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Future perspectives on treatment with erythropoiesis-stimulating agents in high-risk patients

Stefan D. Anker[1] and Robert Toto[2]

[1]Division of Applied Cachexia Research, Department of Cardiology, Charité, Campus Virchow-Klinikum, Berlin, Germany and
[2]The University of Texas Southwestern Medical Center, Dallas, Texas, USA

Abstract

Patients with chronic kidney disease (CKD) have a high burden of mortality and cardiovascular morbidity. Additional strategies to modulate cardiovascular risk in this population are needed. Anaemia has been associated with adverse outcomes in CKD populations, and the ability to modify this parameter with the use of erythropoiesis-stimulating agents has been a topic of much debate. Data on the effects of anaemia correction on cardiovascular outcomes and survival in CKD have been both discordant and controversial. It is hoped that the ongoing Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) will help to redress the current clinical gaps and the uncertainty over the optimal management of anaemia in patients with CKD and type 2 diabetes mellitus. Anaemia is also increasingly being recognized as an important comorbid condition in patients with symptomatic heart failure. The ongoing Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF^{TM}) trial is designed to determine whether the treatment of anaemia improves outcomes in such patients.

Keywords: anaemia correction; cardiovascular disease; chronic kidney disease; erythropoiesis-stimulating agents; non-erythropoietic effects

Use of erythropoiesis-stimulating agents in the treatment of anaemia in patients with chronic kidney disease

Chronic kidney disease (CKD) appears to have a major impact on the risk of mortality and major non-fatal cardiovascular events, including myocardial infarction, heart failure and stroke. Despite the many advances in our understanding of the management of these cardiovascular risk factors, cardiovascular disease (CVD) is still the leading cause of death and hospitalization among patients with CKD. Anaemia is now also recognized as a risk factor for CVD in patients with CKD, for worse outcomes in CKD patients with existing CVD, and for progression of CKD [1,2]. While new therapeutic strategies are needed to address the burden of CVD in patients with CKD, definitive evidence demonstrating that treatment of anaemia can improve cardiovascular outcomes has not yet been provided by any prospective clinical trial.

Lack of evidence for benefit to CVD with full anaemia correction

The impact of normalization of haematocrit versus a lower haematocrit on mortality and non-fatal cardiovascular events in patients on haemodialysis was first tested in a large, randomized, open-label trial, the Normal Hematocrit Treatment trial [3]. The study enrolled only haemodialysis patients with clinical evidence of chronic heart failure (CHF) or ischaemic heart disease, half of whom had diabetes. The median duration of treatment was 14 months, target haematocrit was 42 ± 3% [haemoglobin (Hb) 14 ± 1 g/dL] in the normal haematocrit group and 30 ± 3% (Hb 10 ± 1 g/dL) in the low-haematocrit group, and the primary endpoint was the length of time to death or first non-fatal myocardial infarction. Although not statistically significant, rates of death or first non-fatal myocardial infarction were higher in patients in the normal haematocrit group compared with the low haematocrit group, with a relative risk of 1.3 [95% confidence interval (CI) 0.9–1.9] (Figure 1). This trial was terminated prematurely when the Data Safety Monitoring Committee concluded that the trial would be unable to reach its pre-stated endpoint of demonstrating improved outcomes in the normal haematocrit group, although it has been suggested that the study population was affected by too many comorbidities to benefit from full anaemia correction [4].

In the Canadian multicentre study in CKD, no association could be made between Hb level and left ventricular mass index (LVMI) when anaemia was prevented and/or corrected by immediate versus delayed treatment with epoetin [5]. While active treatment led to a sustained difference in Hb levels between study groups in the 152 patients

Correspondence and offprint requests to: Stefan D. Anker, Division of Applied Cachexia Research, Department of Cardiology, Charité, Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany. Tel: +49-30-450-553463; Fax: +49-30-450-553951; E-mail: s.anker@cachexia.de

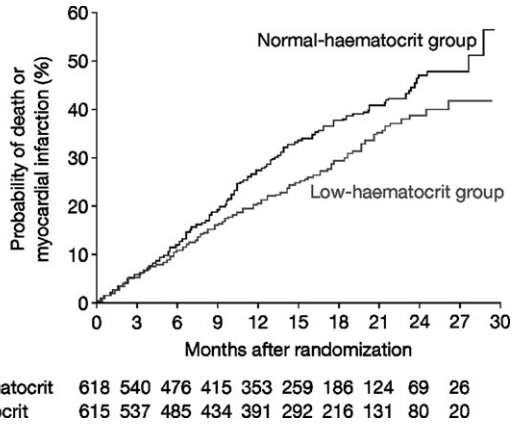

Fig. 1. Probability of death or a first non-fatal myocardial infarction in both patient groups in the Normal Haematocrit Treatment trial [3] (© 1998 Massachusetts Medical Society). All rights reserved.

