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HSR&D

Treatment of Anemia in Patients with Heart Disease: A Systematic Review

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PREFACE

Health Services Research & Development Service's (HSR&D's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

HSR&D provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of HSR&D field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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INTRODUCTION

Anemia is very common in patients with heart disease: about one-third of congestive heart failure (CHF) patients and 10 to 20 percent of coronary heart disease (CHD) patients are anemic, though prevalence estimates vary according to the definition used and illness burden in the population being studied.[1-3] The etiology of anemia in heart disease remains incompletely understood, though there are a number of factors that likely contribute including: comorbid chronic kidney disease, blunted erythropoietin production, hemodilution, aspirin-induced gastrointestinal blood loss, the use of renin-angiotensin-aldosterone system (RAAS) blockers, cytokine-mediated inflammation (anemia of chronic disease), and gut malabsorption with consequent nutritional deficiency. Iron deficiency is also common. Cytokine mediated sequestration of iron in the reticuloendothelial system may contribute to a functional iron deficiency, while an absolute deficiency can result from decreased oral iron absorption associated with cytokine induced hepcidin synthesis.[4]

Anemia is associated with poor outcomes in patients with heart disease, but it is unclear whether anemia directly and independently contributes to these poor outcomes, or whether it simply reflects more severe underlying illness and comorbidities.[5-7] Strategies to correct anemia and/or iron deficiency have included erythropoiesis-stimulating agents, iron supplementation, and red blood cell transfusions. The purpose of this systematic review is to summarize the health outcome effects of each of these treatment strategies in adult medicine patients with heart disease.

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METHODS

TOPIC DEVELOPMENT

The review was commissioned by the Department of Veterans Affairs' Evidence-based Synthesis Program. We conferred with VA and non-VA experts to select the patients and subgroups, interventions, outcomes, and setting addressed in the review. We addressed the following key questions in our review of the literature:

In patients with CHF or CHD,

Key Question 1. What are the health outcome benefits and harms of treating anemia with erythropoiesis-stimulating agents (ESAs)?

Key Question #2. What are the health outcome benefits and harms of using iron to treat iron deficiency with or without anemia?

Key Question #3. What are the health outcome benefits and harms of treating anemia with red blood cell transfusions?

The criteria for patient population, treatment and comparator interventions, outcomes of interest, and patient care setting are outlined below:

Patients: Adult patients with symptomatic CHF (with or without reduced systolic function) or CHD (acute coronary syndrome, post-acute coronary syndrome, history of MI or angina,) and anemia or iron deficiency.

Interventions:

- ESAs with or without iron: These include erythropoietin and darbepoeitin
- Iron: Intravenous or oral
- Red blood cell transfusion

Comparator: Usual care, placebo

Outcomes: Mortality (all-cause and disease specific), hospitalization (all-cause and disease-specific), exercise tolerance or duration (any metric, most commonly NYHA class, 6-minute walk test), quality of life, cardiovascular events (myocardial infarction, heart failure exacerbation, need for revascularization)

Setting: Inpatient or outpatient

Figure 1 illustrates the analytic framework that guided our review and synthesis.

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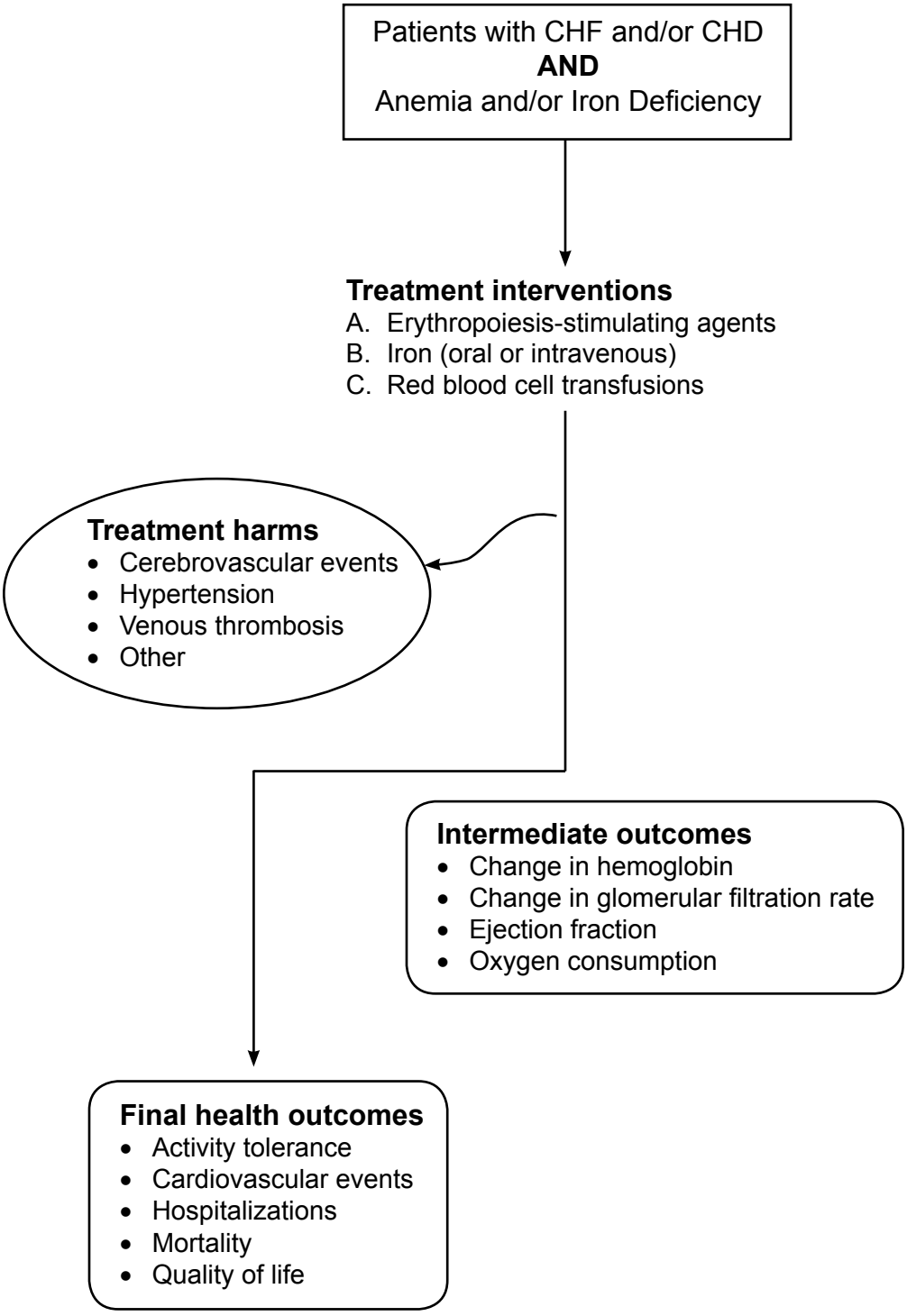
Figure 1. Analytic Framework



SEARCH STRATEGY

We conducted a search in Medline® and the Cochrane database of systematic reviews of literature published from 1947 to November 2010. Appendix A provides the search strategy in detail. We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, editorials, and by consulting experts. We also searched for information about unpublished studies on ClinicalTrials.gov. All citations were imported into an electronic database (EndNote X1).

STUDY SELECTION

Three reviewers assessed for relevance the abstracts of citations identified from literature searches. Two reviewers independently assessed for inclusion full-text articles of potentially relevant abstracts based on the eligibility criteria shown in Appendix B. Disagreements were resolved through a consensus process.

Eligible articles had English-language abstracts and provided primary data relevant to the key questions. We included studies of anemic patients (hemoglobin < 13 g/dL in men, < 12 g/dL in women) with symptomatic CHF (with or without reduced systolic function), CHD (acute coronary syndrome, post-acute coronary syndrome, history of MI or angina), or both. Further eligibility criteria varied depending on the question of interest, as described below.

To evaluate the efficacy of ESAs, we considered prospective, controlled clinical trials of ESAs compared either to placebo or to less intensive ESA use in patients with anemia and heart disease. In evaluating the efficacy of iron, we included studies with mixed populations of anemic and non-anemic patients, but then described how treatment effects might differ for anemic and non-anemic patients. We did include studies of broader patient populations as long as they separately reported outcomes data for the subpopulation of patients with heart disease.

Included studies had to report at least one prespecified patient-centered health outcome which we defined as clinically important outcomes apparent to the patient (Appendix B). We excluded studies reporting only intermediate physiologic outcomes such as change in ejection fraction or oxygen delivery metrics.

Based on an initial exploratory search of red blood cell transfusions in patients with heart disease, we recognized there was a dearth of controlled clinical trial data and that current recommendations for blood transfusion use in heart disease patients are largely based on interpretation of observational studies. Therefore, to better understand the evidence currently guiding clinical practice, we included observational studies as well as controlled clinical trials that reported at least one of the above listed health outcomes. Given the complex technique of cardiac surgery, involving induction of hypothermia, cardioplegia, and establishment of an extracorporeal circuit, we felt that the potential confounding factors were too vast to permit use of observational data to guide decision-making. Therefore, for this population, we elected to consider controlled trials only.

To evaluate the harms of ESAs, iron, and blood transfusion, we collected adverse events data from all the included trials, and we specifically gathered data on the following events from each trial: hypertension, venous thromboembolic events (including deep venous thrombosis, pulmonary embolism, and vascular access thrombosis), and ischemic cerebrovascular events.

DATA ABSTRACTION

From each study, we abstracted the following: study design, objectives, setting, population characteristics (including sex, age, left ventricular ejection fraction, baseline NYHA class, definition of CHD), subject eligibility and exclusion criteria, number of subjects, years of enrollment, duration of follow-up, the study and comparator interventions (including route and dosage), important co-interventions (i.e., iron administration in ESA studies), baseline hemoglobin, change in hemoglobin, health outcomes, and adverse events.

STUDY QUALITY

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration.[8] Disagreements were resolved through discussion. This tool asks the following questions about the methodologic characteristics of each study to guide assessment of the risk of bias:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a high risk of bias? (We assessed whether or not there were extreme baseline differences between groups.)

Each study was then given an overall summary assessment of either low, high, or unclear risk of bias. The risk of bias within a given study can vary according to outcome. For instance, the risk of bias associated with lack of blinding might be low for mortality outcomes, but high for more subjective outcomes such as quality of life or symptom scores.

Though there is no widely accepted standard for quality assessment of observational studies, we used the following questions to guide a comparison of observational study methodologic characteristics:

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)
2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Was the duration of follow-up reasonable for investigated events?

Within question 6, we specifically assessed whether each study: 1) conducted an analysis adjusting for patient propensity to receive a blood transfusion, 2) accounted for bleeding

complications – whether procedurally related or not – in the study population, and 3) accounted for the timing of transfusion given the potential for issues such as survival bias in which patients who died could not have received a transfusion.

We do not report an overall summary assessment for observational studies because there are no validated criteria for doing so and all would be poorly valid in determining the health outcome effects of blood transfusions.

Appendix C provides the details of our quality assessment of trials and observational studies.

RATING THE BODY OF EVIDENCE

We assessed the overall quality of evidence for outcomes using a method developed by the GRADE Working Group.[9] The GRADE method 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 as follows:

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low = Any estimate of effect is very uncertain.

DATA SYNTHESIS

We performed meta-analyses of ESA trials for each of the following outcomes: mean difference in the change of NYHA class, exercise duration during the six-minute walk test, all-cause mortality, hospitalizations, cardiovascular events, hypertension events, and ischemic cerebrovascular events. We abstracted the number of events and total subjects from each treatment arm, and obtained a pooled estimate of relative risk (RR) using a random effects model.[10] We did not meta-analyze quality of life outcomes because we felt a quantitative summary estimate of effect would be less meaningful than a descriptive approach given the variety of assessment tools used.

In order to determine the influence study quality may have had on summary results, we ran analyses for all outcomes excluding those studies with high or unclear risk of bias. To determine whether the effects of ESAs were modified by anemia characteristics, we conducted analyses according to baseline hemoglobin and mean change in hemoglobin in the intervention group, using 11g/dL and 2 g/dL, respectively, as the cutpoints based on distribution of values among included studies. If only the hematocrit was reported, we used a conversion of 3:1 to approximate the hemoglobin value.

Statistical heterogeneity was assessed by Cochran's Q test and I^2 statistic.[8] Because of the small number of trials that could be combined, we did not perform assessments for publication bias.[11] All analyses were performed using Stata 10.0 (StataCorp, College Station, TX, 2007).

Because there were only three trials examining the effects of iron therapy, with one large trial dominating results, we decided to only qualitatively synthesize these results. We also qualitatively synthesized the mostly observational blood transfusion literature.

PEER REVIEW

A draft version of this report was sent to the technical expert panel and additional peer reviewers. The comments and suggestions we received from reviewers and our responses in revising the report are provided in Appendix D.

