Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

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Abstract

Introduction: Heart failure (HF) is always complicated with anemia and is associated with bad prognosis in this patient population. Several studies have assessed the potential role of erythropoietin-stimulating agent (ESA) in improving cardiac function and reducing the number of hospitalizations in anemic patients with HF.

Aim: We performed a meta-analysis to assess the potential role of ESA in the treatment of anemic patients with HF.

Material and methods: A literature and Medline search was performed to identify studies with control groups that examined the efficacy of ESA therapy in patients with HF and anemia.

Results: A total of 11 studies were included (n = 3044 subjects) in the final analysis. Compared to placebo, ESA therapy was associated with increased hemoglobin levels (1.89 g/dl; 95% CI: 1.64–2.14, p < 0.00001), increased left ventricular ejection fraction (LVEF) to 6.88 (95% CI: 0.49–13.28, p = 0.03), decreased B-type natriuretic protein (–272.20; 95% CI: (–444.52)–(–99.89), p = 0.002), improvement in New York Heart Association functional class to –0.33 mean difference (95% CI: (–0.44)–(–0.23), p < 0.00001), and decreased hospitalization (OR = 0.61, 95% CI: 0.39–0.94, p = 0.02). There was no significant between-group difference in all-cause mortality (OR = 0.78, 95% CI: 0.51–1.21, p = 0.27).

Conclusions: The treatment of anemia with ESA therapy did not reduce the rate of all-cause mortality among patients with heart failure, but ESA therapy made a potential important contribution to patients’ symptomatic improvement.

Key words: meta-analysis, heart failure, randomized controlled trials, anemia, erythropoietin-stimulating agents.

Introduction

Heart failure (HF) is always complicated with anemia and is associated with bad prognosis in this patient population. Depending on the definition used and specific patient population studied, the prevalence rate of anemia in HF patients widely varies from 9% to 70% [1–4]. In a meta-analysis of HF patients, presence of anemia almost doubled the mortality risk [5]. Anemia in HF patients not only causes a higher mortality rate, but is also associated with higher rate of various morbidity such as increased number of hospitalizations [6], worse New York Heart Association (NYHA) functional class [7], worse exercise capacity [8], cognitive impairment [9], and reduced quality of life [10].

The safety of erythropoiesis-stimulating agent (ESA) therapy in patients with renal failure and malignancies is not confirmed, but this is an effective therapy of anemia in chronic kidney disease (CKD) and cancer [11, 12]. Erythropoiesis-stimulating agent therapy can improve the health-related quality of life (HRQL) and fatigue of patients with CKD and cancer, and this improvement is both statistically and clinically significant [13]. Several studies have explored the potential therapeutic effects of ESA in improving heart function and reducing the hospitalization rate in patients with HF. Other studies, however, have shown that HF patients have higher levels of erythropoietin, which may lead to higher mortality [14].

Aim

We performed a meta-analysis to assess the potential role of ESA in the treatment of anemic patients with HF.

Material and methods

Search strategy

The electronic databases MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials, and the Web of Science were searched from inception to July 2015.
This search included the following terms: “heart failure”, “congestive heart failure”, “chronic heart failure”, “CHF”, “darbepoitin”, “erythropoiesis”, “stimulating proteins”, “erythropoiesis stimulating protein”, “recombinant erythropoietin”, “EPO/erythropoietin” and “randomized controlled trials”. The search was limited to English language articles of studies in adult humans. We also hand-searched potentially relevant studies, investigated registers of ongoing trials, and contacted the lead authors if necessary.

**Study selection criteria**

Two investigators (H.L.Z. and P.Z.) searched and evaluated all titles, abstracts and full articles independently using predesigned inclusion and exclusion criteria. Any uncertainties were resolved by consensus or consultation with the third investigator (J.Q.Y.) if necessary, which was infrequent. We excluded studies that 1) concerned non-clinical research; 2) included subjects without HF; 3) included subjects without anemia; 4) did not involve the administration of erythropoietin or darbepoitin; 5) included patients less than 18 years old; 6) were published in abstract form only; 7) were not published in English.

**Statistical analysis**

The study was conducted following Cochrane Collaboration meta-analysis review methodology, and data analysis was performed with the RevMan 5.3 and STATA 12.0 software package. Continuous variables with normal distribution are presented as mean ± standard deviation (SD). When studies did not directly supply the SD of the mean for the calculation of effect size, it was manually calculated from the standard error (SE) or the 95% confidence interval (CI). Treatment effects for continuous variables were evaluated as weighted mean difference (WMD). We pooled the results from the individual studies and performed tests of heterogeneity between studies using the $\chi^2$ test and quantified by the $I^2$ statistic. When significant heterogeneity was detected between studies, the random effects model was used. Possible publication bias was estimated with a funnel plot and Egger’s test. Meta-regression analyses were performed to explore the potential sources of significant heterogeneity. To reduce the risk of over-fitting of the regression model, a minimum of nine studies was set to identify each influential factor.

