INPLASY PROTOCOL

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Conflicts of interest:
None.

Efficacy of metformin monotherapy or combined therapy in cardiac, macrovascular, and microvascular risk of people with type 2 diabetes mellitus

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ABSTRACT

Review Question: **Does metformin as monotherapy or add-on treatment reduce the cardiac, macrovascular, and microvascular risk of people with type 2 diabetes mellitus?**

Rationale: **Roles of metformin monotherapy or combined therapy in cardiac, macrovascular, and microvascular risk of people with type 2 diabetes mellitus.**

Condition being studied: **Diabetes mellitus, a heterogeneous mix of physical condition characterized by glucose dysregulation, is an enormous public health issue worldwide. It is estimated that 26, 9.4, and 91.8 million adults have diagnosed diabetes, undiagnosed diabetes, and prediabetes in United States, respectively. CVD is the greatest cause of morbidity and mortality associated with type 2 diabetes, which needs intensive management of glucose, lipid, and blood pressure to minimise risk of complications and disease progression. Currently, T2DM is incurable and some therapeutics antihyperglycaemic drugs bear poor efficacy and adverse effects. The majority of patients fail to be diagnosed until an advanced stage, which is susceptible to suffering from CVD, the most common diabetic complication. Thereby, it is urgent to explore a novel drug to improve the cardiovascular outcomes of T2DM.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 March 2020 and was last updated on 31 March 2020 (registration number INPLASY202030018.

INTRODUCTION

Objectives / Review question: **Does metformin as monotherapy or add-on treatment reduce the cardiac, macrovascular, and microvascular risk of people with type 2 diabetes mellitus?**

Condition being studied: **Diabetes mellitus, a heterogeneous mix of physical condition characterized by glucose dysregulation, is**

an enormous public health issue worldwide. It is estimated that 26, 9.4, and 91.8 million adults have diagnosed diabetes, undiagnosed diabetes, and prediabetes in United States, respectively. CVD is the greatest cause of morbidity and mortality associated with type 2 diabetes, which needs intensive management of glucose, lipid, and blood pressure to minimise risk of complications and disease progression. Currently, T2DM is incurable and some therapeutics antihyperglycaemic drugs bear poor efficacy and adverse effects. The majority of patients fail to be diagnosed until an advanced stage, which is susceptible to suffering from CVD, the most common diabetic complication. Thereby, it is urgent to explore a novel drug to improve the cardiovascular outcomes of T2DM.

METHODS

Participant or population: Inclusion Criteria:1) adults (more than 18 y) with type 2 diabetes Exclusion Criteria: 1) children, pregnant women, and people with only prediabetic state, impaired fasting glucose, or insulin resistance.

Intervention: Oral administration of metformin, or metformin analogue (metformin hydrochloride, metformin sustained release tablet, Glucophage, et al).

Comparator: 1) Placebo; 2) no intervention; 3) lifestyle intervention; 4) antidiabetics.

Study designs to be included: RCT.

Eligibility criteria: 1) adults (≥18 y) with type 2 diabetes irrespective of age, gender, and race; 2) comparing any dose and preparation of oral metformin/metformin analogue (metformin hydrochloride, metformin sustained release tablet, Glucophage, et al) with no intervention, or with placebo or a lifestyle intervention; 3) comparing combination of any dose and preparation of oral metformin/metformin analogue (metformin hydrochloride, metformin sustained release tablet, Glucophage, et al) and antidiabetics with the same antidiabetics; 4) reporting mortality, cardiac, macrovascular, microvascular, or cardio-metabolic outcomes (cardiovascular mortality, myocardial infarction, stroke, heart failure, ischemic heart disease); 5) randomized controlled trial (RCT) irrespective of blinding or arm. Please note that 2) or 3) is either-or situation.

Information sources: We searched PubMed and Embase from inception to the present by using medical subject headings (MeSH), Emtree, and text word with no language limitations. The full electronic search strategy of PubMed and Embase was according to the Biondi-Zoccai's and Wong's methods , respectively with minor revision. Chinese publications are translated by a reviewer (Yue Yin). Other non-English publications will be posted on Cochrane TaskExchange for voluntary interpreter. Moreover, the references of relevant studies, reviews, editorials, and letters were also searched manually. 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 (Heng Ma) for final decision.

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

Additional outcome(s): 3) all cardiac events; 4) all macrovascular events; 5) all microvascular events.

Data management: Two reviewer (Tian Li and Nan Mu) independently extracted data. Any disagreement will be resolved by discussion until consensus is reached or by consulting a third reviewer (Heng Ma). The collected data includes: trail No., reference No., first author, journal, publication year,

region, intervention/control group, sample size, age, male percentage, trial duration, diabetes duration, HbA1c (%), and outcomes, which were summarized in a standardized Excel (Microsoft Corporation, Redmond, USA). The outcomes include all-cause mortality, cardiovascular mortality, all CVD events. Data management was used by EndNote X9.

Quality assessment / Risk of bias analysis: The risk of bias was applied according to the Cochrane guidelines including 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 sources. Only RCT will be asseesed.

Strategy of data synthesis: Dichotomous data were calculated as relative risks (RRs) or odds ratio (OR), with 95% confidence intervals (CI). All tests were two tailed and a P value less than 0.05 was deemed statistically significant. Data were analyzed by the STATA 16.0 (Stata Corp LLC, College Station, Texas, USA) and RevMan 5.3 (Nordic Cochrane Center, Copenhagen, Denmark).

Search strategy: PubMed and Embase amd takes PubMed for example:((((Diabetes Mellitus [MeSH] OR Type 2 Diabetes Mellitus OR Diabetes OR Type 2 Diabetes OR Diabetes Mellitus OR Diabetic)) AND (Metformin[MeSH] OR Dimethylbiguanidine OR Dimethylguanylguanidine OR Metformin)) AND (Cardiovascular Diseases[MeSH] OR Diabetic Nephropathies[MeSH] OR Diabetic Retinopathy[MeSH] OR Peripheral Vascular Diseases[MeSH] OR heart OR cardiovascular OR myocardial OR stroke OR hypertension OR coronary heart disease OR coronary heart diseases OR mortality OR ischemia OR ischemic OR peripheral vascular disease OR peripheral vascular diseases OR atherosclerosis OR Kidney Diseases OR Kidney Disease OR Retinal Disease OR Retinal Diseases OR Peripheral Vascular Disease)) AND ((randomized controlled trial[Publication Type] OR randomized[TIAB] OR randomised[TIAB] OR placebo[TIAB])) NOT (Review[Publication Type]) NOT (meta-analysis[Publication Type]) NOT (Comment[Publication Type]) NOT (Letter[Publication Type])).

Subgroup analysis: Regions, different control group, different types of CVD, et al might be considered for subgroup analysis to provide a clear understanding for readers.

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

Language: English.

Countries involved: China.

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