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 morbidities 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.

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This search included the following terms: "heart failure", "congestive heart failure", "chronic heart failure", "CHF", "darbepoetin", "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 darbepoetin; 5) included patients less than 18 years old; 6) were published in abstract form only; 7) were not published in English.

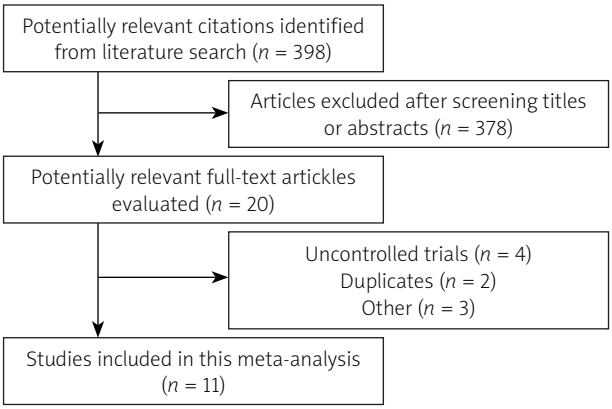


Figure 1. Process of study selection. Flowchart shows the literature search process and the final number of studies included

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 χ^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

Table I. Characteristics of included studies

Study (first author, year)	*N*	Age [years]		Anemia definition, hemoglobin level [g/dl]	ESA therapy		Follow-up [months]
		ESA	Control		ESA	Control	
Cleland, 2005	24	69	74	< 12.5	DA	Placebo	2
Ghali, 2008	319	68	69	9–12	DA + iron	Placebo + iron	12
Kaurea, 2008	41	73	65	< 12.5	DA + iron	Placebo + iron	3
Mancini, 2003	23	87	63	Hematocrit < 35%	EPO + iron	Placebo + iron	3
Palazzuoli, 2006	38	72	75	< 11	EPO + iron	Placebo + iron	9
Palazzuoli, 2007	51	74	72	< 11.5	EPO + iron	Placebo + iron	8
Parissis, 2008	32	72	69	< 12.5	DA + iron	Placebo + iron	3
Ponikowski, 2007	41	70	72	9–12	DA + iron	Placebo + iron	6
Silverberg, 2001	32	75	72	10–11.5	EPO + iron	Iron	8
Swedberg, 2013	2278	71	72	9–12	DA + iron	Placebo + iron	28
Veldhuisen, 2007	165	71	71	9–12	DA + iron	Placebo + iron	6

EPO – erythropoietin, DA – darbepoetin 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