**Results**

The primary electronic search yielded 398 studies. After screening the titles and abstracts, 20 articles were retrieved for full-text assessment. According to the inclusion criteria, 9 articles were excluded and a total of 11 studies [15–25] were included (Figure 1). All of those studies were published in full-text form.

**Study characteristics**

This meta-analysis include 11 studies comprising 3044 patients, and the characteristics of those studies

| Study (first author, year) | N | Age [years] | Anemia definition, hemoglobin level [g/dl] | ESA therapy | Follow-up [months] |
|---------------------------|---|-------------|------------------------------------------|-------------|-------------------|
| Cleland, 2005             | 24| 69          | < 12.5                                   | DA          | Placebo 2         |
| Ghali, 2008               | 319| 68          | 69                                       | DA + iron   | Placebo + iron 12 |
| Kaurea, 2008              | 41| 73          | < 12.5                                   | DA + iron   | Placebo + iron 3  |
| Mancini, 2003             | 23| 87          | < 12.5                                   | EPO + iron  | Placebo + iron 3  |
| Palazzuoli, 2006          | 38| 72          | < 12.5                                   | EPO + iron  | Placebo + iron 9  |
| Palazzuoli, 2007          | 51| 74          | < 12.5                                   | EPO + iron  | Placebo + iron 8  |
| Parissis, 2008            | 32| 72          | < 12.5                                   | DA + iron   | Placebo + iron 3  |
| Ponikowski, 2007          | 41| 70          | 9–12                                     | DA + iron   | Placebo + iron 6  |
| Silverberg, 2001          | 32| 75          | 10–11.5                                  | EPO + iron  | Iron 8           |
| Swedberg, 2013            | 2278| 71           | 9–12                                     | DA + iron   | Placebo + iron 28 |
| Veldhuisen, 2007          | 165| 71          | 9–12                                     | DA + iron   | Placebo + iron 6  |

EPO – erythropoietin, DA – darbepoitin alfa, ESA – erythropoiesis-stimulating agent.
are summarized in Table I. Of those patients, 1564 received ESA therapy and 1480 were in the control group. Baseline characteristics of the two study groups were well balanced and no significant differences were reported. All of the participants had typical symptoms of heart failure with left ventricular ejection fraction (LVEF) < 40%. The baseline hemoglobin level ranged from 9.0 to 12.5 g/dl. The type of ESA therapy is darbepoetin alfa or erythropoietin. The dose regimen and target hemoglobin level were variable.

**Therapeutic effects of erythropoiesis-stimulating agent**

Nine studies provided data on the effect of ESA therapy on hemoglobin levels with an average increase of 1.89 g/dl (95% CI: 1.64–2.14, \( p < 0.00001 \)) compared to placebo (Figure 2 A). Five studies comprising 321 participants reported left ventricular ejection fraction at baseline and after ESA treatment, and the overall beneficial change was 6.88 (95% CI: 0.49–13.28, \( p = 0.03 \); Figure 2 B). In three studies, administration of ESA therapy was correlated with a decrease in B-type natriuretic protein (BNP) levels, with a mean change of −272.20 (95% CI: (−444.52)–(−99.89), \( p = 0.002 \); Figure 2 C). The use of ESA therapy led to an improvement in NYHA functional class in five studies and the mean difference was −0.33 (95% CI: (−0.44)–(−0.23), \( p < 0.00001 \); Figure 2 D). With regard to the type of exercise test, ESA therapy compared with control improved 6-minute walk distance (6-MWD) by 81.48 m (95% CI: 14.57–148.39, \( p = 0.02 \); Figure 2 E), exercise duration by 79.12 s (95% CI: 14.53–143.72, \( p = 0.02 \); Figure 2 F), and peak

