP, three studies[18, 19, 39] adopted MA, one study[30, 31] adopted acupoint application. Control groups included wait list group[12, 20, 30-34, 36-38, 40], sham acupuncture group[12, 20, 32-35, 39], acupoints on the NAM group[12, 18-20, 32-34]. For duration of acupuncture therapy, treatment duration lasted from two weeks to one month and treatment sessions varied from 10 times to 60 times. Needle retention of EA and MA ranged from 20 to 30 minutes, each treatment time of acupressure lasted 2 minutes. For outcomes measures, frequency of angina attacks[12, 18, 19, 30-37, 39], severity of angina (thereinto, seven studies[12, 18, 19, 32-34, 37, 39] measured severity of angina by visual analog scale (VAS), two studies[30, 31, 35] did not report measure method), the

number of participants with changes in ECG[30, 31, 36, 40], 6-MWT[12, 32-35, 37], nitroglycerin intake[30-33, 36, 37], SAQ[12, 19, 20, 32-34, 39], intensity of anxiety (six studies[12, 19, 34, 35, 37, 39] all adopted self-rating anxiety scale (SAS) to measure intensity of anxiety), intensity of depression (all studies[12, 19, 34, 35, 37, 39] used self-rating depression scale (SDS)), HRV[12, 19, 40], ET[32, 33, 40], CRP[18, 30, 31], BNP[18], retention[12, 18-20, 32, 33, 35-37, 39, 40], adverse events[12, 18, 19, 30, 31, 36, 40] were reported. Characteristics of included trials were displayed in Table 1.

Risk of Bias Assessment

For random sequence generation, eleven studies[12, 18-20, 30-35, 37-39] were assessed by low risk of bias, thereinto, eight studies[18, 19, 30, 31, 34, 35, 37-39] used random number table, two studies[12, 32, 33] adopted central randomization system, one study[20] adopted statistical software to generate random sequence. The other two studies[36, 40] did not describe randomization method. For allocation concealment, two studies[12, 32, 33] concealed allocation by central randomization system, one study[20] used sequentially numbered, opaque, sealed envelopes, the others[18, 19, 30, 31, 34-40] did not report concealment of allocation. For blinding of participants and personnel, three studies[12, 18, 39] were assessed as ‘low risk of bias’, in which participants were treated in a single treatment room; seven studies[20, 30-33, 36-38, 40] were judged to be at ‘high risk of bias’, the other studies[19, 34, 35] did not report the detailed approach of blinding. For blinding of outcome assessment, outcome assessors were masking to allocation in seven studies[12, 18, 20, 32-35, 37], six studies[19, 30, 31, 36, 38-40] did not report related information. For incomplete outcome data, eleven studies[12, 18-20, 32-38, 40] were judged to be at ‘low risk of bias’, two studies had no enough information and were assessed as ‘unclear risk of bias’. For selective reporting, five studies[12, 18, 19, 37, 39] published protocol in journal or registered in website, the other studies[20, 30-36, 38, 40] had no available protocols. For other bias, eleven studies were judged to be at ‘low risk of bias’, and two studies[20, 32, 33] were assessed as ‘high risk of bias’. Table 2 presented risk of bias summary.

Table 2. Risk of bias of included studies.

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Chen 2015							
Chen 2017							
Huang et al. 2004							
Jing 2016							
Lan 2016							
Li et al. 2008							
Wang et al. 2015							
Xie 2014							
Yang et al. 2019							
Yin 2018							
Zhang 2018							
Zhang and Sun 2015							
Zhao et al. 2019							

: low risk of bias; : high risk of bias; : unclear risk of bias.

Effects of intervention

Quality of evidence for outcomes was presented in Table 3. Figures for following meta-analyses were showed in additional file 2.

Frequency of angina attacks

Six studies compared the effect of DAM group and wait list group and the combined result found no difference in frequency of angina attacks (n=376; MD, -2.21; 95% CI -5.74 to 1.32; p=0.22; heterogeneity: $X^2=128.96$, $p<0.00001$, $I^2=96\%$). Removing four studies with high risk of bias from the meta-analysis did not reduce heterogeneity (n=219; MD, 1.65; 95% CI -6.35 to 9.66; p=0.69; heterogeneity: $X^2=5.55$, $p=0.02$, $I^2=82\%$). In subgroup analysis, EA group and wait list

group had no statistic difference (n=349; MD, -1.26; 95% CI -4.92 to 2.41; p=0.50; heterogeneity: $X^2=121.89$, $p<0.00001$, $I^2=97\%$), however, acupoint application group and wait list group had statistic difference (n=27; MD, -10.38; 95% CI -18.06 to -2.70; p=0.008).

The combined result presented that the effect of DAM group and sham acupuncture group in frequency of angina attacks had no differences (n=288; MD, -0.82; 95% CI -4.90 to 3.26; p=0.69; heterogeneity: $X^2=50.27$, $p<0.00001$, $I^2=92\%$). There was high heterogeneity after removed one study with high risk of bias (n=268; MD, 0.13; 95% CI -3.70 to 3.96; p=0.95; heterogeneity: $X^2=12.76$, $p=0.005$, $I^2=76\%$). In subgroup, EA group and sham acupuncture group had no statistic difference (n=262; MD, -0.55; 95% CI -5.38 to 4.27; p=0.82; heterogeneity: $X^2=47.37$, $p<0.00001$, $I^2=94\%$), heterogeneity did not reduce by removing one study with high risk of bias (n=242; MD, 0.95; 95% CI -3.27 to 5.18; p=0.66; heterogeneity: $X^2=5.97$, $p=0.05$, $I^2=67\%$), MA group and sham acupuncture group had no statistic difference (n=26; MD, -1.92; 95% CI -5.64 to 1.80; p=0.31).

There was no statistic difference between DAM group and NAM group in frequency of angina attacks (n=304; MD, -0.01; 95% CI -2.22 to 2.19; p=0.99; heterogeneity: $X^2=16.31$, $p=0.003$, $I^2=75\%$). Removing of study with high risk of bias cannot decrease heterogeneity to 50% (n=284; MD, 0.39; 95% CI -2.10 to 2.89; p=0.76; heterogeneity: $X^2=9.91$, $p=0.02$, $I^2=70\%$). In subgroup, EA group and NAM group had no statistic difference (n=240; MD, 0.81; 95% CI -2.20 to 3.82; p=0.60; heterogeneity: $X^2=9.96$, $p=0.007$, $I^2=80\%$), after removed study with high risk of bias, the heterogeneity significantly decrease (n=220; MD, 2.40; 95% CI 1.33 to 3.46; $p<0.0001$; heterogeneity: $X^2=0.11$, $p=0.74$, $I^2=0\%$), MA group and NAM group also had no statistic difference (n=64; MD, -1.30; 95% CI -3.35 to 0.75; p=0.22; heterogeneity: $X^2=0.00$, $p=0.95$, $I^2=0\%$).

