The effects of erythropoiesis stimulating therapy for anemia in chronic heart failure: A meta-analysis of randomized clinical trials

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A B S T R A C T

Background: Although anemia is common in chronic heart failure (CHF), the use of erythropoiesis stimulating agents (ESAs) in CHF patients remains controversial. In this meta-analysis, we sought to clarify the efficacy and safety of ESAs in anemic patients with CHF.
Methods: We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, the U.S. National Institutes of Health registry of clinical trials. We included 13 randomized clinical trials (RCTs) in the meta-analysis. The co-primary outcome was all-cause mortality and rehospitalization. The safety analysis outcome was thromboembolic events.
Results: Preliminary analysis showed that ESA-treatment did not have any effect for all-cause mortality and rehospitalization. However, we revealed a significant small-study bias, and used the trim-and-fill method to reduce this bias. The summary effect of ESA-treatment was insignificant for all-cause mortality (risk ratio [RR] 0.91, 95% confidence interval [CI] 0.59–1.42, p = 0.69) and for rehospitalization (RR 0.91, 95% CI 0.67–1.23, p = 0.53). Regarding symptoms, ESA-treatment improved dyspnea (NYHA grade improvement: 1.63, 95% CI 0.65–2.62, p < 0.001) and quality-of-life measured by subjective questionnaires. However, in safety analysis, ESAs increased the over-all risk for thromboembolic events (RR 1.28, 95% CI 1.03–1.58, p = 0.026), however, no specific increase was observed in severe thromboembolic events. Subgroup analysis showed no difference in ESA-treatment according to the type of ESAs (darbepoetin vs. erythropoietin) and between studies of different follow-up durations (<6 months or ≥6 months).
Conclusion: Among CHF patients with anemia, ESA-treatment has a neutral effect on all-cause mortality and rehospitalization and improves symptoms, but has harmful effects on thromboembolic events.

1. Introduction

Chronic heart failure (CHF) is a major public health concern, with high morbidity and mortality and an increasing prevalence [1,2]. Among the various comorbidities accompanying CHF, anemia is common and is associated with increased mortality and morbidity. Anemia affects the pathophysiology of the failing heart in a complex and multifactorial manner [3,4]. Basically, various factors cause anemia in CHF, such as impaired erythropoiesis in the bone marrow, hemodilution due to volume overload, neurohormonal and proinflammatory cytokine activation, defective iron utilization and inappropriate erythropoietin production [3]. In particular, iron deficiency is the most common cause of anemia, which may be an important mechanism that contributes to adverse outcomes in heart failure [5]. As a treatment for anemia, iron supplementation has proven to improve symptoms, functional capacity, and quality of life, in patients with heart failure [6,7]. Another therapeutic option is the administration of erythropoiesis stimulating agents (ESAs). Although previous meta-analysis suggested that ESA-treatment could improve symptoms and clinical outcomes [8], a recent large trial showed no difference in death or hospitalization between placebo and ESA group, whereas thromboembolic adverse events were more common in the ESA group [9]. Based on previous study results, the current guidelines do not recommend the use of ESAs, neither to improve the outcomes nor to ameliorate the subjective symptoms, particularly in patients with mild-to-moderate anemia [10,11]. Despite current data, ESAs are commonly used in clinical practice based on some studies and meta-analysis showing symptom improvement [12–14]. In addition, patients with heart failure commonly have concomitant renal disorders, so called the cardio-renal syndrome [15] where the use of ESAs is generally accepted. Particularly in

