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CORONARY HEART DISEASE (S. VIRANI AND S. NADERI, SECTION EDITORS)

Anemia in Cardiovascular Disease: Marker of Disease Severity or Disease-modifying Therapeutic Target?

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Abstract

Purpose of the Review In this review paper, we examine the latest evidence regarding the use of iron supplementation, erythropoiesis-stimulating agents (ESAs), and blood transfusions as therapeutic targets for anemia to mitigate morbidity and mortality in patients with cardiovascular disease.

Recent Findings Intravenous ferric carboxymaltose (FC) injections in heart failure (HF) have resulted in improved self-reported patient symptoms; higher exercise capacity, as measured by 6-min walk test distance in anemic patients; and lower re-hospitalization rates in iron deficient patients. Darbepoetin alfa has shown evidence of improved Kansas City Cardiomyopathy Questionnaire scores. No mortality benefits have been noted thus far with FC injections or darbepoetin in HF, with an increase in adverse events with darbepoetin. Aggressive transfusions (Hg < 10 g/dL) are not associated with improved outcomes in cardiovascular disease.

Summary Quality of life metrics, rather than mortality, appear to improve with IV FC and ESA use in HF. More studies are required to see if these treatments have a role in coronary artery disease. Current evidence suggests that anemia is a marker of underlying disease severity, with a limited role in disease modification. Further studies are required to solidify our understanding of this topic.

Keywords Anemia · Heart disease · Iron supplements · Erythropoiesis-stimulating agents · Red blood cell transfusions

This article is part of the Topical Collection on *Coronary Heart Disease*

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Introduction

Anemia, defined by the World Health Organization (WHO) as a Hg < 13 g/dL in males and < 12 g/dL in females, affects nearly a third of the global population [1–4]. Although often comorbid with a variety of chronic diseases, anemia alone has a nearly identical association with mortality as do chronic diseases such as kidney disease and diabetes mellitus [5]. Given that anemia is estimated to be prevalent in approximately 30% to 70% of patients with heart failure (HF) and 10% to 43% of patients with coronary artery disease (CAD) who present with acute coronary syndrome, its significance as both a risk factor for incident heart disease and contributor to overall cardiovascular (CV) morbidity and mortality has been the focus of much interest over the past two decades [3, 6].

Anemia and Cardiovascular Disease

The Anemia and Increased Cardiovascular Disease study may have been the first to suggest that anemia is an

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independent risk factor for cardiovascular disease (CVD). The study examined a cohort of 14,410 subjects in four US communities without CVD at baseline and found that during a mean follow-up of 6.1 years, patients with anemia (both men and women) had an increased risk of CVD, with a hazard ratio of 1.41 (95% CI = 1.01–1.95, $p = 0.04$) [7]. A separate pooled analysis that included the Anemia and Increased Cardiovascular Disease study and three community-based studies (Cardiovascular Health Study, Framingham Heart Study, and the Framingham Offspring Study) further supported the notion that anemia is a risk factor for CVD but that the association was primarily seen in patients with chronic kidney disease [8].

Several studies have also suggested an increased risk of mortality and morbidity in anemic patients in the setting of acute coronary syndrome and HF. For example, in a pooled analysis of 41,637 patients with acute coronary syndrome in 16 clinical trials, Sabatine et al. found increased CV mortality at 30 days for each 1 g/dL drop in hemoglobin below 14 g/dL, with an adjusted OR of 1.21 (95% CI = 1.12–1.30, $p < 0.001$) [9]. In chronic HF, anemia has been associated with an increased risk of death and HF hospitalization. In a retrospective cohort of 655 Medicare patients, McClellan et al. found a 1-year mortality rate of 50% for patients with a hematocrit < 30%, with significantly lower mortality rates for higher hematocrit levels (Chi squared for trend = 7.37, $p = 0.007$) [10]. A separate and larger cohort study (1061 patients) conducted by Horwich et al. found that a lower hemoglobin level was predictive of increased mortality (RR 1.129; CI 1.018–1.251) [11]. The correlation between increased mortality and hemoglobin levels was further evidenced in analyses of the *Randomized Etanercept North American Strategy to Study Antagonism of Cytokine* (RENAISSANCE) trial (risk of mortality was 15.8% lower for every 1 g/dl increase in hemoglobin, $p = 0.0009$) and the *Prospective Randomized Amlodipine Survival Evaluation* (PRAISE) trial (11% higher risk of death for every 1% decrease in hematocrit < 37.6%, $p < 0.01$) [12, 13]. Numerous studies have shown that anemia is also associated with increased HF hospitalizations in addition to mortality. In fact, a large meta-analysis using 21 studies looking at the impact of anemia on HF showed that in the majority of these studies, anemia was an independent predictor of both increased mortality and higher hospitalization rates [14].

Given that anemia is a significant risk factor for CVD and is associated with poor outcomes, recent research has examined the effects of several treatment modalities for anemia on heart disease. In this review paper, we summarize our current understanding of the pathophysiologic mechanisms of anemia in CVD and the latest evidence regarding the use of iron supplementation, erythropoiesis-stimulating agents (ESAs), and red blood cell (RBC) transfusions as therapeutic targets to mitigate morbidity and mortality. A summary of some of the important studies regarding the treatment of anemia in CVD is provided in Table 1. In this review, we identify recent developments in this field of study and highlight current gaps in our knowledge that require further investigation.

Pathophysiologic Features of Anemia in Cardiovascular Disease

The pathophysiologic features of the development of anemia in CVD are complex and multifactorial but revolve around an abnormal erythropoietin (EPO) response and iron homeostasis, which drive bone marrow dysfunction through a variety of upstream mediators. These include chronic inflammation, renal dysfunction, renin–angiotensin–aldosterone system inhibition, nutritional deficiencies and malabsorption, and occult blood loss (Fig. 1).

Erythropoietin

Chronic inflammation mediates anemia in CVD through impaired EPO production and resistance to EPO [2, 3, 15]. Both HF and CAD are characterized as inflammatory disorders with evidence of increased levels of cytokines, such as tumor necrosis factor (TNF)-alpha and C-reactive protein (C-RP) [2, 15–20]. Inflammatory cytokines directly interfere with EPO production by inhibiting its transcription at the molecular level [21–24]. Furthermore, TNF-alpha activates transcriptional pathways involving GATA-1 and NF-κB that directly inhibit the bone marrow's response to EPO by inhibiting erythroid precursor differentiation [22].