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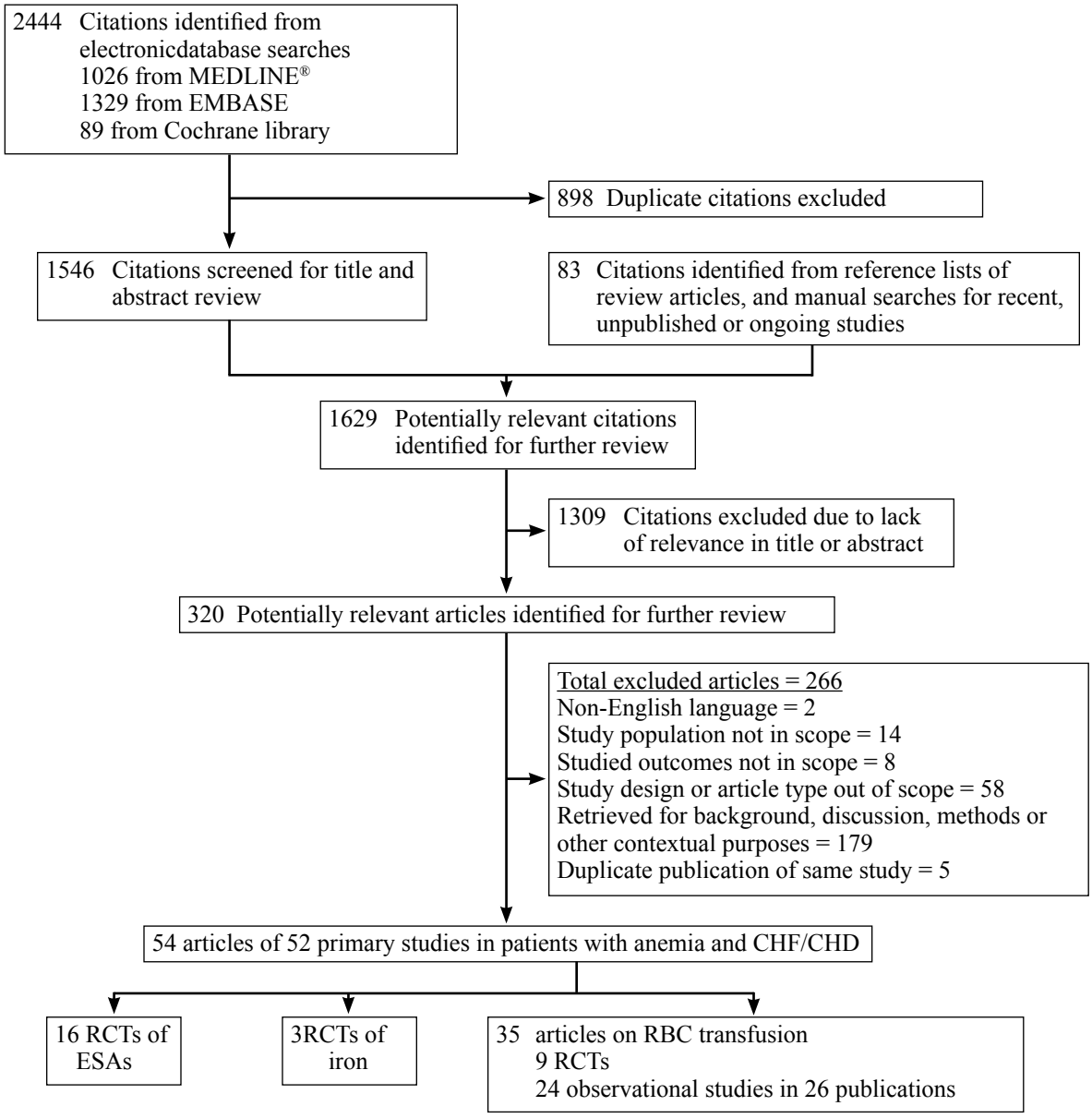
RESULTS

LITERATURE FLOW

We reviewed 1,546 titles and abstracts from the electronic search, and identified an additional 83 from reviewing reference lists, and performing manual searches for recently published studies, and unpublished or ongoing studies.

After applying inclusion/exclusion criteria at the abstract level, 320 full-text articles were reviewed, as shown in Figure 2. Of the full-text articles, we rejected 266 that did not meet our inclusion criteria.

Figure 2. Literature Flow – Anemia and CHF



KEY QUESTION #1. In patients with CHF or CHD, what are the health outcome benefits and harms of treating anemia with ESAs?

Summary

Sixteen randomized, controlled trials evaluated the impact of ESAs in patients with heart disease (Table 1).[12-27] We excluded one study[28] whose patient population was included in a subsequent publication.[21, 28] Eleven trials enrolled patients with CHF, and in the 10 trials reporting systolic function, the mean ejection fraction was ≤ 35%. Most patients had comorbid CHD. Two trials included roughly even proportions of patients with CHD and CHF,[14, 26] and only one trial focused exclusively on patients with CHD.[27] The most commonly reported health outcomes were exercise tolerance measures such as NYHA (nine trials), and exercise duration as measured by the six-minute walk test (five trials) or the Naughton protocol (two trials). Nine trials reported mortality and seven trials reported hospitalizations. Two trials were primarily designed to assess the comparative effects of ESAs titrated to high or low hemoglobin targets in anemic patients with chronic kidney disease, but included a large proportion of patients with heart disease for whom adequate subgroup data are reported.[13, 14]

Overall, we found little good quality evidence that ESA use consistently improves health outcomes. Some studies found ESA use improved exercise tolerance and duration, but this body of evidence is limited by inconsistency of findings and important methodologic weaknesses. The potential benefits of ESA use seen in some studies may be further tempered by the finding that ESA use is associated with serious harms such as mortality and vascular thrombosis, especially in patients with comorbid chronic kidney disease.

Methodologic Considerations

We characterized the quality of each of the included studies according to the impact methodologic flaws could have on an outcome of interest. For example, flaws such as the lack of patient and/or outcome assessor blinding could lead to biased results for subjective outcomes such as exercise tolerance. Five trials contained serious methodologic flaws which could have biased key findings,[12, 15, 21, 24, 25] and unclear reporting made it difficult to assess the risk of bias in one trial.[17] Additionally, there was some evidence for multiple publication bias: in two cases we found multiple publications reporting results for apparently overlapping populations.[16, 18, 21, 28] The methodologic characteristics of each study are detailed in Appendix C, Table 1.

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Table 1. Characteristics of randomized controlled trials of ESA therapy in patients with CHF or CHD

Study ID Setting Months of follow-up	N (T v C); Demographics: % male; % race/ethnicity; mean age (yr)	Clinical subgroup (CHF/CAD); Mean LVEF %; % on RAAS blockers (T v C)	Baseline kidney function, GFR or Serum Cr (T v C)	Intervention (Drug, Dose) v Control	Baseline measures of iron stores (T v C)	Iron in Tx group	Iron in Control group	Baseline Hgb (T v C)	Mean change in Hgb (T v C)	Funding source
Studies conducted in patients with CHF										
Comin-Colet, 2009[12] Single-center Spain 15.3 months	N: 27 v 38 male: 70.4 v 50.0 mean age: 74 v 74	Advanced CHF + CRI: LVEF: 34.5 v 34.6 NYHA III: 66.7 v 81.6 NYHA IV: 33.3 v 18.4 Ischemic etiology: 66.7 v 55.3 ACEI/ARB: 70.4 v 76.3 Aldo antag: 74.1 v 60.5	GFR: 48.1 v 50.3	Epoeitin 4000u IV weekly, adjusted to target Hgb 12.5-14.5 + iron sucrose IV 200mg weekly x 5-6 wks to target ferritin>400, then q 4-6 wks. Control group was not given a placebo.	ferritin: 220.7 v 140.7 TSAT%: 23.2 v 19.9	Y	N	10.9 v 10.9	1.7 v 0.4	NR
Ghali, 2008[19] STAMINA-HeFT Multicenter (65), phase 2 study 12 months; most endpoints at 6 months	N: 162 v 157 male: 57 v 68 white: 77 v 85 black: 14 v 11 mean age: 68 v 69	LVEF: 35 v 36. NYHA I: 1 v 2 NYHA II: 38 v 32 NYHA III: 59 v 62 NYHA IV: 2 v 3 RAAS blockers: 90 v 90	GFR: 47.2 v 47.5	Darbepoeitin alfa 0.75mcg/kg sc q 2 wks titrated to target Hgb ~ 14 vs. "matching placebo"	ferritin: 121 v 124 TSAT%: 23.5 v 23.5	Y, daily elemental oral iron	Y, daily elemental oral iron	11.5 v 11.3	Median Hgb change at 27 weeks: 1.8 v 0.3 53 weeks: 2.1 v 0.5	Amgen
Kourea, 2008[17] Single-center Greece 3 months	N: 21 v 20 male: 76 v 75 mean age: 73 v 65	LVEF: 2 v 8 NYHA II: 38 v 45 NYHA III: 62 v 55 Ischemic CM: 62 v 60 ACEI: 71 v 65 ARB: 19 v 20 Aldo antag: 57 v 55	Cr: 1.7 v 1.7	Darbepoeitin alfa 1.5 mcg/kg sc q 20 days titrated to target Hgb ~ 14 vs. 0.9% saline	ferritin: 144 v 159 Iron: 45 v 59	Y, oral iron 250 mg BID	Y, oral iron 250 mg BID	10.9 v 11.4	1.6 v -0.9	none
Mancini, 2003[24] Single center US 3 months	N: 15 v 8 male: 86.7 v 62.5 race/ethnicity NR mean age: 60 v 55	NYHA 3-4 LVEF: 24 v 21 h/o CAD: 53.3 v 50 RAAS blockers not different between both groups; most were on RAAS blockers (NOS)	Cr: 1.6 v 1.6	Epoetin 5000 sc TIW - titrated up to 10,000 TIW if Hgb did not increase 1 g/dL vs. saline	NR	Y, oral iron 325 mg daily	N	10.9 v 11.0	3.3 v 0.6 (T increased from 11 to 14.3 and C 10.9 to 11.5)	NIH
Palazzuoli, 2007[21] Single-center Italy 12 months	N: 26 v 25 male: 58 v 64 mean age: 74 v 72	LFEF: 30 v 31 NYHA III: 69 v 68 NYHA IV: 30.8 v 32 Mean NYHA: 3.4 v 3.6 ACEI: 69 v 64 ARB: 19 v 28	GFR: 43 v 45	Beta erythropoeitin 6000 IU sc twice weekly to goal Hgb 12-12.5 vs. saline	NR	Y, oral iron gluconate 300 mg daily	Y, oral iron gluconate 300 mg daily	10.4 +/- 0.6 v 10.6 +/- 0.7	2.0 v -0.1	none

Study ID Setting Months of follow-up	N (T v C); Demographics: % male; % race/ethnicity; mean age (yr)	Clinical subgroup (CHF/CAD); Mean LVEF %; % on RAAS blockers (T v C)	Baseline kidney function, GFR or Serum Cr (T v C)	Intervention (Drug, Dose) v Control	Baseline measures of iron stores (T v C)	Iron in Tx group	Iron in Control group	Baseline Hgb (T v C)	Mean change in Hgb (T v C)	Funding source
Palazzuoli, 2009[15] Single-center Italy 12 months	N: 26 v 25 No demographic information reported	LVEF 30.1 vs 30.8 RAAS blockers NR	Cr: 2.3 vs 2.4	Epoetin 6000 sc BIW vs. saline placebo for first four months	NR	FeGluconate 300 mg QD	FeGluconate 300 mg QD	9.6 v 9.3	Final Hgb: 12.4 v 10.4	NR
Parissis, 2008[18] Single center Greece 3 months	N: 21 v 11 mean age: 72 v 69	LVEF: 26 v 28 NYHA II: 19 v 27 NYHA III: 81 v 73 Ischemic related: 90 v 82 ACEI: 71 v 73 ARB 19 v 18 Aldo antag: 57 v 55	Cr: 1.7 v 1.8	Darbepoeitin alfa 1.5mcg/kg sc q 20 days vs. 0.9% saline	ferritin: 153 +/- 119 v 170 +/- 135.	Y, oral iron sulfate 125 mg BID	Y, oral iron sulfate 125 mg BID	11.0 v 11.4	Final Hgb: 12.8 v 11.8	NR
Parissis, 2009[16] Single center Greece 3 months	N: 15 v 15 mean age: 71 v 67 male: 73.3 v 66.7	LVEF: 28 v 27 NYHA II: 53.3 v 60 NYHA III: 46.7 v 40 Ischemic: 86.7 v 73.3 ACEI: 93.3 v 86.7 ARB: 6.7 v 2/15	Cr: 1.6 v 1.5	Darbepoeitin alfa 1.5 mcg/kg q 20 days vs. 0.9% saline	ferritin: 133 +/- 126 v 127 +/- 112.	Y, oral iron sulfate 125 mg BID	Y, oral iron sulfate 125 mg BID	11.2 v 11.5	1.6 v 0.4	none
Ponikowski, 2007[23] Multicenter 6 months (27 weeks)	N: 19 v 22 male: 63 v 45 white: 95 v 100 asian: 5 v 0 mean age: 72 v 70	NYHA I: 0 v 5 NYHA II: 58 v 36 NYHA III: 42 v 59 Ischemic: 84 v 86 RAAS blockers NR	GFR: 59 v 52	Darbepoeitin alfa 0.75mcg/ kg sc q 2 wks, titrated to Hgb 13-15 vs. placebo "in identical single-dose vials"	median ferritin (25th and 75th): 71 (46, 143) v 161 (83, 256). TSAT%: 25.3 (SD 6.6) v 34.6 (SD 12.8).	N, not specified	N, not specified	11.8 v 11.6	2.4 v 0.9	Amgen
Silverberg, 2001[25] Single center Israel 12.4 ± 8.2 months	N: 16 v 16 mean age: 75.3 v 72.2 male: 69 v 75	LVEF: 30.8 v 28.4 Mean NYHA: 3.8 v 3.5 Ischemic: 69 v 62.5 ACEI: 87.5 v 87.5 ARB: 6.6 v 12.5	Cr: 1.7 v 1.4	Erythropoeitin 4000 IU sc weekly adjusted to goal Hgb 12.5 Control not reported.	ferritin: 221 (SD 165) v 264 (SD 162), NS. TSAT%: 25.1 (SD 12.9) v 22.5 (SD 16.7), NS.	Y, IV ferric sucrose 200 mg q 2 weeks	N	10.3 v 10.9	2.6 v -0.1	none
Van Veldhuisen, 2007[22] Multi-center (44 sites, 15 countries) 6 months	N: 110 v 55 male: 56 v 62 white: 93 v 89 black: 5 v 7 asian: 3 v 4 mean age: 71 v 71	LVEF: 29 v 27 NYHA I: 3 v 2 NYHA II: 36 v 44 NYHA III: 59 v 53 NYHA IV: 2 v 2 Ischemic: 69 v 64 ACEI: 77 v 75 ARB: 18 v 20 ACE/ARB: 94 v 91	GFR: 56.5 v 53.5	Darbepoeitin alpha 0.75 mcg/ kg sc q 2 wks OR 50 mcg (fixed dose) vs. identical placebo provided by Amgen	ferritin: 198 (SD 232) v 200 (SD 224). TSAT%: 26 (SD 9) v 25 (SD 8).	Y, 200 mg oral iron daily	Y, 200 mg oral iron daily	11.5 v 11.4	1.87 (0.75 mcg/kg) v 0.07	Amgen