| Study or subgroup | ESAs | Control | Weight | Mean difference | Mean difference |
|------------------|------|---------|--------|----------------|----------------|
|                  | Mean | SD     | Total  |               | IV, random, 95% CI |
| Ghali 2008       | 1.9  | 1.162  | 0.3    | 162 17.9      | 1.60 (1.38, 1.82) |
| Kourea 2008      | 1.6  | 1.3    | 21     | 9.5 2.1       | 2.50 (0.87, 4.13) |
| Mancini 2003     | 5.3  | 0.9    | 18     | 6.6 8.5       | 2.70 (1.77, 3.63) |
| Palazzuoli 2006  | 1.2  | 0.5    | 20     | −0.8 18 14.6  | 2.00 (1.65, 2.35) |
| Palazzuoli 2007  | 2    | 0.7    | 26     | −0.1 25 13.9  | 2.10 (1.72, 2.48) |
| Parissis 2008    | 1.8  | 1.05   | 21     | 0.4 11 7.3   | 1.40 (0.66, 2.14) |
| Ponikowski 2007  | 2.4  | 0.4    | 19     | 0.9 22 16.5  | 1.50 (1.22, 1.78) |
| Silverberg 2001  | 2.6  | 1.2    | 16     | −0.1 16 7.7  | 2.70 (1.99, 3.41) |
| van Veldhuisen 2007 | 1.8  | 0.95  | 110    | 0 11 14.7   | 1.80 (1.45, 2.15) |

Total (95% CI) 413 332 100.0 1.89 (1.64, 2.14)

Heterogeneity: \( t^2 = 0.08; \chi^2 = 22.69, df = 8 (p = 0.004); I^2 = 65% \)

Test for overall effect: \( Z = 14.90 (p < 0.00001) \)

| Study or subgroup | ESAs | Control | Weight | Mean difference | Mean difference |
|------------------|------|---------|--------|----------------|----------------|
|                  | Mean | SD     | Total  |               | IV, random, 95% CI |
| Kourea 2008      | 5    | 5      | 21     | −5 12 18.9    | 10.00 (4.32, 15.68) |
| Palazzuoli 2007  | 6.8  | 6.75   | 26     | −1.5 25 20.9  | 8.30 (4.78, 11.82) |
| Parissis 2008    | 5    | 6      | 21     | −3 5.5 11 20.4 | 8.00 (3.86, 12.14) |
| Silverberg 2001  | 5.5  | 12.3   | 16     | −5.4 16 17.6  | 10.90 (3.89, 17.91) |
| van Veldhuisen 2007 | 1.8  | 0.95  | 110    | 0 11 22.3    | −12.9 (−1.67, −0.91) |

Total (95% CI) 194 127 100.0 6.88 (0.49, 13.28)

Heterogeneity: \( t^2 = 47.78; \chi^2 = 72.75, df = 4 (p < 0.00001); I^2 = 95% \)

Test for overall effect: \( Z = 2.11 (p = 0.03) \)

| Study or subgroup | ESAs | Control | Weight | Mean difference | Mean difference |
|------------------|------|---------|--------|----------------|----------------|
|                  | Mean | SD     | Total  |               | IV, random, 95% CI |
| Kourea 2008      | −340 | 433    | 21     | 179 685 20 15.5 | −519.00 (−871.74, −166.26) |
| Palazzuoli 2006  | −246 | 254    | 20     | −47 294 18 30.5 | −299.00 (−374.61, −23.39) |
| Palazzuoli 2007  | −246 | 253.5  | 26     | −50 344 25 31.5 | −396.00 (−362.37, −29.63) |
| Parissis 2008    | −441 | 1.029  | 21     | 424 705.5 11 6.8 | −865.00 (−1471.23, −258.77) |
| Ponikowski 2007  | −90.5| 269.4  | 19     | −26.5 787.6 22 15.7 | −64.00 (−414.70, 286.70) |

Total (95% CI) 107 96 100.0 −272.20 (444.52, −99.89)

Heterogeneity: \( t^2 = 17341.68; \chi^2 = 79.2, df = 4 (p = 0.09); I^2 = 50\% \)

Test for overall effect: \( Z = 3.10 (p = 0.002) \)

**Figure 2.** Effects of erythropoiesis-stimulating agent therapy in heart failure patients with anemia at follow-up compared to baseline.
D. Comparison of NYHA functional class

| Study               | ESAs       | Control     | Weight | Mean difference | Mean difference |
|---------------------|------------|-------------|--------|-----------------|----------------|
| Ghali 2008          | –0.19      | 0.04        | 162    | –0.03           | 0.17           |
| Palazzuoli 2006     | –0.7       | 0.55        | 20     | 0.2             | 0.5            |
| Palazzuoli 2007     | –0.6       | 0.55        | 26     | 0.1             | 0.45           |
| Parissis 2008       | –0.7       | 0.45        | 21     | 0.5             | 0.55           |
| Silverberg 2001     | –0.6       | 0.55        | 16     | 0.4             | 0.5            |
| van Veldhuisen 2007 | –0.6       | 0.06        | 110    | –0.23           | 0.08           |

