Treatment of Anemia in Patients With Heart Disease

A Systematic Review

Devan Kansagara, MD, MCR; Edward Dyer, MD; Honora Englander, MD; Rongwei Fu, PhD; Michele Freeman, MPH; and David Kagen, MD

Background: The benefits of anemia treatment in patients with heart disease are uncertain.

Purpose: To evaluate the benefits and harms of treatments for anemia in adults with heart disease.

Data Sources: MEDLINE, EMBASE, and Cochrane databases; clinical trial registries; reference lists; and technical advisors.

Study Selection: English-language trials of blood transfusions, iron, or erythropoiesis-stimulating agents in adults with anemia and congestive heart failure or coronary heart disease and observational studies of transfusion.

Data Extraction: Data on study design, population characteristics, hemoglobin levels, and health outcomes were extracted. Trials were assessed for quality.

Data Synthesis: Low-strength evidence from 6 trials and 26 observational studies suggests that liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols (combined relative risk among trials, 0.94 [95% CI, 0.61 to 1.42]; $I^2 = 16.8\%$), although decreased mortality rates occurred in a small trial of patients with the acute coronary syndrome (1.8% vs. 13.0%; $P = 0.032$). Moderate-strength evidence from 3 trials of intravenous iron found improved short-term exercise tolerance and quality of life in patients with heart failure. Moderate- to high-strength evidence from 17 trials of erythropoiesis-stimulating agent therapy found they offered no consistent benefits, but their use may be associated with harms, such as venous thromboembolism.

Limitations: Few trials have examined transfusions in patients with heart disease, and observational studies are potentially confounded by indication. Data supporting iron use come mainly from 1 large trial, and long-term effects are unknown.

Conclusion: Higher transfusion thresholds do not consistently improve mortality rates, but large trials are needed. Intravenous iron may help to alleviate symptoms in patients with heart failure and iron deficiency and also warrants further study. Erythropoiesis-stimulating agents do not seem to benefit patients with mild to moderate anemia and heart disease and may be associated with serious harms.

Primary Funding Source: U.S. Department of Veterans Affairs.

Ann Intern Med. 2013;159:746-757. www.annals.org

For author affiliations, see end of text.

Approximately one third of patients with congestive heart failure (CHF) and 10% to 20% of those with coronary heart disease (CHD) also have anemia (1–3). Anemia is associated with more symptoms, a greater hospitalization rate, and increased mortality rates both in patients with CHF (4–6) and CHD (7, 8). It is unclear whether anemia directly leads to these poor outcomes or simply reflects more severe underlying illness. Indeed, many factors probably contribute to the development of anemia in heart disease, including comorbid chronic kidney disease, blunted erythropoietin production, hemodilution, aspirin-induced gastrointestinal blood loss, the use of renin–angiotensin–aldosterone system blockers, cytokine-mediated inflammation, gut malabsorption, and iron deficiency (9, 10).

For many years, the epidemiologic data and biological plausibility supporting a link between anemia and poor outcomes in patients with heart disease prompted many physicians to advocate treatment of anemia with more aggressive use of blood transfusions. Interest in erythropoiesis-stimulating agents (ESAs) and iron supplementation to treat anemia in heart disease has also been growing. An increasing body of literature has recently tested whether these strategies improve health outcomes in patients with heart disease. This review summarizes and updates a report commissioned by the U.S. Department of Veterans Affairs' Evidence-based Synthesis Program and the Clinical Guidelines Committee of the American College of Physicians, which evaluated the health outcome effects of each of these strategies in adult patients with heart disease (11).

See also:

Print
Related article 770

Web-Only
Supplement

METHODS

Data Sources and Searches

We conducted a search for literature published in MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from database inception to August 2012. We searched EMBASE through November 2010 because we could not retain our license for this database beyond that time frame. The search strategy included such terms as *anemia*, *congestive heart failure*, *coronary heart disease*, *ischemic heart disease*, *erythropoiesis-stimulating agents*, *iron*, and *red blood cell transfusion*. The detailed search strategy is provided in **Table 1** of the **Supplement** (available at www.annals.org). We obtained additional articles from systematic reviews; refer-

ence lists of pertinent studies, reviews, and editorials; and consulting experts. We also searched for ongoing and recently completed studies on ClinicalTrials.gov and included reports of trials that had been published as of April 2013.

Study Selection

The analytic framework that guided our review and synthesis of the literature is provided in **Appendix Figure 1** (available at www.annals.org). Eligible articles had English-language abstracts and provided primary data about the effects of ESAs, iron, or blood transfusions in adult populations with anemia (hemoglobin levels <13 g/dL in men and <12 g/dL in women) and symptomatic CHF (with or without decreased systolic function) or CHD (the acute coronary syndrome, the postacute coronary syndrome, and history of myocardial infarction [MI] or angina). We included trials with mixed populations of patients with and without anemia as long as data specific to the anemia subgroup were reported. We considered trials comparing interventions with placebo or those comparing more intensive with less intensive interventions (that is, trials examining different transfusion thresholds or hemoglobin targets). Because few trials of red blood cell transfusion were found, we included observational studies to characterize the evidence on which current transfusion practice is based. Outcomes of interest included mortality, hospitalization, exercise tolerance, cardiovascular events, quality of life, and adverse effects of treatment.

Three investigators reviewed the titles and abstracts of citations identified from literature searches, and 2 reviewers independently assessed the selected full-text articles for inclusion on the basis of the eligibility criteria shown in **Table 2** of the **Supplement**. Disagreements were resolved by consensus.

Data Extraction and Quality Assessment

From each study, we abstracted study design, objectives, setting, population characteristics (including sex, age, left ventricular ejection fraction, baseline New York Heart Association [NYHA] class, and CHD definition), participant eligibility and exclusion criteria, number of participants, years of enrollment, duration of follow-up, the study and comparator interventions, important cointerventions, baseline hemoglobin levels, change in hemoglobin levels, health outcomes, and adverse effects. If only the hematocrit was reported, we used a conversion of 3:1 to approximate the hemoglobin value. To evaluate harms, we collected data on adverse effects from all included trials and specifically gathered data from each ESA trial on hypertension, venous thromboembolic events (including deep venous thrombosis, pulmonary embolism, and vascular access thrombosis), and ischemic cerebrovascular events. In trials examining blood transfusions, we specifically looked for reporting of transfusion reactions.

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration (12). Disagreements were resolved by discussion. Each study was given an overall summary assessment of low, high, or unclear risk of bias. We assessed the overall quality of evidence for outcomes using a method developed by the Grading of Recommendations Assessment, Development, and Evaluation Working Group (13), which considers the consistency, coherence, and applicability of a body of evidence, as well as the internal validity of individual studies, to classify the grade of evidence across outcomes.

Although there is no widely accepted standard for quality assessment of observational studies, we adapted existing tools (14, 15) relevant to this review and specifically assessed whether each observational blood transfusion study conducted an analysis adjusting for patient propensity to receive a blood transfusion, accounted for bleeding complications (regardless of whether they were procedure-related), and accounted for the timing of transfusion given the potential for survival bias in which patients who died could not have received a transfusion. The detailed assessment of quality for each study is provided in **Tables 3** to **6** of the **Supplement**. We do not report an overall summary assessment for observational studies because there are no validated criteria for doing so.

Data Synthesis and Analysis

We did meta-analyses of study-level data evaluating the effects of liberal compared with restrictive transfusion strategies on short-term mortality rates (defined as death during or within 30 days after the hospital stay) and cardiovascular events (defined as MI, CHF exacerbation, arrhythmia, or cardiac death—we distinguished in-hospital events from those occurring during longer-term follow-up). We abstracted the number of events and total participants from each treatment group and obtained a pooled estimate of relative risk (RR) using a random-effects model (16). We preferentially used 30-day mortality for the analysis, followed by in-hospital and 72-hour mortality. We conducted a sensitivity analysis on the basis of the definition of short-term mortality. If trials included mixed populations of patients with and without heart disease, we contacted authors for subgroup information if it was not available in published reports.

We also did meta-analyses of ESA trials for each of the following outcomes: mean difference in the change in NYHA class, exercise duration during the 6-minute walk test, all-cause mortality, hospitalizations, cardiovascular events, hypertension events, and ischemic cerebrovascular events. Given the variety of assessment tools used, we did not do meta-analyses of quality-of-life outcomes. We ran sensitivity analyses for all outcomes, excluding studies with high or unclear risk of bias.

All analyses were done using Stata 10.0 (StataCorp, College Station, Texas). Statistical heterogeneity among the trials combined in meta-analysis was assessed by the Cochran Q test and I^2 statistic (12). Publication bias was

not assessed because of the small number of trials that could be combined (17).

We qualitatively synthesized the results of trials of iron therapy because only 3 trials examined the effects of iron, with 1 large trial dominating.

Role of the Funding Source

The U.S. Department of Veterans Affairs Quality Enhancement Research Initiative supported this review but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

We reviewed 1740 titles and abstracts from the electronic search and identified an additional 79 from reviewing reference lists and doing manual searches for recently published and unpublished or ongoing studies (**Appendix Figure 2**, available at www.annals.org). After inclusion and exclusion criteria were applied at the abstract level, 404 full-text articles were reviewed. Fifty-five articles comprising 52 primary studies met our inclusion criteria. Detailed results for each intervention are presented in the following sections, and the overall findings are summarized in **Table 1**.

Blood Transfusions

Six trials compared liberal and restrictive transfusion protocols (18–20, 23–25) (**Table 7** of the **Supplement**). Three of these were conducted in nonoperative settings among critically ill patients or those with the acute coronary syndrome (23, 25, 26). Three studies were conducted in patients with and without known heart disease in perioperative settings (18–20), but only 1 of these studies had CHD-specific subgroup information available (20).