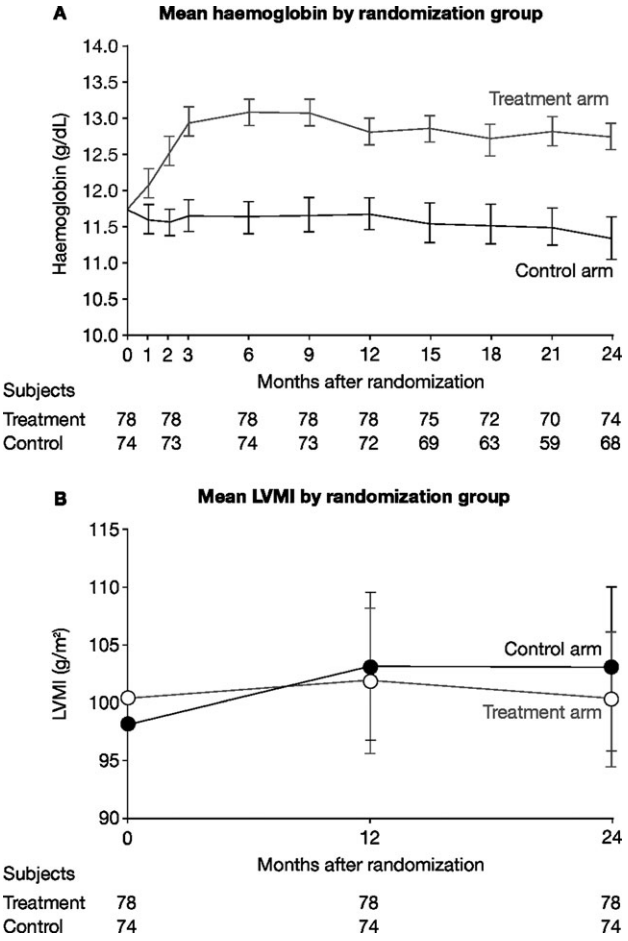

Fig. 2. Mean Hb levels (**A**) and mean LVMI (**B**) in both patient groups in the Canadian multicentre study in CKD. LVMI, left ventricular mass index. Reprinted from [5], Copyright (2005), with permission from Elsevier.

eligible for analysis, there was no statistically significant difference between groups for the primary outcome of the mean change in LVMI from baseline to 24 months (Figure 2) suggesting that active treatment of anaemia with epoetin in CKD patients had no effect on the change in LVMI or growth.

A lack of beneficial cardiac effect with Hb normalization was also evident in the Canadian–European Normalization study in 596 incident haemodialysis patients without symptomatic cardiac disease or left ventricular dilation [6]. While Hb targets were achieved with epoetin treatment over 24 weeks, and maintained for an additional 72 weeks, the percentage changes in left ventricular volume index and LVMI between baseline and last recorded value were not significantly different between the two groups.

A more recent retrospective observational study of 5848 haemodialysis patients investigated whether there was any association between predialysis use of erythropoiesis-stimulating agents (ESAs) in the treatment of anaemia of CKD and postdialysis cardiovascular outcomes [7]. While the data suggested that the risk of developing a cardiovascular event was significantly lower in patients who received ESA treatment prior to dialysis compared with ESA-untreated patients [relative risk (RR) 0.70 (95% CI, 0.61–0.82)], it is not possible to conclude whether such improvements in cardiovascular outcomes are due to improved Hb levels resulting from ESA therapy, or because of the higher rates of concomitant medication use in the ESA-treated patients, compared to the untreated patients.

Large-scale studies on the impact of anaemia therapy

The need for new randomized clinical trials to address critical knowledge deficits, particularly with regard to the impact of anaemia therapy on CVD and survival, has previously been recognized [8,9].

