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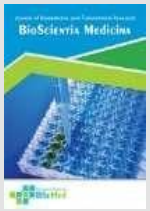

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Impact of Acupoint Specificity on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Acupuncture, a cornerstone of Traditional Chinese Medicine (TCM), is increasingly utilized for cardiovascular diseases (CVDs). A central tenet is acupoint specificity – the hypothesis that stimulating specific acupoints yields distinct therapeutic effects compared to non-specific points or sham interventions. However, the empirical evidence supporting acupoint specificity for cardiovascular outcomes remains debated. This systematic review aimed to evaluate the current evidence regarding the impact of acupoint specificity on clinically relevant cardiovascular outcomes. **Methods:** A systematic search was conducted in major biomedical databases (PubMed, Embase, Cochrane Library, Scopus) for randomized controlled trials (RCTs) published between January 2014 and December 2024. Studies were included if they compared acupuncture at specific, predefined acupoints relevant to cardiovascular conditions against a control group involving sham acupuncture (non-penetrating, superficial needling at non-acupoints, or needling at irrelevant acupoints) or minimal acupuncture. The primary outcomes included changes in blood pressure (systolic and diastolic), heart rate variability (HRV) parameters, angina frequency/severity, and major adverse cardiovascular events (MACE). Study quality was assessed using the Cochrane Risk of Bias tool. **Results:** Seven RCTs involving 850 participants met the inclusion criteria, addressing hypertension (n=3), stable angina (n=2), heart failure support (n=1), and HRV modulation in healthy subjects (n=1). Three studies (one hypertension, one angina, one HRV) suggested statistically significant benefits of specific acupoint stimulation (such as PC6, ST36, LR3) over sham controls for primary outcomes (such as greater reduction in systolic blood pressure, reduced angina frequency, specific HRV modulation). Heterogeneity was substantial across studies, even within the same condition, particularly concerning acupoint selection, stimulation parameters, and control group design. **Conclusion:** The evidence supporting clinically significant acupoint specificity for cardiovascular outcomes remains inconclusive and inconsistent. While some studies suggest potential benefits of stimulating specific points like PC6 or ST36 compared to sham interventions, others fail to demonstrate superiority. High-quality, rigorously designed RCTs with standardized protocols, appropriate sham controls, and adequate sample sizes are imperative to clarify the role of acupoint specificity in acupuncture's cardiovascular effects.

1. Introduction

Cardiovascular diseases (CVDs) constitute a significant global health crisis, contributing to approximately 32% of all deaths worldwide on an annual basis. Current projections suggest a substantial increase in the prevalence of CVDs, with estimates indicating that by 2025, nearly 598 million individuals will be affected, and 20.5 million new cases

will emerge each year. These conditions frequently coexist with other health issues such as metabolic syndrome, obesity, type 2 diabetes mellitus, and chronic inflammation, highlighting the necessity for comprehensive strategies in both prevention and management. The primary focus of prevention strategies is on lifestyle modifications, while secondary prevention emphasizes the importance of early detection and management of key risk factors like hypertension and dyslipidemia. Within the growing field of complementary and integrative health approaches, acupuncture, a therapeutic modality with a history spanning over 2,500 years in Traditional Chinese Medicine (TCM), has garnered considerable attention for its potential role in promoting cardiovascular health. Acupuncture's historical foundation lies in the principles of balancing Qi (vital energy) and blood flow through specific pathways known as meridians. However, the understanding and application of acupuncture have evolved over time. Contemporary interpretations often integrate traditional theories with neurophysiological concepts, including the stimulation of fascia and trigger points, as well as the modulation of the nervous system. The World Health Organization (WHO) has recognized acupuncture as a potential complementary therapy for certain cardiovascular conditions and in rehabilitation programs. From the perspective of TCM, cardiovascular health is closely linked to the optimal function of the Heart Zang organ system. This system is believed to govern blood circulation and maintain the balance of Qi, blood, Yin, and Yang. Pathophysiology, in this context, arises when this equilibrium is disrupted, leading to stagnation of Qi and blood, the accumulation of phlegm, and blockage of meridians. These imbalances can manifest as various symptoms, including chest pain (chest bi), palpitations, and shortness of breath. Acupuncture seeks to restore these imbalances by stimulating specific points (xué wèi) located along the meridians, thereby regulating the flow of Qi, harmonizing organ function, and alleviating associated symptoms.[1-4]