Renal dysfunction also contributes to bone marrow suppression via decreased EPO production in CVD. Renal disease is estimated to be coexist in 25% to 50% of HF patients and 25% to 40% of CAD patients [25, 26]. Progressive renal deterioration results in decreased absolute production of EPO [2, 27]. A linear correlation has been noted between a progressive decline in hemoglobin values and a reduction in the glomerular filtration rate [3, 28].

Finally, iatrogenic renin–angiotensin–aldosterone system inhibition through angiotensin-converting enzyme inhibitors and angiotensin receptor blockers decreases EPO production, particularly in HF. Angiotensin II potently stimulates EPO production by decreasing renal blood flow and inducing subsequent local hypoxia [3, 15]. As a result, multiple studies have noted reduced EPO levels in HF patients and even in hemodialysis and healthy patients treated with renin–angiotensin–aldosterone system inhibition [29–32].

Iron homeostasis

Independent of their effect on EPO, inflammatory cytokines also alter iron homeostasis in CVD. Specifically, chronic

Table 1 Selected clinical trials of treatment of anemia in patients with HF and CAD

Trial/author	Study design	Intervention	Result
Treatment of iron deficiency in heart failure			
Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. The New England journal of medicine. 2009;361(25):2436–48	Multicenter across 75 sites in 11 countries, randomized, double-blind, placebo-controlled 459 participants with NYHA II symptoms and LVEF ≤ 40% (19%) or NYHA III symptoms and LVEF < = 45% (81%), Hemoglobin (Hgb) 9.5–13.5 g/dL, and ferritin < 100 µg/L or ferritin < 100–299 µg/L and transferrin saturation < 20% were randomly assigned 2:1 to ferric carboxymaltose (FC) or placebo and followed up for 24 weeks	Intravenous FC 4 ml (200 mg iron) or saline dosed weekly until iron repletion was achieved (8 or 12 weeks) and then every 4 weeks (maintenance phase) Total repletion iron dose, as determined by Ganzoni's equation for iron deficiency	Primary outcomes at week 24: • Self-reported Patient Global Assessment: 50% much or moderately improved in FC group vs. 28% in placebo group (2.51 OR for improving rank; 95% CI 1.75–3.61; $p < 0.001$) • NYHA class I-II: 47% in FC group vs. 30% in placebo group (OR for improvement by one class 2.40; 95% CI 1.55–3.71; $p < 0.001$) Secondary outcomes: • Use of FC improved self-reported Patient Global Assessment and NYHA class vs. placebo at week 4 and 12 (all $p < 0.001$) • Significant improvement in 6-min walk test and quality of life (EQ-5D visual assessment score and overall Kansas City Cardiomyopathy score) at weeks 4, 12, and 24 (all $p < 0.001$) Similar treatment effect in patients with and without anemia (Hgb < 12 g/dL at baseline) No severe allergic reactions reported. Treatment stopped early in 5.3% of patients receiving FC and 9.0% of those receiving saline
Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015;36(11):657–68	Multicenter across 41 centers in 9 countries, randomized, prospective, placebo-controlled, double-blind, two-arm 304 participants with NYHA II (57%) or III (43%), depressed LVEF, elevated natriuretic peptides, Hgb < 15 g/dL, and ferritin < 100 µg/L or ferritin < 100–300 µg/L and transferrin saturation < 20% were randomly assigned 1:1 to FC or placebo and followed up for 52 weeks	Intravenous FC dosed at baseline and week 6 (therapy phase) and 500 mg of FC at weeks 12, 24, and 36 if iron deficiency was present Therapy dose prescribed based on weight and Hgb at screening between 500 and 2000 mg of FC	Primary outcome (6-min walk test at week 24): • Improved 18 ± 8 m in the FC group vs. decrease of 16 ± 8 m in the placebo group (difference 33 ± 11 m, $p = 0.002$) Secondary outcomes: • Self-reported Patient Global Assessment improved in the FC group vs. placebo at weeks 12, 24, 36, and 52 (all $p < 0.05$) • Significant change in 6-min walk distance at week 36 (42 m) and 52 (36 m) vs. baseline • Significant reduction vs. placebo in fatigue score at weeks 12, 24, 36, and 52 • Beneficial effect on Kansas City Cardiomyopathy Questionnaire score at weeks 12, 36, and 52 (all $p < 0.05$ vs. baseline) • Beneficial effect on EQ-5D health state score vs. placebo significant only at week 36 ($p = 0.002$) Median dose of iron 1500 mg during 1-year study period (range = 500–3500 mg iron) No difference was found between groups in adverse events or treatment discontinuation

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet (London, England). 2020;396(10266):1895–904	Multicenter across 121 sites in 15 countries, randomly assigned, placebo-controlled, double-blind 1132 participants admitted for acute heart failure, LVEF < 50%, clinically stable and ready for discharge with serum ferritin < 100 ng/mL or 100–299 ng/mL and transferrin saturation < 20% were randomly assigned 1:1 to FC or placebo and followed up for 52 weeks	Intravenous FC prior to discharge and at week 6. Additional doses at weeks 12 and 24 for patients with persistent iron deficiency and Hgb 8–15 g/dL Dose was determined based on weight and Hgb at each treatment visit, either 500 mg or 1000 mg iron	Primary outcome (composite of total HF hospitalizations and CV death within 52 weeks): • 52.5% in ferric carboxymaltose group vs. 67.6% in placebo group (RR 0.80; 95% CI 0.65–1.00; $p = 0.059$) Secondary outcomes (ferric carboxymaltose vs. placebo): • Total CV hospitalizations and CV death: 370 vs. 451 (RR 0.80; 95% CI 0.64–1.00; $p = 0.050$) • CV death: 13.8% vs. 14.2% (HR 0.96; 95% CI 0.70–1.32; $p = 0.81$) • Total HF hospitalizations: 217 vs. 294 (RR 0.74; 95% CI 0.58–0.94; $p = 0.013$) • First HF hospitalization or CV death: 32% vs. 38% (HR 0.80; 95% CI 0.66–0.98; $p = 0.030$) • Days lost to HF hospitalization or CV death per 100 patient-years: 369 vs. 548 (RR 0.67; 95% CI 0.47–0.97; $p = 0.035$) Patients received a mean of 1352 mg of FC up to maximum treatment period of 24 weeks Serious adverse events: 45% vs. 51%
Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM et al. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical Trial. JAMA. 2017;317(19):1958–66	Multicenter, randomly assigned, placebo-controlled, double-blind 225 participants with reduced LVEF and NYHA II (67%) or III (33%) who were stable on medical therapy with Hgb 9–15 g/dL (men) or 9–13.5 g/dL (women) and ferritin 15–100 ng/mL or 100–299 ng/mL with transferrin saturation < 20% were randomly assigned 1:1 to oral iron polysaccharide or placebo and followed up for 16 weeks	Oral administration of iron polysaccharide, 150 mg twice daily for 16 weeks	Primary end point (change in peak oxygen uptake after 16 weeks): • + 23 mL/min (95% CI − 84 to 142 mL/min) vs. − 2 mL/min (95% CI − 110 to 104 mL/min); between-group difference 21 mL/min (95% CI − 34 to 76 mL/min, $p = 0.46$) • No significant difference after normalizing for body weight, men vs. women, with vs. without anemia, with vs. without baseline venous congestion, or with and without a marker of maximum volitional effort Secondary end points (at 16 weeks): • No significant differences in 6-min walk distance, NT-proBNP levels, KCCQ score, O2 uptake kinetics, or ventilatory efficiency Observed adverse event rates were similar, with time to first adverse event not differing significantly