Study ID Setting Months of follow-up	N (T v C); Demographics: % male; % race/ethnicity; mean age (yr)	Clinical subgroup (CHF/CAD); Mean LVEF %; % on RAAS blockers (T v C)	Baseline kidney function, GFR or Serum Cr (T v C)	Intervention (Drug, Dose) v Control	Baseline measures of iron stores (T v C)	Iron in Tx group	Iron in Control group	Baseline Hgb (T v C)	Mean change in Hgb (T v C)	Funding source
Studies conducted in patients with CAD										
Bellinghieri, 1994[27] Single-center Italy 24 months	N: 26 v 10 male: 50 vs. 70 race NR mean age: 62.4 v 64.2	CAD (at least one episode of angina or dysrhythmia in last year) RAAS blockers NR	All pts ESRD on HD	Epoeitin IV 25 IU/kg post each HD Control not reported.	NR	NR	NR	NR in both groups	8.1 to 8.97 in Tx group	NR
Studies conducted in patients with CHF or CAD										
Besarab 1998,[26] 2008[20] Multicenter US 30 months	N: 618 v 615 male: 50 v 48 white: 45 v 42 black 41 v 44 Hispanic: 8 v 9 mean age: 65 v 64	CHF (44 v 47) or CHD LVEF NR RAAS blockers: no significant difference between groups (NOS)	All pts ESRD on HD	Epoetin IV or SQ to target Hct 42 ±3 vs. Epoetin IV or SQ to target Hct 30 ± 3	ferritin: 334 v 403 (p = 0.002) TSAT%: 26.8 v 26.3	IV iron dextran in 526/618 pts	IV iron dextran in 464/615 pts	Hct: 30.5 v 30.5	Change in Hct: approx 10 v 0%	Amgen
Studies analyzing a CHF/CAD subgroup of patients with CKD										
Pfeffer, 2009[14] Heart disease subset of TREAT Multi-center, international 29 months	N: 1287 v 1355 (2,636/4,044 enrolled had CVD Hx) male: 46 mean age: 70 white 69 black: 19 Hispanic: 9.3	CVD: 67.9 CHF: 50.2 PAD: 31.8 RAAS blockers: 77.7	GFR: 34	Darbepoeitin alpha titrated to high (13.0 g/dL) vs. low (9.0 g/dL) Hgb target	TSAT%: 23 ferritin: 134	N	N	10.4	For overall cohort (n=4,044) Median achieved Hgb 12.5 (change of 2.1) v 10.6 (change of 0.1)	Amgen
Szczech, 2010[13] CHF subset of CHOIR 36 months	N: 192 v 183 mean age (Hgb 13.5 group v Hgb 11.3 group): 70.2 v 69.5 male: 46.4 v 56.3 black: 29.3 v 27.3 Hispanic: 9.4 v 12.0	CHF	GFR: 26.9 v 26.0	Epoeitin alpha titrated to high (13.5 g/dL) vs. low (11.3 g/dL) Hgb target	ferritin (Hgb 13.5 group vs Hgb 11.3 group): 159.5 v 193.5, p=0.050. TSAT%: 22.1 v 24.1, p=0.043.			Hgb 13.5: 10.0 Hgb 11.3: 10.0		CHOIR funded by Ortho Biotech and Johnson & Johnson. This secondary analysis by NIH.

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Exercise Tolerance and Duration

Overall, though there is some data that ESAs may improve exercise tolerance, the body of evidence is limited by inconsistent results and the methodologic weaknesses of some studies. Pooled results from nine trials reporting change in NYHA scores were highly heterogeneous and found a decline in NYHA scores in ESA-treated patients while control patients generally maintained stable scores or worsened (mean difference in NYHA scores treatment vs. control, -0.77, 95% CI -1.21 to -0.32, I^2=96.0%, Figure 3). However, this improvement was significantly attenuated when we limited the analysis to the four methodologically stronger trials (mean difference in NYHA scores -0.15; 95% CI -0.36 to 0.06; I^2=62.1%, Figure 4). The largest of these trials randomized 319 patients to twice-monthly darbepoietin or saline placebo, and measured exercise duration, tolerance and quality of life outcomes at 27 weeks.[19] The authors found darbepoietin had no effect on any of the outcomes despite raising hemoglobin by 1.8 g/dL on average.

Figure 3. Change in NYHA scores in CHF patients: mean difference comparing ESA to control group

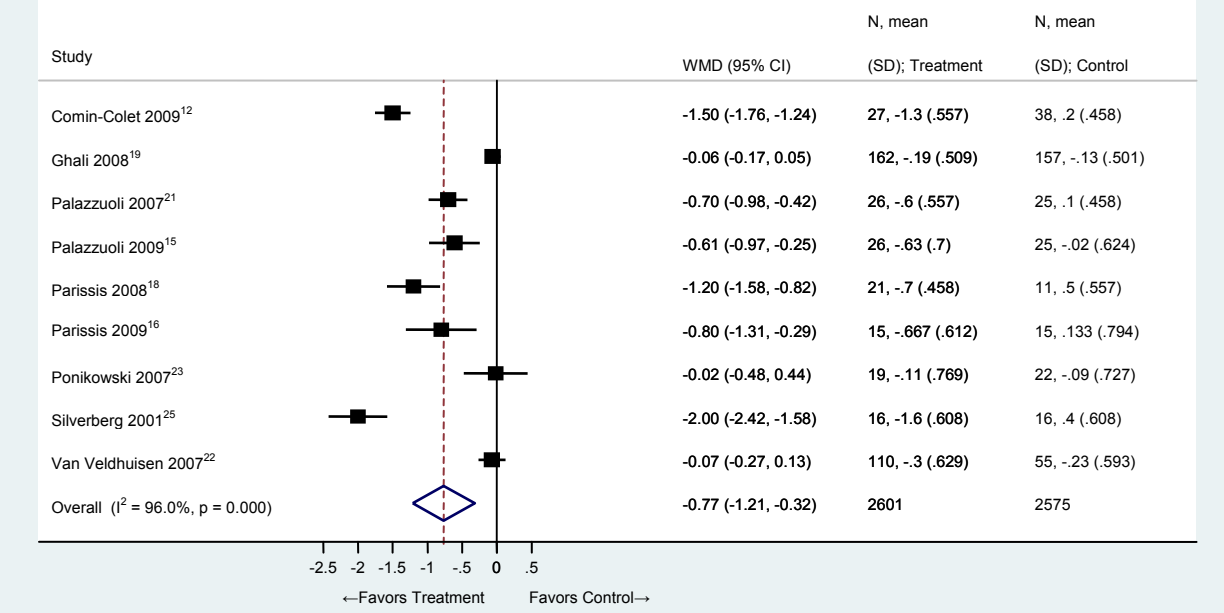

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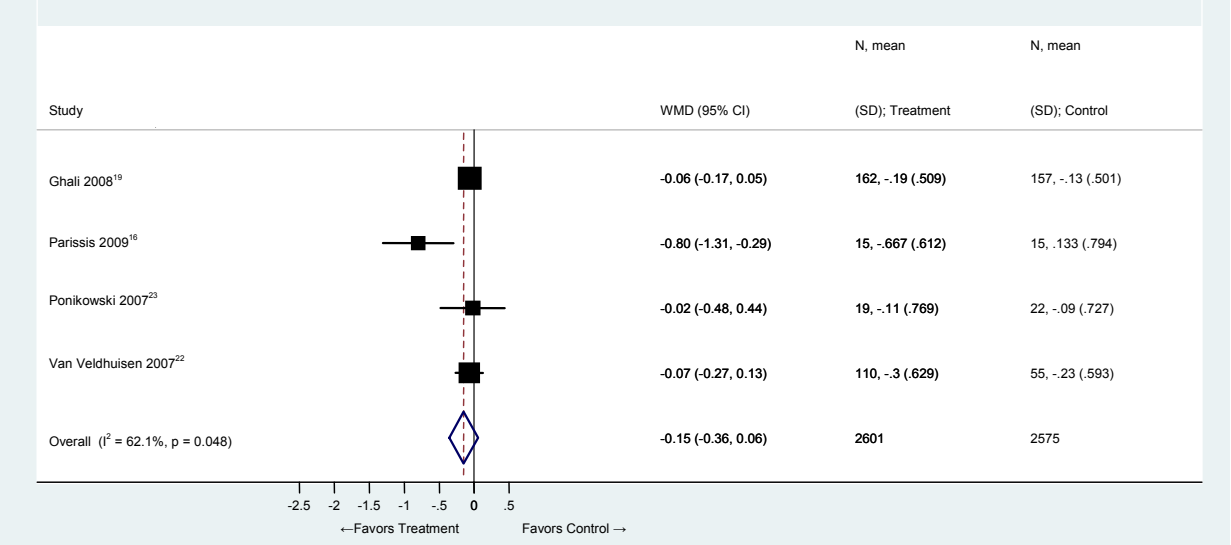
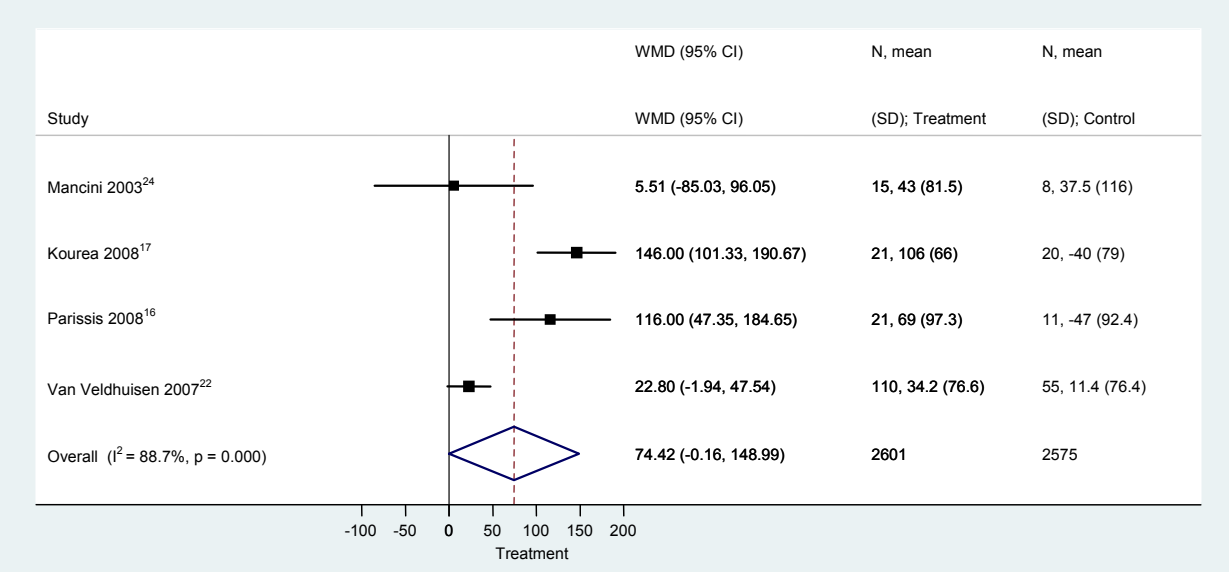
Figure 4. Change in NYHA scores in CHF patients – studies with low risk of bias, and excluding studies with duplicate patient populations: mean difference comparing ESA to control group



Six trials reported exercise distance or duration. Four of these trials reported the mean change in six-minute walk distance and found ESA use was associated with a marginally significant increase in distance walked, though results were quite different among the trials (mean change in meters walked: 74.[4]; 95% CI -0.16 to 149.0; I^2=88.7%) (Figure 5). Two trials reported change in exercise treadmill time using the Naughton protocol; the larger trial found no improvement associated with ESA use,[19] while a smaller trial found ESA use was associated with a small increase in exercise duration.[28] Exclusion of poorer quality studies did not alter results substantially, but such analyses are limited by the very small number of studies.