Severity of angina

Low quality evidence suggested that acupuncture on DAM significantly lessened the severity of angina compared to wait list group (n=296; SMD, -0.49; 95% CI -0.73 to -0.26; $p<0.0001$; heterogeneity: $X^2=5.81$, $p=0.21$, $I^2=31\%$). Subgroup analysis showed that there were significantly statistic differences between EA group and wait list group (n=269; SMD, -0.44; 95% CI -0.68 to -0.20; p=0.0004; heterogeneity: $X^2=3.44$, $p=0.33$, $I^2=13\%$), in addition, acupoint application significantly improving severity of angina (n=27; SMD, -1.13; 95% CI -1.98 to -0.28; p=0.009).

Meta-analysis showed that acupuncture on DAM significantly attenuated severity of angina compared to sham acupuncture group (n=288; SMD, -0.25; 95% CI -0.48 to -0.01; p=0.04; heterogeneity: $X^2=5.39$, p=0.25, $I^2=26\%$). For subgroup analysis, the effect of EA on DAM was better than EA on sham acupoints in alleviating severity of angina (n=262; SMD, -0.33; 95% CI -0.57 to -0.08; p=0.009; heterogeneity: $X^2=0.35$, p=0.95, $I^2=0\%$), nevertheless, MA on DAM did not significantly improve severity of angina compared to MA on sham acupoints (n=26; SMD, 0.63; 95% CI -0.17 to 1.43; p=0.12).

There was no evidence of difference between DAM group and NAM group in severity of angina (n=304; MD, 0.13; 95% CI -0.40 to 0.66; p=0.63; heterogeneity: $X^2=9.40$, p=0.05, $I^2=57\%$).

Moreover, the effect of EA on DAM did not improve severity of angina compared with EA on NAM (n=240; MD, -0.23; 95% CI -0.54 to 0.08; p=0.14; heterogeneity: $X^2=0.18$, p=0.92, $I^2=0\%$), MA on DAM significantly alleviating severity of angina compared with MA on NAM (n=64; MD, 0.94; 95% CI 0.24 to 1.64; p=0.008; heterogeneity: $X^2=0.14$, p=0.71, $I^2=0\%$).

Number of participants with changes in ECG

The meta-analysis of four studies showed that there was difference in DAM group and wait list group (n=278; RR, 1.27; 95% CI 1.09 to 1.49; p=0.002; heterogeneity: $X^2=0.86$, p=0.84, $I^2=0\%$). For subgroup analysis, EA group and wait list group had significant statistical difference (n=151; RR, 1.25; 95% CI 1.07 to 1.47; p=0.005; heterogeneity: $X^2=0.49$, p=0.78, $I^2=0\%$), acupoint application group and wait list group had no statistical difference (n=27; RR, 1.62; 95% CI 0.70 to 3.73; p=0.26). No study reported number of participants with changes in ECG in sham acupuncture group and NAM group.

6-MWT

There was evidence of effect of EA on DAM in 6-MWT as adjunctive therapy (n=269; MD, 19.84; 95% CI 3.84 to 35.83; p=0.02; heterogeneity: $X^2=1.89$, p=0.60, $I^2=0\%$). In the meantime, EA on DAM was found to be more effective than EA in sham acupoints in 6-MWT (n=262; MD, 26.08; 95% CI 10.19 to 41.96; p=0.001; heterogeneity: $X^2=0.17$, p=0.98, $I^2=0\%$). Whereas, there was no difference of difference between EA on DAM and EA on NAM in 6-MWT (n=240; MD, -10.11; 95% CI -26.85 to 6.63; p=0.24; heterogeneity: $X^2=3.35$, p=0.19, $I^2=40\%$).

Nitroglycerin intake

DAM group and wait list group had statistical difference in reducing nitroglycerin intake (n=157;

SMD, -0.63; 95% CI -0.95 to -0.30; $p=0.0002$; heterogeneity: $X^2=3.60$, $p=0.31$, $I^2=17\%$). In subgroup analysis, EA was effective in decreasing nitroglycerin intake ($n=130$; SMD, -0.56; 95% CI -0.91 to -0.20; $p=0.002$; heterogeneity: $X^2=2.67$, $p=0.26$, $I^2=25\%$), acupoint application was also effective in reducing nitroglycerin intake ($n=27$; SMD, -1.00; 95% CI -1.84 to -0.17; $p=0.02$). Only one study reported nitroglycerin intake of SAP participants after treatment of EA on DAM or sham acupoints, and there was no evidence of difference between EA group and sham acupuncture group ($n=20$; MD, -2.40; 95% CI -5.15 to 0.35; $p=0.09$). One study reported nitroglycerin intake in DAM group and NAM group, DAM group and NAM group had no difference in rescue medicine intake ($n=20$; MD, -1.00; 95% CI -2.57 to 0.57; $p=0.21$).

SAQ

A total of four studies discussed the difference between DAM group and wait list group in SAQ. The combined results presented that EA on DAM combined basic therapies significantly improved physical limitation ($n=299$; MD, 2.63; 95% CI 1.19 to 4.07; $p=0.0003$; heterogeneity: $X^2=1.38$, $p=0.71$, $I^2=0\%$), angina stability ($n=299$; MD, 40.15; 95% CI 27.46 to 52.83; $p<0.00001$; heterogeneity: $X^2=19.58$, $p<0.0001$, $I^2=90\%$), angina frequency ($n=299$; MD, 8.02; 95% CI 5.69 to 10.35; $p<0.00001$; heterogeneity: $X^2=0.16$, $p=0.98$, $I^2=0\%$), and had higher score in treatment satisfaction ($n=299$; MD, 17.10; 95% CI 10.51 to 23.68; $p<0.00001$; heterogeneity: $X^2=11.04$, $p=0.01$, $I^2=73\%$) and disease perception ($n=299$; MD, 4.82; 95% CI 2.23 to 7.42; $p=0.0003$; heterogeneity: $X^2=1.77$, $p=0.62$, $I^2=0\%$) compared to basic therapies. For meta-analysis of angina stability score, removing studies with high risk of bias reduced heterogeneity ($n=219$; MD, 33.20; 95% CI 28.07 to 38.32; $p<0.00001$; heterogeneity: $X^2=0.36$, $p=0.55$, $I^2=0\%$). For meta-analysis of treatment satisfaction score, removing studies with high risk of bias also influenced heterogeneity ($n=219$; MD, 12.56; 95% CI 8.79 to 16.33; $p<0.00001$; heterogeneity: $X^2=0.47$, $p=0.49$, $I^2=0\%$). For physical limitation score, DAM group had no statistic difference from sham acupoint group ($n=328$; MD, 0.82; 95% CI -0.88 to 2.52; $p=0.35$; heterogeneity: $X^2=7.86$, $p=0.10$, $I^2=49\%$); in subgroup analysis, the effect of EA on DAM was not different from that of EA on sham acupoints ($n=302$; MD, 1.09; 95% CI -0.63 to 2.81; $p=0.21$; heterogeneity: $X^2=3.05$, $p=0.38$, $I^2=2\%$), however, the effect of MA on DAM was better than that of MA on sham acupoints ($n=26$; MD, -12.52; 95% CI -24.56 to -0.48; $p=0.04$). In addition, there were differences between DAM group and sham acupuncture group in angina stability ($n=328$; MD, 16.63; 95% CI 8.15 to 25.10;

