INPLASY PROTOCOL

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Conflicts of interest: **No.**

Efficacy and safety of ACEI / ARB drugs in patients with COVID-19 combined with diabetes mellitus: A protocol for systematic review and meta-analysis of Randomized Controlled Trials

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Review question / Objective: **In this study, we compared the effects of ACEI / ARB and non ACEI / ARB drugs on mortality, incidence of serious complications and healing in covid-19 patients with diabetes mellitus through extensive collection of randomized controlled trials.**
Condition being studied: **Existing studies have found that age, diabetes, hypertension and obesity increase the morbidity and mortality of COVID-19. However, diabetes is a chronic inflammatory disease. Metabolic disorders, chronic inflammatory, coagulation state and endothelial damage in diabetes are closely related to the high morbidity of obesity, hypertension and cardiovascular diseases.Diabetic cardiovascular complications and diabetic renal complications are important risk factors for severe complications in patients with covid-19. Blood glucose and diabetes are independent risk factors for mortality and morbidity in SARS patients. Other studies have found that the clearance of SARS-COV-2 in diabetic patients is delayed. Therefore,There is a very close relationship between COVID-19 and diabetes. ACEI / ARB drugs are considered to have significant immunomodulatory effects, which are beneficial for COVID-19 infection by reducing cytokines, reducing lung inflammation and systemic inflammatory response. However, some people think that ACEI / ARB drugs can increase the level of angiotensin-2 (ACE2). ACE2 is the receptor of SARS-COV-2, which may increase coronavirus infection. According to the above argument, we want to know whether ACEI / ARB drugs are safe and beneficial for the treatment of COVID-19 combined with diabetes based on large-scale data analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 June 2020 and was last updated on 30 June 2020 (registration number INPLASY202060111).

INTRODUCTION

Review question / Objective: **In this study, we compared the effects of ACEI / ARB and non ACEI / ARB drugs on mortality, incidence of serious complications and healing in covid-19 patients with diabetes mellitus through extensive collection of randomized controlled trials.**

Rationale: Existing studies have found that age, diabetes, hypertension and obesity increase the morbidity and mortality of COVID-19. ACEI / ARB drugs are considered to have significant immunomodulatory effects, which are beneficial for COVID-19 infection. However, it may also increase the level of angiotensin-2 (ACE2). ACE2 is the receptor of SARS-COV-2, which may increase coronavirus infection.

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METHODS

Search strategy: Computer retrieval three English database including PubMed, EMBASE, the Cochrane Library, and 4 Chinese databases including China National Knowledge Infrastructure (CNKI) database, Wanfang Data Knowledge Service Platform, the VIP information resource integration service platform (cqvip), China Biology Medicine Disc (Sino Med) will be searched from their inception to June 1 2020, with language limitation of English and Chinese. In addition, Google scholar and Baidu Scholar will be used to find out potential missing papers.

Participant or population: Patients who are diagnosed as COVID-19 combined with diabetes mellitus.

Intervention: ACEI/ARB drugs.

Comparator: Patient without ACEI/ARB drugs.

Study designs to be included: Only RCTs evaluating the efficacy and safety of ACEI/ ARB drugs.

Eligibility criteria: Eligibility Criteria : We will formulate our participant's eligibility criteria using PICOS (participants, interventions, comparison, outcomes and study designs)description model. Participants. Patients confirmed with diabetes mellitus and COVID-19. without restriction of age, gender, course of disease. At any clinical stage of the disease, thus mild, moderate or severe/critical case. With or without other comorbid conditions. Intervention. ACEI/ARB drugs of any dose. Comparator. ACEI/ARB placebo or standard of care. Outcomes /endpoints. Primary endpoints. Blood lymphocyte count Time to clinical recovery. All-cause mortality. Secondary endpoints. Incidence of severe complications Blood glucose fluctuation Study design. Randomized controlled clinical trials.

Information sources: Computer retrieval three English database including PubMed, EMBASE, the Cochrane Library, and 4 Chinese databases including China National Knowledge Infrastructure (CNKI) database, Wanfang Data Knowledge Service Platform, the VIP information resource integration service platform

(cqvip), China Biology Medicine Disc (Sino Med) will be searched from their inception to June 1 2020, with language limitation of English and Chinese. In addition, Google scholar and Baidu Scholar will be used to find out potential missing papers.

Main outcome(s): Blood lymphocyte count; Time to clinical recovery; All-cause mortality.

Additional outcome(s): Incidence of severe complications. Blood glucose fluctuation.

Data management: All the retrieved papers will be transferred to EnDnote 7 and duplicates will be removed. Two investigators will independently assess the title and abstract of all the retrieved papers based on the eligibility criteria. The two investigators will independently evaluate the full texts. Disagreements between the two investigators will be settled through discussion, and if persisted, the third investigator will be involved as arbitrator.

Quality assessment / Risk of bias analysis: The Cochrane risk of bias tool will be used to assess the risk of bias for each included study. The risk of bias of each trial will be judged by two independent investigators as 'Low', 'Some concerns' or 'High' based on the critical domains, including bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Disagreements will be resolved by discussion among the two investigators. If the disagreements persist, the third investigator will chip in as an arbitrator.

Strategy of data synthesis: Data analysis will be conducted in Review Manager Version 5.3 and stata 14.0 software for Mac. The risk ratio (RR) was used as the analysis statistic and 95% CI was provided. The heterogene- ity of the results was analyzed by x2 test (the test level was a = 2 0.1), and the degree of heterogeneity was determined byI . If there is no statistical heterogeneity between the results of each study, the fixed effect model is used for meta-analysis; if there is statistical heterogeneity between the results of each study, the source of heterogeneity is further analyzed. After excluding the influence of obvious clinical heterogeneity, the random effect model is used for meta-analysis. The level of meta-analysis is set as a=0.05. Significant clinical heterogeneity was treated by subgroup analysis or sensitivity analysis, or only descriptive analysis.

Subgroup analysis: subgroup analysis will be carried out between studies with different duration of follow-up, age of participants, severity of the disease, comorbidities, settings and quality of studies for risk of bias. Following the subgroup analysis, we will look at the data for heterogeneity, and if acceptable, we will perform a meta-analysis. If the data are heterogeneous, we will do a narrative description of findings. To see the robustness of pooled data, sensitivity analysis will be conducted between low and Subgroup analysis will be carried out between studies (at least 10 trials) are available in this study.

Sensibility analysis: To ensure the stability of the results, we will conduct sensitivity analysis of the results by excluding each of the studies included in the analysis one by one. If there is one or more very large study, we will repeat the analysis excluding them to determine how much they dominate the results.

Language: English and Chinese.

Country(ies) involved: China.

Other relevant information: None.

Keywords: COVID-19, diabetes, ACEI/ARB drugs, efficacy and safety, protocol, systematic review and meta-analysis, RCTs.

Dissemination plans: There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-

reviewed journals and present at international and national conferences.

Contributions of each author:

Author 1 - Yan Yang.
Author 2 - Yan Liu.
Author 3 - Yalin Chen.
Author 4 - Wen Zhong.
Author 5 - Yuan Tian.
Author 6 - Xiaoke Liu.