Table 1 (continued)

Trial/author	Study design	Intervention	Result
van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A et al. Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency. Circulation. 2017;136(15):1374–83	Multicenter, randomized controlled, open label 172 participants with stable NYHA HF II (67%) or III (33%) on optimal HF therapy for at least 4 weeks without recent dose change, LVEF ≤ 45%, decreased exercise capacity (peak VO_2 of 10–20 mL/kg/min), and serum ferritin < 100 ng/mL or 100–299 ng/mL and transferrin saturation < 20% were randomly assigned 1:1 to ferric carboxymaltose vs. standard care and followed up for 24 weeks	Intravenous FC was given at day 0 and week 6. Additional dose was given at week 12 if iron deficiency persisted Dose was determined based on weight and Hgb at each treatment visit, either 500 mg or 1000 mg of iron	Change in peak VO_2 at 24 weeks: FC − 0.16 ± 0.37 vs. placebo − 1.19 ± 0.39 mL/min/kg ($p = 0.020$) • Sensitivity analysis without imputed missing values showed no significant difference • No interaction between changes in Hgb and peak VO_2 NYHA functional class improved vs. placebo at 6, 12, and 24 weeks ($p < 0.05$, with and without missing data imputation) Patients received a mean of 1204 mg of FC over a maximum treatment period of 12 weeks Hgb increased from 12.9 ± 1.3 to 13.2 ± 1.4 g/dL vs. 13.0 ± 1.5 to 13.2 ± 1.4 g/dL in placebo ($p < 0.05$)
Erythropoietin in Heart Failure			
Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000;35(7):1737–44	Single center, single treatment arm 142 participants enrolled from 1 HF clinic After 6 months of standard treatment, 26 patients with NYHA class III or IV with Hgb < 12 g/dL and resistance to maximal tolerated HF therapy were selected for intervention and followed up for a mean 7.2 ± 5.5 months (range, 4–15 months)	All patients received subcutaneous EPO once weekly; the dose was started at 2000 IU per week and adjusted to achieve and maintain target Hgb 12 g/dL All patients received intravenous ferric sucrose (200 mg/150 mL saline) per week until serum ferritin > 400 µg/L, iron saturation > 40%, or Hgb > 12 g/dL	Mean Hgb increased from 10.16 to 12.10 g/dL ($p < 0.001$) Mean dose of EPO used was 5227 ± 455 IU per week Mean dose of IV Fe used was 185.1 ± 57.1 mg per month Four patients achieved target Hgb despite stopping EPO for > 4 months No significant change in serum creatinine No significant change in mean systolic or diastolic blood pressure LVEF increased from 27.7 ± 4.8% to 35.4 ± 7.6% ($p < 0.001$) NYHA class decreased from 3.66 ± 0.47 to 2.66 ± 0.70 ($p < 0.05$) 24 of 26 patients improved at least 1 functional class Compared with a similar period of time before intervention, mean hospitalizations fell from 2.72 ± 1.21 to 0.22 ± 0.65 per patient ($p < 0.05$)

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation. 2003;107(2):294–9	Single center, randomized, single-blind, placebo-controlled 23 participants with NYHA III-IV symptoms on stable medical regimen for 4 weeks with Hct < 35%, serum creatinine < 2.5 mg/dL, and erythropoietin level < 100 mU/mL were randomly assigned 2:1 to erythropoietin vs. placebo and followed up for 3 months	Subcutaneous injection of EPO 5000 U three times per week. If Hgb increased < 1 g/dL at 4 weeks, the EPO dose was increased to 10,000 U three times per week. Treatment was continued for 3 months or until Hct > 45% Patients who were randomly assigned to EPO were prescribed ferrous gluconate 325 mg daily and folate 1 mg daily	• EPO was well tolerated without thrombotic complications or hypertension • Hgb increased in the EPO group (11 ± 0.6 to 14.3 ± 1.2 g/dL, $p < 0.0001$) vs. unchanged in the placebo group (10.9 ± 1.1 to 11.5 ± 1.3 g/dL, p = NS) • Exercise: • Peak VO2 increased significantly from 11 ± 0.8 to 12.7 ± 2.8 mL/kg/min ($p < 0.05$) in the EPO group vs. declined from 10.0 ± 1.9 to 9.5 ± 1.6 mL/kg/min (p = NS) • VO_2 at anaerobic threshold, exercise capacity, and 6-min walk distance each increased in the EPO group without significant improvement in the placebo group • Significant positive correlation was observed between change in Hgb and change in peak VO2 ($p < 0.05$) • Quality of life: • 80% in EPO group improved vs. 13% in placebo ($p < 0.05$) • Minnesota Living with Heart Failure Questionnaire score decreased (improved) from 46 to 37 ($p < 0.04$) in the EPO group vs. increased (worsened) from 56 to 66 Multiple measures of muscle oxidative metabolism and forearm vasodilation did not significantly change in either group