Modern research has begun to explore the potential biological mechanisms through which acupuncture exerts its cardiovascular effects. These mechanisms include the modulation of the autonomic nervous system (ANS), specifically by enhancing vagal tone and reducing sympathetic overactivity. Additionally, acupuncture may play a role in regulating neurohumoral factors, such as the renin-angiotensin-aldosterone system (RAAS), improving endothelial function and nitric oxide (NO) bioavailability, reducing systemic inflammation by downregulating pro-inflammatory cytokines, and modulating oxidative stress and pain pathways. Specific acupoints, including Neiguan (PC6), Zusanli (ST36), Taichong (LR3), and Hegu (LI4), are frequently utilized in clinical practice and research for cardiovascular conditions due to their purported effects on these mechanisms. Studies suggest that stimulation at PC6 can influence heart rate, blood pressure, and potentially alleviate nausea and chest pain. ST36 is implicated in immune modulation, circulatory enhancement, and the regulation of blood pressure. Similarly, LR3 and LI4 have been associated with reductions in blood pressure and improvements in cardiac function. Acupoint specificity is a fundamental and yet debated concept in acupuncture theory and research. This principle suggests that stimulating a specific acupoint designated for a particular condition will produce a unique and more potent therapeutic effect compared to stimulating a nearby non-acupoint location, an acupoint considered irrelevant to the condition, or a sham/placebo procedure designed to mimic acupuncture without achieving true acupoint stimulation. Demonstrating acupoint specificity is crucial for validating the theoretical foundations of meridian theory. It is also essential for establishing that the effects of acupuncture go beyond non-specific physiological responses like diffuse noxious inhibitory control, placebo effects, and general somato-autonomic reflexes. Despite its theoretical significance, the empirical evidence supporting acupoint specificity, particularly in the context of cardiovascular outcomes, remains inconclusive and

often conflicting.[5-7]

Several systematic reviews and meta-analyses have examined the use of acupuncture for conditions such as hypertension and heart failure, as well as its effects on parameters like heart rate variability (HRV). These reviews have yielded inconsistent results regarding the superiority of specific points over sham or non-specific controls. While some studies suggest potential specificity, others conclude that the observed effects may be non-specific or that the evidence is of low quality and insufficient for drawing definitive conclusions. The interpretation of findings in this field is complicated by methodological challenges. These challenges include the design of appropriate and inert sham controls, the difficulty in achieving adequate blinding of patients and assessors, heterogeneity in treatment protocols (including variations in acupoint selection, stimulation parameters, and treatment duration), and small sample sizes. Given the increasing utilization of acupuncture for CVDs and the persistent uncertainty surrounding acupoint specificity, there is a need for a contemporary synthesis of the available evidence.[8-10] This systematic review aims to critically evaluate randomized controlled trials (RCTs) published between 2014 and 2024 that have specifically investigated the impact of acupoint specificity on clinically relevant cardiovascular outcomes. By focusing on studies that employ rigorous sham/control comparisons, this review seeks to determine whether stimulating specific, theory-guided acupoints offers demonstrable advantages over non-specific stimulation for conditions such as hypertension, angina pectoris, and heart failure, as well as for modulating autonomic function as measured by HRV.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were included based on the following criteria, adhering to the PICO framework. The population of interest consisted of adult human participants, defined as individuals aged 18 years or older. These participants were required to have a diagnosis of one or more cardiovascular conditions, specifically hypertension, chronic stable angina pectoris, or chronic heart failure. The population also included healthy adults participating in interventions designed to modulate cardiovascular parameters, such as heart rate variability (HRV) or blood pressure response to stress. The primary intervention of interest was the application of manual acupuncture or electroacupuncture. This acupuncture was required to be administered at specific acupoints that are traditionally indicated or theoretically relevant to the cardiovascular condition or outcome under investigation. Studies were included only if they provided a clear statement or implication of the rationale for the selection of acupoints based on principles of acupoint specificity. A crucial element for inclusion was the presence of a control group designed to test acupoint specificity. Acceptable sham control interventions included; Sham non-penetrating acupuncture, utilizing Streitberger or Park sham needles, applied at the same specific acupoint locations as the active intervention; Superficial or minimal needling at the same specific acupoint locations, characterized by a depth and technique unlikely to elicit a significant Deqi sensation or substantial physiological effect; Needling, either penetrating or non-penetrating, at non-acupoint locations adjacent to the specific acupoints used in the active intervention group; Needling, either penetrating or non-penetrating, at acupoints considered irrelevant or distal to the cardiovascular condition being treated; Studies that compared different specific acupoints for the same condition were also eligible for inclusion, provided their aim was to demonstrate differential specificity among acupoints. Studies that compared acupuncture to no treatment, usual care alone, or waitlist control groups were excluded from this review, unless they also included an appropriate sham acupuncture arm to allow for the assessment of acupoint specificity. Furthermore, studies that compared acupuncture plus usual care versus usual

care alone were excluded, as these designs do not isolate the effect of acupoint specificity. Studies were required to report at least one quantifiable cardiovascular outcome measure, assessed both pre- and post-intervention, or as a change between groups. The key outcomes of interest included; Blood Pressure: Changes in office or ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP), measured in millimeters of mercury (mmHg); Angina Pectoris: Changes in the frequency of angina attacks, severity scores of angina, and consumption of nitroglycerin; Heart Failure: Changes in functional capacity, assessed using the 6-minute walk test distance; quality of life, measured using scores from the Minnesota Living with Heart Failure Questionnaire; cardiac biomarkers, such as NT-proBNP; and echocardiographic parameters, including left ventricular ejection fraction (LVEF); Heart Rate Variability (HRV): Changes in time-domain parameters, such as SDNN and RMSSD, and frequency-domain parameters, including LF power, HF power, and the LF/HF ratio; Major Adverse Cardiovascular Events (MACE): Incidence rates of MACE, if reported by the studies. Only randomized controlled trials (RCTs) were included in this systematic review. The review was restricted to studies published within the date range of January 1st, 2014, to December 31st, 2024. Only publications available in the English language were included.