Overall, low-strength evidence from the 6 trials suggests that liberal transfusion protocols do not reduce 30-day mortality rates compared with restrictive transfusion protocols (RR, 0.94 [95% CI, 0.61 to 1.42]; $I^2 = 16.8\%$). Exclusion of the 2 studies in which CHD subgroup-specific information was not available (18, 19) yielded similar results (RR, 0.86 [CI, 0.46 to 1.62]; $I^2 = 50.0\%$) (**Figure 1**).

However, more aggressive transfusion protocols may be associated with lower risk for cardiovascular events (5 trials; RR, 0.64 [CI, 0.38 to 1.09]; $I^2 = 0.0\%$). As previously described, exclusion of the 2 studies in which CHD subgroup information was not available did not affect the findings (RR, 0.60 [CI, 0.34 to 1.03]; $I^2 = 0.0\%$) (**Appendix Figure 3**, available at www.annals.org).

Aside from cardiovascular events, which we report in a subsequent section, there were no reports of excess adverse effects from more aggressive transfusion in the trials, although harms reporting was sparse and only 1 trial recorded transfusion reactions (23).

Nonoperative Setting

Low-strength evidence from 3 trials (23–25) (combined RR, 0.58 [CI, 0.23 to 1.48]; $I^2 = 29.9\%$) and 23 observational studies (8, 27–48) suggests that more aggressive transfusion does not decrease mortality rates in patients who are critically ill with heart disease or those with the acute coronary syndrome (**Table 1**).

Results among studies, however, were conflicting. A recent multicenter, randomized, controlled trial of 110 patients compared transfusion thresholds of 10 and 8 g/dL in patients with the acute coronary syndrome or stable angina having cardiac catheterization (25). The liberal transfusion strategy was associated with a lower 30-day mortality rate (1.8% vs. 13.0%; $P = 0.032$), but the rates of MI (9.1% vs. 13.0%; $P = 0.52$) and unscheduled coronary revascularization (0.0% vs. 3.7%; $P = 0.24$) were similar in both groups. Another trial of patients with acute MI compared similar transfusion thresholds but found that the liberal transfusion group had a greater rate of the primary end point, a composite of in-hospital death, recurrent MI, or new or worsening heart failure (38% vs. 13%; $P = 0.046$), with most of the difference explained by a greater incidence of new or worsening CHF (23). An older trial of patients without bleeding who were critically ill and had anemia compared transfusion hemoglobin thresholds of 10 and 7 g/dL. The overall trial population included 838 patients with and without heart disease and found no difference in mortality or cardiovascular event outcomes (49). In a post hoc subgroup analysis of the 257 patients with known ischemic heart disease, 30-day mortality rates were also similar between the liberal and restrictive transfusion groups (21.2% vs. 26.1%; RR, 0.81 [CI, 0.52 to 1.26]) (24).

Twenty-three observational studies were done in patients having percutaneous coronary intervention or hospitalized with the acute coronary syndrome, MI, or decompensated heart failure (**Table 8** of the **Supplement**). There was little evidence in nearly all studies that transfusions at hemoglobin levels greater than 8 to 9 g/dL were associated with improved outcomes, although there were 2 exceptions (8, 45). However, many observational studies found that transfusions at hemoglobin levels greater than 9 to 10 g/dL were associated with an increased risk for death. Whether these findings reflect a true effect of transfusion or confounding by indication is unclear.

No studies examined transfusions in stable outpatients with a history of CHD.

Perioperative Setting

Low-strength evidence from 3 trials in hip fracture and vascular surgery patients with heart disease found no short-term mortality benefit from a liberal compared with a conservative transfusion strategy (RR, 1.35 [CI, 0.80 to 2.25]; $I^2 = 0.0\%$) (18–20). However, fewer cardiovascular events occurred with more aggressive use of transfusions in patients having surgery. A recent large trial randomly as-

Table 1. **Summary of Evidence for Effects of ESAs, Iron, and Blood Transfusions for Anemia, by Patient Population and Outcome**

Outcome, by Treatment	Trials With Low Risk of Bias (Participants)/Trials With High or Unclear Risk of Bias (Participants), *n*	Summary of Findings, Treatment vs. Control Group*	GRADE Classification†	Comment
Stable CHF				
Blood transfusions				
All outcomes	3 (unknown)/0	No significant difference	Insufficient	3 trials included a small number of patients with CHF. Data specific to patients with isolated CHF and no CHD were available in only 1 trial of patients who had hip fracture surgery, which found no difference in mortality or MI outcomes.
Iron				
Exercise tolerance and duration	2 (499)/1 (35)	Improvements in NYHA class, 6-min walk distance, and Patient Global Assessment of symptoms	Moderate	Most data come from 1 large trial, although the smaller trials found similar results. Data are most applicable to patients with NYHA class III symptoms and ferritin levels <224.7 pmol/L.
Quality of life	2 (499)/1 (35)	Improvement in quality of life	Moderate	Most data come from 1 large trial, although the smaller trials found similar results. Data are most applicable to patients with NYHA class III symptoms and ferritin levels <224.7 pmol/L.
Mortality	1 (459)/1 (35)	No significant difference	Insufficient	The 1 large trial showed a trend toward benefit but was not powered for this outcome.
Cardiovascular events	1 (459)/0	27.6% vs. 50.2% ($P = 0.01$)	Low	This was not a prespecified end point, and outcome definition was unclear.
Serious harms	2 (499)/1 (35)	No significant difference	Moderate	
ESAs				
Exercise tolerance and duration (change in NYHA score)	4 (555)/5 (231)	Studies with low risk of bias: RR, −0.15 (95% CI, −0.36 to 0.06) All studies: RR, −0.77 (CI, −1.12 to −0.32)	Moderate	Overall, studies with low risk of bias found no significant effect.
Quality of life	4 (2803)/2 (64)	No consistent, clinically significant difference in quality of life	Moderate	Inconsistent results and the variety of instruments used limit the evidence base. The largest study found no clinically significant change, although there was statistically significant improvement in quality of life with ESA treatment.
Mortality	6 (4098)/4 (217)	RR, 1.07 (CI, 0.98 to 1.16)	High	1 of the large trials included both CHF and CHD subgroups, which may limit applicability to CHF-only populations, although another large trial in patients with CHF found similar results.
Hospitalizations	4 (3901)/4 (207)	Studies with low risk of bias studies: RR, 0.97 (CI, 0.87 to 1.10) All studies: RR, 0.69 (CI, 0.52 to 0.93)	High	Although smaller, methodologically limited studies found improvement, the largest and best-quality studies found no effect.
Cardiovascular events	7 (6710)/2 (92)	RR, 0.94 (CI, 0.82 to 1.08)	High	3 of the large trials included patients with advanced kidney disease, although a fourth large trial included patients without advanced kidney disease and found similar results.
Harms	Venous thromboembolism: 4 (3988)/0 Ischemic stroke: 4 (2706)/0 Hypertension: 7 (2899)/0	Venous thromboembolism: RR, 1.36 (CI, 1.17 to 1.58) Ischemic stroke: RR, 1.33 (CI, 0.93 to 1.89) Hypertension: RR, 1.20 (CI, 0.90 to 1.59)	Moderate	1 of the large trials finding increased risk for venous thromboembolism included both CHF and CHD subgroups and was conducted in patients with ESRD, which may limit applicability.
Decompensated CHF				
Blood transfusions				
Mortality	0	–	Insufficient	2 observational studies found conflicting results: 1 showed harm, and the other a possible benefit.
Iron				
All outcomes	0	–	–	No evidence
ESAs				
All outcomes	0	–	–	No evidence

Continued on following page

Table 1—**Continued**

Outcome, by Treatment	Trials With Low Risk of Bias (Participants)/Trials With High or Unclear Risk of Bias (Participants), *n*	Summary of Findings, Treatment vs. Control Group*	GRADE Classification†	Comment
CHD				
Blood transfusions				
Mortality	All patients: 4 (1207)‡/0 Acute coronary syndrome: 2 (144)/0 Noncardiac surgery: 1 (796)§/0	All patients: RR, 0.86 (CI, 0.46 to 1.62) Acute coronary syndrome: RR, 0.23 (CI, 0.05 to 1.02) Noncardiac surgery: RR, 1.44 (CI, 0.81 to 2.54)	Low	Imprecision and the small number of trials limit the evidence base. The lack of mortality effects may not apply to the acute coronary syndrome population. Much of the data come from post hoc subgroup analyses of 2 trials. A large body of observational studies also found no mortality benefit, although the validity of these studies is limited.
Cardiovascular events	All patients: 3 (958)‡/0 Acute coronary syndrome: 2 (144)/0 Noncardiac surgery: 1 (804)§/0	All patients: RR, 0.60 (CI, 0.34 to 1.03) Acute coronary syndrome: RR, 0.70 (CI, 0.24 to 2.07) Noncardiac surgery: RR, 0.52 (CI, 0.27 to 1.01)	Low	Imprecision, inconsistencies across populations, and the small number of studies limit the evidence base. Most events come from a subgroup analysis of 1 large trial of patients who had hip fracture surgery.
Iron				
All outcomes	0/0	–	–	No evidence
ESAs				
Mortality	2 (unknown)/0	Increased mortality	Low	2 large trials included a large subgroup of patients with CHD, but subgroup-specific data are not available. Patients with advanced CKD; unclear application to other populations.
Quality of life	0‖/1 (unknown)	No effect on functional status of quality-of-life measures	Low	1 large trial of patients with heart disease included a large subgroup of patients with CHD, but subgroup-specific data are not available. Patients with ESRD; unclear application to other populations.
Cardiovascular events	2 (unknown)/1 (36)	No effect on cardiovascular events	Low	2 large trials included a large subgroup of patients with CHD, but subgroup-specific data are not available. Patients with advanced CKD; unclear application to other populations.
Serious harms	2 (unknown)/0	Increased risk for venous thromboembolic disease	Low	Based on 2 large trials that included large subgroups of patients with CHD, although subgroup-specific harms data were not available. Patients had advanced kidney disease, and application to other populations is unclear.
All other outcomes	0/0	–	–	No evidence

CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; ESRD = end-stage renal disease; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; MI = myocardial infarction; NYHA = New York Heart Association; RR = risk ratio.