Figure 5. Change in six-minute walk distance (meters) in CHF patients: mean difference comparing ESA to control group



Quality of Life

Five trials reported quality of life measures as a primary or secondary outcome,[17, 19, 22-24] but analysis was limited by the variety of and inconsistency among specific instruments used. Most trials used several different methods for evaluating quality of life. Four trials evaluated change in the Patient Global Assessment scale.[19, 22-24] In two of these studies, a significantly greater proportion of treatment patients reported improvement than controls, but one of these studies had several important methodologic flaws, including lack of blinding, that could bias these subjective results.[24] The other trial found no improvement in two simultaneously measured QOL instruments including the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).[23] Four trials reported MLHFQ scores,[19, 22-24] but only one trial with high risk of bias showed a significant improvement in scores associated with treatment.[24] Kourea et al. found treatment was associated with improvement in the Duke Activity Status Index (DASI), Beck Depression Inventory (BDI) and Zung Self-rating Depression Scale (SDS).[17]

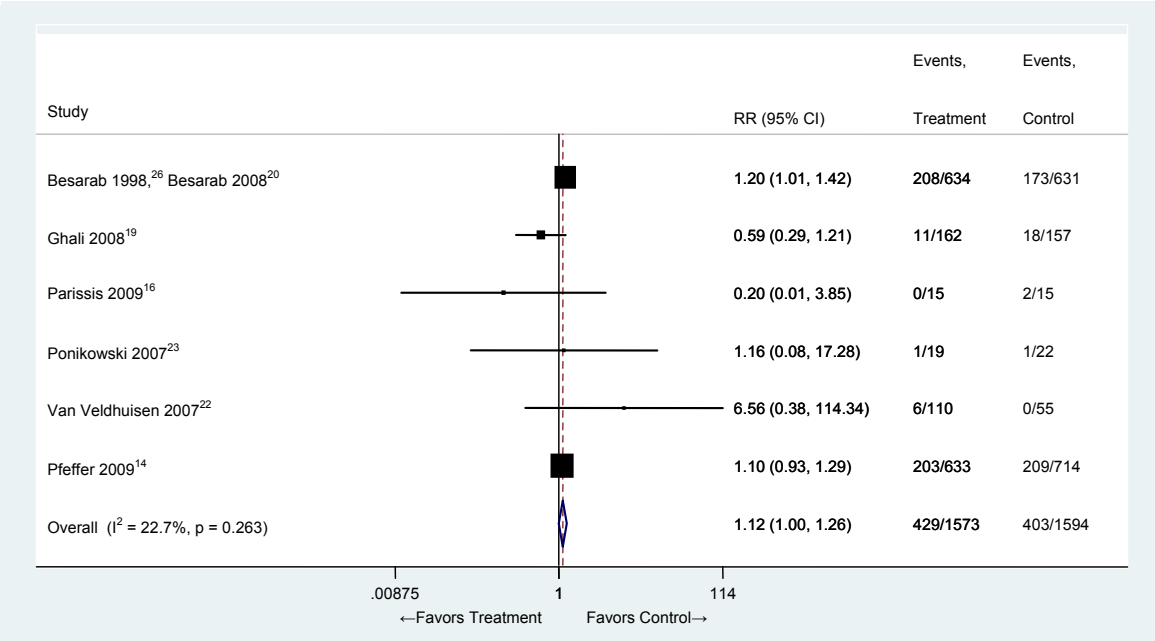
The KCCQ measures quality of life in multiple domains which can be combined into summary scores to facilitate interpretation. Three trials reported different types of KCCQ summary scores without defining which domains were used in each summation.[17, 22, 23] One trial reported a significant difference between groups in mean change from baseline of a KCCQ "total symptom score": 8.2 v 1.5, p=0.027.[22] Another trial noted significant improvements in a KCCQ "functional score" (21 +/- 19 v 2 +/- 11, p=0.004), as well as a KCCQ "summary" score (20 +/- 20 v 6 +/- 14, p=0.04).[17]

Mortality

Nine trials reporting at least one death in the treatment or control group found ESA use was associated with a marginally significant increased mortality risk (RR 1.11; 95% CI 0.99 – 1.24; I^2=0.0%). An analysis of the six trials with low risk of bias found very similar results (Figure 6).

These findings are largely driven by two large trials with extended follow-up and very high event rates. Indeed, a sensitivity analysis without these two trials showed ESAs had a neutral effect on mortality (RR 0.79, 95% CI 0.51 – 1.22; I^2=0.0%). One of the trials compared aggressive (goal hematocrit 42%) to less aggressive (goal hematocrit 30%) epoietin titration in patients with end-stage renal disease and heart failure and/or ischemic heart disease.[26] After a prolonged follow-up of 29 months, the authors found a 20 percent increase in the risk of all-cause mortality, and most of the events were of cardiovascular origin. Another large trial compared darbepoietin to placebo in patients with type 2 diabetes and chronic kidney disease. A prespecified analysis of the large subgroup with comorbid heart disease showed a non-significant increased risk of death in the treatment group after a similarly long follow-up period.[14, 29]

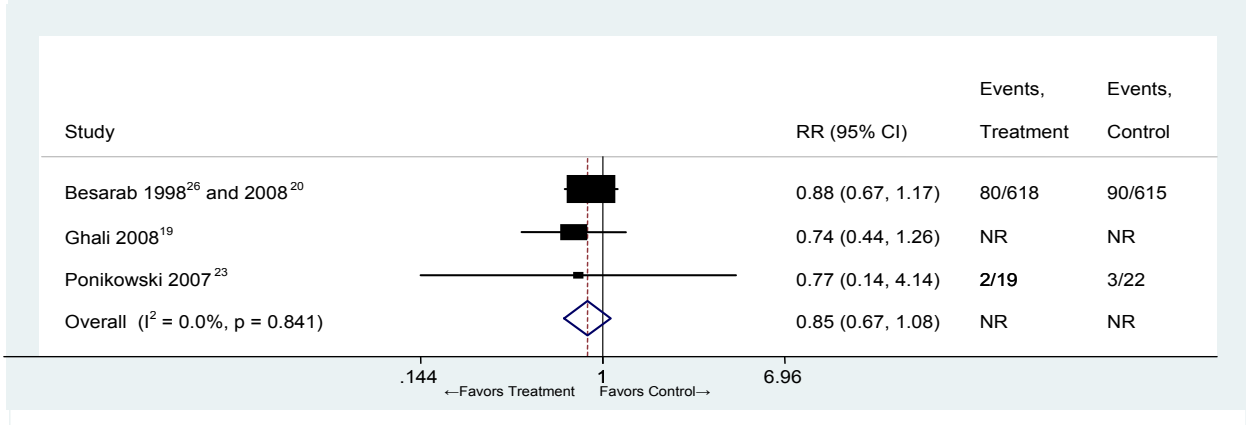
Figure 6. All-cause mortality in patients with CHF or CHD – studies with low risk of bias: ESA vs. control



Hospitalizations

Six trials found ESA treatment was associated with a reduction in hospitalizations (RR 0.70, 95% CI 0.57 – 0.87; I^2=37.7%), but, again, this benefit largely disappeared when we included only the higher quality trials (Figure 7).

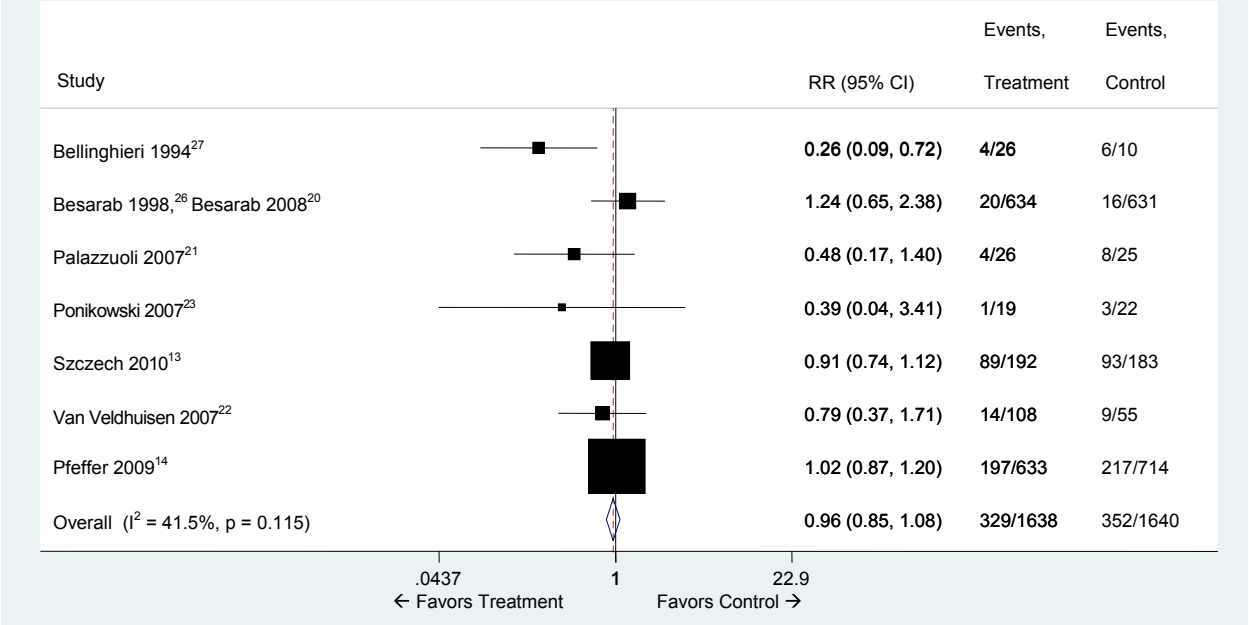
Figure 7. Risk of one or more hospitalizations in patients with CHF or CHD – studies with low risk of bias: ESA vs. Control



Cardiovascular Events

ESAs had a neutral effect on the occurrence of cardiovascular events across seven trials (RR 0.96, 95% CI 0.85 – 1.08; I^2=41.5%, Figure 8). The only trial showing a benefit focused on CHD patients, and had many significant methodologic weaknesses which threaten the validity of the results.[27]

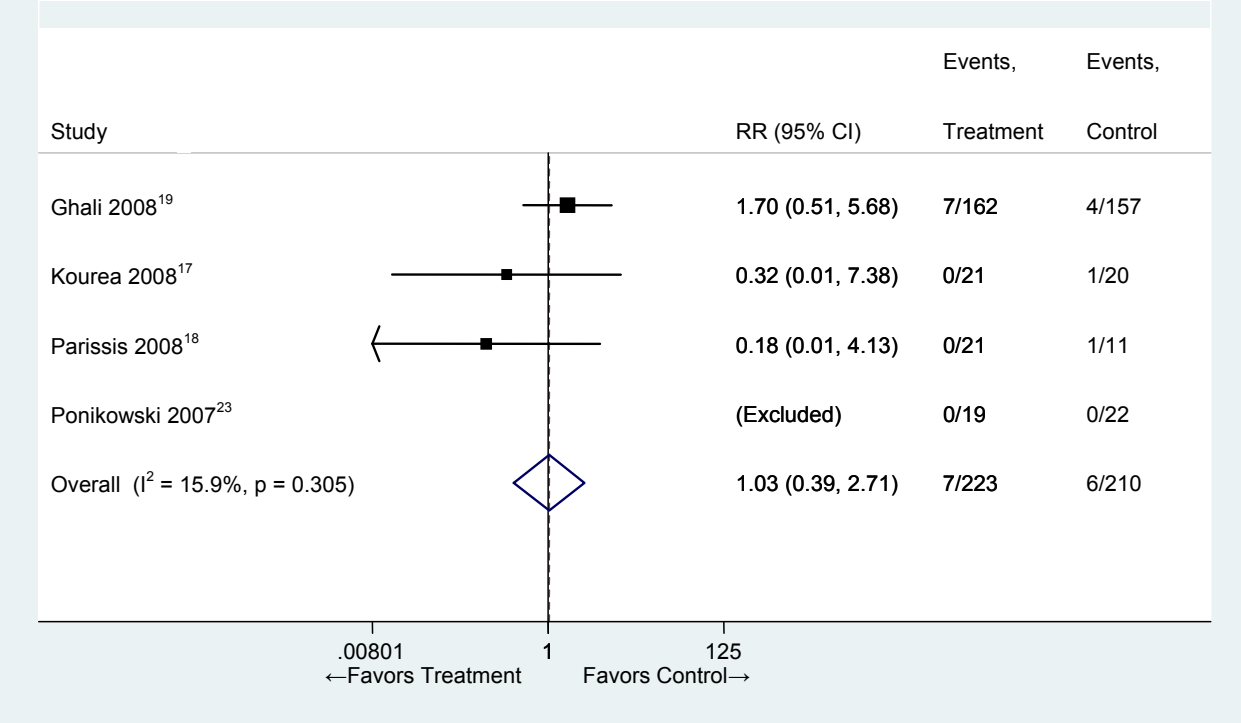
Figure 8. Cardiovascular events in patients with CHF or CHD: ESA vs. control



Cerebrovascular Events

There were very few cerebrovascular events among the four trials reporting this outcome (Figure 9). There was an increased risk of stroke associated with ESA use in the TREAT trial among patients with diabetes and chronic kidney disease (RR 1.92, 95% CI 1.38 – 2.68),[30] but these data are not reported separately for the large subgroup of heart disease patients.

