INPLASY PROTOCOL

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Conflicts of interest:
No conflicts of interest in this work.

The effect of nebivolol on erectile function in the cases with coronary artery bypass surgery: A protocol for a systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **In recent years, the clinical trials of nebivolol on erectile function in the cases with coronary artery bypass grafting have increased, multiple studies confirm that nebivolol exerts protective effects on erectile function against the disruptive effects of CPB in patients undergoing CABG. But its quality and efficacy have not been systematically evaluated.The purpose of this systematic review is to evaluate the efficacy of nebivolol for erectile function in the cases with coronary artery bypass surgery men, provide evidence-based medical evidence and suggestion for further research in the future.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 June 2020 and was last updated on 29 June 2020 (registration number INPLASY202060110).

INTRODUCTION

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the cases with coronary artery bypass surgery men, provide evidence-based medical evidence and suggestion for further research in the future.

Condition being studied: Erectile dysfunction (ED) refers to the inability of men to obtain and maintain adequate penile erection to maintain satisfactory sexual intercourse, and it is one of the most common male sexual dysfunctions.During the last two decades, significant advances in the pathophysiology of erectile dysfunction revealed that erectile dysfunction is of vascular origin in the majority of cases, and thus its prevalence is higher in patients with overt cardiovascular disease or cardiovascular risk factors.Ischemic cardiac diseases are common health problems for elderly population and despite the new treatment methods, coronary artery bypass grafting (CABG) are still commonly perform. CABG with the use of cardiopulmonary bypass (CPB) may cause endothelial dysfunction by reducing the synthesis and release of plasma nitric oxide (NO),Endothelial dysfunction is a major cause of ED, the use of beta-blockers after CABG surgery is common and one of the important side effects is the impact on one's sexual life.

METHODS

Search strategy: A combination of medical subject headings(Mesh) and text words will be used to develop the literature search strategies, mainly including① nebivolol; ② Erectile disfunction, ED; ③ coronary artery bypass; ④ clinical trial or randomized controlled trial. Two researchers (Yali Yang, Shanshan Yong) will independently perform the literature search in the form of "back-to-back", and only studies reported in English or Chinese language will be included due to resource limits. Citations obtained from database searching will be managed using Endnote X8 software.

Participant or population: Male patients after diagnosis of coronary artery disease and who are referred to coronary artery bypass, and having regular sexual partner. Regardless of whether they had ED, no limit with age. All medications used in the preoperative or postoperative period were recorded.

Intervention: All RCTs which contrast nebivolol with other drugs or placebo will be included whether nebivolol is an intervention or control measure. If nebivolol is used as a control in the trial and another drug is an intervention, we consider reversing the order of the 2 interventions in this systematic review, that is, nebivolol will be regarded as an intervention measure, and the other drug as a control measure. Limited to RCTs for drug therapy. Drug therapy in intervention group defined as nebivolol.

Comparator: Other adrenoceptor beta blockers will be included. The control measure can be 1 drug or combination of more than 1 drug.

Study designs to be included: Randomized controlled trials (RCTs) that meet the eligibility criteria will be included.

Eligibility criteria: Randomized controlled trials (RCTs) will be included.

Information sources: We will systematically search English literature in Cochrane library, EMBASE, PubMed, and Chinese literature in China National Knowlege Infrastructure (CNKI), Chinese biomedical document service system (SinoMed), VIP Chinese Science and Technology Journal Database (VIP), WANFANG data. The literature publication deadline is August 31, 2020 in each platform or database and the search work will be done in September, 2020. The literature search update will be executed again before the systematic review is completed. Subject heading, free text words will be used to search in Cochrane library, EMBASE, PubMed. In Cochrane library and EMBASE, the using of free words will be limited within title, abstract and keywords, but in PubMed, limited in tittle/abstract. The "topic" field will be used for the search of CNKI and WANFANG, and the "title or keyword" filed

for the search of VIP. The subject heading plus free words form will be used to retrieve SinoMed.

Main outcome(s): IIEF-5 score.

Additional outcome(s): Adverse events: all adverse events reported in the included studies.

Quality assessment / Risk of bias analysis: The risk assessment of the bias will be independently taken by 2 reviewers (Yali Yang, Shanshan Yong) based on the extracted data information. Any inconsistencies will be discussed and resolved with the third author (Fuhao Li). This process will be based on the Cochrane Collaboration's tool for assessing risk of bias. Assessment items according to the information of random sequence generation, assignment hiding, blind to patients and researchers and blind measurement, data integrity, selective reporting, other bias. The results of the assessment will be shown as high risk, unclear, and low risk.The outcome of the assessment of risk of bias will be presented in tabular form or a specific figure made by using Review Manager 5.3 software.

Strategy of data synthesis: If the clinical heterogeneity between the included clinical trials is significant, or the data from the original study cannot be extracted, we will perform descriptive analysis or narrative synthesis. Only when the apparent clinical heterogeneity between studies is excluded and the data are sufficiently similar and homogeneous, the meta-analysis is conducted.Chi-square test will be used to test the heterogeneity and I2 statistic will be used to test the size of heterogeneity. There is heterogeneity when the P-value of the Chi-square test ≤ .10, but no heterogeneity while the Chi-square test P-value >.10.We define I2 ≤ 50% for acceptable heterogeneity in multiple studies. In this case, the fixed model will be applied to calculate mean differences (MDs) by inverse variance and risk ratios (RRs) by Mantel–Haenszel method. When I2 > 50%, high heterogeneity between studies is considered. In this case, the causes of heterogeneity such as the age, the severity of the condition, the dose and the length of the intervention will be analyzed and subgroup analysis will be used[11,12]. If there still have higher heterogeneity after the above methods processed, random model will be conducted in meta-analysis. MDs and 95% confidence intervals (CIs) will be used for the effect size of the numerical variable, and RRs and 95% CIs for the effect size of dichotomous variable. The effect size will be measured by Z test, and the P-value ≤ .05 is statistically significant .The results of the meta-analysis will be presented as forest plots by RevMan 5.3.

Subgroup analysis: Subgroup analysis will be performed according to age, body mass index, blood pressure, baseline level, different time point of outcome measurement.

Sensibility analysis: We will use sensitivity analysis to test the stability and reliability of meta-analysis. It will be conducted by 2 methods: eliminating each study one by one; using random-effect model (DerSimonian & Laird method) to test the results after using the fixed effect model.

Country(ies) involved: China.

Keywords: nebivolol; erectile dysfunction; coronary artery bypass; IIEF-5; systematic review.

Contributions of each author:
Author 1 - Yali Yang.
Author 2 - Shanshan Yong.
Author 3 - Fuhao Li.
Author 4 - Liang Dong.