* Results according to studies' risk-of-bias rating are presented only when the sensitivity analyses indicated that the risk-of-bias rating significantly influenced summary effects.

† GRADE classification: high = further research is very unlikely to change our confidence on the estimate of effect; moderate = further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

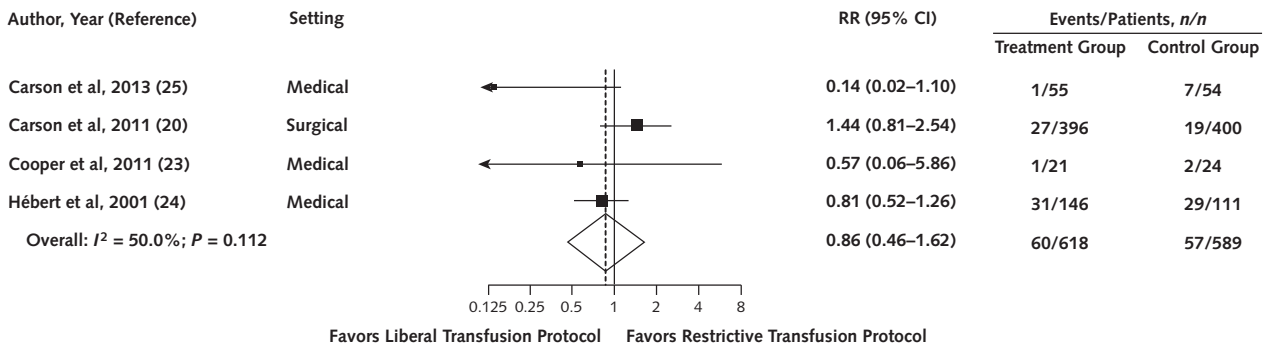
‡ The 2 trials (n = 183) for which CHD-specific subgroup information was not available (18, 19) are not included in these summary estimates. Analyses including these trials yielded similar results for mortality (RR, 1.35 [95% CI, 0.80 to 2.25]) and more imprecise results for MI (RR, 0.63 [CI, 0.25 to 1.60]), in part because these trials only contributed 3 MI events to the analysis. Data from 1 of the included trials (20) are from the CHD subgroup. Sensitivity analyses examining the effects of different definitions of cardiac disease (i.e., including patients with CHF or peripheral vascular disease) yielded similar results.

§ Analysis using a broader definition of cardiovascular disease to include patients with CHD, CHF, peripheral vascular disease, and stroke yielded similar results for mortality (n = 1252; RR, 1.24 [CI, 0.79 to 1.85]) and cardiovascular event outcomes (n = 1267; RR, 0.50 [CI, 0.27 to 0.91]). The 2 trials (n = 183) for which CHD-specific subgroup information was not available (18, 19) are not included in these summary estimates.

‖ One trial was classified as high risk of bias for quality-of-life outcomes but low risk of bias for mortality outcomes (21, 22).

signed patients who had hip fracture surgery and a history of, or risk factors for, cardiovascular disease to a liberal (hemoglobin level threshold of 10 g/dL) or restrictive transfusion strategy (symptoms of anemia or at the physician's discretion for hemoglobin levels <8 g/dL) (20). As expected, more patients in the liberal transfusion group received 1 or more transfusions than the restrictive group (96.7% vs. 41.0%; $P < 0.001$). In a post hoc analysis of the subgroup of 796 patients with known CHD, 30-day mortality rates in the 2 groups were similar (RR, 1.44 [CI, 0.81 to 2.54]), but the liberal transfusion strategy was associated with a reduced risk for in-hospital MI that approached statistical significance (RR, 0.52 [CI, 0.27 to 1.01]). When we used a broader definition of cardiovascular disease to include patients with CHF, peripheral vascular disease, or cerebrovascular disease, the reduction in MI reached statistical significance (1267 patients; RR, 0.50 [CI, 0.27 to 0.91]). Of note, among the 748 patients without known cardiovascular disease, the liberal transfusion strategy had no effect on mortality rates (RR,

Figure 1. **30-d mortality among patients with congestive heart failure or coronary heart disease in liberal versus restrictive blood transfusion protocols.**



RR = risk ratio.

1.12 [CI, 0.50 to 2.50]) or MI (RR, 1.02 [CI, 0.39 to 2.69]).

In the observational cohorts, transfusion did not seem to offer any protection, and in 1 vascular surgery study, mortality and MI rates were greater overall in the transfusion group (**Table 8** of the **Supplement**) (50–52).

Iron

Moderate-strength evidence from 3 trials (53–55) found that intravenous iron improved exercise tolerance, quality of life, and cardiovascular events in patients with heart failure (**Tables 1** and **2**). Results are dominated by 1 large, multicenter trial that found intravenous ferric carboxymaltose improved 6-month exercise tolerance and quality of life in patients with heart failure (55, 56). Most patients had NYHA class III symptoms and moderate to severe systolic dysfunction. Only one half of the patients had anemia (hemoglobin levels ≤12 g/dL), but most had ferritin levels less than 224.7 pmol/L. Intervention patients were more likely to report they were greatly or moderately improved on the Patient Global Assessment (50% vs. 28%; odds ratio, 2.51 [CI, 1.75 to 3.61]) and showed improvement in NYHA functional class (odds ratio for improvement by 1 class, 2.40 [CI, 1.55 to 3.71]). Results were similar in patients with hemoglobin levels less than and greater than 12 g/dL for the Patient Global Assessment (*P* value for interaction with hemoglobin level = 0.98), NYHA class (*P* value for interaction = 0.51), and quality-of-life (*P* value for interaction = 0.59) outcomes (56). There were fewer cardiac events in the intervention group (27.6% vs. 50.2%; *P* = 0.01), although this outcome was poorly defined and not prespecified. Mortality rates were similar in both groups (3.4% vs. 5.5%), but the trial was not powered for mortality outcomes. Serious adverse effects were uncommon, although there was a trend toward increased gastrointestinal events in the intervention group (**Table 2**). The long-term effects of iron treatment are unknown.

Two small trials, 1 with low risk of bias (53) and 1 with high risk of bias because of lack of patient blinding (54), found that intravenous iron sucrose improved symptoms and exercise tolerance.

ESAs

Seventeen randomized, controlled trials of ESAs in patients with heart disease were published in 19 reports (**Table 9** of the **Supplement**) (21, 22, 57–73). Twelve trials enrolled patients with CHF, and the mean ejection fraction was 35% or less among 11 trials that reported systolic function. Most patients had comorbid CHD. Two trials included roughly equal proportions of patients with CHD and CHF (22, 59), and only 1 trial focused exclusively on patients with CHD (70). Two trials were primarily designed to assess the comparative effects of ESAs titrated to high or low hemoglobin targets in patients with anemia and chronic kidney disease but included a large proportion of patients with heart disease for whom adequate subgroup data were reported (58, 59).

Overall, there is high-strength evidence that ESA use has no beneficial effects on mortality rates, cardiovascular events, and hospitalizations (**Table 1**). Moderate-strength evidence suggests that ESAs do not consistently improve quality of life either. Although some studies found that ESA use improved exercise tolerance and duration, no improvement was seen on combining trials with low risk of bias (mean difference in NYHA score change, −0.15 [CI, −0.36 to 0.06]). By contrast, moderately strong evidence in patients with CHF shows that ESA use may be associated with serious harms, such as hypertension and venous thromboembolism, and possibly increased mortality rates (**Figure 2**). The study characteristics, quality assessment, and meta-analyses of the ESA trials are shown in detail in **Tables 6** and **9** of the **Supplement** and **Appendix Figures 4** to **11** (available at www.annals.org).

The Reduction of Events With Darbepoetin Alfa in Heart Failure trial, by far the largest trial (to our knowl-

Table 2. **RCTs of Iron Therapy in Patients With CHF or CHD**

Study, Year (Reference); Setting; Follow-up	Patient Characteristics (Treatment vs. Control Group)	Clinical Characteristics (Treatment vs. Control Group)	Baseline Kidney Function (Treatment vs. Control Group)	Intervention (Treatment vs. Control Group)	Baseline Measures of Iron Stores (Treatment vs. Control Group)
Anker et al, 2009 (55), and Comín-Colet et al, 2013 (56); multicenter, international RCT; 24 wk	Patients: 304 vs. 155 Male: 47.6% vs. 45.2% White: 99.7% vs. 100% Mean age: 67.8 vs. 67.4 y	Mean LVEF: 31.9% vs. 33.0% NYHA class II: 17.4% vs. 18.7% NYHA class III: 82.6% vs. 81.3%. RAAS blockers: 92.4% vs. 91.0%	GFR: 63.8 vs. 64.8 mL/min/1.73 m^2	Ferric carboxymaltose, 200 mg weekly IV, until repleted, then every 4 wk, vs. saline, 4 mL	Ferritin level: 118 vs. 135 pmol/L TSAT: 17.7% vs. 16.7%
Okonko et al, 2008 (54); RCT in 2 centers in Europe; 18 wk	Patients: 24 vs. 11 Male: 71% vs. 73% White: 88% vs. 91% Mean age: 64 vs. 62 y	CAD: 79% vs. 73% LVEF: 30% vs. 29% RAAS blockers: 96% vs. 91%	Baseline creatinine level: 109.7 vs. 103.4 μmol/L (1.23 vs. 1.17 mg/dL)	Iron sucrose IV in varied doses (according to a formula in paper) weekly for 4 wk then every 4 wk for 4 mo; no control	Ferritin level: 139 vs. 198 pmol/L TSAT: 20% vs. 21%
Toblli et al, 2007 (53); RCT; 6 mo	Patients: 20 vs. 20 Male: NR White: NR Mean age: 76 vs. 74 y	CAD: 60% vs. 55% Mean LVEF: 31.3% vs. 30.8% RAAS blockers: 95% vs. 100%	Baseline GFR: 39.8 vs. 37.7 mL/min/1.73 m^2	Iron sucrose, 200 mg IV, vs. saline, 200 mL, weekly for 5 wk	Ferritin level: 164 vs. 159 pmol/L TSAT: 20% vs. 20%

CAD = coronary artery disease; CHD = coronary heart disease; CHF = congestive heart failure; EQ-5D = EuroQol-5 dimension; GFR = glomerular filtration rate; GI = gastrointestinal; HR = hazard ratio; IV = intravenous; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living With Heart Failure Questionnaire; NR = not reported; NYHA = New York Heart Association; OR = odds ratio; PY = patient-year; RAAS = renin–angiotensin–aldosterone system; RCT = randomized, controlled trial; TIA = transient ischemic attack; TSAT = transferrin saturation.
* See **Table 5** of the **Supplement** (available at www.annals.org) for details on quality assessment.

edge) to examine ESA use specifically in patients with CHF, randomly assigned 2278 patients with systolic heart failure and hemoglobin levels of 9 to 12 g/dL to darbepoietin titrated to a target hemoglobin level of 13 g/dL or to placebo (71). There were no differences in any health outcomes, other than a greater rate of thromboembolic events in the intervention group (13.5% vs. 10.0%; $P = 0.009$) after a median 28-month follow-up.