Two large-scale studies evaluated the effect of different levels of anaemia correction on treatment with ESAs on cardiovascular morbidity and mortality in patients with CKD [10,11], while another large-scale study is ongoing to determine if there is a morbidity and mortality benefit to anaemia treatment with ESAs in this patient population [1,2].

The Cardiovascular risk Reduction by Early Anaemia Treatment with Epoetin beta (CREATE) trial investigated the effect of early anaemia correction on cardiovascular risk in a large sample of patients with mild-to-moderate anaemia (defined as Hb 11.0–12.5 g/dL at the time of the study) and CKD not yet requiring renal replacement therapy [10]. In this multicentre, open-label, parallel-group study, 603 patients were randomized to receive early or late treatment with epoetin. The primary endpoint was time to cardiovascular event. The early treatment group started epoetin therapy immediately, aiming for a target Hb level of 13–15 g/dL. The late or routine treatment group started epoetin therapy once the Hb level had decreased to below 10.5 g/dL (target Hb level 10.5–11.5 g/dL). During the 3-year study, early and complete correction of anaemia did not reduce the risk of cardiovascular events compared with partial correction although there was a significant improvement in all major quality of life scores in the treatment group aiming for the higher target Hb level. A major limitation of the study was that the rate of cardiovascular events was considerably lower than anticipated. Consequently, CREATE was underpowered to demonstrate a difference between the two groups.

In the Correction of Hemoglobin and Outcomes in Renal insufficiency (CHOIR) study, a total of 1432 patients not receiving dialysis were randomly assigned to receive epoetin doses targeted to achieve a Hb level of 13.5 g/dL (high Hb group) or 11.3 g/dL (low Hb group) [11]. The primary endpoint was time to death or cardiovascular endpoint. CHOIR showed a 34% increased risk of complications and death from cardiovascular causes in the high Hb group [11]. The study was terminated by a Data and Safety Monitoring Board at a mean and median follow-up of 16 months, when it was determined that the likelihood of demonstrating a benefit for the high Hb level was <5%. However, a number of concerns about the study remain, including the high patient dropout rate, the imbalance in baseline characteristics between treatment arms, the doses of epoetin used and the fact that the protocol was changed with regard to target Hb levels after around one-third of the cohort had been randomized.

CREATE and CHOIR are the largest cardiovascular outcomes studies in non-dialysis CKD patients published to date. Both tested the hypothesis that higher Hb levels would lead to improved patient outcomes; however, in contrast to expectations, the results from both studies were negative. These trials have helped to focus on the need for appropriately designed randomized, double-blind, placebo-controlled trials, but have not sufficiently determined the effect of anaemia therapy on cardiovascular outcomes in patients with CKD. This effect, therefore, needs to be rigorously tested in a robust randomized clinical trial. The ongoing Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) is a 4000-patient, multicentre, double-blind, randomized, placebo-controlled phase III clinical trial [1] in which the objectives are fundamentally different to those of CREATE and CHOIR [2]. CREATE and CHOIR aimed to determine the impact of early versus late anaemia correction or degree of anaemia correction, respectively, on mortality and cardiovascular morbidity in patients with CKD. TREAT, however, aims to determine the impact of no anaemia intervention with an ESA (placebo) versus anaemia intervention with darbepoetin alfa, a long-acting ESA, on mortality and non-fatal cardiovascular events in anaemic patients with CKD and type 2 diabetes mellitus. Subjects are randomized 1:1 to either darbepoetin alfa therapy (to achieve and maintain a target Hb level of 13 g/dL) or placebo control (to maintain Hb levels ≥9 g/dL). The placebo arm permits rescue therapy with darbepoetin alfa when Hb levels are <9 g/dL until the Hb level is again ≥9 g/dL, when placebo will resume. TREAT is event driven and has a composite primary endpoint of death or the development of myocardial infarction, myocardial ischaemia, stroke or CHF. The components of the composite primary endpoint were chosen for their clinical importance and anticipated response to anaemia therapy. The clinical endpoints in TREAT will be key factors in determining the cost effectiveness of, and ultimately access to, anaemia therapies in CKD. It is hoped that the study will provide data that are critical to the evolution of cardiovascular risk management in this high-risk population. Enrolment in TREAT was completed in December 2007, with 4047 patients randomized, meaning that TREAT has enrolled more patients than CHOIR and CREATE combined.

