INPLASY PROTOCOL

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Corresponding author:
Heng Ma

179799693@qq.com

Author Affiliation:
Fourth Military Medical University

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Conflicts of interest:
None.

Metformin may reduce the mortality and cardiac events in patients with cardio-cerebrovascular diseases, irrespective of concurrent diabetes: a meta-analysis of randomized controlled trails and cohort studies

Li, T[1]; Jin, S[2]; Jiang, W[3]; Mu, N[4]; Wang, Y[5]; Li, X[6]; Yin, Y[7]; Liu, M[8]; Yu, L[9]; Chang, A[10]; Gu, C[11]; Ma, H[12].

Review question / Objective: **It is highly controversial whether metformin monotherapy or combined therapy may reduce the all-cause mortality, cardiovascular mortality, or cardio-cerebrovascular mortality in patients with cardiovascular diseases, irrespective of concurrent diabetes.**
Condition being studied: **Diabetes mellitus, a heterogeneous mix of physical condition characterized by glucose dysregulation, is an enormous public health issue worldwide. Metformin is recommended as first-line oral glucose-lowering by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). However, there remains controversy regarding the cardiovascular roles of metformin in CVD in the last three decade. Recent publications have shown that metformin can reduce or fail to reduce the mortality and cardiovascular risk of CVD patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 June 2020 and was last updated on 02 June 2020 (registration number INPLASY202060008).

INTRODUCTION

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American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). However, there remains controversy regarding the cardiovascular roles of metformin in CVD in the last three decade. Recent publications have shown that metformin can reduce or fail to reduce the mortality and cardiovascular risk of CVD patients.

METHODS

Search strategy: ((((Myocardial Ischemia[MeSH] OR Myocardial Infarction[MeSH] OR Coronary Artery Disease[MeSH] OR Angina Pectoris[MeSH] OR Heart Failure[MeSH] OR Stroke[MeSH] OR Cardiovascular Diseases[MeSH] OR Ischemic Heart Disease OR Cardiac Ischemia OR Ischemic Heart Diseases OR Myocardial Infarctions OR Cardiovascular Stroke OR Coronary Atherosclerosis OR Coronary Artery Disease OR Coronary Heart Diseases OR Angina OR Cardiac Failure OR Myocardial Failure OR Cerebrovascular Accident OR Cardiovascular Disease OR Heart Diseases OR Heart Disease)) AND (Metformin[MeSH] OR Dimethylbiguanidine OR Dimethylguanylguanidine OR metformin hydrochloride OR Dimethylbiguanide hydrochloride OR Metformin)) AND (Mortality[MeSH] OR Myocardial Ischemia[MeSH] OR Myocardial Infarction[MeSH] OR Coronary Artery Disease[MeSH] OR Angina Pectoris[MeSH] OR Heart Failure[MeSH] OR Stroke[MeSH] OR Cardiovascular Diseases[MeSH] OR Peripheral Vascular Diseases[MeSH] OR mortality OR Ischemic Heart Disease OR Ischemic Heart Diseases OR Cardiac Ischemia OR Myocardial Infarctions OR Myocardial Infarction OR Cardiovascular Stroke OR Coronary Atherosclerosis OR Coronary Heart Diseases OR Angina OR Cardiac Failure OR Myocardial Failure OR Cerebrovascular Accident OR Cardiovascular Disease OR Heart Diseases OR Heart Disease OR peripheral vascular disease OR Heart Failure)) AND ((randomized controlled trial[Publication Type] OR randomized[TIAB] OR randomised[TIAB] OR placebo[TIAB] OR cohort studies[MeSH] OR Observational Study[Publication Type] OR cohort OR STROBE OR observational[TIAB]) NOT (Review[Publication Type]) NOT (meta-analysis[Publication Type]) NOT (Comment[Publication Type]) NOT (Letter[Publication Type]) NOT (Case-Control Studies[Publication Type])).

Participant or population: Adults (≥18 y) with myocardial ischemia (angina, myocardial infarction, coronary heart disease, or myocardial ischemia), stroke, or heart failure, irrespective of gender, and race, irrespective of concurrent diabetes.

Intervention: 1) Patient receiving metformin. 2) Patient receiving metformin and other hypoglycemic drug(s).

Comparator: 1) Patient receiving no intervention, or with placebo or a lifestyle intervention 2) Patient receiving metformin and other other hypoglycemic drug(s).

Study designs to be included: Randomized controlled trials and cohort studies.

Eligibility criteria: Adults (≥18 y) with myocardial ischemia (angina, myocardial infarction, coronary heart disease, or myocardial ischemia), stroke, or heart failure, irrespective of gender, and race, irrespective of concurrent diabetes.

Information sources: PubMed and Embase from inception to Jun 2020 will be searched. Additional search will be conducted through reviewing the list of articles retrieved. No restrictions on language or publication date will be applied during the literature search process. The eligibility was based on the full text and supplement files, which was acquired from the Libraries of The Fourth Military Medical University and Xi'an Jiao Tong University. We will also seek for full text of published articles in DingXiangYuan (http://www.dxy.cn/) and TaskExchange (https://taskexchange.cochrane.org/), if the literature were not available in the libraries. In addition, we also seek for full text and missing raw data from the references of published articles via our institutional

email. Any inconsistency will be sent to a third reviewer for final decision.

Main outcome(s): 1) all-cause mortality; 2) cardiovascular mortality; 3) Cardiovascular events.

Additional outcome(s): NA.

Data management: For dichotomous outcomes, the Mantel-Haenszel method will be applied to pool odds ratios (ORs)/ relative risks (RRs). Continuous variables reported as median and interquartile range will be converted to mean and standard deviation for meta-analysis using the reported approaches. For survival data or outcomes, we will use the inverse variance technique for meta-analysis of hazard ratios (HRs).

Quality assessment / Risk of bias analysis: Cochrane risk of bias assessment tool for RCTs and the Newcastle–Ottawa Scale (NOS) for cohort studies will be applied for risk of bias assessment.

Strategy of data synthesis: Data were analyzed by the STATA 16.0 (Stata Corp, College Station, TX, USA) and RevMan 5.3 (Nordic Cochrane Center, Copenhagen, Denmark). We will apply a random/fixed effects model to combined dichotomous outcomes and continuous outcomes using HR/RR/OR and standardised mean differences (SMDs) with their corresponding 95% confidence intervals (95% CI). Sensitivity analysis will be conducted using leave one out approach. I^2 statistics will be quantified for heterogeneity assessment for each main outcome. Publication bias will be assessed using Begg's and Egger's test.

Subgroup analysis: Myocardial infarction; Revascularization; Angina; Heart failure; Stroke; etc.

Sensibility analysis: Sensibility analysis will be applied if the heterogeneity is obvious.

Language: English.

Country(ies) involved: China.

Keywords: Metformin; Type 2 diabetes mellitus; Mortality; Cardiovascular diseases; Myocardial ischemia.

Contributions of each author:
Author 1 - Tian Li.
Author 2 - Shanshan Jin.
Author 3 - Wenhua Jiang.
Author 4 - Nan Mu.
Author 5 - Yishi Wang.
Author 6 - Xiaokang Li.
Author 7 - Yue Yin.
Author 8 - Manling Liu.
Author 9 - Lu Yu.
Author 10 - Alex Chia Yu Chang.
Author 11 - Chunhu Gu.
Author 12 - Heng Ma.