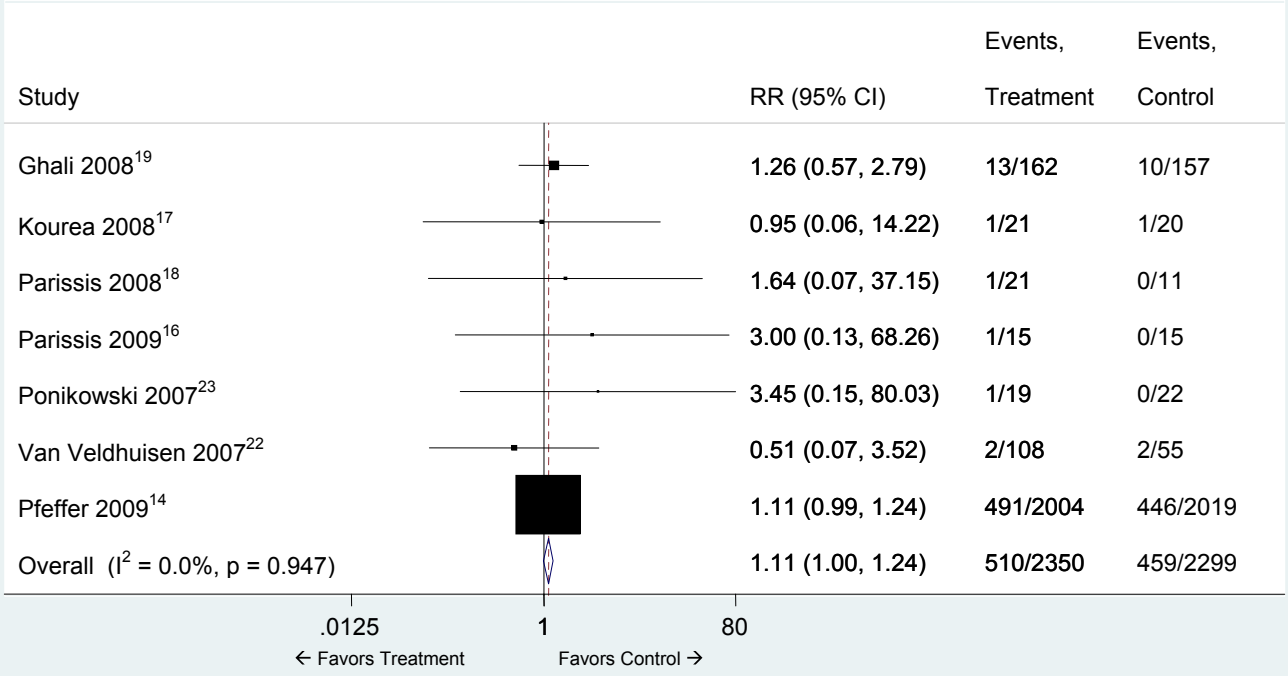
Figure 9. Cerebrovascular events in patients with CHF or CHD: ESA vs. control



Other Harms

Combined results from seven trials suggest ESA use may be associated with excess risk of hypertension (RR 1.11, 95% CI 1.00 – 1.24; I^2= 0.0%), though the findings are again dominated by one large trial.[14] The finding of excess risk became non-significant when we excluded this trial (RR 1.25, 95 % CI 0.65 – 2.38; I^2=0.0%). Reported hypertension events in the other trials were rare, but the quality of adverse event reporting was unclear and the definitions used varied widely (Figure 10).

Figure 10. Hypertension events in patients with CHF or CHD: ESA vs. control



One large trial in end-stage renal disease patients found an increase in the risk of thrombosis – mainly of vascular access sites – associated with aggressive epoietin titration (RR 1.37, 95% CI 1.17 – 1.61).[26] The risk of venous thromboembolism was similarly increased in another trial of patients with chronic kidney disease and diabetes (RR 1.80, 95% CI 1.08 – 2.98), though data for the cardiac disease subgroup were not reported separately.[14] On the other hand, only two other studies reported the occurrence of venous thromboembolic events with no difference seen between groups.[19, 22]

Hemoglobin Target

We were not able to determine how anemia severity and hemoglobin change influenced outcomes in the placebo-controlled trials. Almost all the small trials comparing ESAs to placebo in heart failure patients included patients with moderate anemia and a mean baseline hemoglobin within the narrow 10 – 12 g/dL range. In all cases, ESA use was associated with a significant increase in hemoglobin (mean increase range 1.6 – 2.8 g/dL). In order to better understand the influence of baseline hemoglobin and change in hemoglobin on outcomes, we conducted the two following sensitivity analyses for all outcomes and found no substantive difference in results:

1) exclusion of studies in which the mean baseline hemoglobin < 11 g/dL; and 2) exclusion of studies in which the mean increase in hemoglobin associated with ESA use was < 2 g/dL. However, the utility of such subgroup analysis is limited by the relatively small number of trials, and also by concurrent characteristics which could influence results. For instance, exclusion of studies with mean baseline hemoglobin < 11 g/dL examining change in NYHA scores left only the poorer quality studies. Furthermore, there may not have been enough variation in mean baseline hemoglobin and change in hemoglobin across studies given the relatively small sample of trials.

The best evidence evaluating the influence of hemoglobin targets comes from the three trials (or subgroups of trials) of patients with comorbid chronic kidney and heart disease, in which ESAs titrated to normal or near-normal targets were compared to ESAs titrated to lower targets (hemoglobin 9 – 11.3 g/dL).[13, 14, 20] None of the trials found a benefit from aggressive ESA use and, in fact, two of the trials found a significant increase in venous thromboembolic risk and a near-significant increase in mortality.[14, 20]

No trials in heart disease patients have evaluated the effects of more moderate hemoglobin targets (e.g. hemoglobin 10 – 12 g/dL) compared to lower targets.

In Progress Trials

Two trials of ESAs in heart failure are ongoing. The Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) study is an international, multicenter, randomized and placebo-controlled trial.[31] The intent is to recruit ~2600 optimally treated patients with low ejection fraction (~40%) and symptomatic CHF with a Hgb concentration 9.0 – 12.0 g/dL. Patients will be administered darbepoetin every two weeks, titrated to a goal Hgb of >= 13.0 g/dL, with oral iron repletion as needed. The primary outcome is time to death from any cause or first hospital admission for worsening CHF. The secondary outcomes include mean change in KCCQ scores at six months. Started in June 2006, this event-driven, industry-sponsored trial is estimated to finish in 2014.

Also expected are results from the Anemia in Heart Failure With a Preserved Ejection Fraction trial.[32] This randomized, placebo-controlled trial is examining the effects of weekly erythropoietin, also titrated to a target hemoglobin of 13 g/dL, in 80 patients with anemia and heart failure and a preserved ejection fraction. They will evaluate the primary outcomes of left ventricular end diastolic volume atsix months, as well as secondary outcomes of peak oxygen consumption, six-minute walk duration, KCCQ scores, hospitalization, and others. Started in July 2007, it is anticipated to be completed by March 2012.

KEY QUESTION #2. In patients with CHF or CHD, what are the health outcome benefits and harms of using iron to treat iron deficiency with or without anemia?

Summary

Two small and one large, well-conducted multicenter trials show that IV iron can improve short-term exercise tolerance and quality of life in patients with symptomatic systolic heart failure and

iron deficiency, with or without anemia. The impact on distal health outcomes such as mortality and cardiovascular events remains undertested, as do the long-term effects of such treatment. The evidence supporting symptomatic benefit most closely applies to patients with NYHA III heart failure and evidence of low iron stores.

Details

We included three trials of IV iron in patients with iron deficiency. Results are largely dominated by one recent trial that studied the effect of iron infusion on patients with iron deficiency with or without anemia.[33]

The FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) trial is a randomized, double-blind, multicenter trial that evaluated the efficacy of intravenous-iron infusion on symptoms and submaximal exercise capacity in a cohort of patients with chronic mild or moderate heart failure due to left ventricular systolic dysfunction. The study enrolled 459 stable outpatients with NYHA class II or III heart failure, low ejection fraction, and iron deficiency as defined by a ferritin < 100 µg/dL or between 100 – 299 µg/dL if the transferrin saturation was < 20 percent. Pre-specified primary endpoints included self-reported Patient Global Assessment and NYHA functional class after 24 weeks of therapy. Secondary endpoints included distance walked in six minutes and health-related quality of life. Patients receiving IV iron received 200 mg infusion of ferric carboxymaltose with repeat dosing until iron repletion was achieved (correction phase) and then every four weeks during the maintenance phase, which started at week eight or week twelve, depending on the required iron-repletion dose. Control patients received an IV saline placebo with the same dosing schedule.

Patient characteristics, which were well-matched between the two groups at baseline, are detailed in Table 2. Most patients had NYHA Class III symptoms and moderate to severe systolic dysfunction. Only half the patients were anemic (HHgb ≤ 12g/dL), but most had ferritin levels < 100.

Patients in the treatment group were more likely to report they were much or moderately improved on the Patient Global Assessment compared with control patients (50 v 28%, OR 2.51; 95% CI 1.75 – 3.61). Iron treated patients also showed improvement in NYHA functional class (OR for improvement by one class, 2.40; 95% CI 1.55 – 3.71). Improvements in Patient Global Assessment and NYHA scores were observed in both prespecified subgroups of patients with and without anemia (Hgb ≤ 12g/dL). Significant improvements were also seen in secondary endpoints, including an increased distance on the six-minute walk test (313 meters compared with 277 meters) and quality of life assessments (EQ5-D, where higher score is better, of 63 vs. 57).

The FAIR-HF trial was large and well-conducted, but there are several limitations of note. It relied on subjective primary endpoints, though the strong study design should minimize the risk of biased results. The size of the study and relatively short follow-up period limit its ability to examine intervention effects on more distal health outcomes such as mortality. Finally, there were too few patients with NYHA class II heart failure to meaningfully apply results to this group of patients.

We also included two smaller trials of iron therapy. The first randomized 40 patients with iron deficiency, anemia, chronic heart failure and chronic kidney disease to receive 200 mg of intravenous iron sucrose or saline weekly for five weeks.[34] Investigators found that after six months, participants who received iron sucrose had significant improvement in MLHFQ score, decreased levels of N-terminal pro-brain natriuretic peptide (117.5 +/- 87.4 pg/ml vs. 450.9 +/-248.8 pg/ml, $p<0.01$) and C-reactive protein (2.3 +/- 0.8 mg/l vs. 6.5 +/-3.7 mg/l, $p <0.01$), an increase in left ventricular ejection fraction percentage (35.7 +/- 4.7 vs. 28.8 +/- 2.4), and distance on the six-minute walk test.

The FERRIC-HF (Ferric Iron Sucrose in Heart Failure) trial randomized 35 patients and measured the effect of 200 mg of intravenous iron sucrose compared with placebo on exercise tolerance and QOL.[35] The lack of blinding contributes to a high risk of bias given the subjective nature of the functional status and QOL outcomes. Also, substantially more patients in the intervention group dropped out of the study (16 v 9%).

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Table 2. Characteristics of randomized controlled trials of iron therapy in patients with CHF or CHD

Study setting and design	Characteristics of patient population, T v C	Results, N(%), T v C	Quality assessment
Anker, 2009[33] FAIR-HF Multicenter randomized controlled trial, international 24 weeks Ferric carboxymaltose IV 200 mg weekly until repleted, then q 4 weeks v saline 4 mL	N: 304 v 155 % male: 47.6 v 45.2 % white: 99.7 v 100 Mean age: 67.8 v 67.4 Mean LEVF%: 31.9 v 33.0 % NYHA II: 17.4 v 18.7 % NYHA III: 82.6 v 81.3 % RAAS blockers: 92.4 v 91.0 Baseline GFR: 63.8 v 64.8 Baseline ferritin: 52.5 v 60.1 Baseline TSAT%: 17.7 v 16.7 Baseline Hgb: 11.9 v 11.9	Mean change in HHgb: 1.1 v 0.6 Mortality: 5 (3.4) v 4 (5.5) Cardiac events: 46 events in 38 pts (27.6%) v 49 events in 33 pts (50.2%), p=0.01 First cardiovascular hospitalization: HR 0.53 (95% CI 0.25-1.09, p 0.08) Functional status/activity tolerance: NYHA, OR for improvement by 1 class: 2.40 (95% CI 1.55-3.71) Patient global assessment, OR for improvement: 2.51 (95% CI 1.75-3.61) 6 minute walk (meters): 313 v 277 Quality of life outcomes: Kansas City Cardiomyopathy Questionnaire Score: 66 v 59 EQ-5D Score: 63 v 57 Adverse events: GI event: 29 events in 24 pts (16.9%) v 7 events in 5 pts (6.9%), p=0.06 Respiratory event: 9 events in 9 pts (6.2%) v 13 events in 10 pts (14.2%), p=0.06	Overall: low risk of bias Funding source: Vifor Pharma
Okonko 2008[35] Randomized controlled trial 2 centers in Europe 18 weeks Iron sucrose IV in varied doses (according to a formula in paper) weekly for four weeks then q 4 weeks for four months; no control	N: 24 v 11 % male: 71 v 73 % white: 88 v 91 Mean age: 64 v 62 % CAD: 79 v 73 LVEF%: 30 v 29 RAAS blockers: 96 v 91 Baseline Cr: 1.23 v 1.17 (mg/dL) Baseline ferritin: 62 v 88 Baseline TSAT%: 20 v 21 Baseline Hgb: 12.6 v 12.2	Mean change in Hgb: 0.5 v 0.4 Mortality: 1/24 (4.2%) v 0 Hospitalizations: 3/24 (12%) v 3/11 (27%) Functional status/activity tolerance: NYHA: 2.1 v 2.6 Mean change NYHA -0.4 v 0.2, p = 0.007 Mean change exercise duration (s): 45 v -15 Patient global assessment: 1.5 v -0.2, p = 0.002 Mean change MLHFQ: -10 v 3, p = 0.07 Adverse events: abdominal pain -2/24 (8%) v 0 TIA - 1/24 (4%) v 0	Overall: unclear risk of bias Funding source: Vifor International
Toblli, 2007[34] Randomized controlled trial 6 months Iron sucrose IV 200 mg v saline 200 ml weekly x 5 weeks.	N: 20 v 20 % male: NR % white: NR Mean age: 76 v 74 % CAD: 60 v 55 Mean LVEF%: 31.3 v 30.8 % RAAS blockers: 95 v 100 Baseline GFR: 39.8 v 37.7 Baseline ferritin: 73.0 v 70.6 Baseline TSAT%: 20 v 20 Baseline Hgb: 10.3 v 10.2	Mean change in Hgb: +1.5 v -0.4 Mean change in CrCl: +5.1 v -6.0, p<0.01Hospitalizations: 0/20 v 5/20 (20%), p<0.01 Functional status/activity tolerance: MLHFQ score: 41 v 59, p<0.01 Mean change in MLHFQ score: -19 v -6 6 minute walk (meters): 240.1 v 184.5 , p<0.01	Overall: low risk of bias.