Publication of the results from CREATE and CHOIR and a large meta-analysis [12] generated much discussion and controversy in the field. This led to recent reviews of the safety of ESAs in CKD patients by the European Medicine's Agency (EMEA) and the US Food and Drug Administration [FDA; the cardiovascular and Renal Drugs Advisory Committee (CRDAC) and Drug Safety and Risk Management Advisory Committee (DSRMAC)]. The EMEA concluded that '. . . the benefits of these products continue to outweigh risks in the approved indications . . .'. Based on positive opinions granted for all centrally authorized ESAs in the European Union by the EMEA's Committee for Medicinal Products for Human Use, and a recent public statement [13], the European Commission has approved updates to the prescribing information. These include a new uniform target Hb range of 10–12 g/dL, with a warning not to exceed a concentration of 12 g/dL. Following a joint meeting on 11 September 2007, the CRDAC and DSRMAC (of the FDA) also recommended that ESA dosing should be individualized to achieve and maintain Hb levels within the range of 10–12 g/dL. After careful and regular review of the safety data from TREAT, in March 2008 the Data Monitoring Committee (DMC) for the ongoing study, for which the target Hb level in the darbepoetin alfa treatment arm is 13 g/dL, have found no evidence to suggest alteration or termination of the trial.

Limitations in the data supporting anaemia management guidelines for patients with CKD underscore a critical point that guidelines should be dynamic documents, evolving as new and better data become available and stimulating clinical investigation by identifying gaps in current knowledge. While CHOIR and CREATE had their limitations, it is hoped that TREAT will provide the conclusive data needed to guide anaemia management in this high-risk population.

Use of ESAs in the early treatment of anaemia in CHF

There is great concern over the devastating impact of CVD during the early stages of CKD on the long-term clinical outcome of patients. This underlines the concept that management of patients with CKD should be focused mainly on strategies that aim to prevent the development of cardiovascular complications. Anaemia has been demonstrated to be a common, comorbid condition in patients with CHF, and a growing body of literature from observational databases and clinical trials suggests that anaemia is an independent risk factor for adverse outcomes in patients with heart failure [14,15]. This relationship persists whether considering Hb concentration as a continuous variable or anaemia as a categorical variable.

In the COMET study, Komajda and colleagues [16] measured the impact of new-onset anaemia on morbidity and mortality in 3029 CHF patients receiving beta blockers. Results showed that RR of all-cause mortality (RR 1.47; $P < 0.0001$), death or hospitalization (RR 1.28; $P < 0.0001$), or hospitalization for heart failure (RR 1.43; $P < 0.0001$) was higher for anaemic patients than for non-anaemic patients. The RR of subsequent mortality was greater in patients

whose Hb decreased from baseline over the course of the study [decrease of >3 g/dL (RR 3.37; $P < 0.0001$) or decrease of 2–3 g/dL (RR 1.47; $P = 0.011$)] than in patients whose Hb increased 0–1 g/dL from baseline, highlighting the importance of adequate Hb control in these patients.

Anaemia is increasingly being recognized as an important comorbid condition in its own right, and one that should be treated in patients with heart failure.

ESAs have become a mainstay in the treatment of anaemia in patients with CKD, and phase II studies directly examining the effect of ESA therapy on clinical outcomes in patients with CHF have been published. Silverberg *et al*. [17,18] have described benefits in several studies after the correction of anaemia in patients with CHF. One of their earlier investigations was a small, randomized, controlled trial of epoetin and intravenous (i.v.) iron in patients with moderate-to-severe CHF [17]. Thirty-two patients with New York Heart Association (NYHA) functional class III to IV heart failure who had a left ventricular ejection fraction (LVEF) of ≤40% (despite maximally tolerated doses of medications for CHF) and whose Hb levels were persistently between 10.0 and 11.5 g/dL were randomized into two groups. Group A received subcutaneous (s.c.) epoetin and i.v. iron to increase the level of Hb to at least 12.5 g/dL, while group B received no treatment for anaemia. A marked improvement in cardiac and patient function was observed in the treated group. The mean NYHA class improved by 42.1% in group A and worsened by 11.4% in group B. LVEF increased by 5.5% in group A and decreased by 5.4% in group B. The number of days spent in hospital compared with the same period of time before entering the study decreased by 79.0% in group A and increased by 57.6% in group B. A subsequent report by the same group described its findings in a series of 78 consecutive patients with symptomatic CHF and anaemia (Hb level <12.0 g/dL) treated with epoetin and, when necessary, i.v. iron sucrose [18]. Over a mean observation period of 20.7 ± 12.1 months, mean Hb levels increased from 10.2 ± 1.1 to 13.5 ± 1.2 g/dL ($P < 0.01$). NYHA functional class and LVEF were significantly improved, and the number of hospitalizations was significantly reduced compared with the period before treatment (all $P < 0.01$).