Total (95% CI) 355 282 100.0 –0.33 (–0.44, –0.23)

Heterogeneity: $t^2 = 0.01; \chi^2 = 105.71, df = 5 (p < 0.00001); I^2 = 95%$

Test for overall effect: $Z = 6.15 (p < 0.00001)$

E. Comparison of 6-minute hall walk

| Study               | ESAs       | Control     | Weight | Mean difference | Mean difference |
|---------------------|------------|-------------|--------|-----------------|----------------|
| Kourea 2008         | 106        | 66          | 21     | –40             | 79             |
| Mancini 2003        | 141        | 100         | 15     | –83             | 143.5          |
| Palazzuoli 2006     | 120        | 141         | 20     | 12              | 147            |
| Parissis 2008       | 69         | 96          | 21     | –47             | 91.5           |
| van Veldhuisen 2007 | 34.2       | 73          | 110    | 11.4            | 10.3           |

Total (95% CI) 187 112 100.0 81.48 (14.57, 148.39)

Heterogeneity: $t^2 = 4777.73; \chi^2 = 39.48, df = 4 (p < 0.00001); I^2 = 90%$

Test for overall effect: $Z = 2.39 (p = 0.02)$

F. Comparison of exercise duration

| Study               | ESAs       | Control     | Weight | Mean difference | Mean difference |
|---------------------|------------|-------------|--------|-----------------|----------------|
| Ghali 2008          | 57.3       | 29.3        | 162    | 46.5            | 30.6           |
| Mancini 2003        | 67         | 113         | 15     | –83             | 143.5          |
| Palazzuoli 2006     | 78         | 72          | 20     | –19             | 57             |
| Ponikowski 2007     | 38         | 50.5        | 19     | –58             | 53             |

Total (95% CI) 216 205 100.0 79.12 (14.53, 143.72)

Heterogeneity: $t^2 = 3622.91; \chi^2 = 46.95, df = 3 (p < 0.00001); I^2 = 94%$

Test for overall effect: $Z = 2.40 (p = 0.02)$

G. Comparison of peak oxygen consumption

| Study               | ESAs       | Control     | Weight | Mean difference | Mean difference |
|---------------------|------------|-------------|--------|-----------------|----------------|
| Mancini 2003        | 1.7        | 2.3         | 15     | –0.5            | 1.75           |
| Palazzuoli 2006     | 2.6        | 2.8         | 20     | –0.5            | 2.8            |
| Ponikowski 2007     | 0.6        | 0.6         | 19     | –0.5            | 0.55           |

Total (95% CI) 54 48 100.0 1.77 (0.02, 3.51)

Heterogeneity: $t^2 = 1.90; \chi^2 = 11.20, df = 2 (p = 0.004); I^2 = 82%$

Test for overall effect: $Z = 1.98 (p = 0.05)$

Figure 2. Cont.

The hospitalization analysis demonstrated a significant protective effect in the ESA treatment group compared with the control group (OR = 0.61, 95% CI: 0.39–0.94, p = 0.02; Figure 3 A), but there was no significant reduction in all-cause mortality (OR = 0.78, 95% CI: 0.51–1.21, p = 0.27; Figure 3 B).

Hospitalizations and all-cause mortality

Potential sources of heterogeneity analysis

A random-effect univariate meta-regression analysis for the hemoglobin level change, hospitalizations and all-cause mortality in heart failure was conducted to explore the potential sources of heterogeneity. Data on the age,
A. Heart failure hospitalizations

| Study               | ESAs   | Control | Weight (%) | Odds ratio (95% CI) |
|---------------------|--------|---------|------------|---------------------|
| Cleland 2005        | 3      | 18      | 6          | 1.9                 |
| Ghali 2008          | 25     | 162     | 31         | 157                |
| Kourea 2008         | 3      | 21      | 5          | 20                  |
| Mancini 2003        | 1      | 16      | 4          | 8                   |
| Palazzuoli 2006     | 4      | 20      | 8          | 18                  |
| Palazzuoli 2007     | 4      | 26      | 8          | 25                  |
| Parissis 2008       | 2      | 21      | 3          | 11                  |
| Ponikowski 2007     | 4      | 19      | 9          | 22                  |
| Swedberg 2013       | 314    | 1136    | 311        | 1142               |
| van Veldhuisen 2007 | 4      | 110     | 4          | 55                  |
| Total (95% CI)      | 1549   | 1464    | 100        | 0.61 (0.39, 0.94)   |

