Efficacy of Acupuncture as Complementary Therapy for Refractory Angina Pectoris: A Systematic Review

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Abstract

Background: Refractory angina pectoris poses a significant public health challenge due to its effects on patients' quality of life, the significant healthcare costs involved, and its increasing prevalence among the aging population. This systematic review aims to offer new insights into understanding the efficacy of acupuncture as an adjunct therapy for this condition.
Methods: This systematic review included randomized controlled trials comparing any modality of acupuncture combined with standard therapy versus standard therapy alone, sham acupuncture, or non-meridian acupuncture without language or time restrictions. We searched in PubMed, CENTRAL, LILACS, and Embase databases. The final search was performed on July 13, 2024. The inclusion criteria comprised adults diagnosed with stable angina pectoris for at least three months, experiencing angina more than once a week, and undergoing treatment for at least four weeks. Patients with severe cardiovascular or systemic conditions and studies with incomplete data were excluded. Risk of bias was assessed via the ROB2 tool.
Results: Five RCTs involving Chinese participants were analyzed, finding that acupuncture significantly reduced the frequency of angina attacks and improved quality of life on the SAQ scale. The dosage of rescue medication was not found to decrease, and further trials are needed to evaluate the effect on pain intensity.
Conclusion: Acupuncture could be an effective complementary treatment for refractory angina pectoris. Limitations of reviewed literature include difficulty in accessing manuscripts and varying quality of trials. Further high-quality trials are needed to corroborate these findings and assess long-term effectiveness.

Introduction

Angina pectoris (AP) is a common manifestation of coronary artery disease (CAD). The ClARIFY study reports that a quarter of CAD patients develop AP that, in most cases, resolve within a year with treatment. In 2019, the European Society of Cardiology (ESC) defined refractory angina pectoris (RAP) as chronic angina persisting for more than three months

despite escalating medical therapy to second and third-line treatments (Davies et al., 2021). Presenting in 5–15% with AP and portends higher cardiovascular risk for patients (Chen et al., 2023; Mesnier et al., 2021). With an aging population, the epidemiological characteristics may be evolving, posing a significant public health challenge due to its effects on loss of quality-adjusted life years (QALYs), diminished life expectancy, and the significant healthcare costs involved (Gallone et al., 2019; Knuuti et al., 2020). Associated with substantial morbidity, frequent hospitalizations, treatment adjustments, and diagnostic procedures, which escalate healthcare resource utilization and contribute to elevated levels of depression and anxiety (Fortunato et al., 2024; Gallone et al., 2019). The current treatment for RAP primarily involves standard pharmacological therapy, and alternative therapies are emerging (Knuuti et al., 2020).

Acupuncture has become integral to pain management due to its convenience and safety compared to conventional allopathic treatments (Wang et al., 2020). Research indicates acupuncture's effectiveness may be attributed to its regulation of proteases, vasoactive substances, and inflammatory mediators, which can promote cardiac function regulation and improve autonomic nervous system function. In chronic stable angina, acupuncture is associated with modulating endothelial function and inflammatory responses involving Tumor necrosis factor-alpha and C-reactive protein, which are linked to left ventricular diastolic dysfunction and angina recurrence (Yu et al., 2020). Acupuncture may enhance nitric oxide production, improve blood perfusion, reduce endothelin levels, and stabilize atherosclerotic plaque by lowering serum matrix metalloproteinase-9 content, potentially preventing coronary adverse events. Acupuncture has also been investigated for its potential to regulate heart rate and treat various cardiovascular conditions, including hypertension, cardiac arrhythmias, and heart failure (Yang et al., 2015; Yang et al., 2021).

Research on acupuncture has predominantly focused on stable angina without distinguishing between its subtypes. Moreover, there is a lack of comparative studies evaluating different acupuncture modalities. However, evidence suggests that acupuncture can effectively serve as an adjunctive therapy alongside medications, lifestyle adjustments, and interventional treatments for managing chronic stable angina when conventional approaches are inadequate. Studies indicate that both traditional acupuncture and electroacupuncture can provide significant symptomatic relief. While acupuncture has shown effectiveness in alleviating symptoms, its im-

pact on reducing medication doses still needs to be more conclusive in current research (Pang et al., 2023; Yang et al., 2021). Finding high-quality evidence in randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses is challenging due to weaknesses in study design, methodology, and small sample sizes (Qi et al., 2022). This review aims to contribute to understanding the effectiveness of acupuncture as a complementary therapy to standard medication for the specific context of RAP as defined by the 2019 ESC Angina Guidelines, which prior reviews have not done.

Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2020 guidelines. The study procedure has been meticulously documented in the OSF Widespread Systematic Review Registration (osf-euygs-v1-records), ensuring the transparency and integrity of the protocol. The protocol can be found in the following link: https://doi.org/10.17605/OSF.IO/EUYGS.

The study design was based on the PICOTT framework: (P) Adults with RAP; (I) Acupuncture plus standard therapy; (C) Standard therapy alone; (O) primary outcome: frequency of angina attacks, secondary outcomes: use of nitroglycerin, pain reduction, and quality of life; (T) No time restrictions; (T) Randomized controlled trials.

Our rationale for selecting the frequency of angina attacks as the primary outcome is its known association with future hospitalization, revascularization, and death, independently of other clinical risk factors (Beatty et al., 2014).

Inclusion and Exclusion Criteria

This review included randomized controlled trials published in peer-reviewed journals, gray literature, or non-free journals, with no language restrictions, and registered in trial databases aligned with the International Clinical Trials Registry Platform (ICTRP). Eligible participants were adults over 18 years old diagnosed with stable angina pectoris for at least three months as per ACC/AHA or CCS definitions, experiencing angina more than once a week, of any ethnicity or gender. Interventions included any acupuncture modality, used alone or with conventional treatment (nitrates, beta-blockers, or calcium antagonists) for a minimum of four weeks. Studies had to report at least one outcome: frequency of angina attacks, nitroglycerin use, angina pain intensity, or quality of life measured by the Seattle Angina Questionnaire. Studies were excluded if

participants had acute coronary syndrome, valvular heart disease, severe arrhythmia, or organ failure, or if the study design included incomplete RCT data, systematic reviews, meta-analyses, or observational studies.

Information Sources and Search Strategy

A systematic search for completed and published RCTs was conducted across PubMed, CENTRAL, LILACS, and Embase databases without language or time restrictions. The preliminary search was performed on May 8, 2024. The primary search concepts in PubMed were Acupuncture [MeSH], Angina pectoris [MeSH], and Randomized Controlled Trials as a topic [MeSH]. These concepts were subsequently adapted for the different databases as detailed in the Supplementary Methods (Search Strategy). ClinicalTrials.gov was also consulted for relevant clinical trials, and Google Scholar was used to identify unpublished literature.

Additionally, a manual search was performed in the reference lists of the selected clinical trials and in systematic reviews related to our PICOT question. Some articles were found by external collaborators who have access to Chinese databases. The final search was performed on July 13, 2024, and papers published up to this date were included (Table 2).

Selection of Studies and Data Extraction

We used the web platform Covidence to manage the systematic review process. Eligibility was determined using predefined inclusion and exclusion criteria. Articles were screened first by title and then by abstract. Studies that met these criteria underwent a full-text review to confirm eligibility. Detailed data extraction was then conducted using a predefined form. Two independent reviewers reviewed each article. A third reviewer resolved any discrepancies or uncertainties regarding study eligibility.

Data Synthesis

Covidence was used to facilitate the data extraction and synthesis process. Consensus was reached with the input of all group members, and the descriptive statistics were summarized using Excel in two tables (Table 1 and Table 3). The information included study methods, characteristics of the reference population, intervention, and results. A large amount of heterogeneity was expected due to different acupuncture modalities and acupoints used and differing follow-up periods, due to which a meta-analysis was unsuitable and, therefore, not

planned.

Risk of Bias Assessment

The ROB-2 tool was used to assess the risk of bias (Figure 2). Two independent reviewers assessed bias, and a third reviewer resolved disagreements.

Results

Description of the Results

In May 2024, a comprehensive literature search was conducted, yielding 489 records: 83 from PubMed, 71 from CENTRAL, 91 from Embase, 201 from Google Scholar, 34 from Lilacs, and nine from citation searching. Among these, 151 duplicates were identified, with three detected manually and 148 using the Covidence platform. Two independent reviewers screened titles and abstracts according to predefined inclusion and exclusion criteria, resulting in the exclusion of 305 studies. Four studies could not be retrieved, leaving 29 articles for full-text evaluation. Two independent reviewers assessed the eligibility of the 29 full-text papers. Further assessment led to the exclusion of 24 articles for the reasons presented in Figure 1. Ultimately, five randomized controlled trials conducted in China were included in the final review. Of these, two articles were originally written in Chinese and translated using AI technologies (DeepL) and Google Translate. These were found in Chinese-language peer-reviewed journals and were publicly registered (Deng et al., 2018; Huang et al., 2021; Wang et al., 2015; Zhang et al., 2019; Zhao et al., 2019).