We found no substantive difference in results when we excluded studies in which the mean baseline hemoglobin levels were less than 11 g/dL or studies in which the mean increase in hemoglobin levels associated with ESA use were less than 2 g/dL. However, these parameters varied little among the trials, which could have made it difficult to detect any true influence of baseline hemoglobin levels or change in hemoglobin levels on outcomes.

Three trials compared ESAs titrated to normal or near-normal targets with those titrated to lower targets (hemoglobin levels, 9 to 11.3 g/dL) (21, 58, 59). None of the trials found a benefit from aggressive ESA use, and in fact, 2 of the trials found a significant increase in venous thromboembolic risk and a near-significant increase in mortality rates (21, 59).

No trials in patients with heart disease have evaluated the effects of more moderate hemoglobin level targets (for example, 10 to 12 g/dL) compared with lower targets.

Discussion

We examined the effects of 3 strategies for treating anemia in patients with heart disease. Overall, despite the epidemiologic and biologically plausible association of anemia with poor outcomes, we did not find consistent evidence that anemia correction improves outcomes in patients with heart disease, although there were notable exceptions.

The effects of more liberal transfusion protocols on outcomes are mixed. Low-strength evidence suggests that more aggressive use of blood transfusions does not consistently decrease mortality rates. However, we found very limited evidence from a small trial of patients with the acute coronary syndrome that a transfusion threshold of 10

Table 2—**Continued**

Baseline Hemoglobin Level (Treatment vs. Control Group)	Mean Change in Hemoglobin Level (Treatment vs. Control Group)	Results (Treatment vs. Control Group)	Adverse Effects (Treatment vs. Control Group)	Risk of Bias*
11.9 vs. 11.9 g/dL	1.1 vs. 0.6 g/dL	Deaths: 5 (3.4%) vs. 4 (5.5%) Cardiac events: 46 events in 38 patients (27.6/100 PYs) vs. 49 events in 33 patients (50.2/100 PYs); $P = 0.01$ First cardiovascular hospitalization: HR, 0.53 (CI, 0.25–1.09); $P = 0.08$ Functional status/activity tolerance: NYHA, OR for improvement by 1 class: 2.40 (CI, 1.55–3.71) Patient Global Assessment, OR for improvement: 2.51 (CI, 1.75–3.61) 6-min walk distance: 313 vs. 277 m Quality-of-life outcomes: change in Kansas City Cardiomyopathy Questionnaire score at 24 wk: 12.8 (SD, 1.3) vs. 6.2 (SD, 1.5); $P < 0.001$ EQ-5D score change from baseline to 24 wk: 6.6 (SD, 1.2) vs. −1.0 (SD, 1.8); $P < 0.001$	GI events: 16.9/100 PYs vs. 6.9/100 PYs; $P = 0.06$ Respiratory events: 6.2/100 PYs vs. 14.2/100 PYs; $P = 0.06$	Low
12.6 vs. 12.2 g/dL	0.5 vs. 0.4 g/dL	Mortality: 1/24 (4.2%) vs. 0 Hospitalizations: 3/24 (12%) vs. 3/11 (27%) Functional status/activity tolerance: NYHA score: 2.1 vs. 2.6 Mean change in NYHA score: −0.4 vs. 0.2; $P = 0.007$ Mean change in exercise duration: 45 vs. −15 s; $P = 0.08$ Patient Global Assessment: 1.5 vs. −0.2; $P = 0.002$ Mean change in MLHFQ: −10 vs. 3; $P = 0.07$ Adverse events: Abdominal pain: 2/24 (8%) vs. 0 TIA: 1/24 (4%) vs. 0	Abdominal pain: 8% vs. 0% TIA: 4% vs. 0%	High
10.3 vs. 10.2	+1.5 vs. −0.4	Mean change in creatinine clearance: +5.1 vs. −6.0 mL/min/1.73 m^2; $P < 0.01$ Hospitalizations: 0/20 vs. 5/20 (20%); $P < 0.01$ Functional status/activity tolerance: MLHFQ score: 41 vs. 59; $P < 0.01$ Mean change in MLHFQ score: −19 vs. +1; $P < 0.01$ 6-min walk distance: 240.1 vs. 184.5 m; $P < 0.01$	NR	Low

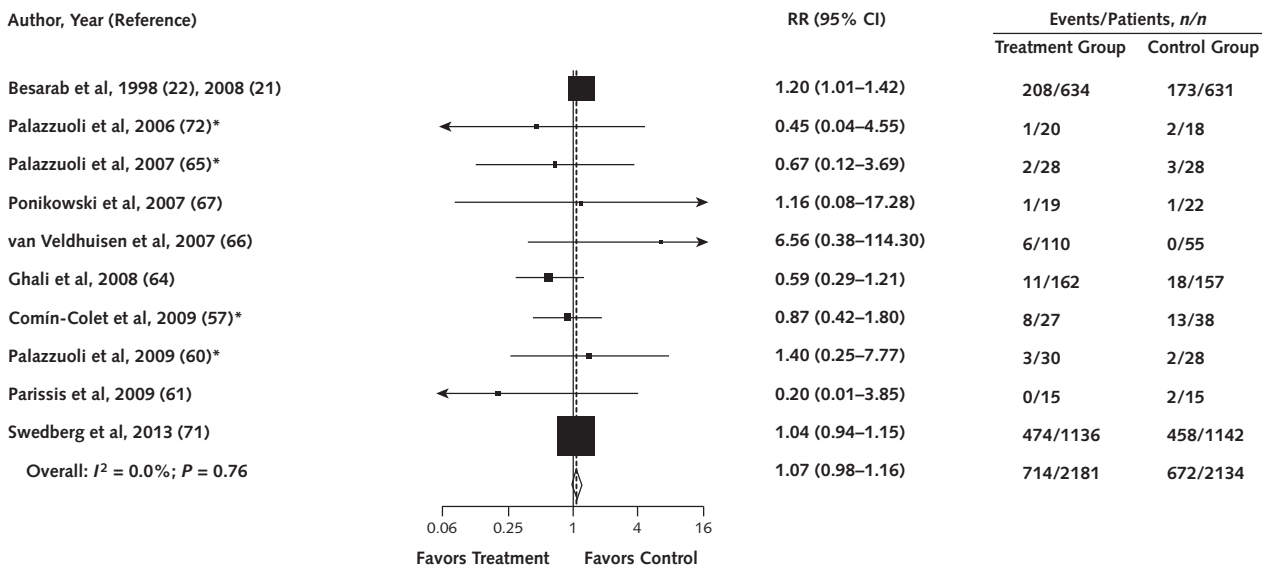
g/dL may decrease mortality rates. Data from a post hoc subgroup analysis of a trial of patients who had hip fracture surgery and heart disease suggest that liberal transfusion strategies may reduce in-hospital MI, although the clinical significance of this finding is unclear in the absence of mortality benefit and in the context of serial troponin measurement (20, 25).

Conflicting biological plausibility arguments have been espoused to support the benefits or harms of transfusions in patients with coronary disease, but surprisingly few trials have tested these biological assumptions (74). The more recent trial data suggesting a potential benefit from more liberal transfusion practices in patients with heart disease urgently need to be confirmed in large-scale trials. In the meantime, the low-strength evidence suggesting a possible benefit needs to be weighed against the well-known potential adverse effects of blood transfusions, which range from relatively common volume overload and febrile reactions to rare infectious and serious hemolytic complications (75). The precise level of harm associated with transfusions in patients with heart disease is unknown because data on adverse effects were inconsistently reported among trials.

We found a large body of observational studies that consistently showed that more aggressive transfusion practices had either neutral or deleterious effects on health outcomes, but the potential for confounding by indication is a limitation (76). The decision to transfuse patients in those studies was based on clinical judgment, which would naturally be influenced by severity of illness, symptoms, and observation of bleeding. Despite very careful propensity adjustment in some studies, the possibility of residual confounding renders this base of evidence fairly tenuous.

Two meta-analyses examining the effects of transfusions were published in 2013, but neither study included CHD-specific subgroup data or more recent data in patients with the acute coronary syndrome (77, 78). One of the meta-analyses focused on a smaller body of 9 observational studies and found that transfusions at greater hemoglobin levels were associated with an increased risk for death in patients with MI, although this risk was not apparent in studies of patients who had ST-segment elevation

Figure 2. **All-cause mortality among patients with congestive heart failure or coronary heart disease treated with erythropoiesis-stimulating agents versus control treatment.**



RR = risk ratio.
* High or unclear risk of bias.