A number of small-scale studies have examined the effect of the longer-acting ESA, darbepoetin alfa, in the treatment of anaemia in CHF patients on various clinical outcomes. van Veldhuisen *et al*. [19] conducted a multicentre, randomized, double-blind, placebo-controlled study to evaluate the effect of darbepoetin alfa on Hb levels and clinical effects in anaemic patients (defined as Hb 9–12.5 g/dL) with CHF. Patients [mean (standard deviation; SD) age 71 [11] years] received placebo ($n = 55$) or s.c. darbepoetin alfa, administered every 2 weeks for 26 weeks to a target Hb level of 14 ± 1.0 g/dL. Patients in the darbepoetin alfa treatment group received either a starting weight-adjusted dose of 0.75 μg/kg ($n = 56$) or a fixed dose of 50 μg ($n = 54$). As expected, mean (SD) Hb rise from baseline [11.5 (0.7) g/dL] in the two darbepoetin alfa treatment groups was greater than in the placebo group (+1.87 ± 1.36 g/dL and +1.64 ± 0.98 g/dL, respectively, versus +0.07 ± 1.08 g/dL). Following treatment with darbepoetin alfa, there was also a significant improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (8.2 versus 1.5 points; $P = 0.027$). In addition, non-significant improvements were seen in the combined darbepoetin alfa group versus the placebo group for the 6-min walk test (6MWT; $P = 0.074$) and the Patient's Global Assessment Score ($P = 0.057$).

In another multicentre, randomized, double-blind, placebo-controlled trial, Ponikowski and colleagues set out to investigate whether treatment with darbepoetin alfa leads to improvements in exercise capacity in anaemic patients with symptomatic CHF [20]. Patients received placebo ($n = 22$) or s.c. darbepoetin alfa ($n = 19$), at a starting dose of 0.75 μg/kg administered every 2 weeks for 26 weeks. Darbepoetin alfa raised Hb levels [+1.5 g/dL (95% CI; 0.5–2.4; $P = 0.005$)] and enabled significant increases in exercise duration [+108 seconds (95% CI; −11 to 228; $P = 0.075$)], compared with patients in the placebo group. Patients receiving darbepoetin alfa also showed a significant improvement in self-reported Patient's Global Assessment of Change (79% versus 41%; $P = 0.01$) compared with patients receiving placebo.

The effects of darbepoetin on quality of life and emotional stress in CHF patients with anaemia were investigated by Kourea and colleagues [21]. Forty-one CHF patients (NYHA functional classes II and III) who were receiving optimal medical treatment, with a documented LVEF of <40%, Hb <12.5 g/dL and a serum creatinine of <2.5 μg/dL, were included in a single-blind study. None of the patients had received erythropoietin treatment within the previous 6 months. The patients were randomized (1:1) to receive either s.c. darbepoetin alfa 1.5 μg/kg every 20 days ($n = 21$) or placebo (0.9% normal saline) ($n = 20$) for 3 months. Both groups received iron sulphate (250 μg twice daily). A whole blood count was performed every 15 days; if Hb exceeded 14 g/dL in patients receiving darbepoetin alfa, therapy was withdrawn for the following 15 days and started again if Hb fell below 12.5 g/dL. Electrocardiographic LVEF, exercise capacity [6MWT and plasma b-type natriuretic peptide (BNP)], quality of life [KCCQ and Duke's Activity Status Index (DASI)] and psychological status [Beck Depression Inventory (BDI) and 20-item Zung Self-rating depression Scale (Zung SDS)] were assessed at baseline and post-treatment.

A significant post-treatment improvement was seen in the following parameters in the darbepoetin alfa group only: LVEF [32 ± 6% (from 26 ± 6%); $P < 0.001$]; Hb [12.8 ± 1.4 g/dL (from 10.9 ± 1.0 g/dL); $P < 0.001$]; 6MWT [274 ± 97 m (from 201 ± 113 m); $P < 0.01$]; plasma BNP [517 ± 579 pg/mL (from 829 ± 858 pg/mL); $P = 0.002$].