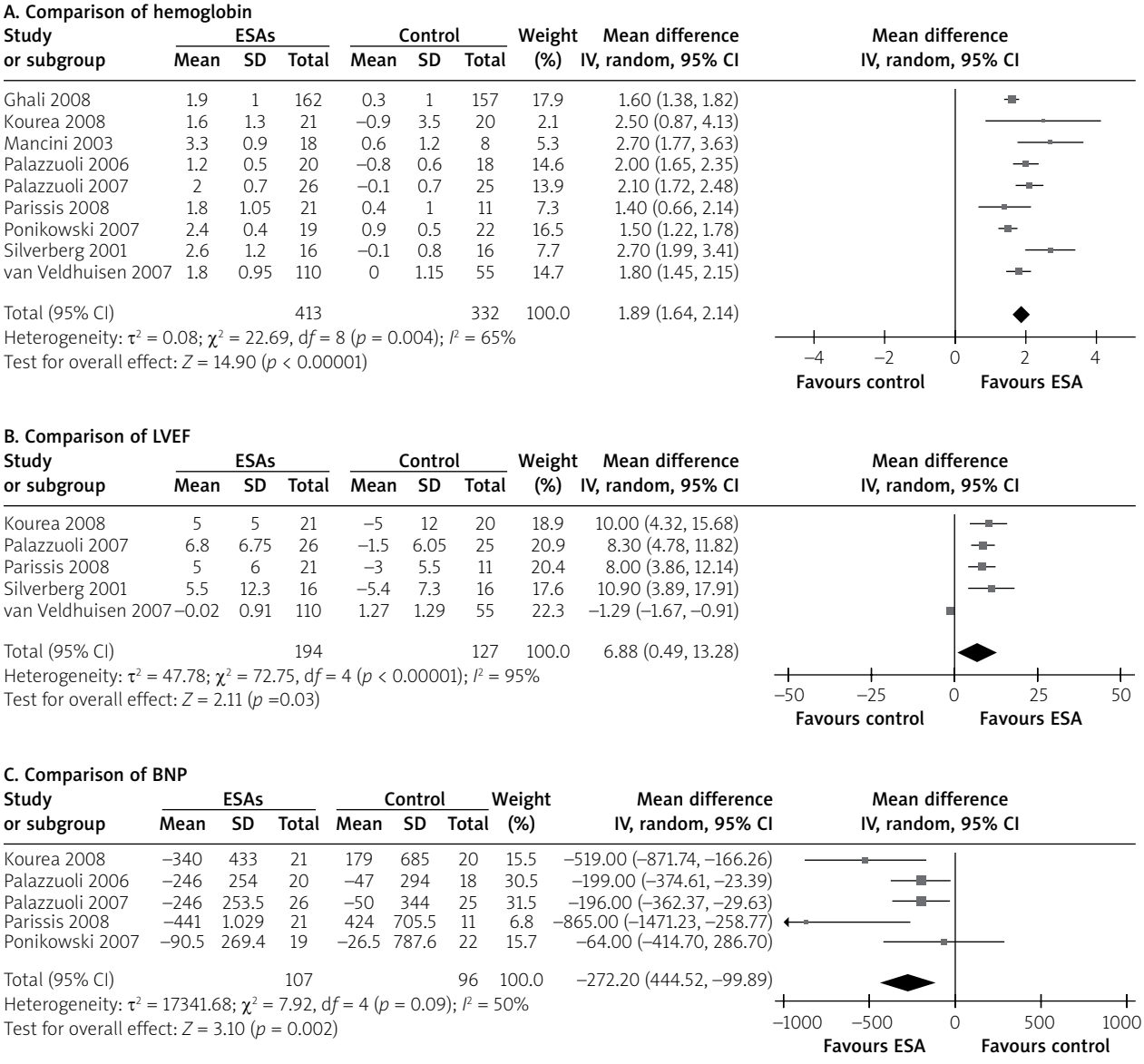
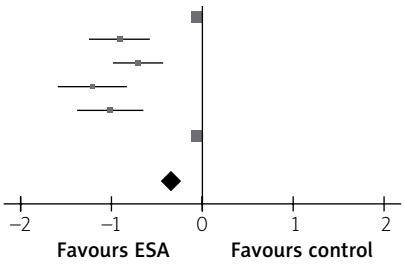


Figure 2. Effects of erythropoiesis-stimulating agent therapy in heart failure patients with anemia at follow-up compared to baseline

D. Comparison of NYHA functional class

Study or subgroup	ESAs Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Ghali 2008	–0.19	0.04	162	–0.13	0.04	157	34.7	–0.06 (–0.07, –0.05)
Palazzuoli 2006	–0.7	0.55	20	0.2	0.5	18	7.8	–0.90 (–1.23, –0.57)
Palazzuoli 2007	–0.6	0.55	26	0.1	0.45	25	10.3	–0.70 (–0.98, –0.42)
Parissis 2008	–0.7	0.45	21	0.5	0.55	11	6.4	–1.20 (–1.58, –0.82)
Silverberg 2001	–0.6	0.55	16	0.4	0.5	16	6.8	–1.00 (–1.36, –0.64)
van Veldhuisen 2007	–0.3	0.06	110	–0.23	0.08	55	34.1	–0.07 (–0.09, –0.05)
Total (95% CI)			355			282	100.0	–0.33 (–0.44, –0.23)

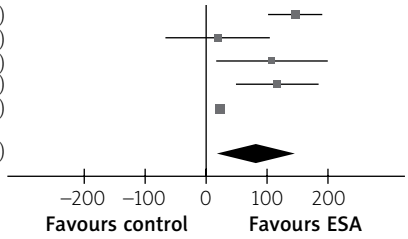
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 105.71$, d$f = 5$ ($p < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 6.15$ ($p < 0.00001$)