Population

The included studies featured sample sizes ranging from 45 to 398 participants, with a total of 841 individuals, of whom 55.29% were females. Most participants were middle-aged or elderly, with reported ages ranging from 50 to 79 years. All participants were of Chinese ethnicity.

Two studies reported dropouts regarding participant retention: Huang et al. (2021) reported 12 dropouts, and Zhao et al. (2019) had five. Reported reasons for dropout included dissatisfaction, lack of compliance, unwillingness to record angina diaries, and changes in contact information.

The frequency of angina at baseline varied, with a minimum average of 5.52 ± 4.48 episodes within four weeks reported by Huang et al. (2021) and a maximum average of 17.9 ± 4.5 episodes over 30 days reported by Wang et al.(2015). All studies provided standard care across both intervention and
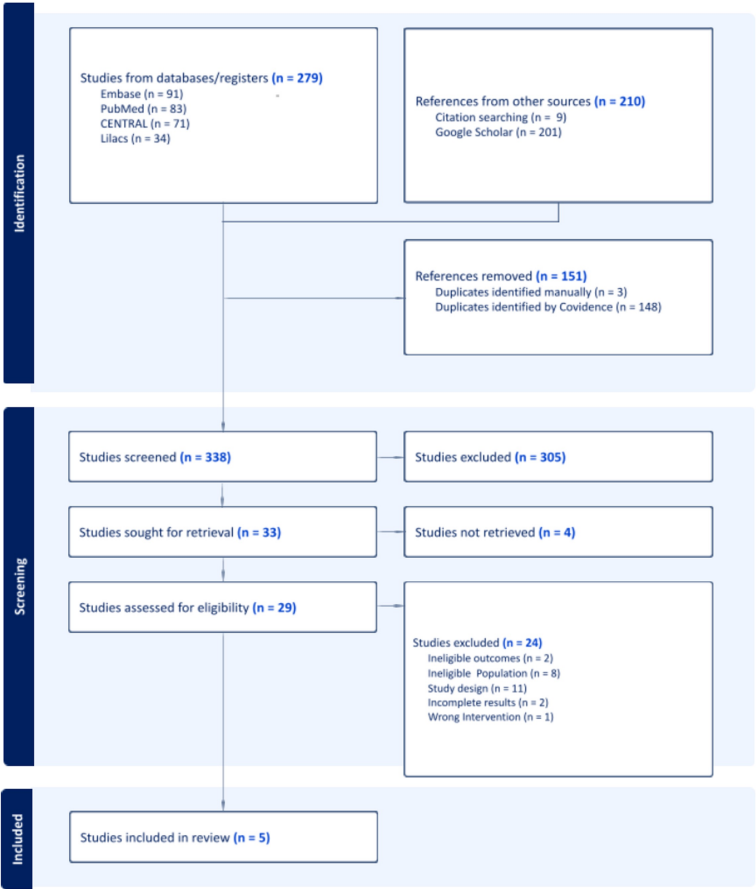
Figure 1: *Flow diagram for the systematic review.*

Figure 2: *Risk of Bias Assesment using ROB-2.*

control arms according to the (Chinese guidelines for the management of patients with Chronic Stable Angina (Chinese Society of Cardiology, 2007). The standard treatment was individualized in all groups.

Intervention Characteristics

Wang et al. (2015) conducted a study with three groups: an intervention group that received both acupuncture and standard medication, a medication-only control group, and a healthy control group without angina. In the intervention group, electroacupuncture was administered at Neiguan acupoints along the pericardium meridian three times a week over a total period of four weeks.

Zhao et al. (2019) conducted a study comparing four groups: Disease-Affected Meridian (DAM), Non-Affected Meridian (NAM), Sham Acupuncture (SA), and a Wait List control group (WL). Each group was followed for 16 weeks. The first three groups received a total of 12 acupuncture sessions lasting 30 minutes each. The DAM group received acupuncture on bilateral acupoints PC6 and HT5. The NAM group received acupuncture on bilateral acupoints LU9 and LU6. The SA group received sham acupuncture only, and the WL group did not receive any acupuncture intervention.

Huang et al. (2021) compared high-sensitivity acupoints to low-sensitivity acupoints. All patients took an acupoint sensitization detection test, based on which the acupuncturist selected the five acupoints with the highest or lowest thresholds. Treatment was administered for four weeks, for a total of 12 sessions. (Deng et al., 2018) compared needle embedding therapy with a control group. In the intervention group, the acupoints stimulated were PC6 (Neiguan), ST36 (Zusanli), and CV4 (Guanyuan). Acupuncture was performed on alternate days, three days a week, with needles remaining embedded for 24 hours. The control group received no acupuncture treatment.