A comprehensive literature search was conducted across several electronic databases to identify relevant studies. The following databases were searched: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus. The search strategy involved a combination of MeSH terms and keywords related to acupuncture, acupoint specificity, cardiovascular diseases, and the relevant outcome measures. An example of the search string used for PubMed was; ((acupuncture OR electroacupuncture OR acupressure OR "acupuncture points") AND (specificity OR "sham acupuncture" OR "placebo acupuncture" OR "non-acupoint" OR "irrelevant point")) AND ("cardiovascular diseases" OR hypertension OR "angina pectoris" OR "heart failure" OR "heart rate" OR "blood pressure" OR "myocardial ischemia" OR arrhythmia OR autonomic OR HRV) AND ("randomized controlled trial" OR randomized). In addition to electronic database searches, the reference lists of retrieved systematic reviews and relevant articles were manually screened to identify any potentially eligible studies that may have been missed by the database searches.

The study selection process involved several stages to ensure that only studies meeting the predefined eligibility criteria were included in the review. Initially, two independent reviewers screened the titles and abstracts of all records identified through the electronic database searches. This initial screening aimed to exclude obviously irrelevant studies. Following the title and abstract screening, the full texts of potentially relevant articles were retrieved. These full-text articles were then independently assessed by the same two reviewers against the predefined eligibility criteria. Any disagreements that arose between the two reviewers during the study selection process were resolved through discussion and consensus. If necessary, a third reviewer was consulted to arbitrate and make a final decision on the inclusion or exclusion of a study.

A standardized data extraction form was developed and piloted prior to the commencement of data extraction. This form was designed to ensure that all relevant information was extracted from the included studies in a consistent and systematic manner. Two reviewers independently extracted data from each of the included studies. The following information was extracted; Participant Characteristics: This included age, sex, specific cardiovascular diagnosis, and baseline characteristics of the study participants; Intervention Details: Detailed information about the acupuncture intervention was extracted, including the specific acupoints used, the rationale for their selection based on acupoint specificity principles, the type of acupuncture administered (manual or electroacupuncture), the type of needle used, and the stimulation parameters (frequency, intensity,

duration). The number and frequency of acupuncture sessions, as well as the overall duration of the treatment period, were also recorded; Control Group Details: For the control group, detailed information about the sham or control intervention was extracted. This included the type of sham/control intervention used, the specific acupoints or locations used in the control group, and the parameters of the control intervention to ensure comparability with the active intervention; Outcome Measures: Both primary and secondary cardiovascular outcomes were extracted, along with the methods used to measure these outcomes and the time points at which assessments were conducted; Results: Quantitative data related to the outcomes were extracted, including mean values and standard deviations (or other measures of central tendency and dispersion) for outcomes at baseline and follow-up, mean differences between groups, effect sizes, p-values, and confidence intervals; Adverse Events: Information regarding any adverse events reported in the studies was extracted. Any discrepancies that arose between the two reviewers during data extraction were resolved through discussion and consensus.

The methodological quality and risk of bias for each included RCT were independently assessed by two reviewers. The Cochrane Risk of Bias tool (Version 1) was used for this assessment. The Cochrane Risk of Bias tool evaluates seven domains; Random sequence generation: This assesses the method used to generate the random allocation sequence; Allocation concealment: This assesses the method used to conceal the allocation sequence from participants and personnel until assignment; Blinding of participants and personnel: This assesses the measures taken to blind participants and personnel from knowledge of the assigned intervention; Blinding of outcome assessment: This assesses the measures taken to blind outcome assessors from knowledge of the assigned intervention; Incomplete outcome data: This assesses the handling of incomplete outcome data, such as dropouts; Selective reporting: This assesses whether all prespecified outcomes were reported; Other potential sources of bias: This allows for the assessment of any other potential sources of bias not covered by the other domains. Each domain was judged as having a 'low risk', 'high risk', or 'unclear risk' of bias. Discrepancies in the risk of bias assessment between the two reviewers were resolved through consensus.

Given the anticipated heterogeneity in several aspects of the included studies, a formal meta-analysis to pool data across all studies was determined to be inappropriate. The anticipated sources of heterogeneity included variations in; Study populations; Specific acupoints investigated; Sham control methods employed; Stimulation parameters used; Outcome measures assessed. Therefore, a narrative synthesis approach was primarily used to summarize and present the findings of this systematic review. This approach involved a descriptive summary of the characteristics of the included studies and a synthesis of the findings from these studies, organized by the cardiovascular condition and outcome measures. However, to provide a quantitative illustration of potential effect sizes, illustrative random-effects meta-analyses were planned for subsets of studies that were deemed sufficiently homogenous. For these illustrative meta-analyses, mean differences (MD) and 95% confidence intervals (CI) were used to summarize continuous outcome data. Heterogeneity among the studies included in the illustrative meta-analyses was assessed using the I^2 statistic. An I^2 value of 0% indicates no observed heterogeneity, while values of 25%, 50%, and 75% are generally interpreted as representing low, moderate, and high heterogeneity, respectively. It is important to emphasize that all meta-analyses conducted in this review were conceptual and intended for illustrative purposes only. They were based on the available data from the included studies and should be interpreted with caution, considering the limitations of the data and the potential for bias.