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H et al. Randomized Double-Blind Trial of Darbepoetin Alfa in Patients With Symptomatic Heart Failure and Anemia. Circulation. 2008;117(4):526–35	Multicenter at 65 centers, randomized, double-blind, placebo-controlled 319 participants with symptomatic HF (35% NYHA II, 61% NYHA III, 3% NYHA IV) for at least 3 months on stable medical therapy, exercise capacity, LVEF ≤ 40%, and Hgb 9–12.5 g/dL were randomly assigned 1:1 to darbepoetin alfa vs. placebo and followed up for 52 weeks	Subcutaneous darbepoetin alfa 0.75 µg/kg was administered once every 2 weeks until Hgb > 13.0/dL and had increased by at least 1.5 g/dL from baseline, at which point the dose was reduced by 25%. Doses were then adjusted to maintain Hgb 13–15 g/dL Daily elemental oral iron was administered unless baseline ferritin was > 800 ng/mL	Primary outcome (change in exercise duration from baseline at week 27): • + 57.3 s in the darbepoetin alfa group vs. + 46.5 s in the placebo group ($p = 0.46$) in a repeated-measures, mixed-effects model Secondary outcomes: • No statistically significant change in NYHA class ($p = 0.34$) • Same rate of improvement in Patient's Global Assessment of Change at week 27 ($p = 0.95$) • No significant difference between groups in Minnesota Living with Heart Failure Questionnaire score ($p = 0.38$) At 53 weeks, the median change in Hgb from baseline was 2.1 (IQR 1.3–2.8) vs. 0.5 (IQR − 0.3 to 1.2) g/dL ($p < 0.001$). 85% in the darbepoetin alfa group achieved target Hgb with ≥ 1.0 g/dL increase from baseline vs. 19% of placebo No significant difference in adverse events between groups

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. The New England journal of medicine. 2013;368(13):1210–9	Multicenter at 453 sites in 33 countries, randomized, double-blind, placebo-controlled 2278 participants with NYHA II (35%) or III/IV (65%) symptoms on medical therapy, LVEF < 40%, and Hgb 9–2 g/dL were randomly assigned 1:1 to darbepoetin alfa or placebo and followed up for median 28 months	Subcutaneous darbepoetin alfa 0.75 μg/kg was administered once every 2 weeks until Hgb > 13.0/dL on two consecutive visits. Maintenance injections were given monthly to maintain Hgb 13.0–14.5 g/dL If transferrin saturation fell < 20% at any time, oral and intravenous iron were administered	Primary outcome (composite of death from any cause or first hospitalization for worsening heart failure): • 50.7% in the darbepoetin alfa group vs. 49.5% in the placebo group (HR 1.01; 95% CI 0.90–1.13, $p = 0.87$); no significant difference adjusting for baseline characteristics and consistent across all subgroups Secondary outcomes (darbepoetin alfa group vs. placebo group): • Death from any cause: 41.7% vs. 40.1% (HR 1.04; 95% CI 0.92–1.19; $p = 0.51$) • Composite of death from CV causes or first hospitalization for worsening heart failure: no significant difference ($p = 0.92$) • Overall summary score (baseline to 6 months): + 6.20 (95% CI 4.71–7.69) vs. + 3.91 points (95% CI 2.42–5.40), $p = 0.01$ • Kansas City Cardiomyopathy Questionnaire (baseline to 6 months): + 6.68 vs. + 4.48 points (treatment difference 2.20 points; 95% CI 0.65–3.75; $p = 0.005$) Hgb was increased from 11.2 to 13.0 g/dL in the darbepoetin alfa group and to 11.5 g/dL in the placebo group ($p < 0.001$). Between-group difference in Hgb was significant at 1 month and persisted throughout follow-up Median monthly dose of darbepoetin alfa was 167 μg (IQR 105–286) Adverse event leading to study-drug discontinuation: 19.5% in the darbepoetin alfa group vs. 20.1% in the placebo group ($p = 0.73$) Embolic and thrombotic events: 13.5% vs. 10.0% ($p = 0.009$) Septic shock: 1.9% vs. 0.6% (reported as significant)

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Erythropoietin in Coronary Artery Disease			
Steppich B, Groha P, Ibrahim T, Schunkert H, Laugwitz KL, Hadamitzky M et al. Effect of Erythropoietin in patients with acute myocardial infarction: five-year results of the REVIVAL-3 trial. BMC Cardiovasc Disord. 2017;17(1):38	Randomized, double-blind, placebo-controlled 138 participants with a first STEMI within 24 h of symptom onset with angiographic LVEF < 50% were randomly assigned 1:1 to receive IV recombinant human epoetin-beta vs. placebo 134 participants completed 5–year follow-up	Intravenous epoetin-beta 33,300 U administered immediately, 24 h after, and 48 h after percutaneous coronary intervention All participants underwent periprocedural antithrombotic therapy of 600 mg clopidogrel orally, 500 mg aspirin, and unfractionated heparin, with or without abciximab intravenously, and post-interventional therapy of clopidogrel (75 mg twice daily for 3 days, followed by 75 mg daily for at least 6 months) and aspirin (100 mg twice daily, recommended indefinitely)	Primary outcome (cumulative incidence of MACE 5 years after randomization): • 25% ($n=17$) of epoetin-beta group vs. 17% ($n=12$) of placebo (RR 1.5; 95% CI 0.8–3.5; $p=0.26$) • No significant differences in MACE when stratified by Hgb quartiles Circulating reticulocytes were increased at 5 days; maximal platelet count increased in the Epoetin-beta group vs. placebo Maximal hemoglobin levels were not increased in the epoetin-beta group vs. placebo
Red Cell Transfusion in Coronary Artery Disease			
Cooper HA, Rao SV, Greenberg MD, Rumsey MP, McKenzie M, Alcorn KW et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol. 2011;108(8):1108–11	Two centers, parallel-group, randomized pilot trial 45 participants admitted with acute myocardial infarction with Hct ≤ 30% within 72 h of symptom onset were randomly assigned 1:1 to conservative and liberal transfusion strategies and followed up daily during hospitalization and at 30 days	Liberal transfusion strategy transfused RBCs for Hct < 30% with the goal of maintaining Hct 30–33% Conservative transfusion strategy transfused RBCs for Hct < 24% with the goal of maintaining Hct 24–27%	Primary clinical safety outcome (composite of in-hospital death, recurrent MI, or new or worsening HF): 38% in the liberal strategy group vs. 13% in the conservative strategy group ($p=0.046$), driven by an increase in the number of new or worsening HF events At 30 days, recurrent MI or new or worsening HF occurred in 60% in the liberal strategy group vs. 20% in the conservative strategy group ($p=0.02$) Average daily Hct was 30.6% in the liberal strategy group vs. 27.9% in the conservative strategy group (difference = 2.7%, $p<0.001$) Average number of units of RBC transfused 2.5 ± 1.3 in the liberal strategy group vs. 1.6 ± 2.0 in the conservative strategy group ($p=0.07$)