Zhang et al. (2019) compared four groups: meridian-specific acupuncture as an intervention, other meridian acupuncture, non-meridian non-acupuncture, and medication-only as a control. The intervention group received electroacupuncture at specified points and was given 30-minute sessions every other day, three days a week, for four weeks.

Primary Outcome: Angina Attack Frequency

All studies, except one (Zhang et al., 2019), reported the outcome of angina attack frequency. Among those that did, three studies (Deng et al., 2018; Wang et al., 2015; Zhao et al., 2019) measured

the monthly number of attacks from baseline to either four or 16 weeks and presented their data as means and standard deviations. Another study (Huang et al., 2021) measured this outcome at 4 and 8 weeks and presented their data as means and incidence ratios.

Secondary Outcomes

Nitroglycerin Consumption: Three studies (Huang et al., 2021; Wang et al., 2015; Zhang et al., 2019) assessed nitroglycerin consumption by quantifying the amount used from baseline up to a maximum of 8 weeks. Two of these studies evaluated this outcome at one month and presented their data as means and standard deviations. One study (Huang et al., 2021) assessed it at 4 and 8 weeks post-intervention and presented their data as odds ratios.

Seattle Angina Questionnaire (SAQ) scores: All studies, except for Huang et al. (2021), assessed the limitation of physical activity, angina stability, angina frequency, satisfaction with treatment, and perception of illness using the SAQ scale from baseline to a maximum of 16 weeks. Three of the studies measured outcomes at four weeks, one at 30 days post-intervention, and one at eight weeks. All the studies presented their data as means and standard deviations.

Pain Severity: Three studies (Wang et al., 2015; Zhang et al., 2019; Zhao et al., 2019) assessed pain intensity using the visual analog pain scale (VAS) ranging from 0 to 10, from a pre-intervention baseline assessment up to 16 weeks (Zhao et al., 2019) and one month (Wang et al., 2015; Zhang et al., 2019), all studies presented their results as means and standard deviations.

The details of the results for each respective study are in Table 3.

Main Results and Heterogeneity

Of the five studies included in this review, three (Huang et al., 2021; Wang et al., 2015; Zhao et al., 2019) reported statistically significant decreases in the frequency of angina attacks at 4 weeks in the acupuncture intervention groups. For Deng et al. (2018), angina attack rates had to be extrapolated from the angina frequency component of the Seattle Angina Score, and no statistically significant difference was found. The studies that showed positive outcomes had significantly higher baseline rates of angina attacks compared to the extrapolated values in the study by Deng et al. (2018) (Table 3). The study by Zhang et al. (2019) did not measure a change in angina attack frequency as an outcome.

Four studies measured the use of nitroglycerin as

Author	Intervention/Control / Total	Number of Participants	Participants age (years)	Participants sex (female/male)	Participants ethnicity	Withdrawals	Duration of Angina (months)	Previous standard medication (Yes/No)	Frequency of Angina attacks (Mean ±SD)
	Healthy	15	56 (52-62)	10-May	Chinese	0	≥3	Yes	0
Wang et al. 2015	Acupuncture	15	59 (55-66)	8-Jul	Chinese	0	≥3	Yes	17.9 ± 4.5
	Comparison	15	57 (53-68)	9-Jun	Chinese	0	≥3	Yes	17.5 ± 5.1
	Total	**45**		**27/18**	**Chinese**			**Yes**	
Deng et al. 2018	Needle-embedding	38	57.12 ± 9.78	Nov-27	Chinese	0	21.38 ± 4.74	Yes	
	Standard treatment	38	56.49 ± 11.36	16/22	Chinese	0	20.29 ± 5.65	Yes	
	Total	**76**		**27/49**	**Chinese**			**Yes**	
Zhao et al. 2019	DAM	99	62.5 (9.9)	64/35	Chinese	1 (change telephone number)	46.2 (47.9) *	Yes	13.52 (5.93)
	NAM	99	61.8 (9.8)	67/32	Chinese	1 (unwilling to follow up)	59.9 (84.3) *	Yes	12.94 (7.28)
	SA	101	62.4 (8.9)	62/39	Chinese	2 (personal reasons)	51.3 (51.1) *	Yes	12.62 (5.64)
	WL	99	63.4 (10.3)	60/39	Chinese	1 (Owing to SAE)	61.5 (69.3) *	Yes	14.14 (10.39)
	Total	**398**		**253/145**	**Chinese**	**5**		**Yes**	
Huang et al. 2021	LSG	93	66.22 ± 10.02	48/45	Chinese	6 (personal reasons)	≥3	Yes	5.52 ±4.48
	HSG	109	66.06 ± 9.11	63/ 46	Chinese	6 (personal reasons)	≥3	Yes	6.34 ±5.81
	Total	**202**		**111/91**	**Chinese**	**12**		**Yes**	
Zhang et al. 2019**	TAAC	30			Chinese	0		Yes	
	TAAOC	30			Chinese	0		Yes	
	NANC	30			Chinese	0		Yes	
	NP	30			Chinese	0		Yes	
	Total	**120**	50 – 79 (68.12±7.45)	47/73			34.75±17.85	**Yes**	