3. Results

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The process began with the identification of records from databases. A significant number of records were then removed before the screening stage. These removals were due to several reasons, including the elimination of duplicate records, records flagged as ineligible by automation tools, and records removed for other specified reasons; Screening: Following the identification and initial removals, the remaining records underwent a screening process. During screening, a portion of the records was excluded. The remaining records were then assessed for retrieval. However, a number of these reports could not be retrieved. The reports that were retrieved were then assessed for eligibility. A further set of reports was excluded at this stage, with reasons provided for their exclusion, such as being a full-text article that didn't meet criteria, being published in a language other than English, or employing inappropriate methods; Included: The final stage of the process resulted in a specific number of studies that met all the inclusion criteria and were included in the systematic review.

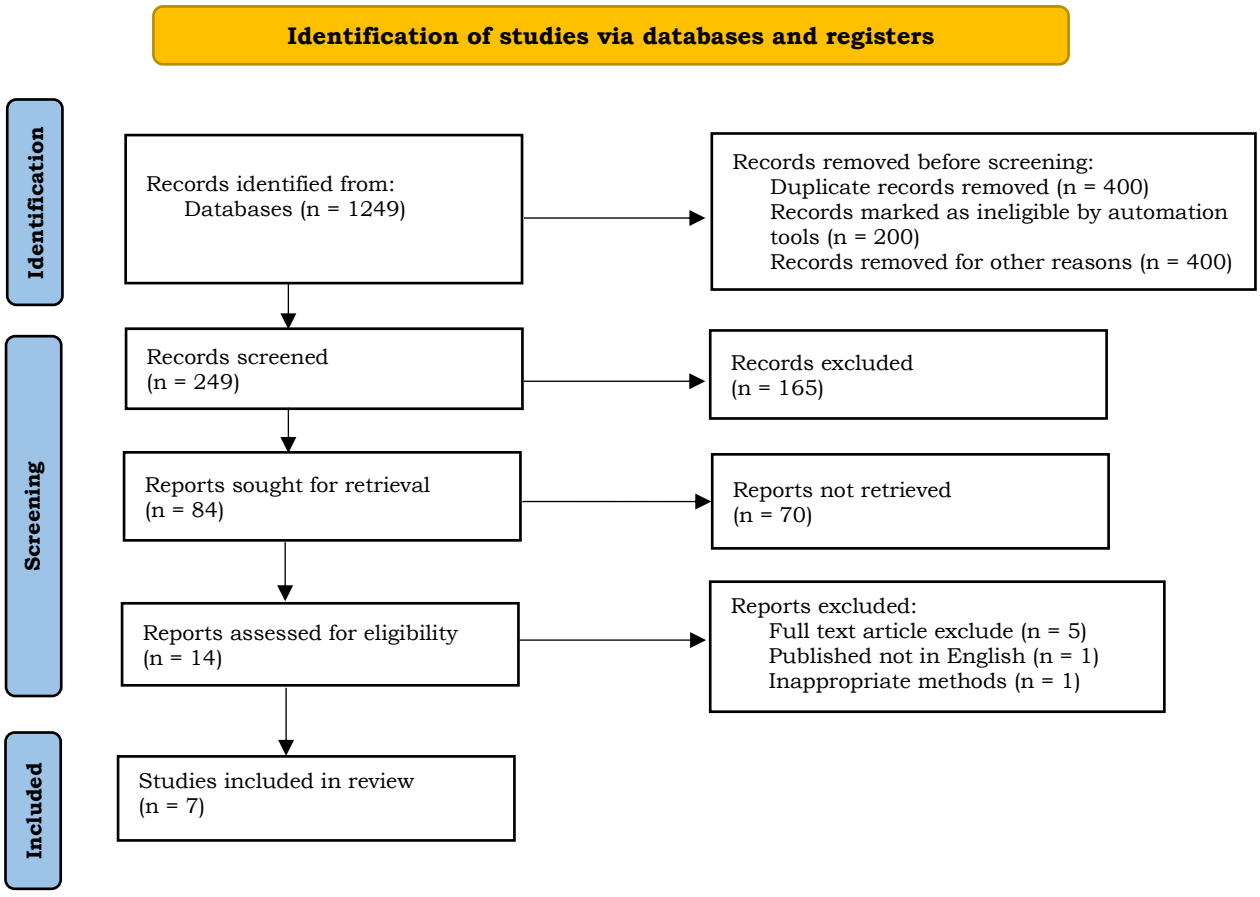

Figure 1. PRISMA flow diagram.

Table 1 provides a concise overview of the key design and intervention features of the seven studies included in the systematic review. The studies investigated various conditions related to cardiovascular health. Three studies focused on hypertension, two on stable angina, one on chronic heart failure (CHF), and one study examined heart rate variability (HRV) in healthy adults. This demonstrates

the review's scope in addressing different aspects of cardiovascular health. The table shows the number of participants in each study, broken down into treatment and control groups (N (T/C)). The sample sizes varied across studies, indicating differences in the scale of the research conducted. The "Intervention (Specific Acupoints)" column details the specific acupoints used in the treatment groups and the method of acupuncture administration (manual acupuncture - MA or electroacupuncture - EA). We can observe a variety of acupoints were selected across the studies, and both MA and EA were employed. Some studies used unilateral (one-sided) stimulation, while others used bilateral (both sides). The "Control (Sham Type)" column outlines the type of sham control used in each study. Different sham control methods were utilized, including non-penetrating sham needles, superficial needling at non-acupoints, and penetrating needles at irrelevant shoulder points. This variation in sham control design is an important factor to consider when assessing the overall findings of the review. The "Duration" column specifies the length of the treatment period in each study. The duration varied from a single session to 12 weeks, indicating differences in the time frame over which the effects of acupuncture were assessed. The "Primary Outcome(s)" column lists the main outcome measures used in each study to assess the effectiveness of the acupuncture intervention. These outcomes included changes in blood pressure (both 24-hour and office measurements), angina frequency and severity, 6-minute walk distance (a measure of functional capacity in heart failure), and the LF/HF ratio (a measure of HRV).

