INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

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Effects of angiotensin-receptor neprilysin inhibitor on exercise capacity, quality of life, and cardiac function in heart failure with preserved ejection fraction: a protocol for meta-analysis

Fukuta, H[1]; Hagiwara, H[2]; Kamiya, T[3].

Review question / Objective: Nearly half of patients with heart failure (HF) have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved EF (HFpEF) are high. Patients with HFpEF are often elderly and their primary chronic symptom is severe exercise intolerance that results in a reduced quality of life (QOL). Thus, improvement of exercise capacity presents another important clinical outcome in HFpEF patients. Left ventricular (LV) diastolic dysfunction is associated with the pathophysiology of HFpEF and LV diastolic dysfunction contributes importantly to exercise intolerance in HFpEF patients. The angiotensin-receptor neprilysin inhibitor (ARNI) sacubitril/valsartan was shown to be associated with better survival in HFpEF patients. However, there is insufficient evidence as to the effects of ARNI on exercise capacity and cardiac function in these patients. Accordingly, the purpose of this meta-analysis is to evaluate the effects of ARNI on exercise capacity and QOL as well as cardiac function in HFpEF patients.

INTRODUCTION

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another important clinical outcome in HFpEF patients. Left ventricular (LV) diastolic dysfunction is associated with the pathophysiology of HFpEF and LV diastolic dysfunction contributes importantly to exercise intolerance in HFpEF patients. The angiotensin-receptor neprilysin inhibitor (ARNI) sacubitril/valsartan was shown to be associated with better survival in HFpEF patients. However, there is insufficient evidence as to the effects of ARNI on exercise capacity and cardiac function in these patients. Accordingly, the purpose of this meta-analysis is to evaluate the effects of ARNI on exercise capacity and QOL as well as cardiac function in HFpEF patients.

Condition being studied: Patients who are symptomatic despite optimal medical therapy.

METHODS

Participant or population: Patients with heart failure with preserved ejection fraction.

Intervention: Angiotensin-receptor neprilysin inhibitor (sacubitril/valsartan).

Comparator: Patients who are on optimal medical therapy.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: Inclusion criteria for this meta-analysis included : (1) included patients with HFpEF; (2) RCTs; (3) used sacubitril-valsartan; (4) compared with optimal medical therapy or placebo control group; and (5) assessed exercise capacity, QOL, LV structure or function.

Information sources: The electronic databases for literature search will include PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov.

Main outcome(s): Exercise capacity (6-minute walking distance).

Additional outcome(s): Health-related QOL and LV structure and function.

Quality assessment / Risk of bias analysis: The Cochrane Risk of Bias tool will be used to assess quality of RCTs included. The quality of evidence for the outcomes will be evaluated by use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The quality of evidence will be evaluated across the domains of risk of bias, consistency, directness, precision, and publication bias.

Strategy of data synthesis: For continuous outcomes, the effect size for the intervention will be calculated by the difference between the means of the intervention and control groups at the end of the intervention. For each outcome, heterogeneity will be assessed using the Cochran's Q and I2 statistic; for the Cochran's Q and I2 statistic, a p value of 50%, will be considered significant, respectively. When there is significant heterogeneity, the data will be pooled using a random-effects model, otherwise a fixed-effects model will be used. Publication bias will be assessed graphically using a funnel plot and mathematically using Egger test. For these analyses, Comprehensive Meta Analysis Software version 2 (Biostat, Englewood, NJ, USA) and STATA 16 software (Stata Corp LP, TX, USA) will be used.

Subgroup analysis: Meta-analysis will be performed separately for RCTs that included patients with EF≥50% and those that included patients with EF≥40%.

Sensitivity analysis: Meta-regression will be used to determine whether the effect of ARNI will be confounded by baseline clinical characteristics.

Language: Only articles published in the English language will be included.

Country(ies) involved: Japan.

Keywords: angiotensin-receptor neprilysin inhibitor; exercise capacity; quality of life; heart failure; meta-analysis.

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