Heterogeneity: $\chi^2 = 0.14, p = 0.10, I^2 = 39$

Test for overall effect: $Z = 2.25 (p = 0.02)$

B. All-cause mortality

| Study               | ESAs   | Control | Weight (%) | Odds ratio (95% CI) |
|---------------------|--------|---------|------------|---------------------|
| Cleland 2005        | 1      | 18      | 1          | 6                   |
| Ghali 2008          | 11     | 162     | 18         | 157                |
| Kourea 2008         | 1      | 21      | 3          | 20                  |
| Mancini 2003        | 1      | 15      | 0          | 8                   |
| Palazzuoli 2006     | 1      | 20      | 2          | 18                  |
| Palazzuoli 2007     | 2      | 26      | 3          | 25                  |
| Parissis 2008       | 0      | 21      | 2          | 11                  |
| Ponikowski 2007     | 1      | 19      | 1          | 22                  |
| Silverberg 2001     | 0      | 16      | 4          | 16                  |
| Swedberg 2013       | 388    | 1136    | 376        | 1142               |
| van Veldhuisen 2007 | 6      | 108     | 0          | 55                  |
| Total (95% CI)      | 1562   | 1480    | 100        | 0.78 (0.51, 1.21)   |

Heterogeneity: $\chi^2 = 0.08, p = 0.30, I^2 = 15$

Test for overall effect: $Z = 1.10 (p = 0.27)$

Figure 3. Effect of erythropoiesis-stimulating agent therapy on hospitalizations and mortality

Discussion

Anemia in HF is related to adverse clinical outcomes, but little is known about the effects of its treatment with ESA on cardiac dimensions and function. Heart failure is associated with elevated pro-inflammatory cytokines, which cause not only decreased erythropoietin (EPO) production, but also resistance to its actions on bone marrow [26, 27]. Erythropoietin levels in HF patients are lower than expected, which is possibly attributed to the action of pro-inflammatory cytokines [26, 28]. Chronic kidney disease or milder forms of renal dysfunction are also common in HF patients, and may contribute to decreased EPO production. Other factors such as inflammation, diabetes, hemo-dilution, gastrointestinal mal-absorption and blood loss, absolute and functional iron deficiency, and drugs such as angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) are believed to contribute to the development of anemia in this patient population [29]. Previous studies have shown that ESA therapy can improve heart function, exercise capacity, and quality of life in HF patients with anemia. However, because of some deficiencies such as small sample sizes and lack of double-blind and/or placebo-controlled design in those studies, no very definite conclusions could be drawn.

In this meta-analysis of 11 RCTs with 3044 patients, we found that ESA therapy leads to a significant improvement in LVEF and BNP compared with placebo. Also we
found that ESA therapy reduced the NYHA functional class, an effect that was partly associated with patient symptomatic improvement. The specific mechanism of the improvement is not very clear. Previous studies have shown that ESA therapy seems to have potential effects to enhance cardiac contractile function and improve cardiac remodeling through its angiogenic and anti-apoptotic properties [30, 31].

Our meta-analysis found that the ESA therapy approach leads to a significant improvement in exercise capacity assessed by 6-MWD, exercise duration, and peak VO₂. There are a number of potential mechanisms such as the treatment of anemia, attenuation of peripheral hypoxia with the concomitant improvement of metabolic status of peripheral muscles and the reduction of volume overloading which may explain the beneficial effects of ESA on exercise tolerance and quality of life in anemic HF patients [17].

As compared with placebo, ESA therapy led to a significant increase in hemoglobin levels and reduction in hospitalizations. However, we found that ESA therapy was not associated with a significant reduction in all-cause mortality compared with placebo. This observation is partly in agreement with the previous studies [32], which suggest that ESA therapy can improve the symptoms of heart failure but does little to reduce all-cause mortality.

Despite employing a random effects model, statistical heterogeneity in the present study was considerable. There are many factors contributing to heterogeneity, such as the baseline disease severity, eligibility criteria, the patient selection and randomization, differences in trial designs, the inclusion of different interventions, the follow-up in the trials and differences in sample size. All of these factors lead to increase in heterogeneity.

Conclusions
We found that the treatment of anemia with ESA therapy did not reduce the rate of all-cause mortality among patients with heart failure. However, a trend of lower BNP, higher LVEF, reduction in hospitalizations and improvement in NYHA functional class was observed. At the same time, ESA therapy led to an increase of exercise tolerance. Consequently, our findings suggest that treatment of anemia with ESA improved the symptoms of heart failure but did not improve clinical outcomes.

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Hengliang Zhang and Pei Zhang contributed equally to this work.

Conflict of interest
The authors declare no conflict of interest.
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