p=0.0001; heterogeneity: $X^2=11.52$, $p=0.009$, $I^2=74\%$), angina frequency (n=328; MD, 5.90; 95% CI 3.73 to 8.08; $p<0.00001$; heterogeneity: $X^2=1.49$, $p=0.83$, $I^2=0\%$), treatment satisfaction (n=328; MD, 8.11; 95% CI 3.45 to 12.77; $p=0.0006$; heterogeneity: $X^2=7.75$, $p=0.10$, $I^2=48\%$) and disease perception (n=328; MD, 4.13; 95% CI 1.76 to 6.51; $p=0.0006$; heterogeneity: $X^2=0.56$, $p=0.97$, $I^2=0\%$). Compared to EA on sham acupoints, EA on DAM was more effective in improving angina stability (n=302; MD, 20.31; 95% CI 16.46 to 24.16; $p<0.00001$; heterogeneity: $X^2=1.44$, $p=0.49$, $I^2=0\%$), angina frequency (n=302; MD, 5.96; 95% CI 3.73 to 8.19; $p<0.00001$; heterogeneity: $X^2=1.44$, $p=0.70$, $I^2=0\%$), treatment satisfaction (n=302; MD, 8.77; 95% CI 3.50 to 14.05; $p=0.001$; heterogeneity: $X^2=7.04$, $p=0.07$, $I^2=57\%$) and disease perception (n=302; MD, 4.02; 95% CI 1.61 to 6.43; $p=0.001$; heterogeneity: $X^2=0.27$, $p=0.97$, $I^2=0\%$). The effect of MA on DAM had no difference from that of MA on sham acupoints in angina stability (n=26; MD, -3.94; 95% CI -18.41 to 10.53; $p=0.59$), angina frequency (n=26; MD, 4.78; 95% CI -4.95 to 14.51; $p=0.34$), treatment satisfaction (n=26; MD, 2.99; 95% CI -8.81 to 14.79; $p=0.62$) and disease perception (n=26; MD, 7.93; 95% CI -6.10 to 21.96; $p=0.27$). For subgroup analysis of EA on DAM in treatment satisfaction, after removed two studies with high risk of bias, heterogeneity was reduced (n=222; MD, 5.71; 95% CI 2.26 to 9.16; $p=0.001$; heterogeneity: $X^2=0.95$, $p=0.33$, $I^2=0\%$).

There were no evidences for differences between DAM group and NAM group in physical limitation (n=328; MD, -0.93; 95% CI -2.79 to 0.93; $p=0.32$; heterogeneity: $X^2=0.54$, $p=0.97$, $I^2=0\%$) and disease perception (n=328; MD, -0.48; 95% CI -3.39 to 2.42; $p=0.74$; heterogeneity: $X^2=3.18$, $p=0.53$, $I^2=0\%$), in subgroup analysis, EA on DAM and EA on NAM had no differences in physical limitation (n=300; MD, -0.90; 95% CI -2.78 to 0.98; $p=0.35$; heterogeneity: $X^2=0.49$, $p=0.92$, $I^2=0\%$) and disease perception (n=300; MD, -0.44; 95% CI -3.45 to 2.57; $p=0.77$; heterogeneity: $X^2=3.17$, $p=0.37$, $I^2=5\%$), MA on DAM and MA on NAM also had no differences in physical limitation (n=28; MD, -2.38; 95% CI -15.28 to 10.52; $p=0.72$) and disease perception (n=28; MD, -1.07; 95% CI -12.25 to 10.11; $p=0.85$). The pooled results showed that DAM group were significantly different from NAM group in angina stability (n=328; MD, 11.05; 95% CI 7.06 to 15.04; $p<0.00001$; heterogeneity: $X^2=1.70$, $p=0.64$, $I^2=0\%$), angina frequency (n=328; MD, 3.96; 95% CI 1.94 to 5.99; $p=0.0001$; heterogeneity: $X^2=1.54$, $p=0.82$, $I^2=0\%$) and treatment satisfaction (n=328; MD, 3.91; 95% CI 1.25 to 6.56; $p=0.004$; heterogeneity: $X^2=3.22$, $p=0.52$,

$I^2=0\%$). Subgroup analysis showed that there were differences between EA group and NAM group in angina stability (n=300; MD, 11.27; 95% CI 7.17 to 15.38; $p<0.00001$; heterogeneity: $X^2=1.49$, $p=0.48$, $I^2=0\%$), angina frequency (n=300; MD, 3.99; 95% CI 1.94 to 6.05; $p=0.0001$; heterogeneity: $X^2=1.51$, $p=0.68$, $I^2=0\%$) and treatment satisfaction (n=300; MD, 4.41; 95% CI 1.64 to 7.18; $p=0.002$; heterogeneity: $X^2=1.60$, $p=0.66$, $I^2=0\%$), nevertheless, there were no differences between MA group and NAM group in angina stability (n=28; MD, 7.14; 95% CI -9.95 to 24.23; $p=0.41$), angina frequency (n=28; MD, 2.86; 95% CI -9.31 to 15.03; $p=0.65$) and treatment satisfaction (n=28; MD, -2.00; 95% CI -11.48 to 7.48; $p=0.68$).

Intensity of anxiety

Compared to wait list group, the intensity of anxiety in DAM group was significantly relieving anxiety (n=249; MD, -2.25; 95% CI -4.12 to -0.39; $p=0.02$; heterogeneity: $X^2=0.92$, $p=0.63$, $I^2=0\%$). There was no evidence of difference in intensity of anxiety between DAM group and sham acupuncture group (n=268; MD, -1.23; 95% CI -2.95 to 0.49; $p=0.16$; heterogeneity: $X^2=1.27$, $p=0.74$, $I^2=0\%$). The pooled analysis of subgroups showed that EA (n=242; MD, -1.33; 95% CI -3.18 to 0.52; $p=0.16$; heterogeneity: $X^2=1.20$, $p=0.55$, $I^2=0\%$) and MA (n=26; MD, -0.65; 95% CI -5.29 to 3.99; $p=0.78$) were not more effective in improving anxiety. DAM group and NAM group had no statistic difference in attenuating anxiety (n=248; MD, -1.07; 95% CI -2.80 to 0.65; $p=0.22$; heterogeneity: $X^2=0.27$, $p=0.87$, $I^2=0\%$). The combined results in subgroups displayed that EA (n=220; MD, -1.25; 95% CI -3.18 to 0.68; $p=0.20$; heterogeneity: $X^2=0.11$, $p=0.74$, $I^2=0\%$) and MA (n=28; MD, -0.36; 95% CI -4.25 to 3.53; $p=0.86$) were not more effective comparing with NAM group.