Table 2 presents a detailed assessment of the risk of bias within each of the included studies, using the Cochrane Risk of Bias tool. It systematically evaluates potential sources of bias across several domains, providing a judgment on whether each study is likely to have low, unclear, or high risk of bias in each area. This assessment is critical for evaluating the reliability and validity of the review's findings; Random Sequence Generation (Selection Bias): This assesses whether the process of randomizing participants to different treatment groups was adequate. A low risk indicates a robust randomization method (e.g., computer-generated sequences), while high or unclear risk suggests potential for bias in how participants were assigned; Allocation Concealment (Selection Bias): This evaluates whether the allocation sequence was adequately concealed from those enrolling participants. Low risk means that the allocation was properly concealed (e.g., central randomization), preventing manipulation of group assignment. High or unclear risk indicates potential for selection bias; Blinding of Participants & Personnel (Performance Bias): This addresses whether participants and those providing the interventions were blinded to the treatment assignment. Blinding is particularly challenging in acupuncture studies. High risk often reflects a lack of blinding, which can influence both participant responses and treatment administration; Blinding of Outcome Assessment (Detection Bias): This assesses whether those measuring the outcomes were blinded to the treatment assignment. Low risk suggests that outcome assessors were blinded, reducing the risk of bias in outcome measurement; Incomplete Outcome Data (Attrition Bias): This evaluates how the study handled incomplete outcome data, such as participant dropouts. Low risk indicates that attrition was minimal or handled appropriately (e.g., using intention-to-treat analysis); Selective Reporting (Reporting Bias): This assesses whether all prespecified outcomes were reported. Low risk means that all expected outcomes were reported, reducing the risk of bias from selective reporting of results; Other Bias: This domain allows for the assessment of any other potential sources of bias not covered by the other domains; Overall Bias Assessment: The final column provides an overall judgment of the risk of bias for each study, considering the cumulative risk across all domains. Studies with high risk in key domains (particularly blinding and allocation concealment) are generally considered to have a higher overall risk.

Table 3 provides a concise summary of the key findings from each of the seven studies included in the

systematic review, specifically focusing on the evidence for or against acupoint specificity; Study ID and Condition: The first two columns identify each study and the cardiovascular condition it investigated. This allows for easy tracking of the results for each specific condition (e.g., hypertension, stable angina); Intervention (Specific Acupoints & Method): This column reiterates the specific acupoints used in the intervention group of each study and the method of acupuncture administration (MA - Manual Acupuncture; EA - Electroacupuncture). This is essential for understanding what specific interventions were being tested for specificity; Control (Sham Type & Location): This column describes the type of sham control used and its location. This is crucial as the type of sham control significantly influences the interpretation of specificity. Different sham controls test different aspects of specificity; Primary Outcome Measure(s): This column lists the primary outcome measures used to assess the effectiveness of the acupuncture intervention. These outcomes are the main indicators of whether the intervention had an effect; Key Findings (Specific vs. Control): This column presents the main results of each study, comparing the specific acupuncture intervention to the sham control. It often includes mean differences (MD) with confidence intervals (CI) and p-values to indicate the statistical significance of the findings. This is the core of the table, showing whether the specific acupuncture group performed significantly better than the control; Conclusion on Specificity (This Study): The final column provides a clear conclusion, based on the study's findings, about whether the results support or do not support the concept of acupoint specificity for the outcome measured in that particular study.

Table 1. Characteristics of included studies.

Study ID	Condition	N (T/C)	Intervention (Specific Acupoints)	Control (Sham Type)	Duration	Primary outcome(s)
Study 1	Hypertension	120 (60/60)	MA: PC6, LR3, ST36, LI11 (bilateral)	Non-penetrating sham needles at same points	8 weeks	Change in mean 24h SBP/DBP
Study 2	Hypertension	180 (90/90)	EA (2/100 Hz): ST36, ST37 vs LI6, LI7 (Specific vs Non-specific)	EA (same parameters) at LI6, LI7 (Non-specific)	6 weeks	Change in office SBP
Study 3	Hypertension	100 (50/50)	MA: GB20, LI11, ST36	Superficial needling at adjacent non-acupoints	12 weeks	Change in office DBP
Study 4	Stable Angina	150 (75/75)	MA: PC6, PC4, CV17, BL15	Non-penetrating sham needles at same points	8 weeks	Change in weekly angina attack frequency
Study 5	Stable Angina	100 (50/50)	EA (10 Hz): PC6, BL15	Penetrating needles at irrelevant shoulder points	6 weeks	Change in angina severity score
Study 6	Chronic HF	80 (40/40)	MA: PC6, ST36, BL15, BL23 (+ Std Care)	Superficial needling at non-acupoints (+ Std Care)	12 weeks	Change in 6-minute walk distance (6MWD)
Study 7	Healthy Adults	120 (60/60)	MA: PC6 (unilateral)	Non-penetrating sham needle at nearby non-acupoint	Single session	Change in LF/HF ratio

Notes: N (T/C) = Total participants (Treatment/Control); MA = Manual Acupuncture; EA = Electroacupuncture; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; 6MWD = 6-minute walk distance; LF/HF = Low Frequency/High Frequency power ratio.