Table 1. DAM= acupoints on the disease-affected meridian; NAM= acupoints on the nonaffected meridian; SA= sham acupuncture; WL= no acupuncture (wait list [WL] group); SAE= serious adverse effect; LSG= low-sensitivity group; HSG= high-sensitivity group; TAAC= taking acupoints along channel; TAAOC= taking acupoints along other channel; NANC= non-acupoints in non-channel; NP= no puncturing.

* In Zhao at the duration of angina: check typing error Mean and SD. The data is the same as the original article but probably has a typo.

** In Zhang they do not describe the age and gender of the participants from each group. This article did not use Frequency of Angina Attacks as an outcome.

Table 1: *Baseline population characteristics.*

rescue medication. Of these, a statistically significant decrease in the frequency of nitroglycerin usage for the intervention group was found in two studies (Wang et al., 2015; Zhang et al., 2019). Two other studies (Huang et al., 2021; Zhao et al., 2019) found no differences in the dosage of nitroglycerine used as rescue medication between control and intervention groups. Three studies measured pain intensity as an outcome. Of these, two (Wang et al., 2015; Zhao et al., 2019) found a significant reduction in pain intensity, as measured by the Visual Analog Scale, for the intervention groups. One study (Zhang et al., 2019) found a decrease in pain intensity for all groups, and the difference between the intervention and control groups was not statistically significant. Considering the limitations of the included research literature, it is still necessary to conduct further high-quality RCTs to assess the effect of acupuncture on pain severity and rescue medication usage for those with refractory angina pectoris.

Three studies found a statistically significant improvement in quality of life as measured by the Seattle Angina Questionnaire (SAQ) for the intervention groups (Huang et al., 2021; Wang et al., 2015; Zhao et al., 2019). Two of these studies showed a statistically significant improvement in the angina frequency scores for the intervention group but differed on the other components (Huang et al., 2021; Zhao et al., 2019). Details for the subsets of the SAQ were not reported in the study by (Wang et al., 2015).

For safety outcomes, Huang et al. (2021) reported one case of bruising at the acupuncture site, leading the patient to withdraw, with no other safety issues. Zhao et al. (2019) recorded 16 mild to moderate acupuncture-related adverse events, including subcu-

taneous hemorrhage, tingling, and sleeplessness, all of which resolved without medical intervention. One serious adverse event occurred in the waitlist group, where a patient died from a myocardial infarction before any acupuncture treatment. Wang et al. (2015) and Zhang et al. (2019) did not report any side effects. Overall, acupuncture-related adverse events were mild, with no unexpected safety issues across studies.

Risk of Bias Assessment

The overall risk of bias in the articles is illustrated in Figure 2. Only two of the five studies (Huang et al., 2021; Zhao et al., 2019) reported a sample size calculation. All studies described their randomization process using either a random number table or a computerized system. Blinding varied between studies; only two studies (Huang et al., 2021; Zhao et al., 2019) clearly described the blinding of both patients and outcome assessors. Two studies had unclear blinding for participants but blinded evaluators and statisticians (Wang et al., 2015; Zhang et al., 2019). One study (Deng et al., 2018) did not mention a blinding procedure. However, the interventionists administering the acupuncture cannot be blinded in any acupuncture study, introducing a potential bias when comparing intervention groups to the medicine-only groups.

A high risk of bias was identified in one study (Deng et al., 2018) due to potential selective reporting of results (McGuinness & Higgins, 2021). This study did not report a complete score for the Seattle Angina Questionnaire and provided an unclear explanation for this omission. This was a secondary outcome for our review, allowing this study to be included.