KCCQ functional [78 ± 14% (from 57 ± 24%); $P < 0.01$] and KCCQ overall [68 ± 20% (from 47 ± 22%); $P < 0.001$], DASI [19 ± 11 (from 14 ± 9); $P < 0.05$], Zung SDS [38 ± 10 (from 47 ± 11); $P < 0.05$] and BDI [11 ± 9 (from 16 ± 10); $P < 0.05$] scores also improved in the darbepoetin-treated patients, remaining unchanged in the placebo group (except for Zung SDS, which worsened [49 ± 8 (from 44 ± 10); $P < 0.05$]. There was also a significant correlation between darbepoetin-induced percent changes in 6MWT and Zung SDS ($R = -0.627$, $P < 0.05$).

Kourea *et al*. [21] concluded that, through amelioration of symptoms, darbepoetin alfa improved the quality of life and

emotional stress of CHF patients with anaemia, with a parallel increase in exercise capacity. They felt that short-term darbepoetin alfa administration was an effective therapeutic approach to correct anaemia and improve quality of life and depressive symptoms in patients with CHF. They also considered that these beneficial effects might have important clinical implications, reasoning that the antidepressant action of darbepoetin might counteract a pathophysiological contributor to CHF progression.

In a study of 32 anaemic CHF patients, Parissis and colleagues [22] evaluated the effects of darbepoetin alfa on left (LV) and right ventricular (RV) function and neurohormonal activation. Patients were randomized 2:1 to receive darbepoetin alfa (1.5 μg/kg every 20 days) plus oral iron ($n = 21$) or placebo plus oral iron ($n = 11$), for 3 months. The F and corresponding P values for the interaction between time of measurement of the studied variables and treatment were calculated. Treatment with darbepoetin alfa led to significant improvements in a number of echocardiographic indices of LV systolic and diastolic function and RV function. Improvements were recorded in LVEF ($F = 22.001$, $P = 0.001$), end-systolic wall stress (ESWS; $F = 4.934$, $P = 0.034$), mitral annulus systolic displacement ($F = 6.710$, $P = 0.015$), isovolumic relaxation time ($F = 4.909$, $P = 0.035$) and E/e ratio (as a marker of LV filling pressures; $F = 7.833$, $P = 0.009$), compared to placebo. Improvements were also noted in the RV systolic pressure ($F = 7.715$, $P = 0.009$) as well as tricuspid annulus systolic displacement and right ventricular ejection fraction ($F = 9.264$, $P = 0.005$). In addition, patients treated with darbepoetin alfa showed improvements in both the 6MWT ($F = 19.926$, $P = 0.001$) and the NYHA functional class ($F = 14.586$, $P = 0.001$). Darbepoetin treatment also correlated with reduced neurohormonal activation in these patients, as indicated by a significant fall in plasma levels of BNP ($F = 14.781$, $P = 0.001$). This was associated with reduction of elevated ESWS in these patients, together with symptomatic improvement. As high plasma levels of BNP appear to be associated with adverse clinical outcomes in CHF, this finding may be of clinical importance.

In the multicentre, randomized, double-blind, placebo-controlled 'Study of Anaemia in Heart Failure Trial' (STAMINA-HeFT), the effect of treating anaemia with darbepoetin alfa on cardiovascular outcomes, exercise capacity and quality of life measures was evaluated in 319 anaemic patients with symptomatic CHF [23]. Patients were randomized 1:1 to placebo or s.c. darbepoetin alfa administered every 2 weeks for 1 year, with a target Hb level of 14.0 ± 1.0 g/dL. While darbepoetin alfa raised and maintained Hb levels within the target range, treatment did not significantly improve exercise duration, NYHA class or quality of life score compared with placebo. Interestingly, a non-significant trend was observed towards a lower risk of all-cause mortality or first hospitalization due to heart failure in darbepoetin alfa-treated patients compared with placebo [hazard ratio 0.68 (95% CI; 0.43–1.08); $P = 0.1$]. These data are supportive of the conduct of a larger adequately powered trial to evaluate the importance of treatment of anaemia in CHF on cardiovascular outcomes.