Intensity of depression

The pooled analysis showed that there was no difference between DAM group and wait list group (n=245; MD, -2.82; 95% CI -6.18 to 0.54; $p=0.10$; heterogeneity: $X^2=6.35$, $p=0.04$, $I^2=68\%$). Heterogeneity was not reduced by removed one study with high risk of bias (n=215; MD, -4.70; 95% CI -9.61 to 0.21; $p=0.06$; heterogeneity: $X^2=2.60$, $p=0.11$, $I^2=61\%$). The moderate quality evidence of outcomes showed that DAM group and sham acupuncture group had no significantly statistic difference in intensity of depression (n=268; MD, -1.81; 95% CI -3.71 to 0.09; $p=0.06$; heterogeneity: $X^2=2.81$, $p=0.42$, $I^2=0\%$). In subgroup analysis, EA on DAM was effective in improving depression comparing with EA on sham acupoints (n=242; MD, -2.55; 95% CI -4.67 to

-0.42; $p=0.02$; heterogeneity: $X^2=0.58$, $p=0.75$, $I^2=0\%$), MA on DAM was not different from MA on sham acupoints ($n=26$; MD, 1.03; 95% CI -3.16 to 5.22; $p=0.63$). The effect of acupuncture therapy on DAM and NAM had no difference in intensity of depression ($n=248$; MD, -1.14; 95% CI -3.18 to 0.90; $p=0.27$; heterogeneity: $X^2=0.28$, $p=0.87$, $I^2=0\%$), furthermore, EA ($n=220$; MD, -1.34; 95% CI -3.71 to 1.02; $p=0.27$; heterogeneity: $X^2=0.17$, $p=0.68$, $I^2=0\%$) and MA ($n=28$; MD, -0.54; 95% CI -4.57 to 3.49; $p=0.79$) at DAM were both different from those at NAM.

HRV

DAM group and wait list group had differences in LF ($n=126$; MD, -48.97; 95% CI -88.90 to -9.04; $p=0.02$) and LF/HF ($n=264$; MD, -0.59; 95% CI -0.85 to -0.34; $p<0.00001$; heterogeneity: $X^2=0.00$, $p=0.95$, $I^2=0\%$), and DAM group and wait list group had no difference in HF ($n=264$; MD, 67.17; 95% CI -53.02 to 187.37; $p=0.27$; heterogeneity: $X^2=14.32$, $p=0.0002$, $I^2=93\%$) and SDNN ($n=126$; MD, 3.40; 95% CI -11.22 to 18.02; $p=0.65$). DAM group was not different from sham acupuncture group in LF ($n=133$; MD, -27.30; 95% CI -63.94 to 9.34; $p=0.14$), HF ($n=133$; MD, 13.10; 95% CI -0.55 to 26.75; $p=0.06$), LF/HF ($n=133$; MD, -0.50; 95% CI -1.04 to 0.04; $p=0.07$), SDNN ($n=133$; MD, -11.11; 95% CI -39.71 to 17.49; $p=0.45$). There were no evidences of differences in LF ($n=133$; MD, -20.24; 95% CI -52.32 to 11.84; $p=0.22$), HF ($n=133$; MD, 10.93; 95% CI -2.47 to 24.33; $p=0.11$), LF/HF ($n=133$; MD, -1.93; 95% CI -5.30 to 1.44; $p=0.26$), SDNN ($n=161$; MD, -9.47; 95% CI -22.27 to 3.33; $p=0.15$; heterogeneity: $X^2=0.50$, $p=0.48$, $I^2=0\%$) between DAM group and NAM group.

ET

The meta-analysis presented difference between DAM group and wait list group ($n=158$; MD, -0.67; 95% CI -1.00 to -0.35; $p<0.0001$; heterogeneity: $X^2=0.35$, $p=0.55$, $I^2=0\%$). DAM group and sham acupuncture group had no significantly statistic difference ($n=20$; MD, -0.32; 95% CI -2.11 to 1.47; $p=0.73$). DAM group and NAM group also had no statistic difference ($n=20$; MD, -1.11; 95% CI -2.97 to 0.75; $p=0.24$).

CRP

The combined result showed that DAM group and wait list group had difference in CRP ($n=27$; MD, -0.99; 95% CI -1.22 to -0.76; $p<0.00001$). However, there was no difference between DAM group and NAM group ($n=36$; MD, -3.50; 95% CI -11.25 to 4.25; $p=0.38$).

BNP

No evidence of difference between DAM group and NAM group was found (n=36; MD, -6.25; 95% CI -47.03 to 34.53; p=0.76).

Retention

DAM group and wait list group had no difference in retention (n=566; RR, 0.99; 95% CI 0.96 to 1.03; p=0.66; heterogeneity: $X^2=1.14$, p=0.98, $I^2=0\%$). The combined result showed no difference between DAM group and sham acupuncture group (n=334; RR, 0.97; 95% CI 0.92 to 1.02; p=0.17; heterogeneity: $X^2=1.81$, p=0.77, $I^2=0\%$). Subgroup analysis presented that EA group and sham acupuncture group had no difference (n=200; RR, 0.97; 95% CI 0.92 to 1.01; p=0.14; heterogeneity: $X^2=1.77$, p=0.62, $I^2=0\%$), MA group and sham acupuncture group also had no difference (n=34; RR, 0.95; 95% CI 0.66 to 1.39; p=0.81). In addition, no evidence showed the difference between DAM group and NAM group (n=378; RR, 0.99; 95% CI 0.95 to 1.03; p=0.61; heterogeneity: $X^2=0.39$, p=0.98, $I^2=0\%$), meanwhile, EA at DAM and EA at NAM had no difference (n=278; RR, 0.99; 95% CI 0.93 to 1.04; p=0.58; heterogeneity: $X^2=0.27$, p=0.87, $I^2=0\%$), MA at DAM and MA at NAM had no difference (n=100; RR, 1.00; 95% CI 0.95 to 1.06; p=1.00; heterogeneity: $X^2=0.00$, p=1.00, $I^2=0\%$).

Safety

The meta-analysis of pooled data showed that there was no difference between DAM group and wait list group (n=218; RR, 0.54; 95% CI 0.05 to 5.51; p=0.60; heterogeneity: $X^2=2.66$, p=0.10, $I^2=62\%$). A total of six studies[12, 18, 19, 30, 31, 36, 40] reported adverse effect, thereinto, four study[18, 30, 31, 36, 40] reports concrete data in each group. The study[12] conducted by Zhao et al. included DAM group, sham acupuncture group, NAM group and wait list group. In their study, 16 (5%) participants in acupuncture groups reported adverse effects, and all recovered; and one (1%) participant in wait list group report serious adverse effect. Huang et al.[36] reported that no participant had adverse effect in DAM group, four (4%) participants had adverse effect, meanwhile, all participants remained in the trial. Zhang[40] reported that there was no difference between DAM group and wait list group in adverse effect. In the study of Lan[19], a total of four (14%) participants reported adverse effects, and all participants recovered without treatment. In the studies of Li et al.[30, 31] and Jing[18], no participants reported adverse effect.

Heterogeneity

Considering the high heterogeneity for some outcomes, sensitivity analysis and subgroup analysis

were conducted. Heterogeneity was reduced by the removal of study assessed as ‘high risk of bias’ or subgroup analysis based on different type of acupuncture therapies in most of meta-analysis in this study, but not all meta-analysis for outcomes. In fact, there were clinical heterogeneity caused by stimulation modes, duration, dosages, choice of acupoints, etc. In addition, basic therapies had differences. In ten studies, participants all received antianginal western medications, and the other studies adopted Chinese medicine as basic therapy, namely *Danshen* dripping pills. On account of the number of included studies, we cannot conduct subgroup analysis on all influence factors and sensitivity analysis in all outcomes.