E. Comparison of 6-minute hall walk

Study or subgroup	ESAs Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Kourea 2008	106	66	21	–40	79	20	22.0	146.00 (101.33, 190.67)
Mancini 2003	141	100	15	123	100	8	17.4	18.00 (–67.81, 103.81)
Palazzuoli 2006	120	141	20	12	147	18	16.7	108.00 (16.18, 199.82)
Parissis 2008	69	96	21	–47	91.5	11	19.5	116.00 (48.11, 183.89)
van Veldhuisen 2007	34.2	7.3	110	11.4	10.3	55	24.4	22.80 (19.76, 25.84)
Total (95% CI)			187			112	100.0	81.48 (14.57, 148.39)

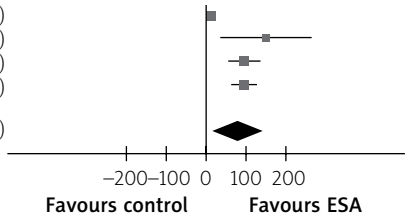
Heterogeneity: $\tau^2 = 4777.73$; $\chi^2 = 39.48$, d$f = 4$ ($p < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 2.39$ ($p = 0.02$)



F. Comparison of exercise duration

Study or subgroup	ESAs Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Ghali 2008	57.3	29.3	162	46.5	30.6	157	29.9	10.80 (4.22, 17.38)
Mancini 2003	67	113	15	–83	143.5	8	15.4	150.00 (35.29, 264.71)
Palazzuoli 2006	78	72	20	–19	57	18	26.7	97.00 (55.90, 138.10)
Ponikowski 2007	38	50.5	19	–58	53	22	28.0	96.00 (64.28, 127.72)
Total (95% CI)			216			205	100.0	79.12 (14.53, 143.72)

Heterogeneity: $\tau^2 = 3622.91$; $\chi^2 = 46.95$, d$f = 3$ ($p < 0.00001$); $I^2 = 94\%$
Test for overall effect: $Z = 2.40$ ($p = 0.02$)



G. Comparison of peak oxygen consumption

Study or subgroup	ESAs Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Mancini 2003	1.7	2.3	15	–0.5	1.75	8	30.0	2.20 (0.52, 3.88)
Palazzuoli 2006	2.6	2.8	20	–0.5	2.8	18	29.0	3.10 (1.32, 4.88)
Ponikowski 2007	0	0.6	19	–0.5	0.55	22	40.9	0.50 (0.15, 0.85)
Total (95% CI)			54			48	100.0	1.77 (0.02, 3.51)

Heterogeneity: $\tau^2 = 1.90$; $\chi^2 = 11.20$, d$f = 2$ ($p = 0.004$); $I^2 = 82\%$
Test for overall effect: $Z = 1.98$ ($p = 0.05$)

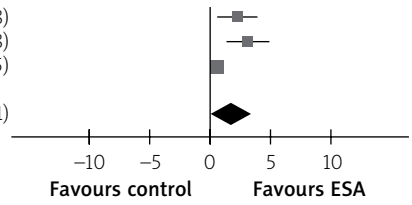


Figure 2. Cont.

oxygen consumption (VO_2) by 1.77 ml/kg/min (95% CI: 0.02–3.21, $p = 0.05$; Figure 2 G).

Hospitalizations and all-cause mortality

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).

