INPLASY PROTOCOL

To cite: Fukuta et al. Hypoxia-inducible factor prolyl hydroxylase inhibitors for anemia in heart failure patients: a protocol for systematic review and meta-analysis. Inplasy protocol 202230103. doi: 10.37766/inplasy2022.3.0103

Received: 20 March 2022

Published: 20 March 2022

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Support: **The faculty research expenses.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Hypoxia-inducible factor prolyl hydroxylase inhibitors for anemia in heart failure patients: a protocol for systematic review and meta-analysis

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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. Hypoxia-inducible 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 on-going prospective 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 efficacy and safety of HIF-PH inhibitors in anemic HF patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2022 and was last updated on 20 March 2022 (registration number INPLASY202230103).

INTRODUCTION

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increased risk of thromboembolic events in anemic HF patients. Hypoxia-inducible 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 ongoing prospective 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 efficacy and safety 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.

Study designs to be included: Prospective cohort studies and randomized controlled trials (RCTs).

Eligibility criteria: Inclusion criteria for this meta-analysis included: (1) included HF patients with anemia; (2) prospective cohort studies or RCTs; (3) administration of HIF-PH inhibitors; (4) compared with usual therapy or placebo control group; and (5) assessed cardiovascular death, all-cause death, hospitalization for HF, HF symptoms, exercise capacity, or health-related quality of life.

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

Main outcome(s): The primary outcome will be cardiovascular death.

Additional outcome(s): The secondary outcomes will be 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 morbidity and mortality, hazard ratios will be pooled. 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 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: Subgroup analysis stratified by study design (prospective 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, meta-analysis.

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