Reporting Bias

Considering the number of included studies was insufficient, funnel plot was not generated by RevMan 5.3.

Discussion

This systematic review and meta-analysis included 13 studies involving 1026 participants with SAP. In summary, acupuncture on DAM had certain differences from no acupuncture treatment, acupuncture on sham acupoints, and acupuncture on NAM.

For primary outcome, there was no evidence that acupuncture therapies on DAM was more effective than no acupuncture treatment, acupuncture on sham acupoints, and acupuncture on NAM. However, in subgroup analysis, acupoint application on DAM could effectively reduce frequency of angina attacks as adjunctive therapy. The quality of these outcomes was low and very low, thus, we could not come to a firm conclusion.

For secondary outcomes, acupuncture therapies on DAM was effective in attenuating severity of angina, anxiety, improving the results in ECG, 6-MWT, SAQ (physical limitation, angina stability, angina frequency, treatment satisfaction, disease perception), HRV, ET and CRP, reducing nitroglycerin intake. Subgroup analysis suggested that EA could be effective in improving severity of angina, the results in ECG, 6-MWT and SAQ (physical limitation, angina stability, angina frequency, treatment satisfaction, disease perception), reducing nitroglycerin intake; acupoint application could be effective in lessening severity of angina and reducing nitroglycerin intake. Compared to sham acupoints, acupuncture therapies on DAM could be more effective in alleviating severity of angina and improving the results in SAQ (angina stability, angina

frequency, treatment satisfaction, disease perception). Compared with NAM, acupuncture therapies on DAM could be more effective in improving the results in SAQ (angina stability, angina frequency, treatment satisfaction). Moreover, acupuncture therapies did not increase the risk of adverse effect.

In this study, 15 percent of selected studies did not report random sequence generation, 77 percent of selected studies did not describe the approach of allocation concealment, 54 percent of selected studies did not mention blinding of participants, 46 percent of selected studies did not mention blinding of outcome assessment, 15 percent of selected studies did not report completeness of outcome data, 62 percent of selected studies did not publish study protocols. In short, seven (54%) studies were rated as 'high risk of bias', five (38%) studies were judged as 'unclear risk of bias', and only one (8%) study was assessed as 'low risk of bias'. Because of quality of outcomes and small number of studies, the conclusions in our study was limited.

Acupuncture has physiologic analgesic effects[41], and our study indicated that acupuncture on DAM could effectively improve SAP. Nevertheless, the mechanisms have not yet comprehensively explained. SAP is relevant to the mismatch between demand and supply of myocardial oxygen[42], which is caused by stable coronary artery plaque when myocardial oxygen consumption increase[43]. Previous studies[44-47] stated that acupuncture on DAM can decrease oxygen demand, infarct size, ventricular arrhythmias, left ventricle dysfunction, and so on. Acupuncture on DAM also has the improvements of myocardial ischemia syndromes in regulating autophagy[48], the expression level of adenosine receptor[49], myocardial enzyme[48], myocardial remodeling[50], microvessel formation[51].

Although we searched international general healthcare databases, regional databases, subject-specific electronic bibliographic databases, citation index database, dissertations and theses database, clinical trials registry platforms, grey literature database without language restriction, we cannot rule out the possibility that there are unpublished studies or studies which are published in other databases. All selected studies were conducted in China. Thus, in consideration of singleness of setting, and difference of compliance in acupuncture therapies and acupuncturists' professional backgrounds, the applicability of acupuncture therapies in improving SAP was restricted.

This study has several limitations. First, the amount of included studies and sample size in most studies was small, and we cannot assess reporting bias by funnel plot. Secondly, high

heterogeneity in some meta-analysis lower the evidence grade. Third, the low quality of some outcomes limited our confidence in the effect of acupuncture on DAM in SAP. Forth, all studies from a single country limited the applicability of acupuncture in SAP.

Six previous studies assessed the effect of acupuncture in treating angina. Chen et al.[22] included participants with all types of angina, however, we both agreed that acupuncture combined with conventional drugs could improve ECG and angina symptoms. Yu et al.[24] also included participants with UAP, not only SAP. They categorized included studies into SAP, UAP, coronary heart disease angina pectoris in subgroup analysis. Their subgroup analysis indicated that acupuncture could effectively improve ECG and reduce the number of participants showing ineffectiveness of SAP relief. Zhang et al.[26] searched electronic database from January 2000 to July 2014 and included participants diagnosed with SAP. They discussed the effect of simple acupuncture therapies, and showed that acupuncture therapies increased clinical effects in angina symptoms and ECG, and we all agreed that acupuncture therapies could reduce nitroglycerin intake. Huang et al.[21] compared the difference between simple acupuncture combined with standard treatment and standard treatment in the outcome of effective rate. And they reached a conclusion that acupuncture therapy had increased markedly effective rate as adjunctive treatment. Although we did not assess the effective rate of acupuncture therapy in SAP, our results showed that acupuncture therapies on DAM could be effective in relieving SAP. Liu et al.[23] evaluated the effect of simple acupuncture and acupuncture combined with medicine and we both produced the results that acupuncture therapy could improve anginal symptoms, ECG results as adjunctive therapy. Their results also pointed out that acupuncture therapy reduced intake rate of nitroglycerin, and our results presented that acupuncture therapy at DAM could decrease consumption of nitroglycerin. Yang et al.[25] searched electronic databases from inception to August 2018, and we both came to same conclusions in the effect of acupuncture therapies in anxiety and depression level, safety compared to wait list group or sham acupuncture group. They included participants in intervention group treated by EA or MA in all acupoints, and we included participants in intervention group treated by various acupuncture therapies on DAM. Due to the differences in inclusion criteria and search time, there were disagreements about whether acupuncture could reduce angina attack frequency, nitroglycerin intake and intensity of angina. The six studies did not discuss the differences of curative effect caused by choice of acupoints.

Conclusions

Acupuncture therapy on DAM could be effective and safe in improving severity of angina, anxiety, ECG results, 6-MWT result, SAQ results, HRV, ET, CRP, and reducing nitroglycerin intake as adjunctive therapy, especially EA and acupoint application. No evidence verified that acupuncture therapy on DAM could reduce angina severity, however, in subgroup analysis, Acupoint application on DAM could reduce frequency of angina attacks. Additionally, acupuncture therapies on DAM had certain differences from acupuncture therapies on sham acupoints or NAM in the effect of improving angina severity and physical function. These results are limited by low quality of most of included studies, thus, strong supporting trials are further needed.