MI or baseline hemoglobin levels less than 10 g/dL. The other meta-analysis found that restrictive transfusion strategies were associated with a lower risk for death that approached statistical significance (RR, 0.85 [CI, 0.70 to 1.03]), but a broad range of patient populations was examined and applicability to patients with heart disease is low.

There is moderate-strength evidence, mainly from 1 large, multicenter trial, that intravenous iron carboxymaltose improves exercise tolerance, quality of life, and exercise duration in patients with chronic, stable systolic heart failure (55). These results are most applicable to patients with NYHA class III heart failure and low ferritin levels. Biological plausibility and test-of-concept studies suggest that iron replacement could play a role in improving symptoms of heart failure even when iron stores are theoretically adequate, because symptoms may be related to a functional misuse of iron rather than absolute deficiency (10). Nevertheless, although the criteria used to define iron deficiency were fairly broad, most patients enrolled in the Assessment in Patients With Iron Deficiency and Chronic Heart Failure trial had evidence of more advanced iron deficiency and limited iron stores. Although the trial results are encouraging and at least 1 study has supported the cost-effectiveness of iron treatment (79), the long-term health implications are uncertain, and harms have not been more widely assessed in this population. In other populations, iron carboxymaltose has not been associated with an increased risk for serious adverse effects, such as anaphylactic reactions, which were possibly linked with older iron preparations, such as iron sucrose (80, 81).

There is moderate- to high-strength evidence that ESAs do not improve health outcomes and may be associated with serious harms in patients with heart disease. The data are most applicable to patients with CHF and systolic dysfunction. Future studies may be useful to clarify the role of ESAs in patients with preserved systolic function or those with CHD only. The balance of benefits and harms is most straightforward for the use of ESAs titrated to normal or near-normal hemoglobin levels. It is unknown whether more modest hemoglobin targets would be safer and yield a net health outcome benefit, but the lack of any functional or quality-of-life benefits from more aggressive use of ESAs suggests that a potential benefit is unlikely.

Anemia is common in patients with heart disease. Greater transfusion thresholds are not consistently associated with mortality benefit, but there are few trials. Recent data suggest a possible benefit in patients with the acute coronary syndrome, but large trials are needed to better clarify the role of transfusions in these patients. Evidence mostly from 1 large trial suggests that intravenous iron treatment may help to alleviate symptoms over the short term in patients with symptomatic heart failure and iron deficiency. Strong evidence shows that ESAs do not improve symptoms or outcomes in patients with mild to moderate anemia and heart disease and may be associated with serious harms.

From Portland Veterans Affairs Medical Center and Oregon Health & Science University, Portland, Oregon.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the U.S. Department of Veterans Affairs or the U.S. government.

Acknowledgment: The authors thank Rose Relevo, MLIS, MS, AHIP, for developing the search strategy and conducting the database searches and Tomiye Akagi, BA, for providing administrative support. They also thank Dr. Jeffrey Carson for his advice and for sharing subgroup data from the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair study.

Grant Support: From the U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative, Evidence-based Synthesis Program (project 05-225).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0078.

Requests for Single Reprints: Devan Kansagara, MD, MCR, Portland Veterans Affairs Medical Center, Mailcode RD71, 3710 Southwest U.S. Veterans Hospital Road, Portland, OR 97239; e-mail, kansagar@ohsu.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Boyd CM, Leff B, Wolff JL, Yu Q, Zhou J, Rand C, et al.** Informing clinical practice guideline development and implementation: prevalence of coexisting conditions among adults with coronary heart disease. J Am Geriatr Soc. 2011; 59:797-805. [PMID: 21568950]

2. **Felker GM, Adams KF Jr, Gattis WA, O'Connor CM.** Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol. 2004;44:959-66. [PMID: 15337204]

3. **Malyszko J, Bachorzewska-Gajewska H, Malyszko J, Levin-Iaina N, Iaina A, Dobrzycki S.** Prevalence of chronic kidney disease and anemia in patients with coronary artery disease with normal serum creatinine undergoing percutaneous coronary interventions: relation to New York Heart Association class. Isr Med Assoc J. 2010;12:489-93. [PMID: 21337818]

4. **O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al; CHARM Committees and Investigators.** Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation. 2006;113:986-94. [PMID: 16476847]

5. **Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM.** The prognostic importance of anemia in patients with heart failure. Am J Med. 2003; 114:112-9. [PMID: 12586230]

6. **Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, et al.** The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. Eur Heart J. 2006;27:1440-6. [PMID: 16717081]

7. **da Silveira AD, Ribeiro RA, Rossini AP, Stella SF, Ritta HA, Stein R, et al.** Association of anemia with clinical outcomes in stable coronary artery disease. Coron Artery Dis. 2008;19:21-6. [PMID: 18281811]

8. **Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, et al.** Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation. 2005;111:2042-9. [PMID: 15824203]

9. **Anand IS.** Heart failure and anemia: mechanisms and pathophysiology. Heart Fail Rev. 2008;13:379-86. [PMID: 18236152]

10. **González-Costello J, Comín-Colet J.** Iron deficiency and anaemia in heart failure: understanding the FAIR-HF trial. Eur J Heart Fail. 2010;12:1159-62. [PMID: 20855375]

11. **Kansagara D, Dyer EA, Englander H, Freeman M, Kagen D.** Treatment of Anemia in Patients with Heart Disease: A Systematic Review. VA-ESP Project no. 05-225. 2011. Accessed at www.hsrd.research.va.gov/publications/esp/anemia.cfm on 18 October 2013.

12. **Higgins JP, Altman DG, Sterne JA, eds.** Part 2, Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.10 (updated March 2011). The Cochrane Collaboration; 2008. Accessed at www.cochrane-handbook.org on 12 June 2013.

13. **Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al; GRADE Working Group.** Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490. [PMID: 15205295]

14. **Norris S, Atkins D, Bruening W, Fox S, Johnson E, Kane R, et al.** Selecting observational studies for comparing medical interventions. In: Methods Guide for Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2010. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/196/454/MethodsGuideNorris_06042010.pdf on 18 October 2013.

15. **Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 1 October 2012.

16. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88. [PMID: 3802833]

17. **Egger M, Davey Smith G, Schneider M, Minder C.** Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34. [PMID: 9310563]

18. **Bush RL, Pevec WC, Holcroft JW.** A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. Am J Surg. 1997; 174:143-8. [PMID: 9293831]

19. **Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, et al.** A pilot randomized trial comparing symptomatic vs. hemoglobin level-driven red blood cell transfusions following hip fracture. Transfusion. 1998;38: 522-9. [PMID: 9661685]

20. **Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al; FOCUS Investigators.** Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011;365:2453-62. [PMID: 22168590]

21. **Besarab A, Goodkin DA, Nissenson AR; Normal Hematocrit Cardiac Trial Authors.** The normal hematocrit study—follow-up [Letter]. N Engl J Med. 2008;358:433-4. [PMID: 18216370]

22. **Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al.** The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584-90. [PMID: 9718377]

23. **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;108:1108-11. [PMID: 21791325]

24. **Hébert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, et al; Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group.** Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med. 2001;29:227-34. [PMID: 11246298]

25. **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. Am Heart J. 2013;165:964-971.e1. [PMID: 23708168]

26. **Hebert PC, Szick S.** The anemic patient in the ICU: how much does the heart tolerate? Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie. 2001;36 Suppl 2:S94-100.

27. **Chase AJ, Fretz EB, Warburton WP, Klinke WP, Carere RG, Pi D, et al.** Association of the arterial access site at angioplasty with transfusion and mortality: the M.O.R.T.A.L study (Mortality benefit Of Reduced Transfusion after percutaneous coronary intervention via the Arm or Leg). Heart. 2008;94:1019-25. [PMID: 18332059]

28. **Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, et al.** Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. JACC Cardiovasc Interv. 2008; 1:202-9. [PMID: 19463301]