KEY QUESTION #3. In patients with CHF or CHD, what are the health outcome benefits and harms of treating anemia with red blood cell transfusions?

Summary

We found 35 studies that examine the association between red blood cell transfusion and clinical outcomes in patients with CHD or CHF. Ten of these studies evaluated transfusion use in the perioperative period; the remaining reports, all but one published since 2001, focused on the non-surgical population. Three of these studies were subgroup analyses of the same registry;[36-38] thus, in the end, we found 23 unique studies of the potential benefits and harms of transfusion outside of the perioperative period in patients with ischemic heart disease and/or CHF.

Outside of the surgical setting, red blood cell transfusion has been evaluated as a treatment for anemia in heart disease in two controlled trials: one found no difference in survival from more aggressive transfusion above a threshold hemoglobin 10 g/dL,[39] while the other found a higher incidence of heart failure in patients transfused to that level, without a difference in survival.[40]

Twenty-one additional observational studies have been conducted in patients undergoing percutaneous coronary intervention (PCI) or admitted with acute coronary syndrome, myocardial infarction, or decompensated heart failure. Inconsistency of findings and methodological weaknesses complicate the interpretation of results, but several themes emerge: 1) the evidence strongly suggests that transfusion has no benefit and may be harmful in patients with heart disease and hemoglobin >10 g/dL, with the possible exception of those with ST-elevation myocardial infarction; 2) outcomes do not appear to improve with transfusion in non-ST-elevation ACS patients with hemoglobin levels down to the 8 – 9 g/dL range; 3) transfusion is consistently associated with higher mortality risk in the unselected PCI population, across multiple studies with mean nadir hemoglobin of 8 – 9 g/dL; and 4) the elevated risk in the PCI population is seen in patients with anemia related or unrelated to bleeding but may be higher in the non-bleeding anemic population. There is no evidence to guide decision-making in the stable coronary disease population, and the two studies in decompensated heart failure have conflicting results.

The literature evaluating the use of perioperative transfusion in patients with heart disease is concentrated primarily on the cardiac surgery population but does include several studies in vascular and orthopedic surgery and one in the general non-cardiac surgery population. Seven perioperative randomized controlled trials have been conducted, and each found no difference in survival or cardiovascular complications between patients transfused to a higher versus lower target hemoglobin. In the observational cohorts, transfusion did not appear to offer any protection; and in one study in the vascular surgery setting, mortality and myocardial infarction rates were higher overall in the transfused group, a harm in subgroup analysis limited to those transfused at a hemoglobin ≥ 9 g/dL.[41]

Non-operative Setting

Randomized Controlled Trials

Only 2 of the 23 studies in nonsurgical populations were randomized controlled trials (Table 3).[39, 40] The TRICC trial, published in 1999, remains the only large controlled trial of transfusion strategies in hospitalized patients.[42] This landmark study randomized 838 euvolemic, non-bleeding, critically ill patients with hemoglobin < 9 g/dL to one of two transfusion thresholds: hemoglobin of 7 g/dL (restrictive transfusion strategy) or 10 g/dL (liberal strategy). They found no significant difference between the two groups in mortality in the hospital or at 30 days, or in other clinical outcomes including cardiac events, pulmonary or infectious complications, organ dysfunction scores, and length of stay. Importantly, the trend suggested the potential for higher mortality and more cardiac events in patients treated to the higher hemoglobin level. In the subgroups of patients younger than 55 years of age or with APACHE II scores of 20 or lower, the mortality rate was statistically significantly higher in the liberally transfused group.

In 2001, the TRICC authors published a post-hoc subgroup analysis focusing on patients with cardiovascular disease in general and ischemic heart disease in particular.[39] Once again, there were no significant differences in any clinical outcome. However, the trend toward improved survival with a restrictive transfusion strategy disappeared in the general cardiovascular disease population, and in the ischemic heart disease subgroup, there was a higher mortality rate in the restrictive group, though the difference was nonsignificant (30 day mortality 21.1% versus 26.1% with liberal and restrictive strategies, respectively; p=0.38). Like the TRICC trial population overall, the ischemic heart disease subgroup was severely ill with multiple comorbidities (mean APACHE II scores of 23, 87% requiring mechanical ventilation).

Cooper et al. performed a pilot trial (CRIT) designed to evaluate conservative versus liberal transfusion strategies specifically in patients with acute myocardial infarction.[40] They randomized 45 patients with hematocrit under 30 percent to a transfusion trigger of 24 percent (conservative strategy), with a target hematocrit 24 – 27 percent, or a trigger of 30 percent (liberal strategy), with a target of 30 – 33 percent. They found a higher rate of the primary endpoint, a composite of in-hospital death, recurrent MI, or new/worsening heart failure, in the liberally transfused group compared to the conservative group (38% versus 13%; p=0.046). The difference was explained entirely by a higher incidence of new or worsening CHF.

An additional study, the Myocardial Ischemia and Transfusion trial, began two years ago and is now collecting final outcomes data.[43] This multicenter, randomized, controlled trial aimed to enroll 200 anemic patients hospitalized with acute coronary syndrome, including both STEMI and NSTE-ACS, or stable CAD undergoing cardiac catheterization during the index hospitalization. Like the TRICC and CRIT trials, patients were assigned to a restrictive (< 8 g/dL) or liberal (< 10 g/dL) transfusion threshold and were observed for clinical outcomes including mortality, myocardial ischemia, stroke, heart failure, infectious complications, and readmission.

Observational Studies

Given the sparse and the inconsistent data from the trial literature, clinical decision-making appears largely guided by an imperfect body of evidence characterized by conflicting

observational data. We reviewed these observational studies, in part to clarify their utility in guiding transfusion treatment decisions (Table 4).

Because of the observational nature of these studies, the decision to transfuse patients was based on clinical judgment which, in turn, would be naturally influenced by severity of illness, symptoms, and observation of bleeding. All the included observational studies suffer from the possibility of residual confounding and are all, therefore, of lower quality than the evidence provided by randomized controlled trials. However, there were methodologic differences amongst observational studies. For instance, some accounted for bleeding and conducted propensity to transfuse adjustments, while others did not. These factors are summarized in Appendix C, Table 3.

Percutaneous Coronary Intervention

Nine observational studies looked exclusively at populations undergoing percutaneous coronary intervention; six included all indications,[36-38, 44-48] and three examined PCI solely in the setting of acute MI.[49-51]

In those studies that recorded it, 1.8 – 6.7 percent of unselected patients undergoing PCI received PRBC transfusion; rates were higher in those studies for which anemia was an inclusion criterion. A substantial proportion of patients who received transfusions did so because of major bleeding (22 – 100%), and median nadir hematocrit prior to transfusion ranged across studies from 24 to 30 percent. After adjustment for potential confounding factors in multivariable analyses, transfusion was associated with worse survival in all studies but one;[36-38] it found no significant relationship between transfusion exposure and death or MI, both in cohorts with hematocrit < 27 percent and 24 – 30 percent. The association between transfusion and increased mortality appeared stronger in non-bleeding patients,[44, 51] but was also noted in several studies that examined patients with major bleeding.[44-46]

Acute Coronary Syndrome/Myocardial Infarction

Twelve observational studies evaluated transfusion in the setting of acute coronary syndrome or myocardial infarction; four included only patients with non-ST-elevation ACS,[52-55] two included patients exclusively with ST-elevation MI,[50, 56] and six examined mixed ST/non-ST elevation ACS populations. Of these, three included predominately STEMI patients,[51, 57, 58] two had a majority NSTE-ACS population,[59, 60] and one did not record the breakdown.[49] PCI rates ranged from 10 to 100 percent and transfusion rates from 4 to 30 percent across cohorts. Nadir hematocrit among patients who were transfused averaged from 25 to 29 percent in those studies that recorded it.

Eight of the ACS/AMI studies did find an association between transfusion and higher risk of death, including the three studies that focused exclusively on AMI patients undergoing PCI;[49-51] three involving patients with high-risk non-ST-elevation ACS,[52-54] and two examining patients primarily with ST-elevation myocardial infarction.[56, 58] One additional study found no relationship between transfusion status and in-hospital mortality in a mixed ST/non-ST-elevation ACS population, regardless of whether the transfusion was bleeding-related or for non-specific anemia.[60]

Six studies examined whether mortality risk varies according to hemoglobin level, but they had varied results and used different thresholds for their stratified analyses, making it difficult to draw firm conclusions.[52, 54, 55, 57-59]

Wu et al. examined a cohort of nearly 79,000 Medicare beneficiaries 65 years of age or older who were hospitalized with confirmed acute MI and were not actively bleeding.[59] They found a consistent association between transfusion and improved survival in patients with hematocrit values on admission of 30 percent or less, stronger in each successively lower hematocrit category. This benefit was lost in patients with hematocrit above 33 percent, and risk of death at 30 days was statistically significantly higher with transfusion once hematocrit rose above 36 percent.

Meanwhile, Rao et al. analyzed 24,112 patients who had been enrolled in three large international ACS trials (GUSTO IIB, PURSUIT, PARAGON B).[52] They found that receipt of transfusion predicted increased risk of death and death/MI at 30 days. After stratifying results by nadir hematocrit, they noted no association between transfusion exposure and mortality with a hematocrit of 25 percent or below, but they found a highly increased probability of death at 30 days with transfusion at a nadir hematocrit of 30 percent or higher.

Sabatine et al. performed a post-hoc meta-analysis of 16 prior TIMI cardiac trials, finding that transfusion appeared to confer a protective effect in terms of cardiovascular mortality in patients with STEMI and admission hemoglobin less than 12 g/dL.[57] Meanwhile, there was a non-significant trend towards worse outcomes in STEMI with transfusion at hemoglobin level greater than 12 g/dL; and in the NSTE-ACS population, they noted an association between transfusion and higher risk for a combined mortality and cardiovascular event endpoint at all hemoglobin levels.

Of the three remaining studies that performed stratified analyses, transfusion was found to be of potential benefit in acute MI patients with nadir hemoglobin 8 g/dL or less,[58] and nonsignificant trends toward improved outcomes were noted in NSTE-ACS patients with hemoglobin at presentation less than 9 g/dL,[54] and NSTE-ACS patients with hematocrit 24 percent or less.[55] In each case, transfusion at hemoglobin or hematocrit levels higher than these thresholds was associated with increased mortality.

Heart Failure

Two observational studies evaluated patients with acute decompensated heart failure,[61, 62] with conflicting results. Garty et al. evaluated 2,335 patients admitted for acute decompensated heart failure to public hospitals in Israel.[61] They found that transfusion appeared to confer lower risk of death at 30 days, with trends toward benefit in-hospital, at one year and at four years. Meanwhile, Kao et al. noted higher adjusted in-hospital mortality with transfusion in a large cohort of patients hospitalized for heart failure in California.[62] This association was noted in both anemic and non-anemic patients but was much stronger in the non-anemic cohort.