List of abbreviations

SAP: stable angina pectoris; IHD: ischemia heart disease; PCI: percutaneous coronary intervention; GABG: coronary artery bypass grafting; MA: manual acupuncture; EA: electroacupuncture; DAM: disease-affected meridian; NAM: nonaffected meridian; RCT: randomized controlled trial; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; AMED: Allied and Complementary Medicine Database; CNKI: China National Knowledge Infrastructure; CBM: China Biology Medicine; UAP: unstable angina pectoris; ECG: electrocardiogram; 6-MWT: 6-minute walk test; SAQ: Seattle Angina Questionnaire; HRV: heart rate variability; ET: endothelin; CRP: C-reactive protein; BNP: brain natriuretic peptide; GRADEpro: GRADEpro; RR: risk ratio; CI: confidence interval; SMD: standardized mean difference; MD: mean difference; VAS: visual analog scale; SAS: self-rating anxiety scale; SDS: self-rating depression scale.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZC and YW contributed equally to this study. ZC, YW, BX, CL, SL and YR participated in the design of study. ZC, YW and YR performed database searching and screening, data extraction, assessment of the risk of bias and evidence quality. ZC, YW, BX, CL and SL analyzed data. ZC and YW drafted this manuscript and YR revised the manuscript. All authors approved the final manuscript.

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Figure legends

Figure 1. Flow diagram for study selection.

Table 1. Characteristics of included trials

Study ID	Country	Study Type	Sample size	Diagnosis	Intervention: acupoints; duration; needle retention	Age (mean±SD or range)	Sex (n)	Duration of stable angina (mean±SD or range)	Previous antianginal medications	Main outcomes
Chen 2015	China	RCT	43	① ACC/AHA guidelines updated in 2007 ② Guideline for diagnosis and treatment of patients with chronic stable angina	G1 (n=11): electroacupuncture and basic therapy (antianginal medications and health education): acupoints on the DAM; 4 weeks (12 sessions); 30 minutes. G2 (n=11): electroacupuncture and basic therapy: acupoints on the NAM; 4 weeks (12 sessions); 30 minutes. G3 (n=11): sham acupuncture and basic therapy: sham acupoints; 4 weeks (12 sessions); 30 minutes. G4 (n=10): basic therapy: 4 weeks.	67.8±9.2 years 64.7±10.2 years 67.1±8.9 years 67.4±6.1 years	M: 6 F: 5 M: 4 F: 7 M: 4 F: 7 M: 2 F: 8	6.1±5.1 years 10.1±12.9 years 7.3±7.3 years 11.8±9.4 years	Not mentioned	Frequency of angina attacks; severity of angina; 6-MWT; intensity of anxiety; intensity of depression; SAQ.
Chen 2017	China	RCT	20	① ACC/AHA guidelines updated in 2007 ② Guideline for diagnosis and treatment of patients with chronic stable angina	G1 (n=9): electroacupuncture and basic therapy (antianginal medications and health education): acupoints on the DAM; 4 weeks (12 sessions); 30 minutes. G2 (n=11): sham acupuncture and basic therapy: sham acupoints; 4 weeks (12 sessions); 30 minutes.	68±8.5 years	M: 6 F: 14	6.52±6.38 years	Not mentioned	Frequency of angina attacks; severity of angina; 6-MWT; intensity of anxiety; intensity of depression; retention.
Huang et al. 2004	China	RCT	80	Nomenclature and criteria for diagnosis of ischemic heart disease	G1 (n=40): electroacupuncture and basic therapy (<i>Danshen</i> dripping pills): acupoints on the DAM; 4 weeks (24 sessions); 30 minutes. G2 (n=40): basic therapy: 4 weeks.	56±15 years 57±14 years	M: 22 F: 18 M: 21 F: 19	5.3±4.5 years 5.2±4.3 years	Not mentioned	Frequency of angina attacks; ECG; nitroglycerin intake; retention; adverse events.
Jing 2016	China	RCT	36	① ACC/AHA guidelines updated in 2007 ② Guideline for diagnosis and treatment of patients with chronic stable angina	G1 (n=18): manual acupuncture and basic therapy (antianginal medications and health education): acupoints on the DAM; 2 weeks (10 sessions); 30 minutes. G2 (n=18): manual acupuncture and basic therapy: acupoints on the NAM; 2 weeks (10 sessions); 30 minutes.	66.67±6.28 years 67.11±5.97 years	M: 8 F: 10 M: 7 F: 11	64.72±56.24 months 54.17±64.43 months	Not mentioned	Frequency of angina attacks; severity of angina; CRP; BNP; retention; adverse events.
Lan 2016	China	RCT	28	① ACC/AHA guidelines updated in 2007 ② Guideline for	G1 (n=14): manual acupuncture and basic therapy (antianginal medications and health education): acupoints on the DAM; 2 weeks (10 sessions); 30 minutes.	64.85±6.03 years	M: 5 F: 9	57.00±50.25 months	Antiplatelet agents, angiotensin-converting enzyme	Frequency of angina attacks; severity of angina; SAQ;

				diagnosis and treatment of patients with chronic stable angina	G2 (n=14): manual acupuncture and basic therapy: acupoints on the NAM; 2 weeks (10 sessions); 30 minutes.	65.78±7.74 years	M: 8 F: 6	55.36±49.77 months	inhibitors, angiotensin receptor blockers, β-blockers, statins, nitrates, calcium channel blockers	intensity of anxiety; intensity of depression; HRV; retention; adverse events.
Li et al. 2008	China	RCT	27	Nomenclature and criteria for diagnosis of ischemic heart disease	G1 (n=17): acupoint application and basic therapy (antianginal medications): acupoints on the DAM; 2 weeks (once in three days). G2 (n=10): basic therapy: 2 weeks.	60.82±5.39 years 60.2±5.63 years	M: 9 F: 8 M: 6 F: 4	Not mentioned	Not mentioned	Frequency of angina attacks; severity of angina; ECG; nitroglycerin intake; CRP; adverse events.
Wang et al. 2015	China	RCT	30	ACC/AHA guidelines updated in 2007	G1 (n=15): electroacupuncture and basic therapy (antianginal medications and health education): acupoints on the DAM; 4 weeks (12 sessions); 30 minutes. G2 (n=15): basic therapy: 4 weeks.	55-66 years 53-68 years	M: 7 F: 8 M: 6 F: 9	More than 6 months More than 6 months	Not mentioned	Frequency of angina attacks; severity of angina; 6-MWT; nitroglycerin intake; intensity of anxiety; intensity of depression; retention.
Xie 2014	China	RCT	40	① Nomenclature and criteria for diagnosis of ischemic heart disease; ② Practice of Internal Medicine	G1 (n=17): electroacupuncture and basic therapy (<i>Danshen</i> dripping pills): acupoints on the DAM; 4 weeks (24 sessions); 30 minutes. G2 (n=16): basic therapy: 4 weeks.	60.55±7.81 years 59.30±6.82 years	M: 7 F: 13 M: 7 F: 13	Not mentioned	Not mentioned	ECG; retention.
Yang et al. 2019	China	RCT	120	① ACC/AHA guidelines updated in 2007 ② Guideline for diagnosis and treatment of patients with chronic stable angina	G1 (n=30): electroacupuncture and basic therapy (antianginal medications): acupoints on the DAM; 4 weeks (12 sessions); 30 minutes. G2 (n=30): electroacupuncture and basic therapy: acupoints on the NAM; 4 weeks (12 sessions); 30 minutes. G3 (n=30): sham acupuncture and basic therapy: sham acupoints; 4 weeks (12 sessions); 30 minutes. G4 (n=30): basic therapy: 4 weeks.	68.12±7.45 years	M: 73 F: 47	36.85±18.75 months	Not mentioned	SAQ; retention.
Yin 2018	China	RCT	26	① ACC/AHA guidelines updated in 2007 ② Guideline for	G1 (n=15): manual acupuncture and basic therapy (antianginal medications): acupoints on the DAM; 2 weeks (10 sessions); 30 minutes.	65.27±5.97 years	M: 6 F: 9	62.33±52.65 months	Nitroglycerin; antiplatelet agents; statins; angiotensin	Frequency of angina attacks; severity of angina; SAQ;