29. **Jani SM, Smith DE, Share D, Kline-Rogers E, Khanal S, O'Donnell MJ, et al.** Blood transfusion and in-hospital outcomes in anemic patients with myocardial infarction undergoing percutaneous coronary intervention. Clin Cardiol. 2007;30:II49-56. [PMID: 18228652]
30. **Jolicoeur EM, O'Neill WW, Hellkamp A, Hamm CW, Holmes DR Jr, Al-Khalidi HR, et al; APEX-AMI Investigators.** Transfusion and mortality in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Eur Heart J. 2009;30:2575-83. [PMID: 19596659]
31. **Kim P, Dixon S, Eisenbrey AB, O'Malley B, Boura J, O'Neill W.** Impact of acute blood loss anemia and red blood cell transfusion on mortality after percutaneous coronary intervention. Clin Cardiol. 2007;30:II35-43. [PMID: 18228650]
32. **Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al.** Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol. 2003; 92:930-5. [PMID: 14556868]
33. **Maluenda G, Lemesle G, Syed A, Collins SD, Ben-Dor I, Li Y, et al.** Should patients who develop anemia (hematocrit (less-than or equal to) 27%) after percutaneous coronary intervention be transfused? J Am Coll Cardiol. 2009; 53:A84.
34. **Maluenda G, Lemesle G, Ben-Dor I, Collins SD, Syed AI, Li Y, et al.** Value of blood transfusion in patients with a blood hematocrit of 24% to 30% after percutaneous coronary intervention. Am J Cardiol. 2009;104:1069-73. [PMID: 19801026]
35. **Maluenda G, Lemesle G, Syed A, Collins SD, Ben-Dor I, Li Y, et al.** Does transfusion for major bleeding after percutaneous coronary intervention impact clinical outcome in patients admitted with normal hematocrit? J Am Coll Cardiol. 2009;53:A72.
36. **Nikolsky E, Mehran R, Sadeghi HM, Grines CL, Cox DA, Garcia E, et al.** Prognostic impact of blood transfusion after primary angioplasty for acute myocardial infarction: analysis from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) Trial. JACC Cardiovasc Interv. 2009;2:624-32. [PMID: 19628185]
37. **Yatskar L, Selzer F, Feit F, Cohen HA, Jacobs AK, Williams DO, et al.** Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic Registry. Catheter Cardiovasc Interv. 2007; 69:961-6. [PMID: 17421023]
38. **Aggarwal C, Panza JA, Cooper HA.** Does the relation between red blood cell transfusion and mortality vary according to transfusion indication? A case-control study among patients with acute coronary syndromes. Coron Artery Dis. 2011; 22:194-8. [PMID: 21169814]
39. **Alexander KP, Chen AY, Wang TY, Rao SV, Newby LK, LaPointe NM, et al; CRUSADE Investigators.** Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. Am Heart J. 2008;155:1047-53. [PMID: 18513518]
40. **Aronson D, Dann EJ, Bonstein L, Blich M, Kapeliovich M, Beyar R, et al.** Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. Am J Cardiol. 2008;102:115-9. [PMID: 18602505]
41. **Athar MK, Bagga S, Nair N, Punjabi V, Vito K, Schorr C, et al.** Risk of cardiac arrhythmias and conduction abnormalities in patients with acute myocardial infarction receiving packed red blood cell transfusions. J Crit Care. 2011;26: 335-41. [PMID: 20869199]
42. **Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al.** Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004;292:1555-62. [PMID: 15467057]
43. **Shishehbor MH, Madhwal S, Rajagopal V, Hsu A, Kelly P, Gurm HS, et al.** Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2009; 2:46-53. [PMID: 19463397]
44. **Singla I, Zahid M, Good CB, Macioce A, Sonel AF.** Impact of blood transfusions in patients presenting with anemia and suspected acute coronary syndrome. Am J Cardiol. 2007;99:1119-21. [PMID: 17437739]
45. **Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM.** Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med. 2001; 345:1230-6. [PMID: 11680442]
46. **Yang X, Alexander KP, Chen AY, Roe MT, Brindis RG, Rao SV, et al; CRUSADE Investigators.** The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol. 2005; 46:1490-5. [PMID: 16226173]
47. **Garty M, Cohen E, Zuchenko A, Behar S, Boyko V, Iakobishvili Z, et al; Heart Failure Survey in ISrael (HFSIS) Investigators.** Blood transfusion for acute decompensated heart failure—friend or foe? Am Heart J. 2009;158:653-8. [PMID: 19781427]
48. **Kao DP, Kreso E, Fonarow GC, Krantz MJ.** Characteristics and outcomes among heart failure patients with anemia and renal insufficiency with and without blood transfusions (public discharge data from California 2000-2006). Am J Cardiol. 2011;107:69-73. [PMID: 21146689]
49. **Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al.** A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409-17. [PMID: 9971864]
50. **Carson JL, Duff A, Berlin JA, Lawrence VA, Poses RM, Huber EC, et al.** Perioperative blood transfusion and postoperative mortality. JAMA. 1998;279: 199-205. [PMID: 9438739]
51. **Bursi F, Barbieri A, Politi L, Di Girolamo A, Malagoli A, Grimaldi T, et al.** Perioperative red blood cell transfusion and outcome in stable patients after elective major vascular surgery. Eur J Vasc Endovasc Surg. 2009;37:311-8. [PMID: 19111480]
52. **Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, et al.** Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology. 2011;114: 283-92. [PMID: 21239971]
53. **Toblli JE, Lombraña A, Duarte P, Di Gennaro F.** Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol. 2007;50:1657-65. [PMID: 17950147]
54. **Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al.** Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol. 2008;51:103-12. [PMID: 18191732]
55. **Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al; FAIR-HF Trial Investigators.** Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436-48. [PMID: 19920054]
56. **Comín-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Lüscher TF, et al.** The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. Eur Heart J. 2013;34:30-8. [PMID: 22297124]
57. **Comín-Colet J, Ruiz S, Cladellas M, Rizzo M, Torres A, Bruguera J.** A pilot evaluation of the long-term effect of combined therapy with intravenous iron sucrose and erythropoietin in elderly patients with advanced chronic heart failure and cardio-renal anemia syndrome: influence on neurohormonal activation and clinical outcomes. J Card Fail. 2009;15:727-35. [PMID: 19879457]
58. **Szczech LA, Barnhart HX, Sapp S, Felker GM, Hernandez A, Reddan D, et al.** A secondary analysis of the CHOIR trial shows that comorbid conditions differentially affect outcomes during anemia treatment. Kidney Int. 2010;77:239-46. [PMID: 19890274]
59. **Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al; TREAT Investigators.** Baseline characteristics in the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT). Am J Kidney Dis. 2009;54:59-69. [PMID: 19501439]
60. **Palazzuoli A, Silverberg DS, Calabrò A, Spinelli T, Quatrini I, Campagna MS, et al.** Beta-erythropoietin effects on ventricular remodeling, left and right systolic function, pulmonary pressure, and hospitalizations in patients affected with heart failure and anemia. J Cardiovasc Pharmacol. 2009;53:462-7. [PMID: 19455052]
61. **Parissis JT, Kourea K, Andreadou I, Ikonomidis I, Markantonis S, Ioannidis K, et al.** Effects of darbepoetin alfa on plasma mediators of oxidative and nitrosative stress in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 2009;103:1134-8. [PMID: 19361602]
62. **Kourea K, Parissis JT, Farmakis D, Paraskevaidis I, Panou F, Filippatos G, et al.** Effects of darbepoetin-alpha on quality of life and emotional stress in

anemic patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2008; 15:365-9. [PMID: 18525396]

63. **Parissis JT, Kourea K, Panou F, Farmakis D, Paraskevaidis I, Ikonomidis I, et al.** Effects of darbepoetin alpha on right and left ventricular systolic and diastolic function in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am Heart J. 2008;155:751.e1-7. [PMID: 18371487]

64. **Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, et al; Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group.** Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation. 2008;117:526-35. [PMID: 18195176]

65. **Palazzuoli A, Silverberg DS, Iovine F, Calabrò A, Campagna MS, Gallotta M, et al.** Effects of beta-erythropoietin treatment on left ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome. Am Heart J. 2007;154:645.e9-15. [PMID: 17892986]

66. **van Veldhuisen DJ, Dickstein K, Cohen-Solal A, Lok DJ, Wasserman SM, Baker N, et al.** Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. Eur Heart J. 2007;28:2208-16. [PMID: 17681958]

67. **Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymlinski R, et al.** Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2007;49:753-62. [PMID: 17306703]

68. **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;107:294-9. [PMID: 12538431]

69. **Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, et al.** The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol. 2001;37:1775-80. [PMID: 11401110]

70. **Bellinghieri G, Savica V, De Gregorio C, De Gregorio G.** Use of erythropoietin in ischemic and arrhythmic cardiopathy of hemodialyzed patients. Contrib Nephrol. 1994;106:135-7. [PMID: 8174359]

71. **Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, et al; RED-HF Committees.** Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med. 2013;368:1210-9. [PMID: 23473338]

72. **Palazzuoli A, Silverberg D, Iovine F, Capobianco S, Giannotti G, Calabrò A, et al.** Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. Am Heart J. 2006;152:1096.e9-15. [PMID: 17161060]

73. **Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al; CHOIR Investigators.** Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-98. [PMID: 17108343]

74. **Gerber DR.** Transfusion of packed red blood cells in patients with ischemic heart disease. Crit Care Med. 2008;36:1068-74. [PMID: 18379229]

75. **Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al; Clinical Transfusion Medicine Committee of the AABB.** Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012;157:49-58. [PMID: 22751760]

76. **Norris SL, Atkins D, Bruening W, Fox S, Johnson E, Kane R, et al.** Observational studies in systemic reviews of comparative effectiveness: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64:1178-86. [PMID: 21636246]

77. **Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D.** Association of blood transfusion with increased mortality in myocardial infarction: a meta-analysis and diversity-adjusted study sequential analysis. JAMA Intern Med. 2013;173:132-9. [PMID: 23266500]

78. **Carson JL, Carless PA, Hébert PC.** Outcomes using lower vs higher hemoglobin thresholds for red blood cell transfusion. JAMA. 2013;309:83-4. [PMID: 23280228]

79. **Gutzwiller FS, Schwenkglenks M, Blank PR, Braunhofer PG, Mori C, Szucs TD, et al.** Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK. Eur J Heart Fail. 2012;14:782-90. [PMID: 22689292]

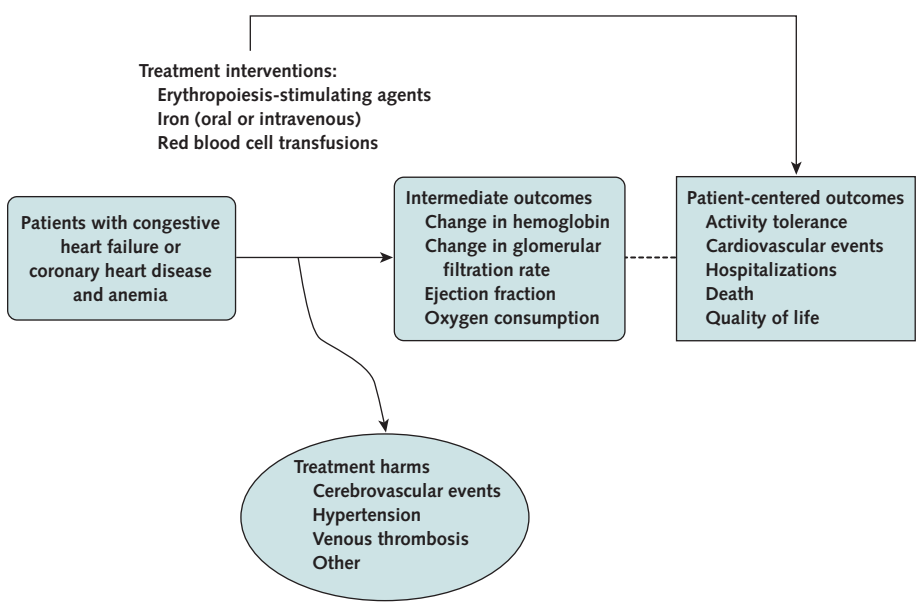
80. **Lyseng-Williamson KA, Keating GM.** Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. Drugs. 2009;69:739-56. [PMID: 19405553]