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. American heart journal. 2013;165(6):964–71.e1	Multicenter across 8 US hospitals, randomized pilot trial 110 participants with Hgb < 10 g/dL and STEMI (30%), NSTEMI (43%), unstable angina (15%), or stable CAD undergoing cardiac catheterization (13%) were randomly assigned 1:1 to liberal vs. restrictive transfusion strategies and followed up daily for the first 3 days, through hospitalization, and then at 30 days and 6 months	Liberal transfusion strategy transfused RBCs to raise and maintain Hgb ≥ 10 g/dL Restrictive transfusion strategy transfused RBCs for any anemia-related symptoms (definite angina requiring symptomatic treatment, unexplained tachycardia, or hypotension). Transfusion was also permitted but not required if Hgb < 8 g/dL	Primary clinical outcome (composite of all-cause mortality, myocardial infarction, or unscheduled coronary revascularization within 30 days): • 30 days: 10.9% in the liberal transfusion group vs. 25.9% (difference 15.0%; 95% CI 0.7–29.3%; $p = 0.054$) in restrictive group • 6 months: 37.0% vs. 27.3% (difference 9.7%; 95% CI − 5.3 to 24.7%; $p = 0.26$) Secondary outcomes: • Death at 30 days: 1.8% in the liberal transfusion group vs. 13.0% in the restrictive transfusion group (difference 11.1%; 95% CI 1.5–20.8%; $p = 0.032$) • Risk of death and of death or MI not significantly different between groups at 30 days or 6 months • 30-day composites of death, MI, unscheduled revascularization, and pneumonia and of death, MI, and unstable angina both significantly decreased in the liberal compared to the restrictive group; all other secondary outcomes were not significantly different Mean Hgb was 1.3–1.8 g/dL higher in the liberal vs. the restrictive transfusion group (all $p < 0.001$). Liberal group participants received 87 RBC units vs. 27 in the restrictive group ($p < 0.001$); 72.7% of the restrictive group participants did not receive a transfusion vs. 0% of the liberal group

Table 1 (continued)

Trial/author	Study design	Intervention	Result
Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I et al. Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial. Jama. 2021;325(6):552–60	Multicenter across 35 centers in France and Spain, open-label, non-inferiority, randomized trial 668 participants with acute myocardial infarction and Hgb 7–10 g/dL were randomly assigned 1:1 to restrictive or liberal transfusion strategy and followed up through hospitalization and at 30 days	Liberal transfusion strategy transfused RBCs for Hgb ≤ 10 g/dL with targeted post-transfusion Hgb ≥ 11 g/dL Restrictive transfusion strategy transfused RBCs for Hgb ≤ 8 g/dL with target post-transfusion Hgb 8–10 g/dL	Primary outcome (composite of all-cause death, non-fatal stroke, non-fatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia at 30 days): • 11.0% in the restrictive group vs. 14.0% in the liberal group (RR 0.79; 1-sided 97.5% CI 0.00–1.19), meeting criteria for non-inferiority; planned superiority analysis did not meet criteria • No significant subgroup differences or interactions Secondary outcomes (restrictive vs. liberal): • All-cause death: 5.6% vs. 7.7% • Recurrent myocardial infarction: 2.1% vs. 3.1% • Emergency revascularization prompted by ischemia: 1.5% vs. 1.9% • Non-fatal ischemic stroke: 0.6% vs. 0.6% Mean Hgb was 1.4 g/dL higher in the liberal vs. restrictive transfusion group (95% CI 1.2–1.6 g/dL). Liberal group participants received 758 RBC units vs. 342 in the restrictive group; 64.3% of the restrictive group participants did not receive a transfusion vs. 0.3% of the liberal group

NYHA New York Heart Association, *FC*, ferric carboxymaltose; *Hgb*, hemoglobin; *LVEF*, left ventricle ejection fraction; *HF*, heart failure; *CV,* cardiovascular; *RR*, relative risk; *CI*, confidence interval; *EPO*, erythropoietin, *HR*, hazard ratio; *MACE*, major adverse cardiovascular events; *STEMI,* ST-elevation myocardial infarction; *Hct*, hematocrit; *NSTEMI*, non-ST elevation myocardial infarction; *CAD*, coronary artery disease; *RBCs*, red blood cells.

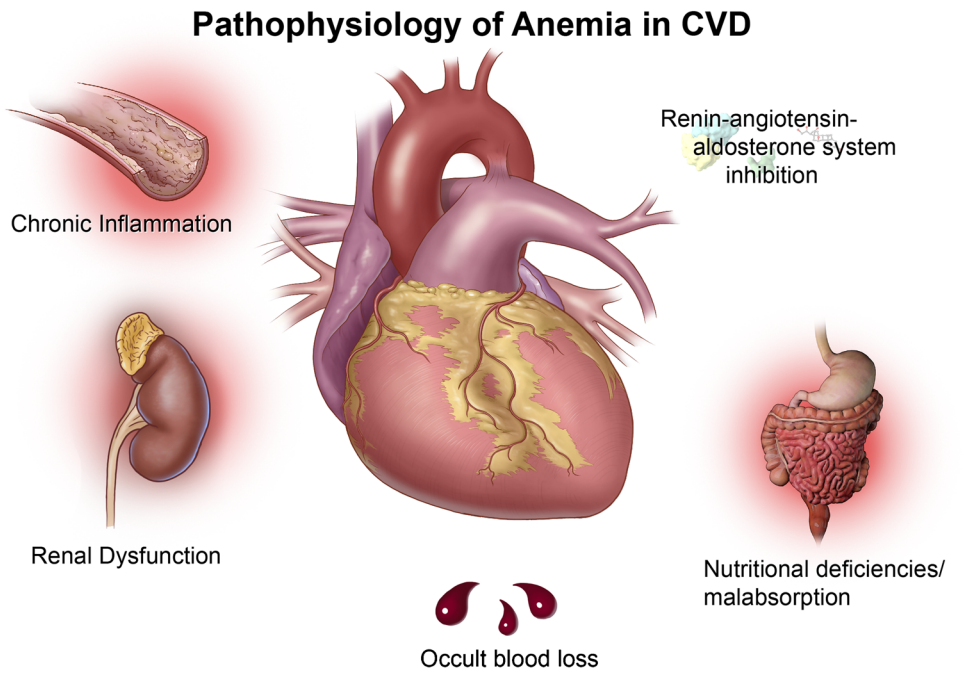

Fig. 1 Pathophysiologic features of anemia in cardiovascular disease (CVD)

inflammation reduces the amount of iron that is available for erythropoiesis by increasing reticuloendothelial iron uptake and inhibiting duodenal iron absorption via increases in hepcidin levels [2, 3]. As a result, inflammation induces an anemia of chronic disease in CVD, resulting in both a functional (inability of the body to use available iron) and absolute state of iron deficiency.

