Efficacy and safety of berberine treatment for cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: What are the therapeutic effects of berberine treatment for cardiovascular disease and the comparison of berberine alone and berberine combined with statins?

Condition being studied: Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall is the foremost cause of premature mortality and of disability-adjusted life years (DALYs) in developed countries, and is also increasingly common in developing countries. The main clinical entities are coronary artery disease (CAD), ischaemic stroke, and peripheral arterial disease (PAD). At present, berberine is widely used in cerebral infarction, coronary heart disease, and atherosclerosis in clinical practice. However, there is not enough evidence to disclose the therapeutic effect of the berberine treatment. The purpose of this study is to conduct a systematic review and meta-analysis of the literature to evaluate the therapeutic effect of berberine in cardiovascular disease.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 April 2022 and was last updated on 21 April 2022 (registration number INPLASY202240128).
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METHODS

Search strategy:
#1 "Cardiovascular Diseases"[MeSH]
#2 cardi*[Title/Abstract] OR heart*[Title/Abstract] OR coronary*[Title/Abstract] OR angina*[Title/Abstract] OR ventric*[Title/Abstract] OR myocard*[Title/Abstract] OR pericard*[Title/Abstract] OR emboli*[Title/Abstract] OR arrhythmi*[Title/Abstract] OR thrombo*[Title/Abstract] OR tachycardi*[Title/Abstract] OR endocard*[Title/Abstract]
#3 atrial*[Title/Abstract] AND fibrillat*[Title/Abstract]
#4 sick*[Title/Abstract] AND sinus*[Title/Abstract]
#5 “Stroke”[MeSH]
#6 stroke*[Title/Abstract] OR apoplex*[Title/Abstract] OR ischem*[Title/Abstract]
#7 cerebr*[Title/Abstract] AND vasc*[Title/Abstract]
#8 brain*[Title/Abstract] AND accident*[Title/Abstract]
#9 (brain*[Title/Abstract] or cerebral*[Title/Abstract] or lacunar*[Title/Abstract]) AND infarc*[Title/Abstract]
#10 “Atherosclerosis”[MeSH]
#11 atherosclero*[Title/Abstract] OR arteriosclero*[Title/Abstract] OR “PAD”[Title/Abstract]
#12 peripheral*[Title/Abstract] AND arter*[Title/Abstract]
#13 “Berberine”[MeSH]
#14 "Berberine" [Title/Abstract] OR "Huanglian" [Title/Abstract] OR "Huangbai" [Title/Abstract]
#15 #1OR#2OR#3OR#4OR#5OR#6OR#7OR#8OR#9OR#10OR#12
#16 #13OR#14
#17 #15AND#16.

Participant or population: Adult patients who were clinically diagnosed with cardiovascular diseases (cerebral infarction, coronary heart disease, atherosclerosis).

Intervention: Berberine alone or combined with statins.

Comparator: Statins, conventional treatment or basic treatment (e.g. vasoactive drugs, neurotrophic drugs, or anti-platelet drugs).

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: Studies were included if they met the following criteria: (1) All studies were randomized controlled trials (RCTs), whether allocation concealment and blinding was used or not. (2) Adult patients who were clinically diagnosed with cardiovascular diseases (cerebral infarction, coronary heart disease, atherosclerosis). (3) The experimental group was treated with berberine or berberine combined with statins, while the control group received statins or conventional treatment. (4) Outcome measures: blood lipids including TC, TG, LDL-C and HDL-C; NIHSS score; inflammatory factors including hs-CRP, IL-6 and TNF-α; carotid atherosclerotic plaque markers including IMT, Crouse score and number of unstable plaques. Studies were excluded if: (1) studies for which the data could not be extracted. (2) the baseline data of patients in two groups were not comparable. (3) repeated publication or duplicate data. (4) Outcome measures were poorly described.

Information sources: The Cochrane Central Register of Controlled Trials(CENTRAL), Cochrane Library, PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), VIP Chinese Science and
Technology Periodical Database (VIP), and Wanfang Data will be searched for relevant information, updated to November 2021. No language or date restrictions will be applied.

**Main outcome(s):**
1. Blood lipids including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C).
2. National Institute of Health stroke scale (NIHSS) score.
3. Inflammatory factors including high sensitive c-reaction protein (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).
4. Carotid atherosclerotic plaque markers including intima-media thickness (IMT), Crouse score and number of unstable plaques.

**Additional outcome(s):** Adverse events.

**Data management:** Two reviewers will independently review the titles and abstracts of the studies retrieved in the searches to identify relevant studies for inclusion. We will record the selection process in sufficient detail to complete a PRISMA flow diagram. Two reviewers will then independently extract the following information from the studies selected for inclusion: authors, year of publication, country, age distribution, gender proportion, study design, intervention condition, diagnosis, intervention period, and outcome measures. If there are disagreements between the two reviewers, a third reviewer will be consulted to determine the final result.

**Quality assessment / Risk of bias analysis:** Two reviewers will independently evaluate the quality of the selected studies according to the Cochrane Collaboration's tool for randomized control trials. Items will be evaluated in three categories: low risk of bias, unclear risk of bias and high risk of bias. The following characteristics will be assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Results from these questions will be graphed and assessed using Review Manager 5.3.

**Strategy of data synthesis:** The meta-analyses will be performed by the Review Manager 5.3 software. The dichotomous variables will be assessed by risk ratios (RR) with 95% confidence intervals (95% CIs) and continuous variables will be analyzed with standard mean difference(SMD) with 95% CIs. Between-study heterogeneity will be assessed using x² test and I² statistic, and substantial heterogeneity is considered when I2 is >50%. The random effects model will be applied to estimate the summary RR, SMD and 95% CIs. Outcomes will be calculated using P values and P<0.05 is considered statistically significant. A sensitivity analysis will be performed to ascertain the results of the meta-analysis by excluding each of the individual studies. Publication bias will be assessed by a funnel plot for meta-analysis, if more than 10 studies were included.

**Subgroup analysis:** If the necessary data are available, subgroup analysis will be done according to berberine alone or combined with statins, different control groups, and different treatment duration.

**Sensitivity analysis:** A sensitivity analysis will be performed to ascertain the results of the meta-analysis by excluding each of the individual studies.

**Language:** No language restrictions.

**Country(ies) involved:** China.

**Keywords:** Cardiovascular disease, berberine, statins, systematic review, meta-analysis.

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