Thus far, no large randomized phase III clinical trials have determined the effect of anaemia treatment on morbidity and mortality in patients with heart failure. However, the ongoing Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF^{TM}) trial is a large, double-blind, multicentre, randomized, placebo-controlled phase III study to assess the efficacy and safety of darbepoetin alfa treatment on morbidity and mortality in patients with symptomatic LV systolic dysfunction and anaemia (Hb >9.0 g/dL and <12 g/dL) [24]. Approximately 3400 patients will be randomized 1:1 to receive either darbepoetin alfa or placebo. Darbepoetin alfa will be initiated at 0.75 μg/kg once every 2 weeks, and will be titrated until the target Hb level of 13.0–14.5 g/dL is achieved. The dose will then be doubled and the administration interval extended to once monthly. The primary endpoint is a composite of all-cause death or first hospitalization for worsening heart failure. The study is planned to end ∼3 years after the first subject has been enrolled, when ∼1450 subjects are anticipated to have experienced a primary endpoint event. The RED-HF^{TM} trial is anticipated to provide the critical data needed to determine whether treatment of anaemia improves outcomes in patients with heart failure. The target Hb level in this trial (13–14.5 g/dL) is no longer in line with the target Hb range most recently recommended by the EMEA (10–12 g/dL) [13]. However, both the Executive Committee and the DMC of RED-HF^{TM} are of the opinion that the adverse findings in CKD patients, from the CREATE and CHOIR trials, cannot be extrapolated to the RED-HF^{TM} trial [25]. In addition, the positive data already obtained in phase II trials in CHF provide further support for the continuation of this study. The DMC has conducted careful and regular reviews of the safety data from this trial, and will continue to do so, and has seen no evidence to suggest that the trial should be stopped due to safety concerns.

Use of i.v. iron in the treatment of anaemia in CHF

In anaemia of CHF, iron metabolism is disturbed, so it is possible that administration of iron might improve outcomes in these patients. In the FERRIC-HF trial, Okonko and colleagues [26] investigated whether i.v. iron improved exercise tolerance in 35 anaemic (Hb <12.5 g/dL) or non-anaemic (Hb 12.5–14.5 g/dL) symptomatic CHF patients with iron deficiency. Iron loading (200 mg i.v. iron sucrose per week until ferritin levels were >500 ng/mL and 200 mg i.v. iron monthly thereafter) improved both exercise capacity and symptoms in patients with CHF, compared with no treatment. The mean increase in Hb in anaemic patients was 0.8 g/dL for those treated with i.v. iron versus a 0.6 g/dL increase in anaemic control patients (P = not significant). Overall, mean changes from baseline in absolute pVO_2 [+96 (95% CI; −12 to 205) mL/min; $P = 0.08$], pVO_2/kg [+2.2 (95% CI; 0.5–4.0) mL/kg/min; $P = 0.01$] and treadmill exercise duration [+60 (95% CI; −6 to 126) seconds; $P = 0.08$] were significantly larger in patients receiving iron compared to patients in the control group, with the most significant benefits evident in anaemic patients. In addition, mean changes from baseline to study end in NYHA functional class and Patient Global Assessment were greater in the i.v. iron treatment group than in the placebo group [−0.6 (95% CI; −0.9 to −0.2);

$P = 0.007$ and 1.7 (95% CI; 0.7–2.6); $P = 0.002$, respectively]. Thus, evidence suggests that, in addition to ESA treatment, the use of i.v. iron in the treatment of anaemia in CHF patients may also be important to their optimal management. The ongoing IRON-HF Study is a multicentre, randomized, double-blind, placebo-controlled trial to assess the effects of oral and i.v. iron supplementation in heart failure patients with anaemia with a primary efficacy endpoint of variation of peak oxygen consumption [27].

Conclusion

Evidence indicates that anaemia is a potent risk factor for mortality and cardiovascular morbidity among patients with CKD. Although not yet conclusive, the available data suggest that anaemia therapy may be beneficial in these patients. TREAT is designed to provide critical and unbiased risk/benefit information that is needed to guide medical practice in this high-risk population and is expected to serve as an example of a robust randomized clinical trial that provides informed and data-driven practice patterns for the benefit of patients with CKD. It is hoped that the ongoing RED-HF^{TM} trial will also provide definitive data on the effect of correcting anaemia in patients with CHF.

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