INPLASY PROTOCOL

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Conflicts of interest:
The authors declare that they have no competing interests.

Enalapril and carvedilol for prevention anthracycline-induced cardiotoxicity: a systematic review and meta-analysis

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Review question / Objective: **P: cancer patients with a anthracycline chemotherapy. I: using enalapril or carvedilol as the cardioprotective agent. C: comparing with a placebo treatment. O: the cardiotoxicity events and the absolute change of left ventricular ejection fraction. S: a systemic review and meta analysis.**
Condition being studied: **Previous studies about enalapril or carvedilol for the prevention of anthracycline-induced cardiac toxicity. But there was a conflict result about them and limited the use of them clinically.**
Information sources: **We will search on the PubMed, Medline, Embase, and Cochrane databases to evaluate all relevant study and excluded studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 June 2020 and was last updated on 01 June 2020 (registration number INPLASY202060005).

INTRODUCTION

Review question / Objective: **P: cancer patients with a anthracycline chemotherapy. I: using enalapril or carvedilol as the cardioprotective agent. C: comparing with a placebo treatment. O: the cardiotoxicity events and the absolute change of left ventricular ejection fraction. S: a systemic review and meta analysis.**

Rationale: **There was a conflict result about enalapril or carvedilol for the prevention of anthracycline-induced cardiotoxicity. We**

will try to find the truth and help get a efficient prevention strategy by making a new systemic review and meta-analysis including both agents.

Condition being studied: Previous studies about enalapril or carvedilol for the prevention of anthracycline-induced cardiac toxicity. But there was a conflict result about them and limited the use of them clinically.

METHODS

Search strategy: All included studies were published before December 31, 2019 from Pubmed, Medline, Embase and Cochrane databases. Search terms included "enalapril(mesh)," "carvedilol(mesh)," "anthracycline(mesh)," "doxorubicin (mesh)," "idarubicin," "daunorubicin," and "cardiotoxicity(mesh)."

Participant or population: Cancer patients with a anthracycline chemotherapy.

Intervention: Using enalapril or carvedilol as the cardioprotecitve agent.

Comparator: Using placebo as the blank control.

Study designs to be included: We only included randomized controlled trial.

Eligibility criteria: We will include studies as follow: (1) RCT about adult tumor patients, (2) plan to have a chemotherapy including anthracycline, (3) used enalapril or carvedilol as cardioprotective agents, (4) had similar primary outcome or secondary outcome.

Information sources: We will search on the PubMed, Medline, Embase, and Cochrane databases to evaluate all relevant study and excluded studies.

Main outcome(s): The happen of cardiotoxicity events and the absolute change of left ventricular ejection fraction.

Data management: Yang and Yuan would help to collect and assess included trials about the characteristic baseline and the outcome of different trials. Disagreement would be discussed and resolved through consensus.

Quality assessment / Risk of bias analysis: According to the Cochrane handbook systematic review of intervention and GRADE, Yang and Yuan will evaluate the included studies and confirme that the low risk of bias brought high quality. We will assess the publication bias by utilizing the funnel plot. If necessarily, we will make a Jadad scale to help assess the bias of all included trials.

Strategy of data synthesis: We will calculate the ORs with 95% CIs using a random-effects model for dichotomous and continuous data respectively. Heterogeneity is assessed by I2 statistics. We will regard the I2 values of 25, 50, and 75% as low, moderate, and high heterogeneity. $P < 0.05$ means a statistical significance.

Subgroup analysis: We will include the different types of cardioprotective agents, average anthracyclie cumulative dosd, and follow-up time in different subgroup analysis. If finding other factors, like age, side effect, which cause heterogeneity, the new more subgroup analysis will be made.

Sensibility analysis: We will use the method by removing the trials one by one to find the source of heterogeneity. The meta-regression analysis will be carried out too.

Language: No. And we will reserch all published articles in English.

Country(ies) involved: China.

Keywords: anthracycline, doxorubicin, enalapril, carvedilol, cardiotoxicity

Contributions of each author:
Author 1 - Yanjun Chen - This author is the guarantor for the veracity and accuracy of the information in the registered protocol.
Author 2 - Junteng Zheng - Author 2 joined in buliding the study protocol and drafted

the manuscript, analyzed all including data and finished the whole paper.
Author 3 - Ye Luo - Author 3 joined in buliding the study protocol and analyzed the including data with author 2.
Author 4 - Huihua Yang - Author 4 helped to collect and assess included trials about the characteristic baseline and the outcome of different trials.
Author 5 - Zhiming Yuan - Author 5 helped to collect and assess included trials about the characteristic baseline and the outcome of different trials with author 4.