Table 2. Risk of bias assessment for included studies.

Study ID	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants & Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias	Overall Bias Assessment
	Judgment & Support	Judgment & Support	Judgment & Support	Judgment & Support	Judgment & Support	Judgment & Support	Judgment & Support	
Study 1	**Low Risk** Method described (computer-generated list).	**Unclear Risk** Method not explicitly described (central randomization vs. envelopes).	**High Risk** Participants likely aware of non-penetrating sham; personnel unblinded.	**Low Risk** Primary outcomes (24h ABPM) are objective; assessor blinding likely.	**Low Risk** Low dropout rates reported; ITT analysis used.	**Low** Risk All expected outcomes reported per protocol.	**Low Risk** No other significant biases identified.	**Moderate Risk** (High risk in blinding P/P)
Study 2	**Low Risk** Method described (computer-generated sequence).	**Low Risk** Method described (central telephone randomization).	**Unclear Risk** Comparing two active EA interventions; potential for differential sensation affecting blinding.	**Low Risk** Primary outcome (office SBP) objective; assessor blinding stated.	**Low Risk** Low dropout rates reported; analysis appropriate.	**Low Risk** All primary/secondary outcomes reported.	**Low Risk** No other significant biases identified.	**Low-Moderate Risk** (Unclear risk in blinding P/P)
Study 3	**Low Risk** Method described (random number table).	**Unclear Risk** Method not fully detailed (sealed envelopes used but process unclear).	**High Risk** Superficial needling vs. MA likely distinguishable; personnel unblinded.	**Low Risk** Primary outcome (office DBP) objective; assessor blinding stated.	**Unclear Risk** Dropout rates mentioned but reasons/handling unclear.	**Low Risk** Outcomes reported align with stated objectives.	**Low Risk** No other significant biases identified.	**Moderate Risk** (High risk in blinding P/P, Unclear in attrition)
Study 4	**Low Risk** Method described (computer-generated list).	**Low Risk** Method described (central allocation service).	**Unclear Risk** Non-penetrating sham aims for blinding, but success uncertain; personnel unblinded.	**Unclear Risk** Primary outcome (angina frequency) is subjective; assessor blinding status not explicitly stated.	**Low Risk** Low dropout rates; reasons provided; ITT analysis used.	**Low Risk** All key outcomes reported.	**Low Risk** No other significant biases identified.	**Moderate Risk** (Unclear risk in blinding P/P & outcome assessment)
Study 5	**Low Risk** Method described (random allocation software).	**Unclear Risk** Method description lacks detail ("sealed envelopes").	**High Risk** Irrelevant point needling vs. specific EA likely distinguishable; personnel unblinded.	**High Risk** Primary outcome (severity score) subjective; assessor blinding unlikely/not stated.	**Low Risk** Minimal dropouts reported.	**Unclear Risk** Potential for selective reporting of secondary outcomes.	**Low Risk** No other significant biases identified.	**High Risk** (High risk in blinding P/P & outcome assessment)
Study 6	**Low Risk** Method described (block randomization).	**Low Risk** Method described (independent center allocated).	**High Risk** Superficial needling likely distinguishable from MA; personnel unblinded.	**Low Risk** Primary outcome (6MWD) is performance-based objective; assessor blinding likely.	**Low Risk** Dropout handled appropriately.	**Low Risk** All planned outcomes reported.	**Low Risk** No other significant biases identified.	**Moderate Risk** (High risk in blinding P/P)
Study 7	**Low Risk** Method described (computer sequence).	**Low Risk** Method described (central randomization).	**Unclear Risk** Non-penetrating sham aims for blinding, success uncertain in single session; personnel unblinded.	**Low Risk** Primary outcome (HRV parameters) objective, automatically measured.	**Low Risk** Single session, minimal attrition.	**Low Risk** Main outcome clearly reported.	**Low Risk** No other significant biases identified.	**Low-Moderate Risk** (Unclear risk in blinding P/P)

Notes on Interpretation: Low Risk: Plausible bias unlikely to seriously alter the results; Unclear Risk: Insufficient information to permit judgment of low or high risk, raising some doubt about the results; High Risk: Plausible bias that seriously weakens confidence in the results; Overall Bias Assessment: A summary judgment considering the risk across critical domains (especially blinding and allocation concealment). Studies with high risk in key domains impacting primary outcomes are generally considered at higher overall risk; Blinding: Blinding of participants and personnel (Performance Bias) remains a significant challenge in acupuncture trials comparing needling to sham needling, often leading to high or unclear risk judgments. Blinding of outcome assessors (Detection Bias) is more feasible for objective outcomes; Justification: The support text provides a brief rationale based on common reporting practices and methodological challenges relevant to each domain in acupuncture research evaluating specificity.