It is important to note that a functional iron deficiency caused by inflammation in CVD is also exacerbated by several modifying factors that are specific to both HF and CAD. In HF, for example, gut wall edema from fluid overload impairs duodenal iron absorption [33, 34]. Furthermore, in CAD, iatrogenic bleeding from anticoagulation with antiplatelet agents has also been hypothesized to further exacerbate iron deficiency [2, 35, 36].

Given the established roles of iron metabolism and EPO as the final common pathways for anemia in chronic heart disease, we focus on current evidence for the use of iron supplementation, ESAs, and RBC transfusions in HF and CAD.

Iron Supplementation

Iron Supplementation in Heart Failure

The role of iron supplementation in improving outcomes in HF has been extensively studied over the past decade (Table 1). *The Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency* (FAIR-HF) trial was one of the first randomized clinical trials to suggest that iron deficiency may be a valid therapeutic target. Specifically, the trial enrolled 459 patients with HF and iron deficiency with or without overt anemia. Importantly, this trial found a significant improvement in both Patient Global Assessment (OR for improvement = 2.51; 95% CI = 1.75–3.61; $p < 0.001$) and NYHA class (OR for improvement = 2.40; 95% CI 1.55–3.71; $p < 0.001$). Significant improvements were also noted in 6-min walk tests and quality of life. Importantly, authors noted similar treatment effects on the primary endpoints in a subgroup analysis of patients with anemia (defined as a Hg < 12 g/dL). However, the mortality rates were similar between both study groups, with a non-significant trend for reduced hospitalization for any cardiovascular cause ($p = 0.08$) and hospitalization for worsening heart failure ($p = 0.11$) in the treatment arm (comprised of anemic and non-anemic iron deficient patients) [37].

In the past few years, two other randomized clinical trials have added further support for the use of IV FC as a therapeutic target in HF. Specifically, the *Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patents with symptomatic heart failure and iron deficiency* (CONFIRM-HF) trial showed evidence of a significant increase in 6-min walk distance at week 24 following FC (mean difference of 33 ± 11 m, $p = 0.002$), with a sustained treatment effect through 52 weeks (36 ± 11 m, $p < 0.001$). Similar to the FAIR-HF trial, treatment effect was also noted in a subgroup analysis of clinically anemic patients (defined as Hg < 12 g/dL). Perhaps, more importantly, the trial was one of the first to show a significant reduction in the risk of hospitalizations for HF (HR 0.39; CI = 0.19–0.82; $p = 0.009$) with no significant impact on mortality [38].

The recently completed *Ferric Carboxymaltose for iron deficiency at discharge after acute heart failure* (AFFIRM-AHF) trial further studied the efficacy of initiating IV FC treatment versus placebo in hospitalized iron deficient HF patients after stabilization, with a primary composite endpoint of total HF hospitalizations and CV death at 52 weeks (RR 0.79; 95% CI 0.62–1.01; $p=0.059$). While the trial missed statistical significance in the primary endpoint, the secondary endpoint analysis demonstrated reduced HF hospitalization in the FC group (RR 0.74; CI 0.58–0.94; $p=0.013$), with no effect on the risk of CV death (13.8% vs. 14.2% [HR 0.96; 95% CI 0.70–1.32; $p=0.81$]). Similar to prior IV FC trials, however, this trial also included a proportion of patients without overt anemia as defined by the WHO (exclusion criteria of Hg > 15 g/dL). [39••].

Despite promising results with FC treatment in symptom improvement, quality of life indicators, and re-hospitalization rates, translation of this approach in current clinical practice may be challenging. Specifically, the IV formulation of FC may be a barrier to many patients with respect to the cost, need for follow-up appointments for infusions, and method of delivery (IV vs. oral). This may be especially challenging to the most vulnerable, socio-economically disadvantaged patients. Unfortunately, more convenient and cost-effective oral iron repletion regimens have failed to show favorable results. For example, the *Effect of Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure* (IRONOUT-HF) randomized clinical trial, which studied the effect of an oral iron repletion regimen, failed to show improvement in exercise capacity as measured by peak oxygen uptake (VO_2) over a 16-week period in a subgroup analysis of anemic, iron deficient patients [40••]. In contrast, the *Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency* (EFFECT-HF) trial, which measured the effects of IV FC on VO_2, showed improvement at 24 weeks ($p=0.02$), although the authors noted that this finding was dependent on a statistical method to account for missing data from patients who died during the trial ($p=0.23$ without the use of the statistical technique). Of note, authors noted no additional benefit with IV FC in a subgroup analysis of anemic patients when compared to non-anemic patients (Hg < 12) [41•].

Iron Supplementation in Coronary Artery Disease

In contrast to HF, the role of iron supplementation in CAD is more controversial, perhaps because of the long-standing belief that iron supplementation, in and of itself, may be harmful in CAD. This concept, known as the "iron hypothesis," was initially suggested by JL Sullivan in 1981, who argued that premenopausal women are more protected from heart disease than are men; this was attributed to higher stored iron levels in men [42]. The hypothesis was initially bolstered by experimental data that elucidated the role of iron in lipid peroxidation, the first step in the formation of atherosclerotic lesions [43]. The results of early epidemiologic studies, primarily from Finland, indicated that iron overload has a role in the progression of atherosclerotic disease and the risk of developing acute myocardial infarction [44, 45]. Furthermore, in one experimental study, iron chelation with deferoxamine improved nitric oxide-mediated vasodilation in patients with CAD [46]. On the other hand, more recent studies have suggested that iron deficiency, as measured by high serum transferrin receptors, are associated with poorer outcomes in CAD [47, 48].

