INPLASY

Effects of hypoxia-inducible factor prolyl hydroxylase inhibitors in anemic heart failure patients: a protocol for systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 October 2024 and was last updated on 15 October 2024.

INTRODUCTION

Review question / Objective Anemia is common in patients with heart failure (HF) and is associated with worse outcomes. Iron supplementation improves symptoms and is associated with reduced risk of hospitalization for HF in iron-deficiency HF patients. However, iron deficiency is present in <30% of anemic HF patients. Erythropoiesis stimulating agents improve symptoms but are associated with increased risk of thromboembolic events in anemic HF patients. Hypoxiainducible factor prolyl hydroxylase (HIF-PH) inhibitors are a new class of agents for the treatment of anemia. These agents work by stabilizing the HIF complex, thereby stimulating endogenous erythropoietin production. Although there are several studies examining the effect of HIF-PH inhibitors in anemic HF patients, there is no evidence as to the effect in these patients. Accordingly, the purpose of this meta-analysis is to evaluate the effects of HIF-PH inhibitors in anemic HF patients.

Condition being studied Heart failure with anemia.

METHODS

Participant or population Heart failure patients with anemia.

Intervention Hypoxia-inducible factor prolyl hydroxylase inhibitors.

Comparator Usual medical therapy or placebo control group. If no comparative study is identified, pre-intervention data from single-arm studies will be used as an internal control for before-and-after comparisons of outcomes.

Study designs to be included Cohort studies and randomized controlledtrials (RCTs).

Eligibility criteria Inclusion criteria for this meta-analysis included: (1) included HF patients with

anemia; (2) cohort studies or RCTs; (3) administration of HIF-PH inhibitors; (4) assessed hemoglobin levels, BNP levels, renal function, all-cause death, hospitalization for HF, HF symptoms, exercise capacity (6-minute walk distance), and health-related quality of life,

Information sources PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov.

Main outcome(s) The primary outcome will be hemoglobin levels.

Additional outcome(s) The secondary outcomes will be BNP levels, renal function, all-cause death, hospitalization for HF, HF symptoms, exercise capacity (6-minute walk distance), and health-related quality of life.

Quality assessment / Risk of bias analysis The Cochrane Risk of Bias tool will be used to assess quality of RCTs included. The quality of prospective cohort studies will be evaluated by Newcastle-Ottawa Scale tool (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). 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. If the outcome is measured on the same scale, the weighted mean difference and 95% confidence interval (CI) will be calculated. Otherwise, the standardized mean difference and 95% CI will be calculated. For morbidity and mortality, hazard ratios will be pooled. For single-arm studies, pre- and post-intervention data will be synthesized using the mean change from baseline, and the corresponding standard error will be used to calculate pooled effect estimates. 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 fixedeffects 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 Subgroup analysis stratified by study design (cohort study or RCT) will be performed.

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

Country(ies) involved Japan.

Keywords anemia; hypoxia-inducible factor prolyl hydroxylase inhibitors; heart failure; systematic review; meta-analysis.

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