81. **Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD.** A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant. 2011;26:1599-607. [PMID: 20929915]

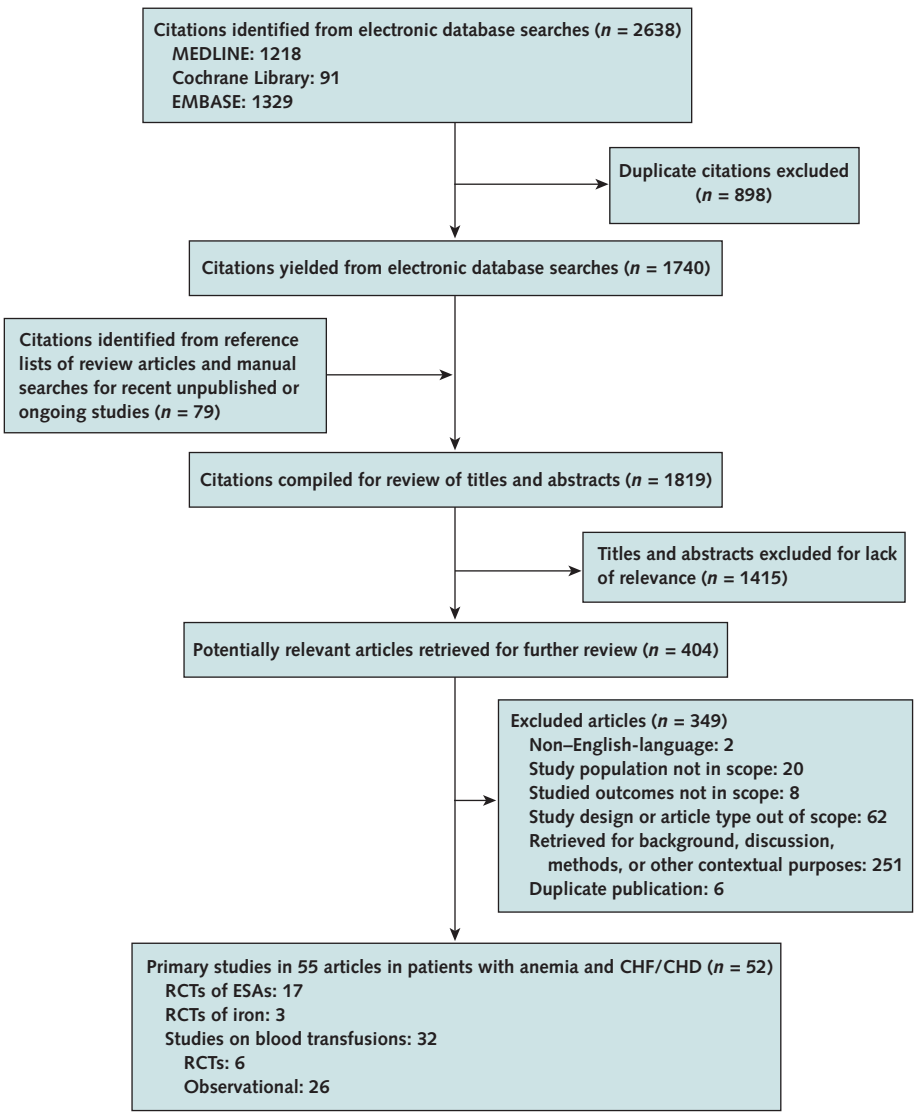
Current Author Addresses: Dr. Kansagara and Ms. Freeman: Portland Veterans Affairs Medical Center, Mailcode RD71, 3710 Southwest U.S. Veterans Hospital Road, Portland, OR 97239.
Drs. Dyer and Kagen: Portland Veterans Affairs Medical Center, Mailcode P3-MED, 3710 Southwest U.S. Veterans Hospital Road, Portland, OR 97239.
Dr. Englander: Oregon Health & Science University, BTE 119, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239.
Dr. Fu: Department of Public Health & Preventive Medicine, Oregon Health & Science University, Mailcode CB669, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239.

Author Contributions: Conception and design: D. Kansagara, H. Englander, D. Kagen.
Analysis and interpretation of the data: D. Kansagara, E. Dyer, H. Englander, R. Fu, D. Kagen.
Drafting of the article: D. Kansagara, H. Englander, D. Kagen.
Critical revision of the article for important intellectual content: D. Kansagara, E. Dyer, H. Englander, R. Fu, M. Freeman, D. Kagen.
Final approval of the article: D. Kansagara, H. Englander, R. Fu, D. Kagen.
Statistical expertise: D. Kansagara, R. Fu.
Administrative, technical, or logistic support: M. Freeman.
Collection and assembly of data: D. Kansagara, E. Dyer, H. Englander, M. Freeman, D. Kagen.

Appendix Figure 1. **Analytic framework.**

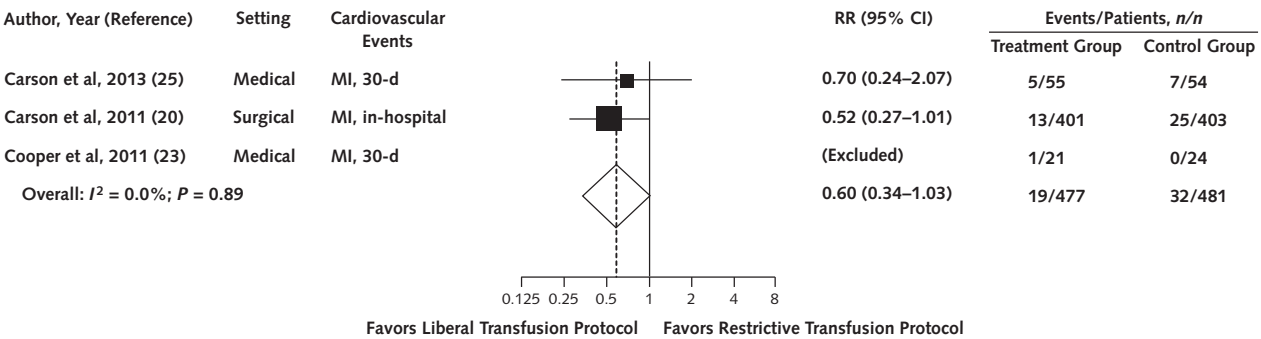


Appendix Figure 2. **Summary of evidence search and selection.**



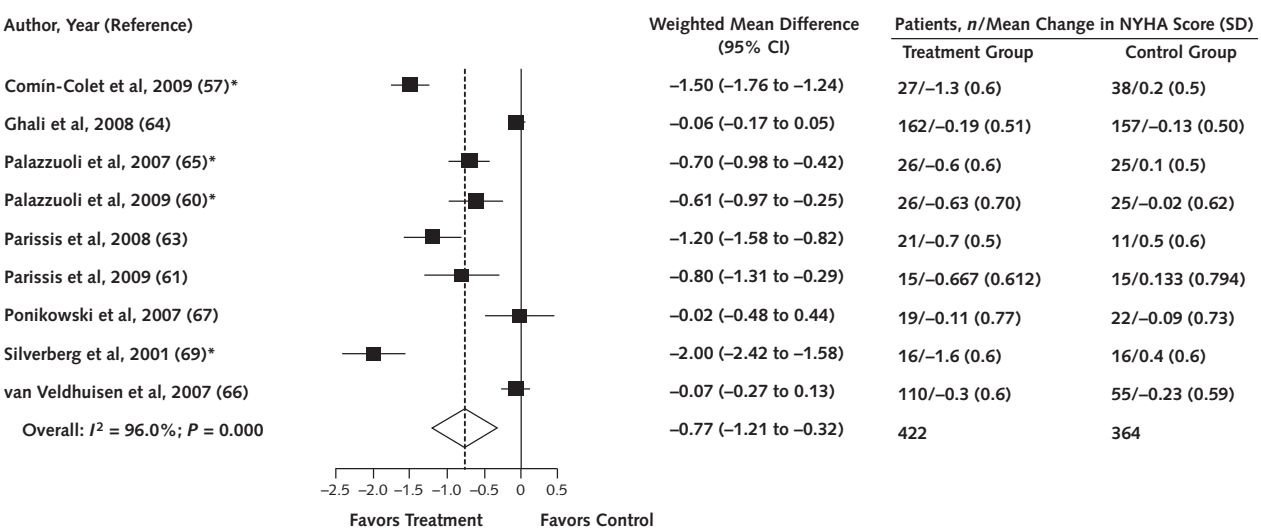
CHD = coronary heart disease; CHF = congestive heart failure; ESA = erythropoiesis-stimulating agent; RCT = randomized, controlled trial.

Appendix Figure 3. **Cardiovascular events among patients with congestive heart failure or coronary heart disease in liberal versus restrictive blood transfusion protocols.**



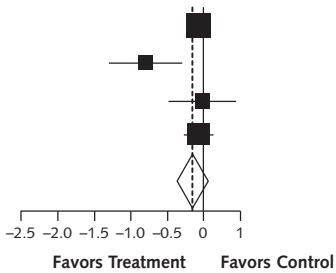
MI = myocardial infarction; RR = risk ratio.

Appendix Figure 4. **Change in NYHA score among patients with congestive heart failure treated with erythropoiesis-stimulating agents compared with control patients.**



NYHA = New York Heart Association.
* High or unclear risk of bias.