Such conflicting data and theories may ultimately reflect the importance of the delicate balance required in iron homeostasis: both too little and too much iron may be detrimental with respect to CV outcomes in CAD. Interestingly, a large retrospective autopsy study involving 48,000 hemochromatosis patients with hemosiderosis found a lower prevalence of significant CAD in iron-overloaded patients (12% vs. 38%, $p=0.01$), as well as a lower prevalence of triple vessel disease (11.1% vs. 33.3%, $p=0.04$) [49]. This suggests that the adverse CV effects of iron overload are independent of CAD and likely secondary to cardiomyopathy from direct damage to cardiomyocytes [50]. Therefore, at this time, more studies and randomized clinical trials are needed to investigate ideal serum iron levels in CAD and determine whether a role for iron supplementation exists.

Erythropoiesis-Stimulating Agents

Erythropoiesis-Stimulating Agents in Heart Failure

Given its importance in the pathophysiologic characteristics of anemia in CVD, the use of ESAs has also been the subject of much study, particularly in HF. Specifically, the results of early small-scale trials suggested that recombinant human EPO is associated with improved quality of life measures and possibly fewer HF hospitalizations (Table 1). For example, Mancini et al. noted improvements in peak VO_2 ($p \leq 0.05$), exercise duration ($p<0.004$), 6-min walk ($p<0.05$), and Minnesota Living with Heart Failure Questionnaire responses ($p<0.04$) after 3 months of treatment with EPO in a randomized, placebo-controlled trial that included 26 anemic patients [51]. A separate retrospective study of 26 patients conducted by Silverberg et al. further indicated improvements in NYHA class ($p<0.05$), LVEF ($p<0.001$), and number of all-cause hospitalizations per patient ($p<0.05$) treated with EPO/IV iron for a mean treatment course of approximately 7 months [52]. On the contrary, the 2008 *Study of Anemia in Heart Failure Trial* (STAMINA-HeFT) which enrolled 319 patients did not find improved exercise duration, NYHA class, or quality of life outcomes with the use of darbepoetin alfa, despite improved

hemoglobin values. Furthermore, the authors of this trial did note a nonsignificant trend towards lower risk in a composite endpoint of death by any cause or first heart failure hospitalization (HR 0.68; CI 0.43–1.08; $p = 0.10$) [53].

Early studies had small sample sizes; *the Reduction of Events with Darbepoetin alfa in Heart Failure* (RED-HF) trial (2013) was the definitive large (2278 patients), randomized, double-blind trial that evaluated the effects of darbepoetin alfa on the primary outcome of death from any cause or first heart failure hospitalization; secondary outcomes included quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire Score. This study failed to meet its primary composite endpoint (HR 1.10; CI 0.90–1.13; $p = 0.87$), with no evidence of decreased mortality or first heart failure hospitalization when assessing outcomes individually ($p = 0.51$, 0.92 respectively); however, it did show improved quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire Score at 6 months (treatment difference = 2.2 points; CI 0.65–3.75; $p = 0.005$) and the symptom frequency score ($p = 0.01$). Importantly, an increased frequency of statistically significant thromboembolic adverse effects was found in the treatment arm ($p = 0.01$). When interpreting the outcome results of this particular trial, it is important to note that the treatment arm in this trial contained a higher proportion of NYHA class III/IV heart failure patients than did the placebo arm (67.4% vs. 63% NYHA class III/IV, $p < 0.05$), which may have affected the results [54].

The routine use of ESAs in the treatment of anemia in HF remains controversial, particularly with the increased thromboembolic adverse events noted in the RED-HF trial. Potential differences in the effects of recombinant EPO and darbepoetin alfa also remain unexplored, given the conflicting data regarding earlier studies (which focused primarily on recombinant EPO) and more recent studies (which focused primarily on darbepoetin alfa).

Erythropoiesis-Stimulating Agents in Coronary Artery Diseas (CAD)

Similar to studies involving iron supplementation, there are limited data regarding ESA use in the correction of anemia in CAD patients. However, the non-hematopoietic effects of ESAs have been uniquely investigated. Specifically, in animal studies, EPO has been shown to be cardioprotective through the inhibition of apoptosis, myocardial inflammatory response following ischemia/reperfusion injury, and even improved cardiac function as a result of direct modulation of the cardiac Na+/K+pump [55]. Unfortunately, the *Efficacy Study of Erythropoietin After Revascularization in Myocardial Infarction* (REVIVAL-3) trial of 138 patients with STEMI who were randomly assigned to receive EPO or placebo 24 and 48 h after PCI failed to find a significant reduction in major adverse CV events at a follow-up period of 5 years (RR 1.5; CI 0.8–3.5; $p = 0.26$). Interestingly, a subgroup analysis of 39 patients with lower hemoglobin levels (defined as Hg < 14.1 g/dL in this trial) found increased (albeit not statistically significant) mortality in EPO-treated patients (6.2% placebo, 21.7% EPO, $p = 0.21$) [56•]. The results of this trial indicate that ESAs have limited utility in CAD complicated by anemia. Nevertheless, our current knowledge with respect to the hematopoietic effects of ESAs on outcomes in CAD remains poorly explored, especially when compared to HF.

Red Blood Cell Transfusions

The use of RBC transfusions in cardiac patients has been controversial, particularly in terms of the effect of specific transfusion thresholds on mortality and CV outcomes. The main source of controversy revolves around two major transfusion thresholds: a restrictive strategy (transfuse below 7–8 g/dL) vs a liberal transfusion strategy (transfuse below 10 g/dL) [57–59, 60••].

The *Transfusion Requirements in Critical Care* (TRICC) trial was the one of the first to evaluate these two transfusion strategies in a critical care population, finding no significant difference in the 30-day mortality rate between the groups (18.7% restrictive, 23.3% liberal, $p = 0.11$), with similar findings in a subgroup analysis of patients with clinically significant cardiac disease (20.5% restrictive, 22.9% liberal, $p = 0.69$). Of note, patients with CV disease comprised approximately 32% of the trial population [57]. This trial has been the basis for the long-standing clinical dogma of "transfuse for Hg < 7 g/dL." However, whether this applies to patients with CVD has been a matter of debate.