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,

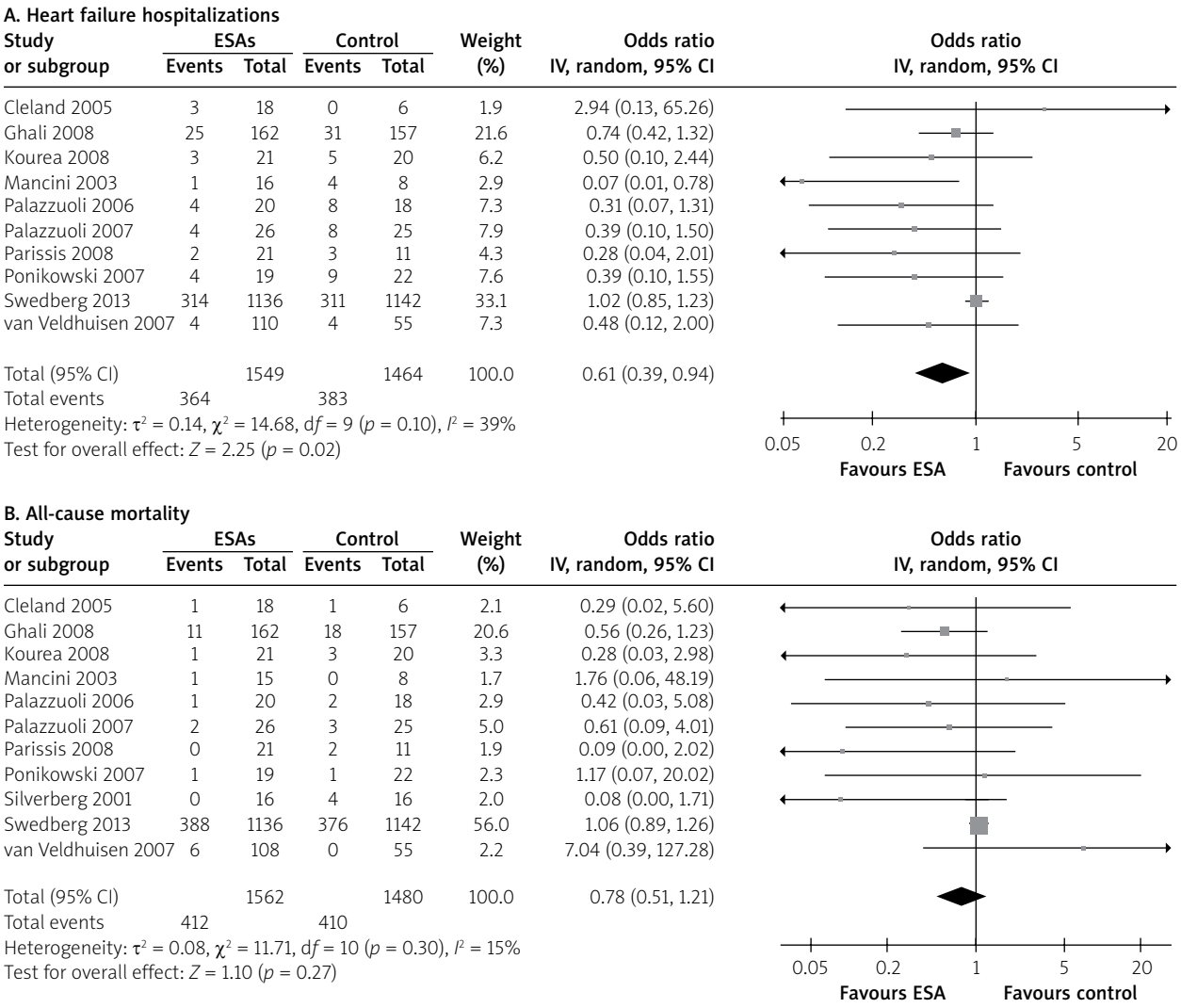


Figure 3. Effect of erythropoiesis-stimulating agent therapy on hospitalizations and mortality

sex (% male), baseline EF, baseline hemoglobin and ESA therapy (DA or EPO) were included. As a result, baseline hemoglobin was the major heterogeneity source identified for hemoglobin level change (adjusted R^2 = 0.21, p = 0.089). The ESA therapy was the major heterogeneity source identified for hospitalizations (adjusted R^2= 0.28, p = 0.093) and all-cause mortality (adjusted R^2 = 0.23, p = 0.035). Age, sex and baseline EF may not contribute to the source of heterogeneity for hemoglobin level change, hospitalizations and all-cause mortality (p > 0.1).

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 malabsorption 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 VO_2. 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.

Acknowledgments

Hengliang Zhang and Pei Zhang contributed equally to this work.

Conflict of interest

The authors declare no conflict of interest.

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