Perioperative Setting

Cardiac Surgery

There were four randomized controlled trials of which two enrolled fewer than 40 patients total and were designed to evaluate primarily hemodynamic and lab parameters, while two were larger, enrolling 400 to 500 patients with primary clinical endpoints (Table 3). All were consistent in finding no difference in survival or cardiovascular complications with a conservative compared to a liberal transfusion strategy.[63-66]

Non-cardiac Surgery

Six studies, including three controlled trials and three observational studies, have reported outcomes based on transfusion status in patients with heart disease undergoing non-cardiac surgery. In the three controlled trials, performed in hip fracture and vascular surgery populations, there was no apparent benefit or harm from a more versus less aggressive transfusion strategy (Table 3).[67-69] By far, the largest of these studies, the FOCUS trial that enrolled over 2,000 patients undergoing hip fracture surgery, has only reported results in abstract form, with full publication expected in the very near future. The authors report no difference in mortality and functional status outcomes between the liberal and conservative transfusion groups. In the observational cohorts, transfusion did not appear to offer any protection, and in one study in the vascular surgery setting, mortality and myocardial infarction rates were higher overall in the transfused group, a harm in subgroup analysis limited to those transfused at a hemoglobin ≥ 9 g/dL (Table 3).[41, 68, 70]

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Table 3. Randomized controlled trials of red blood cell transfusion for anemia in patients with CHD or CHF, stratified by patient setting

Study ID	Patient Population	N	Intervention		Transfusion Rate (%)		Rate of Major Bleeding (%)	Mean Achieved Hgb/Hct		Outcome	%		HR/OR adj or P value
			Liberal Hgb/Hct trigger	Restrictive Hgb/Hct trigger	Liberal	Restric-tive		Liberal	Restric-tive		Liberal	Restric-tive	
Non-operative settings													
Cooper, 2011[40] CRIT trial	AMI (40% STEMI, 55.6% PCI) Hct ≤30% multicenter US, 2003-2009	45	Hct 30	Hct 24	100	54	0 (exclusion criterion)	Hct 30.6	Hct 27.9	mortality, in-hospital death/MI/CHF, in-hospital CHF, in-hospital mortality, 30 d death/MI/CHF, 30 d	5 38 38 5 60	8 13 8 8 20	p=1.0 p=0.046 p=0.03 p=1.0 p=0.02
Hebert, 2001[39] TRICC trial	ICU, 1° or 2° cardiovascular dx Hgb ≤9 g/dL post-hoc analysis, multicenter RCT Canada, 1994-1997	357 (44.8% restrictive)	Hgb 10	Hgb 7	100 (full study)	67 (full study)	0 (exclusion criterion)	Hgb 10.3	Hgb 8.5	mortality, 30 d mortality, 60 d	22.8 26.9	22.5 26.2	0.79 (0.45-1.43) p=0.9
	Known ischemic heart disease only	257 (43.2% restrictive)								mortality, 30 d mortality, 60 d	21.1 24.5	26.1 28.8	p=0.38 p=0.48
Non-cardiac surgery													
Bush, 1997[67]	Vascular surgery (aortic/ infrainguinal) (25% previous MI, 10% CHF) single center US, 1995-1996	99	Hgb 10	Hgb 9	NR	NR	NR	Hgb 11.0	Hgb 9.8	mortality, 30 d MI, 30 d cardiac events, 48 hrs	8 4 16	8 2 16	p>0.6 for all
Carson, 1998[68]	Hip fracture surgery (45.2% CV disease), Hgb <10 g/dL single center US, 1996-1997	84	Hgb 10	Hgb 8	100	45	NR	Hgb 10.7	Hgb 9.7	mortality, 60 d death/immobility, 60 d	4.8 45.2	11.9 39.0	NS NS
Carson, 2009[69]	Hip fracture surgery CAD or risk factors (40% known CAD) post-op Hgb <10 g/dL multicenter N. America, 2003-2009	2016	Hgb 10	Hgb 8	100	NR	NR	Hgb 9.2	Hgb 7.9	mortality, 60 d death/immobility, 60 d readmissions falls fatigue	7.6 35	6.5 35	1.19 (0.76-1.86) 1.03 (0.85-1.23) NS NS NS
Cardiac surgery													
Bracey, 1999[65]	Cardiac surgery single center US, 1997	428	Hgb 9	Hgb 8	64	60	NR	NR	NR	mortality, in-hospital MI, in-hospital	2.7 0.5	1.4 0	p=0.32 NS
Hajjar, 2010[66]	Cardiac surgery single center Brazil, 2009-2010	502	Hct 30	Hct 24	78	47	NR	Hct 31.8	Hct 28.4	mortality, 30 d death/shock/ARDS/ dialysis, 30 d cardiac complications	5 10 21	6 11 24	p=0.93 p=0.85 p=0.27
Johnson, 1992[64]	Cardiac surgery single center US, dates NR	39	Hct 32	Hct 25	100	80	NR	Hct 31.3	Hct 28.4	mortality, in-hospital MI/CVA/CHF, in-hospital	0 11.1	0 5	NS NS
Weisel, 1984[63]	Cardiac surgery single center Canada, dates NR	27	Hgb 12 (plus plasma for volume)	Hgb 7 (plus crystalloid for volume)	NR	NR	NR	Hgb 12.1	Hgb 8.9	mortality, 72 hrs MI, 72 hrs	0 0	0 0	NS NS

Table 4. Observational studies of red blood cell transfusion for anemia in patients with CHD/CHF

Study ID	Patient Population	Design	Number	Transfusion Rate (%)	Rate of Major Bleeding (%)	Mean/Median Nadir Hct, Transfused Cohort (%)	Outcome	Crude % Trans-fused	Crude % Not Trans-fused	HR/OR adj
Percutaneous Coronary Intervention										
Chase, 2008[48]	PCI, all indications (64.9% ACS, STEMI rate NR) 4 centers in British Columbia, 1999-2005	Observational cohort, registry	38872	2.5	NR	NR	mortality, 30 d mortality, 1 yr	12.6 22.9	1.3 3.2	4.01 (3.08-5.22) 3.58 (2.94-4.36)
		Propensity score matched cohort	914	50			mortality, 30 d propensity matched mortality, 1 yr propensity matched	7.7 19.3	2 5.7	3.9 (1.89-8.0) 3.38 (2.22-5.14)
Doyle, 2008[47]	PCI, all indications (65.4% urgent/ emergent; STEMI rate NR) Mayo Clinic, 1994-2005	Observational cohort, administrative database	17901	6.7	4.8 (overall) 38 (transfused cohort)	NR	mortality, 30 d 1-2 units ≥3 units mortality, 1 yr	 24.6	 13	 8.9 (6.3-12.6) 18.1 (13.7-24.0)
Jani, 2007[49]	PCI, MI within prior 7 d (STEMI rate NR) anemia pre-PCI multicenter Michigan (BCBS),1997-2004	Observational cohort, registry	4623	22.3	NR	Hgb 10.0 (overall) transfused cohort NR but 87.8% Hgb <10	mortality, in-hospital MACE, in-hospital stroke/TIA	14.52 20.81 2.42	3.01 5.13 0.84	2.02 (1.47-2.79)
		Propensity score matched cohort	1196				mortality, in-hospital, propensity matched stroke/TIA, propensity matched	12.71 2.01	7.36 2.01	
Jolicoeur, 2009[50]	PCI, STEMI multicenter multinational, 2004-2006	Observational cohort, post-hoc analysis of APEX-AMI trial	5532	3.9	81.7 (transfused cohort)	Hgb 8.7	mortality, 90 d CV death, 90 d MI, 90 d CHF, 90 d CVA, 90 d	26 16.7 7.8 15.2 4.9	4.1 3.5 2.6 4.4 1	2.16 (1.20-3.88)
Kim, 2007[45]	PCI, all indications (ACS/STEMI rates NR) Hct drop >10% single institution 2000-2002	Observational case-control, registry	146 txfused pts, 292 controls	NR	100	24	mortality, in hospital mortality, 1 yr	11 26	3.1 10.3	p=0.0008 2.42 (1.32-4.46)
Kinnaird, 2003[44]	PCI, all indications (2.4% AMI, 67.2% unstable angina) single center US, 1991-2000	Observational cohort, registry	10974	5.4	5.4 (overall) 41.8 (transfused cohort)	24.7	mortality, in-hospital major bleeding no bleeding mortality, 1 yr major bleeding no bleeding	9.2 10.6 10.3 28.4 22.7 36.8	0.6 5.1 0.4 5.4 13.6 5	2.0 (1.1-3.2) 1.9 (1.4-2.5)
Maluenda, 2009[38]	PCI, all indications (ACS/STEMI rates NR) Hct ≤ 27% post-PCI single US institution 2003-2007	Observational cohort, registry	379	53.5	NR	24.1	death/MI, 1 yr	26.6	17.2	1.1 (0.7-1.6)

Study ID	Patient Population	Design	Number	Transfusion Rate (%)	Rate of Major Bleeding (%)	Mean/Median Nadir Hct, Transfused Cohort (%)	Outcome	Crude % Trans-fused	Crude % Not Trans-fused	HR/OR adj
Maluenda, 2009[36]	PCI, all indications (ACS/STEMI rates NR) Hct 24-30% post-PCI single US institution 2003-2007	Observational cohort, registry	625	30.2	9.6 (overall) 22.8 (transfused cohort)	26.5	death/MI, 30 d mortality, 30 d death/MI, 1 yr mortality, 1 yr	15.8 15.3 28.6 27.5	7.1 6.9 19.6 18.5	1.4 (0.8-2.5) 1.4 (0.9-2.0)
	subgroup analysis, MI/shock		202				death/MI, 30 d death/MI, 1 yr			1.3 (0.6-2.8) 0.9 (0.5-1.9)
	subgroup analysis, major bleeding		60		 100 (transfused cohort)		death/MI, 30 d death/MI, 1 yr	14 27.9	11.8 17.6	NS NS
Maluenda, 2009[37]	PCI, all indications (ACS/STEMI rates NR) normal Hct pre-PCI w/ major bleeding single US institution 2003-2007	Observational cohort, registry	3738	1.6	100 (transfused cohort)	NR	death/MI, 1 yr	16.4	3.7	1.93 (0.81-4.17)
Nikolsky, 2009[51]	PCI, AMI (88% STEMI) multicenter multinational, 1997-1999	Observational cohort, post-hoc analysis of CADILLAC trial	2082	4	40.2 (transfused cohort)	29.9 (53.7% Hct >30)	mortality, 30 d mortality, 1 yr MACE, 1 yr	13.4 23.9 41	 3.4 16.6	4.71 (1.97-11.26) 3.16 (1.66-6.03)
	subgroup analysis, txfusion for major bleeding vs no bleed		33 major bleeding			28.5 (bleeding) \	mortality, 30 d mortality, 1 yr mortality, 30 d	6.1 19 18.4		
			49 no bleed			30.4 (no evident bleeding)	mortality, 1 yr	29.3		
Yatskar, 2007[46]	PCI, all indications (41.9% urgent/ emergent; 24.0% AMI, STEMI rate NR) multicenter US, 1997-1999, 2001-2002	Observational cohort, registry	6656	1.8	1.8 (overall) 100 (transfused cohort)	NR	mortality, in-hospital mortality, 1 yr	9.9 18.8	1.2 4.7	3.59 (1.66-7.77) 1.65 (1.01-2.70)
Acute Coronary Syndrome/Acute MI										
Aggarwal, 2011[60]	ACS (40% STEMI, 61% PCI) single center US, 2002-2006	Observational case-control	103 txfused pts, 185 controls	NA	42 (transfused cohort)	26.2	mortality, in-hospital non-specific anemia overt bleeding	19.4	10.8	1.8 (0.6-5.1) 0.9 (0.3-2.4) 2.7 (0.7-10.0)

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Study ID	Patient Population	Design	Number	Transfusion Rate (%)	Rate of Major Bleeding (%)	Mean/Median Nadir Hct, Transfused Cohort (%)	Outcome	Crude % Trans-fused	Crude % Not Trans-fused	HR/OR adj
Alexander, 2008[55]	High-risk NSTE-ACS (61.2% PCI) multicenter US, 2004-2005	Observational cohort, registry (CRUSADE)	44242	10.4 (0.9%-79.2% lowest-highest quartile)	11.9 (overall; not given for transfused cohort)	25.7	mortality, in-hospital			
							Hct ≤ 24	11.8	15	0.67 (0.45-1.02)
							Hct 24.1-27	9.3	9.1	1.01 (0.79-1.30)
							Hct 27.1-30	7.3	6.1	1.18 (0.92-1.50)
							Hct >30	12.2	2.6	3.47 (2.30-5.23)
							death/MI, in-hospital			
							Hct ≤ 24	15.9	17.4	
							Hct 24.1-27	13.1	12.5	
							Hct 27.1-30	10.6	8.3	
							Hct >30	18.2	4	
							CHF, in-hospital			
							Hct ≤ 24	17.4	9.4	
							Hct 24.1-27	19.1	12.8	
							Hct 27.1-30	16.4	11.5	
							Hct >30	17.9	5.3	
Aronson, 2008[58]	AMI (81.8% STEMI; 27.8% PCI, 23.2% lytics) single Israeli institution, 2000-2006	Observational cohort, registry	2358	8.1	NR	Hgb 8.8	mortality, 6 mo, all	28.1	11.7	1.9 (p=0.001)
							Hgb ≤ 8			0.13 (CI 0.03-0.65)
							Hgb > 8			2.2 (CI 1.5-3.3)
							death/MI/CHF, 6 mo, all	41.1	19.6	1.4 (p=0.05)
							Hgb ≤ 8			0.24 (CI 0.07-0.75)
							Hgb > 8			1.6 (CI 1.1-2.2)
Rao, 2004[52]	NSTE-ACS (PCI rate NR) multicenter multinational, 1994-1999	Observational cohort, post-hoc meta-analysis of 3 RCTs (GUSTO IIB, PURSUIT, PARAGON B)	24112	10	NR (tracked bleeding and adjusted for but didn't report)	29	mortality, 30 d	8	3.1	3.94 (3.26-4.75)
							Hct 20			1.59 (0.95-2.66)
							Hct 25			1.13 (0.70-1.82)
							Hct 30			168.6 (7.5-3797.7)
							Hct 35			291.6 (10.3-8273.8)
							death/MI, 30 d	29.2	10	2.92 (2.55-3.35)
Sabatine, 2005[57]	ACS (63.7% STEMI, 34.8% revascularized), multicenter multinational, 1989-2001	Observational cohort, post-hoc meta-analysis of 16 TIMI trials	39922	3.9 (overall) 4.6 (STEMI) 2.7 (NSTE-ACS)	80 (transfused cohort)	NR	CV mortality, 30d, STEMI			
							Hgb < 12			0.42 (CI 0.20-0.89)
							Hgb ≥ 12			1.42 (CI0.94-2.17)
							MACE, 30 d, NSTE-ACS			1.54 (CI 1.14-2.09)
Shishehbor, 2009[56]	STEMI (18.5% PCI) multicenter multinational, 1994-1995	Observational cohort, post-hoc analysis of GUSTO IIB trial	3575	8.6	97 (transfused cohort) 0.6 (non-transfused)	25.1	mortality, 30 d	13.7	5.5	3.89 (2.66-5.68)
							MI, 30 d			3.44, p<0.001
							mortality, 6 mo	19.7	6.9	3.63 (2.67-4.95)
							MI, 6 mo			2.69, p<0.001
							mortality , 1 yr	21.8	8.7	3.03 (2.25-4.08)
		Propensity score matched cohort	316				mortality, 30 d, propensity matched			5.44 (3.21-9.22)
							mortality, 6 mo, propensity matched			4.81 (3.00-7.71)
							mortality, 1 yr, propensity matched			3.10 (2.18-4.40)

