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Benefits and Safety of Zhigancao Decoction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus：A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202430133

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 March 2024 and was last updated on 31 March 2024.

INTRODUCTION

Review question / Objective We conducted an extensive review of both domestic and foreign literature to impartially assess the benefits and safety of ZGCD on cardiovascular outcomes in patients with type 2 diabetes mellitus, aiming to shed light on clinical treatment approaches.

Condition being studied Cardiovascular diseases are of major importance in patients with type 2 diabetes, accounting for up to 80% of the excess mortality in these patients. In light of the unsatisfactory outcomes associated with current treatments, clinicians are taking a closer look at Traditional Chinese Medicine (TCM) as an adjuvant or alternative treatment. Zhigancao decoction (ZGCD), can activate qi, supplement blood, and return pulse, is derived from “Treatise on Febrile Diseases”written by Zhang Zhongjing in the Han dynasty have been widely used in treating all forms of cardiovascular for thousands of years in China.

METHODS

Participant or population Patients with diabetic cardiovascular disorder.

Intervention Zhigancao decoction or Zhigancao decoction combine with western medicine.

Comparator Western medicine alone.

Study designs to be included All controlled trials that reported the utilization of ZGCD for the treatment of DCD were included in this study. No restrictions were placed on publication status or language.

Eligibility criteria Inclusion Criteria - 2.2.1. Types of Participants. The study did not impose any limitations based on age, gender, or race. The participants included individuals who had received a diagnosis of DCD based on a well-defined definition or internationally recognized diagnostic criteria.

2.2.2. Types of Interventions. The intervention implemented in this study entailed ZGCD. In the ZGCD group, ZGCD was exclusively employed as the positive intervention, contrasting with the control group. No limitations were imposed on the dosage or duration of medication.
2.2.3. Types of Comparison. The use of WM treatment, including hypoglycemic agents, insulin, and others, has been shown to effectively lower blood glucose levels and enhance cardiovascular function. The control groups in the studies employed the same specifications and dosage of WM as the treatment groups.
2.2.4. Types of Outcomes. The primary outcome measure was the total effective rate, while secondary outcomes included LVEDV, LVESV, LVEF, LVDD, LA, E/A, C-D, SV, P, SBP, DBP, BNP, IL6, TNF-α, SDNN, SDANN, PNN50, adverse reactions, hypotension, headache and dizziness. All included literature reported at least one result from the aforementioned outcomes.
2.2.5 Types of Study Design. All controlled trials that reported the utilization of ZGCD for the treatment of DCD were included in this study. No restrictions were placed on publication status or language.
The exclusion criteria were set as followed. (1) Non-CTs or animal studies. (2) Control group included methods of TCM, such as acupuncture, Chinese patent medicine, herbal extracts and so on. (3) Repeated publication or repeated clinical data. (4) Original and unpublished data that could not be obtained and extracted after contacting the authors. (5) Outcome effect was not clear: The data were incomplete, the outcome effect was not clear, the statistical method was incorrect, and the data could not provide the mean and standard deviation.

Information sources To identify relevant studies on biological therapeutic interventions for DCD, an extensive search was conducted across several databases, including China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journals Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, EMBASE, Web of Science, and Cochrane Library. The retrieval period encompassed the entire duration of databases up until March 2024. No restrictions were placed on language, systemic conditions of participants, or publication year within the scope of this study. The search strategy employed a comprehensive approach, utilizing both MeSH terms and keywords, with a specific emphasis on the topics of "Diabetic Cardiovascular Disorders" and "Zhigancao Decoction". Additionally, the search encompassed intervention measures and diseases associated with these topics, such as Zhigancao Soup, Fumai Decoction and Diabetic Cardiovascular Outcomes etc. Furthermore, a manual search was conducted in the journal literature available to complement the initial search and identify any potential omissions.

Main outcome(s) The primary outcome measure was the total effective rate, while secondary outcomes included LVEDV、LVESV、LVEF、LVDD、LA、E/A、C-D、SV、P、SBP、DBP、BNP、IL6、TNF-α、SDNN、SDANN、PNN50、adverse reactions.

Data management The data extraction process for the studies was conducted by two independent reviewers. To facilitate this process, a study-specific spreadsheet was created in Excel, encompassing variables such as authors, publication date, country, study design, sample size, average age, gender, intervention measures, follow-up duration, and outcome measures.

Quality assessment / Risk of bias analysis The Cochrane Handbook for Systematic Reviews was utilized to evaluate the risk of bias in all studies included in this analysis. These studies were categorized as having a low, high, or unclear risk of bias based on seven specific criteria: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) selective reporting; and (7) other potential risks of bias. In cases where there was disagreement, a third reviewer investigator was consulted to reach a resolution.

Strategy of data synthesis The meta-analysis was conducted utilizing Review Manager 5.4 and Stata 17.0 software. The odds ratio (OR) was employed to evaluate the binary variables, while the mean difference (MD) or standardized mean difference (SMD) was utilized to depict the distinction between groups for continuous variables, depending on whether the results were in similar or different units of measure, respectively. The outcomes were presented with a 95% confidence interval (CI). The presence of heterogeneity was assessed using the chi-square test. If the P-value exceeded 0.1 or the I2 statistic was below 50%, it was concluded that heterogeneity was absent, and the fixed-effects model was selected. Conversely, if the P-value was equal to or less than 0.1 or the I2 statistic was equal to or greater than 50%, the random effects model was utilized. Furthermore, in order to assess the stability of each outcome, a sensitivity analysis was performed. Additionally, the Egger test was

employed to detect any potential publication bias. Moreover, the utilization of the GRADE pro software was instrumental in evaluating the robustness of the evidence and augmenting the credibility of the findings.All data were cross-verified and imported into Rev Man software (V.5.4).

Subgroup analysis Subgroup analysis was performed on the clinical characteristics to investigate the causes of clinical heterogeneity.

Sensitivity analysis By excluding one study at a time, sensitivity analysis was used to examine whether low-quality studies affected the robustness and stability of the overall meta-analysis. Begg's test funnel plot and Egger's test were used to evaluate publication bias.

Country(ies) involved China.

Keywords Zhigancao decoction; Diabetic cardiovascular disorder; Systematic Review and Meta-analysis; Traditional Chinese medicine.

Contributions of each author

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