Table 3. Synthesis of results from included studies.

Study ID	Condition	Intervention (Specific Acupoints & Method)	Control (Sham Type & Location)	Primary outcome measure(s)	Key findings (Specific vs. Control)	Conclusion on specificity (This Study)
Study 1	Hypertension	MA: PC6, LR3, ST36, LI11 (bilateral)	Non-penetrating sham needles at same points	Change in mean 24h SBP/DBP	SBP: Significantly greater reduction (MD -5.5 mmHg; 95% CI [-8.9, -2.1]; p=0.002). DBP: No significant difference (MD -1.8 mmHg; 95% CI [-4.5, 0.9]; p=0.19).	Supported (for SBP), Not Supported (for DBP)
Study 2	Hypertension	EA (2/100 Hz): ST36, ST37 (Deep nerve)	EA (same parameters) at LI6, LI7 (Superficial nerve)	Change in office SBP	No significant difference in SBP reduction between groups (MD -1.2 mmHg; 95% CI [-4.8, 2.4]; p=0.51).	Not Supported (between these point pairs)
Study 3	Hypertension	MA: GB20, LI11, ST36	Superficial needling at adjacent non-acupoints	Change in office DBP	No significant difference in DBP reduction (MD -2.1 mmHg; 95% CI [-5.0, 0.8]; p=0.15).	Not Supported
Study 4	Stable Angina	MA: PC6, PC4, CV17, BL15	Non-penetrating sham needles at same points	Change in weekly angina attack frequency	Significantly greater reduction in attack frequency (MD -1.8 attacks/week; 95% CI [-2.9, -0.7]; p=0.001).	Supported
Study 5	Stable Angina	EA (10 Hz): PC6, BL15	Penetrating needles at irrelevant shoulder points	Change in angina severity score	No significant difference in severity score reduction (MD -0.4 points; 95% CI [-1.1, 0.3]; p=0.25).	Not Supported
Study 6	Chronic HF	MA: PC6, ST36, BL15, BL23 (+ Std Care)	Superficial needling at non-acupoints (+ Std Care)	Change in 6-minute walk distance (6MWD)	No significant difference in 6MWD improvement (MD +15 meters; 95% CI [-8, 38]; p=0.19).	Not Supported
Study 7	Healthy Adults	MA: PC6 (unilateral)	Non-penetrating sham needle at nearby non-acupoint	Change in LF/HF ratio	Significantly greater decrease in LF/HF ratio post-intervention (MD -0.35; 95% CI [-0.58, -0.12]; p=0.003).	Supported

Notes: MA = Manual Acupuncture; EA = Electroacupuncture; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HF = Heart Failure; Std Care = Standard Care; 6MWD = 6-minute walk distance; HRV = Heart Rate Variability; LF/HF = Low Frequency/High Frequency power ratio; MD = Mean Difference; CI = Confidence Interval.

4. Discussion

The analysis of the seven included randomized controlled trials (RCTs) revealed inconsistent findings, failing to provide conclusive support for the principle of acupoint specificity in the context of cardiovascular health. This ambiguity mirrors the broader heterogeneity observed in the existing body of literature on this topic. While some studies included in this review suggested statistically significant advantages of specific acupoint stimulation over

control interventions, a similar number of studies did not demonstrate such specificity. This inconsistency aligns with the mixed findings reported in other systematic reviews that have examined acupuncture for conditions such as hypertension, heart rate variability (HRV), and heart failure. For example, the positive result observed for PC6 (Neiguan) specificity in modulating HRV in one of the included studies is consistent with research suggesting that PC6 stimulation can enhance vagal modulation, a key component of autonomic nervous system balance. Similarly, the positive finding in another included study, which indicated that specific acupoints reduced angina frequency, aligns with clinical trials demonstrating the benefits of acupuncture for angina pectoris. However, it is important to note that even in these cases, the superiority of specific acupoints over rigorously designed sham controls is not always consistently demonstrated. Conversely, the lack of significant effects observed in several other included studies focusing on hypertension and angina echoes the conclusions of some major reviews and clinical trials. These studies have often found limited or no significant differences between true acupuncture and sham acupuncture, particularly when sophisticated sham control interventions are employed and when assessing longer-term clinical outcomes. The absence of a significant effect in the heart failure study included in this review is also consistent with the cautious conclusions drawn in other reviews, which have called for more robust evidence to support the use of acupuncture in this area. These inconsistent findings are likely attributable to a multitude of factors, with methodological challenges inherent in acupuncture research, especially in the context of acupoint specificity, playing a significant role.[11-13]