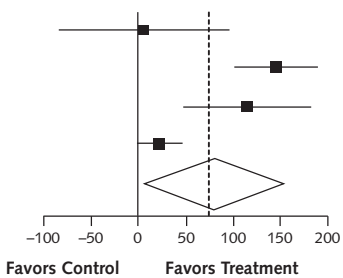
Appendix Figure 5. **Change in NYHA score among patients with congestive heart failure treated with erythropoiesis-stimulating agents versus control patients in studies with low risk of bias.**



Author, Year (Reference)	Weighted Mean Differece (95% CI)	Patients, *n*/Mean Change in NYHA Score (SD)	
		Treatment Group	Control Group
Ghali et al, 2008 (64)	–0.06 (–0.17 to 0.05)	162/–0.19 (0.51)	157/–0.13 (0.50)
Parissis et al, 2009 (61)	–0.80 (–1.31 to –0.29)	15/–0.667 (0.612)	15/0.133 (0.794)
Ponikowski et al, 2007 (67)	–0.02 (–0.48 to 0.44)	19/–0.11 (0.77)	22/–0.09 (0.73)
van Veldhuisen et al, 2007 (66)	–0.07 (–0.27 to 0.13)	110/–0.3 (0.6)	55/–0.23 (0.59)
Overall: I^2 = 62.1%; P = 0.048	–0.15 (–0.36 to 0.06)	306	249

NYHA = New York Heart Association.

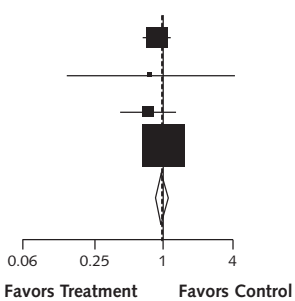
Appendix Figure 6. **Change in 6-minute walk distance among patients with congestive heart failure treated with erythropoiesis-stimulating agents compared with control patients.**



Author, Year (Reference)	Weighted Mean Difference (95% CI)	Patients, *n*/Mean Change in 6-Minute Walk Distance, *m*	
		Treatment Group	Control Group
Mancini et al, 2003 (68)*	5.51 (–85.03 to 96.05)	15/43 (82)	8/37.5 (110)
Kourea et al, 2008 (62)*	146.00 (101.33 to 190.67)	21/106 (66)	20/–40 (79)
Parissis et al, 2008 (63)	116.00 (47.35 to 184.65)	21/69 (97)	11/–47 (92)
van Veldhuisen et al, 2007 (66)	22.80 (–1.94 to 47.54)	110/34.2 (76.6)	55/11.4
Overall: I^2 = 88.7%; P = 0.000	74.42 (–0.16 to 148.99)	167	94

* High or unclear risk of bias.

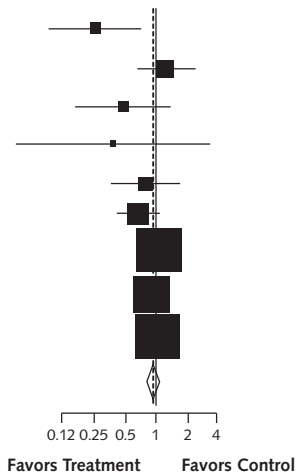
Appendix Figure 7. **Risk for hospitalization among patients with congestive heart failure or coronary heart disease treated with erythropoiesis-stimulating agents versus control patients in studies with low risk of bias.**



Author, Year (Reference)	RR (95% CI)	Events/Patients, *n/n*	
		Treatment Group	Control Group
Besarab et al, 1998 (22), 2008 (21)	0.88 (0.67–1.17)	80/618	90/615
Ponikowski et al, 2007 (67)	0.77 (0.14–4.14)	2/19	3/22
Ghali et al, 2008 (64)	0.74 (0.44–1.26)	NR	NR
Swedberg et al, 2013 (71)	1.01 (0.89–1.16)	314/1136	311/1142
Overall: I^2 = 0.0%; P = 0.58	0.97 (0.87–1.10)	NR	NR

NR = not reported; RR = risk ratio.

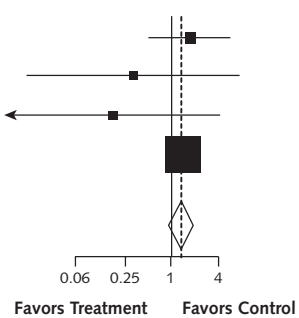
Appendix Figure 8. **Cardiovascular events among patients with congestive heart failure or coronary heart disease treated with erythropoiesis-stimulating agents compared with control patients.**



Author, Year (Reference)	RR (95% CI)	Events/Patients, *n/n*	
		Treatment Group	Control Group
Bellinghieri et al, 1994 (70)*	0.26 (0.09–0.72)	4/26	6/10
Besarab et al, 1998 (22), 2008 (21)	1.24 (0.65–2.38)	20/634	16/631
Palazzuoli et al, 2007 (65)*	0.48 (0.17–1.40)	4/26	8/25
Ponikowski et al, 2007 (67)	0.39 (0.04–3.41)	1/19	3/22
van Veldhuisen et al, 2007 (66)	0.79 (0.37–1.71)	14/108	9/55
Ghali et al, 2008 (64)	0.68 (0.43–1.08)	NR	NR
Pfeffer et al, 2009 (59)	1.06 (0.93–1.20)	494/1287	485/1355
Szczech et al, 2010 (58)	0.91 (0.74–1.12)	89/192	93/183
Swedberg et al, 2013 (71)	1.02 (0.93–1.12)	513/1136	506/1142
Overall: I^2 = 44.4%; P = 0.072	0.94 (0.82–1.08)	NR	NR

NR = not reported; RR = risk ratio.
* High or unclear risk of bias.

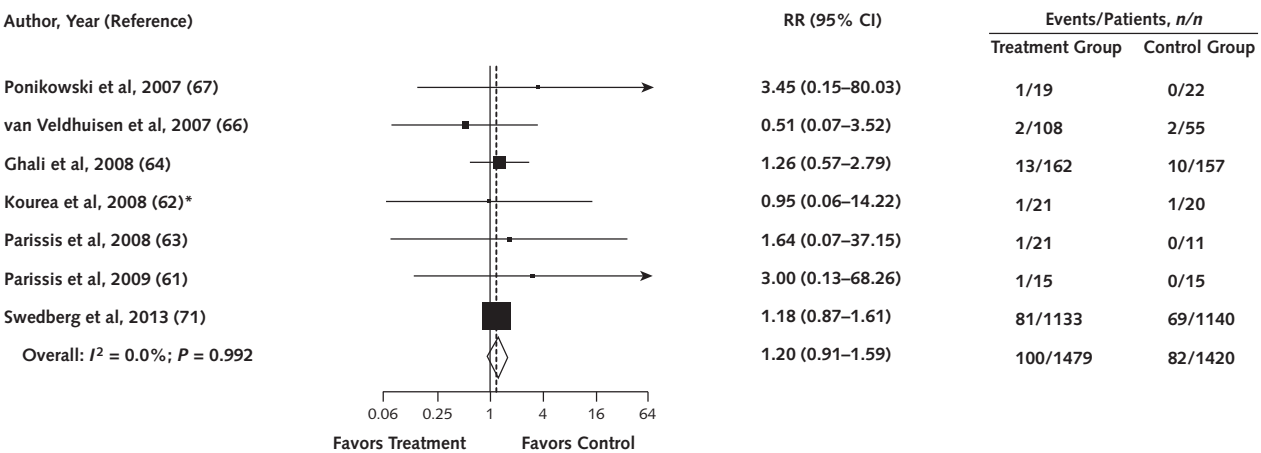
Appendix Figure 9. **Cerebrovascular events among patients with congestive heart failure or coronary heart disease treated with erythropoiesis-stimulating agents compared with control patients.**



Author, Year (Reference)	RR (95% CI)	Events/Patients, *n/n*	
		Treatment Group	Control Group
Ghali et al, 2008 (64)	1.70 (0.51–5.68)	7/162	4/157
Kourea et al, 2008 (62)*	0.32 (0.01–7.38)	0/21	1/20
Parissis et al, 2008 (63)	0.18 (0.01–4.13)	0/21	1/11
Swedberg et al, 2013 (71)	1.36 (0.94–1.99)	61/1133	45/1140
Ponikowski et al, 2007 (67)	(Excluded)	0/19	0/22
Overall: I^2 = 0.0%; P = 0.98	1.33 (0.93–1.89)	68/1356	51/1350

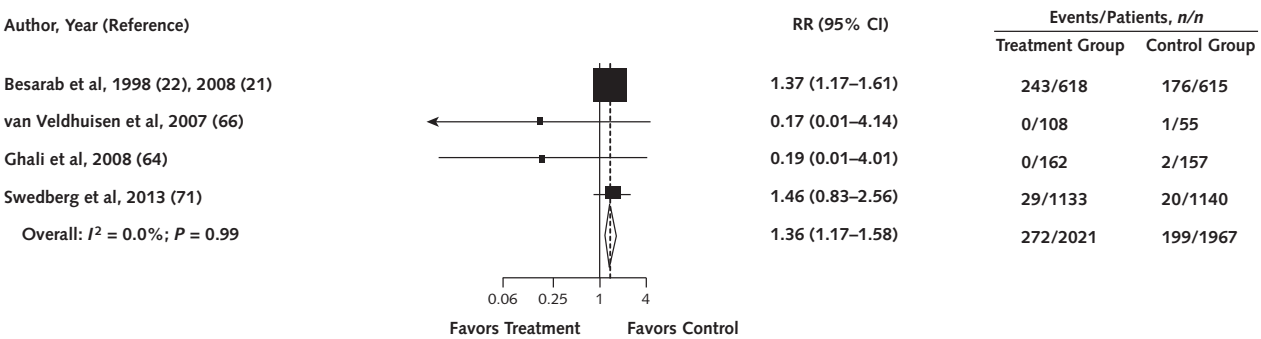
RR = risk ratio.
* Unclear risk of bias.

Appendix Figure 10. **Hypertension events among patients with congestive heart failure or coronary heart disease treated with erythropoiesis-stimulating agents compared with control patients.**



RR = risk ratio.
* Unclear risk of bias.

Appendix Figure 11. **Venous thromboembolic events among patients with congestive heart failure or coronary heart disease treated with erythropoiesis-stimulating agents compared with control patients.**



RR = risk ratio.