				diagnosis and treatment of patients with chronic stable angina	G2 (n=11): manual acupuncture and basic therapy: sham acupoints; 2 weeks (10 sessions); 30 minutes.	62.73±6.79 years	M: 4 F: 7	43.00±34.54 months	receptor blocker; β-blockers; calcium channel blockers; angiotensin-converting enzyme inhibitors; Chinese patent medicine; others.	intensity of anxiety; intensity of depression; retention.
Zhang 2018	China	RCT	138	Evaluation criteria for effect of coronary heart disease angina and electrocardiogram	G1 (n=69): electroacupuncture and basic therapy (<i>Danshen</i> dripping pills): acupoints on the DAM; 4 weeks (24 sessions); 30 minutes. G2 (n=69): basic therapy: 4 weeks.	40-78 years	NA	2-10 years	Not mentioned	ECG; HRV; ET; retention; adverse events.
Zhang and Sun 2015	China	RCT	40	① ACC/AHA guidelines updated in 2007 ② Guideline for diagnosis and treatment of patients with chronic stable angina	G1 (n=10): electroacupuncture and basic therapy (antianginal medications and health education): acupoints on the DAM; 4 weeks (12 sessions); 30 minutes. G2 (n=10): electroacupuncture and basic therapy: acupoints on the NAM; 4 weeks (12 sessions); 30 minutes. G3 (n=10): sham acupuncture and basic therapy: sham acupoints; 4 weeks (12 sessions); 30 minutes. G4 (n=10): basic therapy: 4 weeks.	64.50±6.67 years 66.60±8.29 years 64.70±7.33 years 68.50±7.38 years	M: 2 F: 8 M:5 F: 5 M:1 F: 9 M:5 F: 5	32.10±19.73 months 32.60±14.79 months 36.10±17.32 months 38.20±21.08 months	Not mentioned	Frequency of angina attacks; severity of angina; 6-MWT; nitroglycerin intake; SAQ; ET; retention.
Zhao et al. 2019	China	RCT	398	ACC/AHA guidelines updated in 2007	G1 (n=99): electroacupuncture and basic therapy (individualized antianginal medications): acupoints on the DAM; 4 weeks (12 sessions); 30 minutes. G2 (n=99): electroacupuncture and basic therapy: acupoints on the NAM; 4 weeks (12 sessions); 30 minutes. G3 (n=101): sham acupuncture and basic therapy: sham acupoints; 4 weeks (12 sessions); 30 minutes. G4 (n=99): basic therapy: 4 weeks.	62.5±9.9 years 61.8±9.8 years 62.4±8.9 years 63.4±10.3 years	M: 35 F: 64 M: 32 F: 67 M: 39 F: 62 M: 39 F: 60	46.2±47.9 months 59.9±84.3 months 51.3±51.1 months 61.5±69.3 months	β-blockers, aspirin, clopidogrel, statins, angiotensin-converting enzyme inhibitors, calcium channel blockers, long-lasting nitrates	Frequency of angina attacks; severity of angina; 6-MWT; SAQ; intensity of anxiety; intensity of depression; HRV; retention; adverse events.

Table 3. Quality of evidence for outcomes.

Outcomes	Group	Number of participants (studies)	Relative effect (95% CI)	Quality of evidence (GRADE)*
Frequency of angina attacks	DAM group versus wait list group	376 (6 studies)	MD -2.21 (-5.74 to 1.32)	⊕⊕⊕⊕
	DAM group versus sham acupuncture group	288 (5 studies)	MD -0.82 (-4.90 to 3.26)	⊕⊕⊕⊕
	DAM group versus NAM group	304 (5 studies)	MD -0.01 (-2.22 to 2.19)	⊕⊕⊕⊕
	DAM group versus wait list group	296 (5 studies)	SMD -0.49 (-0.73 to -0.26)	⊕⊕⊕⊕
	DAM group versus sham acupuncture group	288 (5 studies)	SMD -0.25; (-0.48 to -0.01)	⊕⊕⊕⊕
Severity of angina	DAM group versus wait list group	304 (5 studies)	MD 0.13 (-0.40 to 0.66)	⊕⊕⊕⊕
	DAM group versus wait list group	278 (4 studies)	RR 1.27 (1.09 to 1.49)	⊕⊕⊕⊕
	DAM group versus wait list group	269 (4 studies)	MD 19.84 (3.84 to 35.83)	⊕⊕⊕⊕
	DAM group versus sham acupuncture group	262 (4 studies)	MD 26.08; (10.19 to 41.96)	⊕⊕⊕⊕
	DAM group versus NAM group	240 (3 studies)	MD -10.11 (-26.85 to 6.63)	⊕⊕⊕⊕
Number of participants with changes in ECG	DAM group versus wait list group	157 (4 studies)	SMD -0.63 (-0.95 to -0.30)	⊕⊕⊕⊕
	DAM group versus wait list group	20 (1 study)	MD -2.40 (-5.15 to 0.35)	⊕⊕⊕⊕
	DAM group versus wait list group	269 (4 studies)	MD 19.84 (3.84 to 35.83)	⊕⊕⊕⊕
	DAM group versus wait list group	262 (4 studies)	MD 26.08; (10.19 to 41.96)	⊕⊕⊕⊕
	DAM group versus wait list group	240 (3 studies)	MD -10.11 (-26.85 to 6.63)	⊕⊕⊕⊕
6-MWT	DAM group versus wait list group	157 (4 studies)	SMD -0.63 (-0.95 to -0.30)	⊕⊕⊕⊕
	DAM group versus wait list group	20 (1 study)	MD -2.40 (-5.15 to 0.35)	⊕⊕⊕⊕
	DAM group versus wait list group	269 (4 studies)	MD 19.84 (3.84 to 35.83)	⊕⊕⊕⊕
	DAM group versus wait list group	262 (4 studies)	MD 26.08; (10.19 to 41.96)	⊕⊕⊕⊕
	DAM group versus wait list group	240 (3 studies)	MD -10.11 (-26.85 to 6.63)	⊕⊕⊕⊕
Nitroglycerin intake	DAM group versus wait list group	157 (4 studies)	SMD -0.63 (-0.95 to -0.30)	⊕⊕⊕⊕
	DAM group versus wait list group	20 (1 study)	MD -2.40 (-5.15 to 0.35)	⊕⊕⊕⊕
	DAM group versus wait list group	269 (4 studies)	MD 19.84 (3.84 to 35.83)	⊕⊕⊕⊕
	DAM group versus wait list group	262 (4 studies)	MD 26.08; (10.19 to 41.96)	⊕⊕⊕⊕
	DAM group versus wait list group	240 (3 studies)	MD -10.11 (-26.85 to 6.63)	⊕⊕⊕⊕