The *Conservative versus liberal red cell transfusion in acute myocardial infarction* (CRIT) trial, which focused on RBC transfusion in acute myocardial infarction in a population of 45 patients, found an increased risk of in-hospital death, recurrent myocardial infarction, or new or worsening HF in the liberal arm (transfuse < 10 g/dL) vs. a restrictive arm (transfuse < 8 g/dL) (38% liberal, 13% restrictive, $p = 0.046$) [58]. On the contrary, the results of a separate larger trial involving 110 patients with acute coronary syndrome or stable angina who were undergoing cardiac catheterization indicated that there was a trend towards fewer cardiac events and deaths in a liberal transfusion strategy (transfuse < 10 g/dL) vs a restrictive strategy (transfuse < 8 g/dL), with statistical significance in 30-day mortality (1.8% liberal, 13% restrictive, $p = 0.032$). A trend for fewer unscheduled hospitalizations was also noted in the liberal transfusion group (16.4% vs. 31.5% for any cause, $p = 0.064$; 5.5% vs 14.8% for cardiac reason, $p = 0.10$). However, it is important to note that in this trial, the mean age of the restrictive arm was older than that of the liberal arm

(74.3 vs. 67.3, $p = 0.004$), and a post hoc analysis to correct for this difference found no statistically significant difference in the composite of 30-day mortality, myocardial infarction, or unscheduled revascularization between the two arms (OR 2.65; CI 0.90–7.78; $p = 0.076$) [59]. The authors of both trials recommended a larger scale randomized trial for further investigation.

The recently completed *Restrictive And Liberal Transfusion Strategies in Patients With Acute myocardial Infarction* (REALITY) randomized clinical trial studied these two transfusion strategies in a population of 668 patients with acute myocardial infarction and anemia. This trial specifically showed the non-inferiority of the restrictive transfusion strategy (transfuse < 8 g/dL) vs. the liberal transfusion strategy (transfuse < 10 g/dL) in the primary composite outcome, including all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization at 30 days (RR, 0.79; CI 0.00–1.19). In the assessment of individual outcomes, a restrictive strategy resulted in lower all-cause death (5.6% vs. 7.7%), recurrent myocardial infarction (2.1% vs. 3.1%), and emergency revascularization (1.5% vs. 1.9%), with similar rates of non-fatal ischemic stroke (0.6%) [60••]. Of note, the authors did not perform statistical significance testing to avoid multiple comparisons of the individual outcomes. Nevertheless, the results of this larger trial indicate that a restrictive transfusion strategy may be appropriate in CV patients.

Latest Treatment Guidelines

The 2013 American College of Physicians guidelines found inconclusive evidence to support IV iron use in patients with HF, given the lack of evidence of long-term outcomes and a limited number of studies at the time of recommendation [61]. In contrast, the 2017 ACC/AHA/HFSA focused update of the 2013 HF guideline states that it may be reasonable to consider IV iron replacement in patients with NYHA class II and III HF with ferritin levels < 100, or between 100 and 299 if transferrin saturation is < 20% (class IIb recommendation). This recommendation reflects new data from the CONFIRM-HF and FAIR-HF trials [62]. Iron treatment in anemic CAD patients remains an area with few guidelines, given the paucity of data.

The American College of Physicians guidelines strongly recommend against the use of ESAs in chronic heart disease [61]. Similarly, the ACC/AHA/HFSA guideline strongly recommend against the use of ESAs to improve morbidity and mortality in chronic HF and anemia (class III recommendation) [62]. No official guideline-directed recommendations exist on ESA use in anemic CAD patients.

The American College of Physicians guidelines recommend a transfusion threshold of 7–8 g/dL in acute coronary syndrome [61]. In contrast, guidelines from the American Association of Blood Banks from 2016 recommend a transfusion threshold of 8 g/dL in patients with pre-existing CVD; however, note that a threshold of 7 g/dL is likely similar to 8 g/dL [63]. Future studies assessing whether true significance exists

Table 2 Current guidelines for the use of IV sron, ESAs, and RBC transfusions in cardiac populations

IV Iron in Heart Failure			
Organization	Recommendation	Grade/Class	Level of evidence
2013 American College of Physicians	Inconclusive	N/A	N/A
2017 ACC/AHA/HFSA	"In patients with NYHA class II and III HF and iron deficiency (ferritin <100ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and quality of life'"	IIb	Moderate quality
ESAs in heart failure			
2013 American College of Physicians	"ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure."	Strong	Moderate quality
2017 ACC/AHA/HFSA	"In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality."	III	Moderate quality
Rbc transfusions in cardiac populations			
2013 American College of Physicians	ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease.	Weak	Low Quality
2016 American Association of Blood Banks	"A restrictive RBC transfusion threshold of 8 g/dL is recommended for patients undergoing orthopedic surgery, cardiac surgery, and those with preexisting cardiovascular disease	Strong	Moderate Quality

ACP, American College of Physicians; *AC*, American College of Cardiology; *AHA*, American Heart Association; *HFSA*, Heart Failure Society of America; *IV*, intravenous; *ESA*, erythropoiesis-stimulating agents; *RBCs*, red blood cells; *NYH*, New York Heart Association; *HF*, heart failure.

between thresholds of 7 g/dL and 8 g/dL would be helpful; however, it may be difficult to practically study. A summary of current recommendations for the treatment of anemia from these various organizations is provided in Table 2 [61–63].

Conclusions

Anemia is an established risk factor for CVD and is associated with unfavorable outcomes in both CAD and HF. Recent studies have assessed the effects of anemia treatment with iron supplementation, ESAs, and RBC transfusions. While IV FC and ESAs in HF have resulted in improved quality of life metrics in clinical trials, with IV FC further showing evidence of reduced re-hospitalization rates in HF, neither iron supplementation, ESAs, nor aggressive RBC transfusions (transfuse for Hg < 10 g/dL vs. < 8 g/dL) have resulted in improved CV and mortality outcomes. ESAs have further been associated with increased adverse thromboembolic events. There are no guideline-based recommendations on iron supplementation and ESAs in anemic CAD patients; further study is required. Differences between recombinant EPO and darbepoetin alfa, differences between transfusion thresholds of 7 g/dL vs. 8 g/dL in heart disease, and long-term studies of IV and PO iron supplementation with an emphasis on anemic populations are also areas for future study.

Anemia in CVD is a marker of underlying disease severity; however, benefits in quality of life, physical function, and hospitalization resulting from anemia treatment suggest that it has a limited role in disease modification. This remains an area of ongoing investigation.

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Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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