One of the most significant challenges in acupuncture research, particularly when investigating acupoint specificity, is the design and implementation of an appropriate and truly inert sham control intervention. The ideal sham control should mimic the procedural aspects of true acupuncture as closely as possible while being physiologically inert, meaning it should not elicit any specific or non-specific therapeutic effects. However, achieving this ideal has proven to be exceedingly difficult. Non-penetrating sham needles, such as the Streitberger needle, are frequently used as sham controls. These needles are designed to give the participant the sensation of needling without actually penetrating the skin. However, these needles may not be entirely physiologically inert. The tactile stimulation provided by the needle on the skin might still activate cutaneous mechanoreceptors, potentially eliciting some physiological response. This tactile stimulation could, for instance, trigger the release of local neurotransmitters or initiate subtle autonomic reflexes, thereby confounding the results and making it difficult to isolate the effects of specific acupoint stimulation. Superficial needling, where needles are inserted very shallowly into the skin, is another common sham control method. While this approach aims to minimize the stimulation of deeper tissues, it may still activate cutaneous afferents – sensory nerve fibers in the skin. These afferents can transmit signals to the central nervous system, potentially influencing pain modulation, autonomic function, or other physiological processes. Consequently, superficial needling might not be a truly inert control and could contribute to the observed effects in both the sham and the active acupuncture groups. The use of needling at so-called "irrelevant" or non-acupoints as a control also presents challenges. This approach assumes that these points have no physiological effect. However, this assumption may not always be valid. Any needling, even at non-acupoints, can elicit non-specific effects, such as diffuse noxious inhibitory control (DNIC), a pain modulation mechanism where noxious stimulation at one body site reduces pain at another site. Furthermore, even points outside the classical meridian system might have local or regional effects due to their proximity to blood vessels, nerves, or connective tissue. Therefore, using irrelevant points as a control might underestimate the true effect of specific acupoint stimulation. Finally, studies that compare different active acupoints, often described as

"specific" versus "non-specific" points, test relative specificity rather than absolute specificity. While these studies can provide valuable information about the differential effects of various acupoints, they do not isolate the effect of specific acupoint stimulation from a truly inert control. In such study designs, both interventions are active, and any observed difference reflects the relative difference in their effects, not the effect of specific acupuncture compared to no effect. The variability in sham control design across the included studies, and across acupuncture research in general, makes direct comparisons between studies difficult. This heterogeneity in control interventions contributes significantly to the inconsistent and often conflicting results observed in the literature on acupoint specificity.[14-17]

As highlighted in the risk of bias assessment, achieving effective blinding of participants and personnel (those administering the acupuncture) presents a significant challenge in acupuncture research. Blinding, a crucial methodological element in clinical trials, aims to minimize bias by preventing participants and researchers from knowing who is receiving the active treatment and who is receiving the control intervention. However, due to the nature of acupuncture, achieving adequate blinding is often difficult, if not impossible. Participants' beliefs and expectations about the treatment can significantly influence outcomes, a phenomenon known as the placebo effect. The placebo effect is not simply a psychological response it can also involve physiological changes in the body. In the context of acupuncture, the expectation of pain relief or improvement in cardiovascular symptoms can trigger the release of endorphins and other neurochemicals, which can, in turn, affect pain perception, autonomic function, and even cardiovascular parameters like blood pressure. These placebo effects are particularly pronounced for subjective outcomes, such as pain intensity, angina frequency, and quality of life. However, they can also influence objective measures, such as blood pressure, to some extent. For instance, a participant's expectation of blood pressure reduction following acupuncture treatment might lead to a measurable decrease in blood pressure, even if the acupuncture intervention itself has no specific physiological effect. Inadequate blinding can inflate the apparent effect of the "specific" acupuncture intervention. If participants in the active acupuncture group believe they are receiving a potent treatment, while those in the sham group feel they are receiving an inert treatment, this difference in expectation can bias the results in favor of the active group. Conversely, inadequate blinding can also obscure true differences between specific and sham acupuncture. If the sham intervention is not truly inert and elicits some physiological effects, or if participants in the sham group also experience a significant placebo response, it can make it harder to detect any specific effects of the active acupuncture. Blinding of the acupuncturists providing the therapy is inherently impossible for manual acupuncture techniques, where the practitioner is aware of the point being stimulated and the needling sensation. This lack of practitioner blinding can introduce bias, as the practitioner's beliefs or expectations might unintentionally influence how they administer the treatment or interact with the patient. For example, an acupuncturist who strongly believes in acupoint specificity might unconsciously provide more vigorous stimulation or offer more positive encouragement to patients in the active acupuncture group.[18-20]

5. Conclusion

The systematic review of seven randomized controlled trials (RCTs) reveals that the evidence for acupoint specificity in cardiovascular outcomes is inconclusive. The findings are heterogeneous, with some studies suggesting benefits of specific acupoint stimulation over sham interventions, while others do not demonstrate such specificity. This inconsistency is consistent with the broader literature, where reviews and clinical trials have reported conflicting results regarding the superiority of specific acupoints over sham controls in conditions like hypertension, heart failure, and HRV modulation. Observed positive

effects, such as PC6 specificity in HRV modulation and specific acupoints reducing angina frequency, align with existing research. However, the absence of significant effects in hypertension and angina studies, and the heart failure study, underscores the uncertainty surrounding acupoint specificity, especially when rigorous sham controls are used. Methodological challenges, particularly the design of truly inert sham controls and the difficulty in achieving adequate blinding, contribute to the inconsistency in findings. Variations in sham control design, potential physiological effects of sham needling, and the influence of placebo effects further complicate the interpretation of results. These factors highlight the need for more rigorously designed studies to clarify the role of acupoint specificity in acupuncture's cardiovascular effects.

6. References

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