

INPLASY PROTOCOL

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Conflicts of interest: No.

Prognostic value of the level of gut microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: a meta-analysis and systematic review

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Review question / Objective: The effect of TMAO on the prognosis of patients with heart failure is unknown, so this study was designed to observe the effect of TMAO on the prognosis of patients with heart failure **P:**patients with heart failure **O:**The relationship between plasma TMAO and all-cause death in patients with heart failure.

Condition being studied: Heart failure is a complex multifactor disease with a wide range of socio-economic consequences. Despite the latest development of new drugs and treatment strategies, CHF related mortality and incidence rate is still high. Targeting the gut microbiome is a new strategy, as people are increasingly aware of its important role in overall health, one of which is heart failure. Trimethylamine nitrogen oxide (tmno) is considered to be a key mediator between intestinal microbiome changes and heart failure, and is associated with poor prognosis in patients with heart failure. We aimed to determine the prognostic value of TMAO in heart failure (HF).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 May 2020 and was last updated on 09 May 2020 (registration number INPLASY202050030).

P:patients with heart failure **O:**The relationship between plasma TMAO and all-cause death in patients with heart failure.

Rationale: Objective: trimethylamine-N-oxide (TMAO), a metabolite of intestinal microbial origin, is considered to be the key mediator between the change of intestinal microflora and heart failure, and is

INTRODUCTION

Review question / Objective: The effect of TMAO on the prognosis of patients with heart failure is unknown, so this study was designed to observe the effect of TMAO on the prognosis of patients with heart failure

associated with poor prognosis in patients with heart failure. The purpose of this meta-analysis was to systematically assess the relationship between plasma TMAO levels and the prognosis of heart failure.

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METHODS

Search strategy: Based on the retrieval strategy, we identified 272 potential studies from our initial search and excluded 260 studies including reviews, experience summaries, animal model experiments, medical record reports and duplicate literatures. The full text of the remaining 12 studies was reviewed, and studies failing to meet the inclusion criteria and the outcome indicators were excluded. Eventually, 6 English-language studies met our inclusion criteria.

Participant or population: Patients with heart failure.

Intervention: No.

Comparator: No.

Study designs to be included: Prospective study.

Eligibility criteria: 1) The research methods are prospective research, and complete data can be obtained from literature; 2) the research methods are basically the same among the studies, the heterogeneity

between groups is small, and the research is comparable; 3) the outcome indicators should include the relationship between TMAO in blood and all-cause mortality.

Information sources: PubMed, Cochrane Library and EMBASE databases were searched for studies up to may 2020.

Main outcome(s): The relationship between plasma TMAO and all-cause death in patients with heart failure.

Additional outcome(s): The relationship between TMAO and rehospitalization in patients with heart failure, TMAO and mace in patients with heart failure, BNP / NT Pro BNP, hsCRP, gender, region, age of patients, ultrasound results, follow-up time, adjustment and other factors on outcome indicators.

Data management: Relevant data were extracted from each individual eligible study using a structured table. Two reviewers (Hua Qu and Lina Miao) extracted data independently and checked with each other. We contacted the authors to obtain the original data if the article lacked key information related to the investigation. Disagreement between the reviewers was resolved by consulting a third investigator (Dazhuo Shi). Basic information and research content were extracted for each study.

Quality assessment / Risk of bias analysis: The bias risk assessment tool described in the Cochrane Handbook 5.3 was used. The literature quality assessment was based on selection bias, implementation bias, measurement bias, follow-up bias, reporting bias and other biases. The risk of bias was categorised as low, high or unknown for each bias type. The extracted literature data was analyzed with Review Manager 5.3.

Strategy of data synthesis: The data were analyzed by Revman 5.3 software and Stata 12.0 meta analysis module. The continuous variables were analyzed with standard

mean difference (SMD) and 95% confidence interval (CI).

Subgroup analysis: If necessary, we will evaluate the impact of TMAO level on outcome indicators according to the TMAO level before and after the patients themselves, and the TMAO level comparison results of heart failure patients and healthy people. And we will conduct subgroup analysis according to research design, gender, region, age of patients, BNP / NT proBNP level, ultrasound results, follow-up time, adjustment and other factors to determine the impact on outcome indicators.

Sensibility analysis: Sensitivity analysis can be used to judge the stability and reliability of research results. By eliminating the literature with high risk of bias and poor quality, meta analysis is carried out again, and the results before and after comparison are made to judge the stability and reliability of the results.

Language: No language limits be imposed on the search.

Country(ies) involved: China, United States of America, UK, Norway, Greece, France, Netherlands, Germany, Norway, Greece, Poland, France, Italy, Japan.

Other relevant information: No.

Keywords: TMAO, Heart failure, prognosis, All cause death.

Dissemination plans: No.

Contributions of each author:

Author 1 - Lina Miao - Literature search, screening, data abstraction, analysis and writing the manuscript.

Author 2 - Hua Qu - Literature search, screening, data abstraction and analysis.

Author 3 - Dazhuo Shi - Conceptualization, methodology.