Database	Number	Concept	Search Strategy	Citations
PubMed	# 1	Acupuncture	"acupunctural" [All Fields] OR "acupuncture" [MeSH Terms] OR "acupuncture" [All Fields] OR "acupuncture therapy" [MeSH Terms] OR ("acupuncture" [All Fields] AND "therapy" [All Fields]) OR "acupuncture therapy" [All Fields] OR "acupunctures"[All Fields] OR "acupunctured" [All Fields] OR "acupunctures" [All Fields] OR "acupuncturing" [All Fields]	44,652
	# 2	Refractory Angina pectoris	"angina pectoris" [MeSH] OR "Refractory angina pectoris" [tw] OR "Chronic refractory angina pectoris"[tw] OR "angina pectoris"[tw] OR "Chest pain" [MeSH] OR "Chest pain"[tw]	93,968
	# 3	Randomized Controlled trial	"randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomized controlled trial"[All Fields]	824,524
	# 4		#1 AND #2 AND #3	40
CENTRAL	# 1	Acupuncture	"Acupuncture" OR "acupuncture analgesia"	20,173
	# 2	Refractory Angina pectoris	"angina pectoris" OR "Angina pectori, Stable" OR "Angina Pectoris, Stable"	10,731
	# 3		#1 AND #2	71
Embase	#1	Acupuncture	('acupunctural'/exp OR 'acupuncture':ti,ab OR 'acupuncture therapy'/exp OR ('acupuncture':ti,ab AND 'therapy':ti,ab) OR 'acupuncture therapy':ti,ab OR 'acupunctures':ti,ab OR 'acupunctured':ti,ab OR 'acupunctures':ti,ab OR 'acupuncturing':ti,ab)	63,536
	#2		'angina pectoris'/exp OR 'refractory angina pectoris':ti,ab OR 'chronic refractory angina pectoris':ti,ab OR 'angina pectoris':ti,ab OR 'chest pain'/exp OR 'chest pain':ti,ab	253,895
	#3		'randomized controlled trial'/exp OR 'randomized controlled trials as topic'/exp OR 'randomized controlled trial':ti,ab	1,125,001
	#4		#1 AND #2 AND #3	91
Google Scholar	# 1	Acupuncture	Acupuncture | acupunctural | "acupuncture therapy" | acupunctures | acupuncturing | acupunctured	
	# 2	Angina pectoris	"angina pectoris" | "Refractory angina pectoris" | "Chest pain"	
	# 3	Randomized Controlled trial	"randomized controlled trial" | "randomised controlled trial"	
	# 4		#1 AND #2 AND #3	200
Lilacs	# 1	Acupuncture	acupuncture OR acupuntura OR acup* OR "acupuncture therapy" OR acupunctered OR acupuncturing OR acupres*	54.672
	# 2	Angina pectoris	"angina pectoris" OR "Refractory angina pectoris" OR "Chronic refractory angina pectoris" OR "angina pectoris" OR "Chest pain" OR "Chest pain" OR "precordalgia" OR "dolor de pecho" OR "angina de pecho"	99.55
	# 3	Randomized Controlled trial	"randomized controlled trial" OR "randomized controlled trials as topic" OR "randomized controlled trial" OR "randomized controlled trial" OR "Ensayo clínico aleatorizado" OR "randomizado" OR "aleatorizado"	1.496.226
	#4		#1 AND #2 AND #3	34