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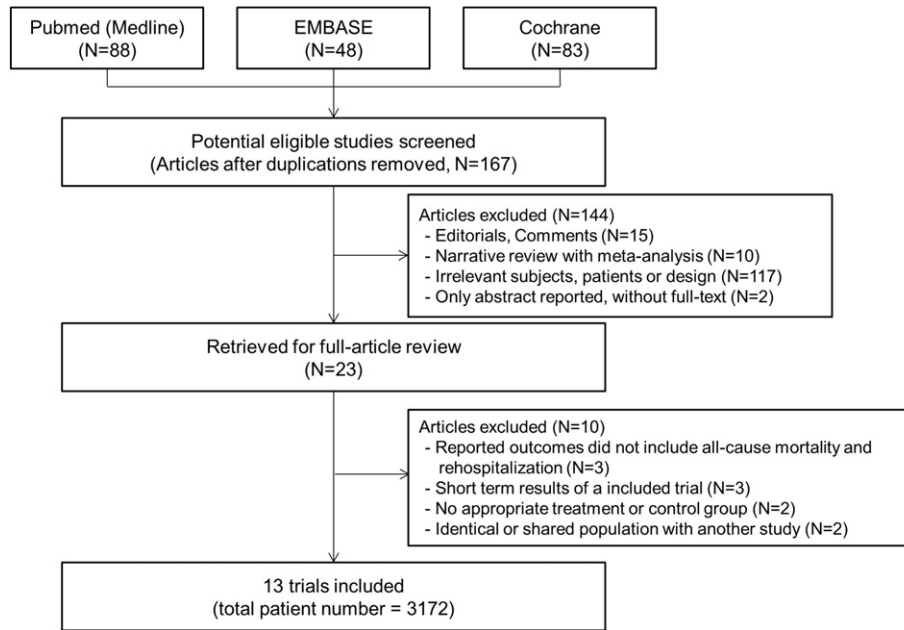[1] These authors contributed equally to this work.

Fig. 1. The study flow diagram.

anemic patients without iron deficiency, no other treatment options, except for the use of ESAs, are available to improve anemia [12].

Therefore, in this systemic review, we sought to clarify the efficacy and safety of ESA-treatment in anemic patients with CHF by using available randomized clinical trials (RCTs).

2. Methods

An expanded description of the study methods are presented in the Supplementary Appendix. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

2.1. Data sources and study strategy

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and the U.S. National Institutes of Health registry of clinical trials, and relevant websites for pertinent published or unpublished studies. Search strategies included both the Medical Subject Heading term (MeSH) and text word searches. The electronic search strategy was complemented by manual review of the reference list of included articles. References of recent reviews, editorials, and meta-analyses were also examined. No restrictions were imposed on language, study period, or sample size.

2.2. Study selection, data extraction and quality assessment

We included RCTs investigating ESAs for adult patients with CHF and anemia in the meta-analysis. Two investigators (J.K and J.P) independently extracted and tabulated data and discrepancies were resolved by group discussion, reference to the original publication, and discussion with the lead author when necessary. The quality of eligible RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias for RCTs (Supplementary Table 1). The last search was performed in August 2015.

2.3. Outcomes and definitions

The co-primary outcome was the all-cause mortality and rehospitalization for worsening heart failure, which were selected based on the review of the trials, and are the most common and well-defined endpoints [16]. Secondary clinical outcomes included the hemoglobin level, NYHA dyspnea grade and the health-related quality of life (QOL) scores. The health-related QOL was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) [17] and the Kansas City Cardiomyopathy Questionnaire (KCCQ) [18]. Also, for safety analysis, we analyzed the thromboembolic event rate.

2.4. Data synthesis and statistical analysis

Statistical analysis regarding the primary outcome involved both the random effects model. Pooled data were analyzed for the weighted mean difference for continuous variables and the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous parameters. The pooled RR was calculated with the DerSimonian and Laird method for random effects. Statistical heterogeneity was assessed using the χ^2 test and I^2 statistics. Publication bias was assessed for outcomes with a sufficient number of trials using funnel plots, Begg's test, and Egger's test. The Duval and Tweedie nonparametric trim-and-fill method [19] was performed to further assess the potential publication bias. $p \leq 0.05$ was considered statistically significant. Analyses were performed on Review Manager version 5 (Nordic Cochrane Centre, Denmark), with STATA/SE 12.1 (Stata Corp LP, USA) and R programming language, version 3.0.2 (R Foundation for Statistical Computing). The present study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the review protocol has not been registered (Supplementary Table 2).

3. Results

3.1. Search results and trial characteristics

Only full-length, peer-reviewed, original journal articles were considered for the study. We identified 167 citations by electronic search, and on initial screening, 144 studies were rejected based on the title and abstract, leaving 23 studies to be retrieved for detailed evaluation. Ten studies were excluded after full-text review. The final analysis included 13 studies with 3172 participants (Fig. 1) [9,20–31]. The baseline characteristics of each individual study are summarized in Table 1, and