	DAM group versus	20	MD -1.00 (-2.57 to	⊕⊕⊕⊕
	NAM group	(1 study)	0.57)	very low
SAQ: physical limitation score	DAM group versus wait	299	MD 2.63 (1.19 to	⊕⊕⊕⊕
	list group	(4 studies)	4.07)	low
	DAM group versus sham	328	MD 0.82 (-0.88 to	⊕⊕⊕⊕
	acupuncture group	(5 studies)	2.52)	moderate
	DAM group versus	328	MD -0.93 (-2.79 to	⊕⊕⊕⊕
	NAM group	(5 studies)	0.93)	moderate
SAQ: angina stability score	DAM group versus wait	299	MD 40.15 (27.46	⊕⊕⊕⊕
	list group	(4 studies)	to 52.83)	very low
	DAM group versus sham	328	MD 16.63 (8.15 to	⊕⊕⊕⊕
	acupuncture group	(5 studies)	25.10)	moderate
	DAM group versus	328	MD 11.05 (7.06 to	⊕⊕⊕⊕
	NAM group	(5 studies)	15.04)	moderate
SAQ: angina frequency score	DAM group versus wait	299	MD 8.02 (5.69 to	⊕⊕⊕⊕
	list group	(4 studies)	10.35)	low
	DAM group versus sham	328	MD 5.90 (3.73 to	⊕⊕⊕⊕
	acupuncture group	(5 studies)	8.08)	moderate
	DAM group versus	328	MD 3.96 (1.94 to	⊕⊕⊕⊕
	NAM group	(5 studies)	5.99)	moderate
SAQ: treatment satisfaction score	DAM group versus wait	299	MD 17.10 (10.51	⊕⊕⊕⊕
	list group	(4 studies)	to 23.68)	low
	DAM group versus sham	328	MD 8.11 (3.45 to	⊕⊕⊕⊕
	acupuncture group	(5 studies)	12.77)	moderate
	DAM group versus	328	MD 3.91 (1.25 to	⊕⊕⊕⊕
	NAM group	(5 studies)	6.56)	moderate
SAQ: disease perception score	DAM group versus wait	299	MD 4.82 (2.23 to	⊕⊕⊕⊕
	list group	(4 studies)	7.42)	low
	DAM group versus sham	328	MD 4.13 (1.76 to	⊕⊕⊕⊕

	acupuncture group	(5 studies)	6.51)	moderate
	DAM group versus	328	MD -0.48 (-3.39 to	⊕⊕⊕⊖
	NAM group	(5 studies)	2.42)	moderate
Intensity of anxiety	DAM group versus wait	249	MD -2.25 (-4.12 to	⊕⊕⊕⊖
	list group	(3 studies)	-0.39)	moderate
	DAM group versus sham	268	MD -1.23 (-2.95 to	⊕⊕⊕⊖
	acupuncture group	(4 studies)	0.49)	moderate
	DAM group versus	248	MD -1.07 (-2.80 to	⊕⊕⊕⊖
	NAM group	(3 studies)	0.65)	moderate
Intensity of	DAM group versus wait	245	MD -2.82 (-6.18 to	⊕⊕⊕⊖
depression	list group	(3 studies)	0.54)	moderate
	DAM group versus sham	268	MD -1.81 (-3.71 to	⊕⊕⊕⊖
	acupuncture group	(4 studies)	0.09)	moderate
	DAM group versus	248	MD -1.14 (-3.18 to	⊕⊕⊕⊖
	NAM group	(3 studies)	0.90)	moderate
HRV: LF	DAM group versus wait	126	MD -48.97 (-88.90	⊕⊕⊖⊖
	list group	(1 study)	to -9.04)	low
	DAM group versus sham	133	MD -27.30 (-63.94	⊕⊕⊖⊖
	acupuncture group	(1 study)	to 9.34)	low
	DAM group versus	133	MD -20.24 (-52.32	⊕⊕⊖⊖
	NAM group	(1 study)	to 11.84)	low
HRV: HF	DAM group versus wait	264	MD 67.17 (-53.02	⊕⊖⊖⊖
	list group	(2 studies)	to 187.37)	very low
	DAM group versus sham	133	MD 13.10 (-0.55 to	⊕⊕⊖⊖
	acupuncture group	(1 study)	26.75)	low
	DAM group versus	133	MD 10.93 (-2.47 to	⊕⊕⊖⊖
	NAM group	(1 study)	24.33)	low
HRV: LF/HF	DAM group versus wait	264	MD -0.59 (-0.85 to	⊕⊕⊖⊖
	list group	(2 studies)	-0.34)	low

HRV: SDNN	DAM group versus sham	133	MD -0.50 (-1.04 to	⊕⊕⊕⊖
	acupuncture group	(1 study)	0.04)	moderate
	DAM group versus	133	MD -1.93 (-5.30 to	⊕⊕⊕⊖
	NAM group	(1 study)	1.44)	moderate
	DAM group versus wait	126	MD 3.40 (-11.22 to	⊕⊕⊕⊖
	list group	(1 study)	18.02)	low
	DAM group versus sham	133	MD -11.11 (-39.71	⊕⊕⊕⊖
	acupuncture group	(1 study)	to 17.49)	low
	DAM group versus	161	MD -9.47 (-22.27	⊕⊕⊕⊖
	NAM group	(2 studies)	to 3.33)	low
ET	DAM group versus wait	158	MD -0.67 (-1.00 to	⊕⊕⊕⊖
	list group	(2 studies)	-0.35)	low
	DAM group versus sham	20	MD -0.32 (-2.11 to	⊕⊕⊕⊖
	acupuncture group	(1 study)	1.47)	very low
	DAM group versus	20	MD -1.11 (-2.97 to	⊕⊕⊕⊖
	NAM group	(1 study)	0.75)	very low
CRP	DAM group versus wait	27	MD -0.99 (-1.22 to	⊕⊕⊕⊖
	list group	(1 study)	-0.76)	very low
	DAM group versus	36	MD -3.50 (-11.25	⊕⊕⊕⊖
	NAM group	(1 study)	to 4.25)	low
BNP	DAM group versus	36	MD -6.25 (-47.03	⊕⊕⊕⊖
	NAM group	(1 study)	to 34.53)	low
Retention	DAM group versus wait	566	RR 0.99 (0.96 to	⊕⊕⊕⊖
	list group	(7 studies)	1.03)	low
	DAM group versus sham	334	RR 0.97 (0.92 to	⊕⊕⊕⊖
	acupuncture group	(5 studies)	1.02)	low
	DAM group versus	378	RR 0.99 (0.95 to	⊕⊕⊕⊖
	NAM group	(5 studies)	1.03)	low
Adverse effect	DAM group versus wait	218	RR 0.54 (0.05 to	⊕⊕⊕⊖

list group	(2 studies)	5.51)	very low
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* GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Figures

Figure 1

Flow diagram for study selection.

Supplementary Files

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