Table 2: *Search strategy.*

Author	Intervention/ Control Groups	Follow-up	Frequency of Angina (Monthly) (Mean/SD)	Nitroglycerin usage (Mean/SD)	Seattle Angina Questionnaire (SAQ) (Mean/SD)	Pain Severity Analog Scale (VAS) (Mean/SD)
Wang et al. 2015	Healthy	Baseline			95.6/3.1	
		After 30 days			96.5/5.2	
	Acupuncture	Baseline	17.9/4.5	16.1/5.9	43.4/11.3	6.8/1.0
		After 30 days	12.9/3.8	10.1/2.2	47.4/10.2	6.0/1.2
	Comparison	Baseline	17.5/5.1	15.9/5.2	45.4/12.3	7.0/1.1
		After 30 days	17.1/4.3	15.1/6.2	45.2/12.8	7.1/1.1
	Main Results: Improvement of angina attacks, nitroglycerin usage, and VAS scores in acupuncture group. All of them have P<0.05. The SAQ score was significantly increased P<0.05 compared with the drug group.					
Deng et al. 2018	Needle-embedding (group A)				SAQ scores: Limitation of motion (76.3/2.9)	
		Baseline	52.63/18.6***		Stable state of angina pectoris (36.1/12.5)	
					Angina attack scores (52.6/18.6)	
		After 4 weeks	61.57/18.5***		SAQ scores: Limitation of motion (76.8/3.1)	
					Stable state of angina pectoris (48.6/14.1)	
					Angina attack scores (61.5/18.5)	
	Standard treatment (group B)	Baseline	39.4/12.5***		SAQ scores: Limitation of motion (75.6/3.2)	
					Stable state of angina pectoris (39.4/12.5)	
					Angina attack scores (48.9/17.6)	
		After 4 weeks	41.4/12.0***		SAQ scores: Limitation of motion (75.7/3.0)	
					Stable state of angina pectoris (41.4/12.0)	
					Angina attack scores (55.5/12.6)	
	Main Results: Significant improvement in Limitation of motion, Stable state of angina pectoris, and Angina attack scores. Group A were statistically higher than those in group B, it had P<0.01.					
Zhao et al. 2019	DAM	Baseline	13.5/5.9			
		After 4 weeks *	5.5/5.1**		72.2/12.4	3.0/1.3
	NAM	Baseline	12.9/7.2		60.7/15.9	3.6/1.3
		After 4 weeks *	3.1/4.0**		69.1/13.6	3.2/1.2
	SA	Baseline	12.6/5.6		59.7/15.9	3.7/1.1
		After 4 weeks *	2.0/4.1**		66.0/13.3	3.4/1.0
	WL	Baseline	14.1/10.3		58.8/16.7	3.5/1.1
		After 4 weeks *	0.4/4.5**		59.2/15.7	3.5/1.2
	Main Results: A greater reduction was observed in the DAM group than in the other groups: 4.07 fewer attacks than in the NAM group P < 0.001. Lower pain severity in DAM group had a P<0.001; Improvement in SAQ scores in DAM group had a P < 0.001. All these results of P values (in main results) are referring after 16 weeks.					
Huang et al. 2021	LSG	Baseline	5.4/4.5			
		After 4 weeks	3.6/3.8			
		After 8 weeks	3.6/3.6			
	HSG	Baseline	6.3/5.7			
		After 4 weeks	2.9/3.4			
		After 8 weeks	2.8/3.4			
	Main Results: The frequency of angina attacks was reduced from baseline in the HSG significantly more than in the LSG at week 4 (P < 0.001) and week 8 (P 0.003).					
Zhang et al. 2019	TAAC	Baseline		10.0/1.8		4.0/0.4
		After 4 weeks		8.9/1.6		3.7/0.2
	TAAOC	Baseline		10.1/1.7		4.0/0.5
		After 4 weeks		9.3/2.0		3.8/0.3
	NANC	Baseline		10.1/1.6		4.0/0.4
		After 4 weeks		9.6/1.9		3.7/0.2
	NP	Baseline		10.5/2.3		4.0/0.5
		After 4 weeks		9.9/2.7		3.8/0.3
	Main Results: After treatment, the dosage of nitroglycerin in the group receiving meridian-specific acupuncture was significantly reduced (P<0.01). After treatment, the pain severity of angina pectoris (VAS score) in the four groups was reduced, with statistically significant differences compared to before treatment (P<0.01).					

DAM= acupoints on the disease-affected meridian; NAM= acupoints on the non affected meridian; SA= sham acupuncture; WL= no acupuncture (wait list [WL] group); LSG= low-sensitivity group (Control Group); HSG= high-sensitivity group (Intervention Group); TAAC= taking acupoints along channel; TAAOC= taking acupoints along other channel; NANC= non-acupoints in non-channel; NP= no puncturing.

*Zhao et al. Also has measured the outcomes after 8 weeks, 12 weeks, and 16 weeks but for comparison this review only used the results after 4 weeks.

** Zhao et al. The authors do not measure the Frequency of Angina after 4 weeks, they put the results as the decreasing frequency of attacks compared at baseline absolute numbers.

*** Deng et al. The authors measured frequency of angina by the SAQ scores and not as the crude value

Table 3: *Primary and secondary results.*

Another study (Wang et al., 2015) also presented a high risk of bias as it relied on participant-reported outcomes in a trial design where participants were likely unblinded, resulting in a high risk of bias for outcome measurement. This trial was included due to the more extended period of follow-up, which was 30 days after intervention.

Two studies performed an intention-to-treat analysis (Huang et al., 2021; Zhao et al., 2019) . One study (Zhang et al., 2019) used a per-protocol analysis. Only one study (Zhao et al., 2019) described using the last-observation-carry-forward method to handle missing data. It was unclear if dropouts could have contributed to attrition bias in one study (Huang et al., 2021), which was judged to have "some concerns" of bias due to missing outcome data.

Discussion

This review is noteworthy because it studies acupuncture as an additional intervention for RAP, which is in line with the modern definition of the disease. Patients received standard medical therapy based on guidelines for chronic stable angina, and the intervention groups received acupuncture in addition to medical therapy. Three of the five studies found that the intervention decreased the frequency of angina attacks, three found a reduction in pain intensity and an improvement in quality of life, and two found a reduction in the frequency of rescue medication usage.

This systematic review has several strengths. First, this review includes various modalities of acupuncture, which increases the generalizability of the results. Second, all trials included a standard of care for participants in accordance with current clinical practice. Additionally, the review focuses on clinically relevant outcomes, providing a practical assessment of the potential benefits of acupuncture in real-world clinical settings. Lastly, we did not limit the search strategy to articles published in English, reducing the risk of language selection bias.

Key methodological issues included blinding, intervention reliability, and generalizability. All studies except Huang et al. (2021) included a control group that received only standard medication and, therefore, was unblinded, increasing the risk of response bias for subjective outcomes (Hróbjartsson et al., 2011). Only Zhao et al. (2019) and Huang et al. (2021) specified licensed acupuncturists, raising questions about intervention reliability. Additionally, the short trial durations limited the ability to assess long-term efficacy. Despite these concerns, these trials were judged to have sufficient quality and included in our review, given that acupuncture as an intervention necessitates unblinding of the acupuncturist,

and there is no evidence suggesting the effectiveness of blinding in this situation (Trinh, 2003).

Additionally, these were the best trials that met the criteria for our research question. Generalizability is also limited as all studies were conducted in China, potentially affecting applicability to other ethnic groups and regions. Factors like participant expectations, regional differences in acupuncture practices, and patient characteristics can influence outcomes (Cao et al., 2020; Linde et al., 2007; Mao et al., 2010). Additionally, the fact that two of the articles were originally in Chinese and required translation may compromise the reproducibility of this review for non-Chinese investigators.

This review indicates that acupuncture could effectively reduce angina attack frequency and improve the quality of life in patients with refractory angina pectoris. The conclusion that acupuncture can reduce angina attack frequency and improve quality of life is primarily supported by three studies (Huang et al., 2021; Wang et al., 2015; Zhao et al., 2019). These studies showed statistically significant reductions in angina attack frequency and improvement in quality of life. The findings suggest acupuncture could be a valuable adjunctive tool for RAP, similar to previous studies in chronic stable angina where acupuncture has demonstrated efficacy in reducing pain (Vickers & Linde, 2014), alleviating anxiety (Tu et al., 2021), and enhancing quality of life (Wang et al., 2018). Additionally, its association with low side effects, risks, and costs makes it appealing for broader clinical implementation, attracting interest from governments and policymakers.

However, two other studies (Deng et al., 2018; Zhang et al., 2019) focusing on nitroglycerin use and pain intensity did not yield significant results. In general, only the article by Zhang et al. (2019) was considered of high quality, and overall, evidence remains limited by the small sample size and heterogeneity of the interventions. Therefore, further high-quality research is necessary to conclude acupuncture's efficacy.

In terms of safety, none of the studies included in this review reported serious adverse events related to acupuncture. Minor side effects, such as subcutaneous bleeding, were observed in two studies (Huang et al., 2021; Zhao et al., 2019). These findings support the general view that acupuncture is a low-risk intervention when performed by trained professionals. However, further research is needed to establish a comprehensive safety profile, particularly in Western populations where acupuncture is less commonly practiced. In China, acupuncture is widely integrated into the healthcare system, while in the Western healthcare system, it is less commonly

incorporated into standard care. Skepticism about its efficacy persists across different ethnicities (Johnson et al., 2019), and access to trained practitioners is limited (Chan, 2005). However, this disparity in acupuncture usage and expertise in Western healthcare stresses the need for more research into the efficacy of acupuncture in different cultural and healthcare settings.

Furthermore, future studies should focus on refining design and methodology, including more extensive and diverse sample sizes, improved blinding techniques, and robust control groups to mitigate biases and enhance study quality. Establishing a standardized treatment protocol for optimal acupoint selection, session duration, and treatment intervals is essential for advancing the clinical application of acupuncture in managing refractory angina.

Conclusion

This systematic review suggests acupuncture could be an effective adjuvant therapy for reducing the frequency of angina attacks in the Chinese population. However, the term RAP has recently been defined, highlighting the need for new randomized controlled trials that are explicitly targeting this population. Given the limitations identified in existing studies, further high-quality research with a more diverse population is essential to provide more robust conclusions that can be generalized to other regions.

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Conflicts of Interest

The authors declare no conflict of interest.

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