Study ID	Patient Population	Design	Number	Transfusion Rate (%)	Rate of Major Bleeding (%)	Mean/Median Nadir Hct, Transfused Cohort (%)	Outcome	Crude % Trans-fused	Crude % Not Trans-fused	HR/OR adj
Singla, 2007[54]	Suspected NSTE-ACS (PCI rate NR) initial Hgb ≤11.5 g/dl single VA hospital, 2001-2005	Observational cohort, registry	370	29.7	NR	NR	mortality, 30 d death/MI, 30 d recurrent MI, 30 d	26.4 33.6 7.3	11.2 14.2 3.5	 2.57 (1.41-4.69)
Wu, 2001[59]	AMI (28.3% STEMI, 24.9% cath, 10.3% PCI) all ≥65 yo multicenter US, 1994-1995	Observational cohort, administrative database	78974	4.7	0 (exclusion criterion)	NR	mortality, 30 d admission Hct 5-25 Hct 24.1-27 Hct 27.1-30 Hct 30.1-33 Hct 33.1-36 Hct 36.1-39 Hct >39			 0.22 (0.11-0.45) 0.48 (0.34-0.69) 0.60 (0.47-0.76) 0.69 (0.53-0.89) 1.13 (0.89-1.44) 1.38 (1.05-1.80) 1.46 (1.18-1.81)
Yang, 2005[53]	High-risk NSTE-ACS (PCI rate NR) multicenter US, 2001-2004	Observational cohort, registry (CRUSADE)	85111 (overall), 74,271 non-CABG	14.9 (overall), 10.3 (non-CABG)	NR	26	mortality, in-hospital death/MI, in-hospital	11.5 13.4	3.8 5.8	1.67 (1.48-1.88) 1.44 (1.30-1.60)
Congestive Heart Failure										
Garty, 2009[61]	CHF, 1° admitting diagnosis multicenter Israel, 2003	Observational cohort, survey	2335	7.1	NR	Hgb 8.7	mortality, in-hospital mortality, 30 d mortality, 1 yr mortality, 4 yrs	10.8 11 39.6 69.5	5.2 8.5 28.5 59.5	0.48 (0.21-1.11) 0.29 (0.13-0.64) 0.74 (0.50-1.09) 0.86 (0.64-1.14)
		Propensity score matched cohort	206				mortality, in hospital, propensity matched mortality, 30 d, propensity matched mortality, 1 yr, propensity matched mortality, 4 yrs propensity matched	8.7 9.7 38.8 72.8	14.6 18.4 42.7 76.7	
Kao, 2011[62]	CHF, 1° admitting diagnosis California hospitals, 2000-2006	Observational cohort, administrative database	596456 `	6.2	NR	NR; 27.1% had ICD-9 dx of anemia	mortality, in-hospital anemic non-anemic	8.37 7.09 17.46	3.96 4.43 3.81	3.8 (3.5-4.1) 1.7 (1.6-1.8)
Critical Illness										
Hebert, 1997[71]	ICU, 1° or 2° cardiovascular diagnosis, multicenter Canada, 1993	Observational cohort	1365	24.2	NR	Hgb 10.7	mortality, ICU Hgb < 9.5 Hgb < 9.5 + APACHE >20 + txfusion ≤6 units 1-3 units 4-6 units 7-10 units >10 units	28.8 31.2 34.3	17.5 27.4 55	 0.61 (0.37-1.00) 0.49 (0.23-1.03) 0.96 (0.39-2.45) 0.64 (0.24-1.69)

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Study ID	Patient Population	Design	Number	Transfusion Rate (%)	Rate of Major Bleeding (%)	Mean/Median Nadir Hct, Transfused Cohort (%)	Outcome	Crude % Trans-fused	Crude % Not Trans-fused	HR/OR adj
Surgery										
Bursi, 2009[41]	Vascular surgery, major elective (hx CAD 26.7%, hx CHF 22.0%) single center Italy, date NR	Observational cohort	359	26.5	8.6	Hgb 9.2	mortality, 30 d	16.8	1.5	5.38 (1.45-20.0)
							Hgb 7-9			0.64 (0.13-3.18)
							Hgb ≥ 9			18.70 (3.12-112.1)
							MI, 30 d	21.1	6.8	2.23 (0.98-5.09)
							death/MI, 30 d	27.4	7.2	3.07 (1.43-6.59)
							Hgb 7-9			0.83 (0.26-2.60)
							Hgb ≥ 9			4.53 (1.69-12.12)
							mortality, 16.3 mo			4.02 (2.24-7.87)
							MI, 16.3 mo			2.02 (1.15-3.57)
							death/MI, 16.3 mo			2.67 (1.71-4.18)
Carson, 1998[68]	Hip fracture surgery, CV disease subgroup all ≥ 60 yo multicenter US, 1983-1993	Observational cohort	3783	42% (overall); NR for CV disease pts	NR		mortality, 30 d			1.07 (0.75-1.52)
							Hgb 7-7.9			NS
							Hgb 8-9.9			NS
							Hgb ≥ 10			NS
Glance, 2011[70]	Noncardiac surgery, non-emergent, cardiac disease, Hct <30%	Observational cohort, National Surgical Quality Improvement Program registry	10,100 (overall); cardiac disease subgroup NR	21.4 (overall)	NR	Baseline Hct 27.1	mortality, 30 d			NS

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SUMMARY AND DISCUSSION

Anemia commonly complicates heart disease. Despite its association with poor outcomes and a biologically plausible argument supporting anemia correction, we found little evidence that use of ESAs or blood transfusions improve health outcomes in patients with heart disease. A limited evidence base consisting mainly of one trial suggests correction of iron deficiency in patients with symptomatic heart failure improves exercise tolerance and quality of life.

By far, the largest number of trials has examined ESAs in patients with heart failure, and most of these included patients with systolic heart failure. Though a grouped analysis of these mainly small, single-center studies shows some initial promise that ESAs may improve exercise tolerance, the evidence base is limited by inconsistent findings across trials, with some finding benefit and others finding no effect. There are a number of possible reasons for the discrepant results including differences in patient populations, treatment dosing and formulation, and outcomes examined. For example, the largest of the trials[19] enrolled slightly older patients and achieved a slightly smaller hemoglobin improvement with ESA use than did other trials finding a benefit. However, our analyses suggest that the clearest contributor to the discrepant findings was the quality of the individual studies themselves, with the poorer quality studies generally supporting a greater benefit from ESAs and the more rigorous trials finding a neutral effect.

Our review differs from a similar recent review of ESAs[72] for three main reasons: 1) we evaluated studies in both heart failure and CHD patients, though most studies focused on heart failure; 2) we conducted additional analyses investigating the impact of study quality on the overall results; and 3) we included studies of patients with advanced kidney disease if there were separately reported data for the subgroup of patients with comorbid heart disease. We felt the latter difference was justifiable because kidney disease is common among patients with heart disease, and we felt these data were important in understanding the potential benefits and harms in this population.

Though there were few excess harms reported in the smaller ESA trials of heart failure patients, the excess risk associated with ESAs in CKD populations[73] and cancer populations[74] is of concern. Moreover, our own analysis suggests the potential for serious harms associated with aggressive ESA use among the large proportion of patients with heart disease and comorbid CKD. On the other hand, these data may not apply to patients with symptomatic heart failure and reduced systolic function, and they do not elucidate the role of less aggressive ESA use, leaving us with very limited evidence with which to truly evaluate the balance of benefits and harms of ESAs in patients with heart disease. While the large RED-HF trial should more definitively establish the balance of benefits and harms of ESA use in patients with heart failure, the current uncertainty of benefit and the possibility of significant harms suggest widespread use of ESAs in patients with heart disease may be premature. For patients with comorbid chronic kidney disease, the recent cautious FDA recommendations seem reasonable, as they acknowledge the uncertainty of the role of ESA use and suggest that, if they are to be used at all, patients should have Hgb of at least < 10 g/dL.[75]

There is good evidence from one methodologically sound, large multicenter trial that intravenous iron carboxymaltose improves exercise tolerance, quality of life, and exercise duration in patients with chronic, stable systolic heart failure.[33] These results are most applicable to iron deficient patients with NYHA class III heart failure; relatively few patients with milder degrees of heart

failure were included. It also may be premature to apply these results to patients with more subtle evidence of relative iron deficiency. Biologic plausibility and test of concept studies suggest iron replacement could play a role in improving symptoms of heart failure even when, theoretically, iron stores are adequate because symptoms may be related to a functional misuse of iron rather than absolute deficiency.[4] Nevertheless, though the criteria used to define iron deficiency were fairly broad, most patients enrolled in the FAIR HF trial had evidence of more advanced iron deficiency and limited iron stores. Finally, though these results are encouraging and have the potential to influence treatment of heart failure, the long-term health and cost implications of this are uncertain, and harms have not been more widely assessed.

Despite a paucity of data to support this contention, for decades, many physicians adhered to the "10/30 rule," transfusing patients with hemoglobin under 10 g/dL and hematocrit under 30 percent for perceived safety reasons.[76] In recent years, the recognition of immunomodulatory effects from leukocyte contamination and changes in RBCs with storage that impair oxygen exchange have led to increased scrutiny of RBC transfusion practice, culminating in the TRICC trial. After its publication, there was widespread adoption of more restrictive transfusion standards. However, because oxygen extraction is already maximized in the coronary circulation, concern has remained that patients with fixed coronary stenoses, who cannot increase blood flow to enhance oxygen delivery, will be more susceptible to ischemia in the setting of anemia and, therefore, should generally be transfused to a higher target than the general population. Often, this continues to be a hemoglobin of 10 g/dL.

In the perioperative literature, accumulating evidence from randomized controlled trials supports use of a conservative hemoglobin trigger no higher than 8 g/dL among heart disease patients in the intra- and postoperative setting. The results of the FOCUS trial, by far the largest study to investigate transfusion use in heart disease with over 2,000 enrolled patients, have thus far been released only in abstract form, but it found no difference in mortality, ability to walk across a room unaided, falls, or readmissions with transfusion at a threshold of 8 versus 10 g/dL.[69] While they have some methodological weaknesses, four randomized controlled trials in cardiac surgery, one additional study in hip fracture, and one trial in vascular surgery all were consistent in finding no difference in mortality or other health outcomes with more restrictive use of transfusion.[63-68] No similar trial has been conducted in the general surgery population.

The data from observational studies in the perioperative setting are congruent with the results from randomized controlled trials. In non-cardiac surgery cohorts, transfusion did not appear to offer any protection.[41, 68, 70] We chose to exclude cardiac surgery observational cohorts from our review; nevertheless, in 13 out of 14 such studies aggregated in two prior reviews, the primary results suggested increased risk of adverse clinical events, and the fourteenth was neutral.[77, 78]

No definitive conclusions about best transfusion practice in heart disease outside of the perioperative setting can be drawn from the evidence from randomized controlled trials. The TRICC subgroup analysis found no significant difference in survival between restrictive and liberal transfusion groups, but mortality was slightly lower in the liberally transfused group, a trend opposite of that noted in the overall population or any other studied subgroup.[39] In any case, it is difficult to extrapolate from this critically ill population, where the mean APACHE II score was 23, most patients were mechanically ventilated, and many had noncardiac primary diagnoses. Meanwhile, the CRIT trial suggests that transfusion leads to heart failure

exacerbations in ACS patients but was too small to properly evaluate for any effect on survival or recurrent myocardial ischemia.[40] Results from the in-progress MINT trial may shed some light, but it is also small and designed only as a pilot, with the plan for a large scale follow-up trial.

Despite the limitations inherent to their design, several themes emerged in our review of the observational data that can potentially help to guide practice: 1) the evidence strongly suggests that transfusion has no benefit and may be harmful in patients with heart disease and hemoglobin > 10 g/dL; 2) outcomes do not appear to improve with transfusion in non-ST-elevation ACS patients with hemoglobin levels down to the 8 – 9 g/dL range; 3) transfusion is consistently associated with higher mortality risk in the unselected PCI population, across multiple studies with mean nadir hemoglobins of 8 – 9 g/dL; and 4) the elevated risk in the PCI population is seen in patients with anemia related or unrelated to bleeding but may be higher in the non-bleeding anemic population. There is no evidence to guide decision-making in the stable coronary disease population, and the two studies in decompensated heart failure have conflicting results.

One of the larger questions remains: at what hemoglobin threshold does transfusion become protective in ACS patients (i.e., the risks of anemia exceed the hazards of transfusion)? Wu et al. found that transfused AMI patients had lower adjusted mortality than nontransfused patients at any hemoglobin level under 10-11 g/dL,[59] and Sabatine et al. noted that STEMI patients appeared to have lower cardiovascular mortality if they received PRBCs at a hemoglobin below a threshold of 12 g/dL.[57] In contrast, Sabatine found increased risk of major adverse cardiac events in NSTE-ACS patients who received transfusion at any hemoglobin level; and Rao et al. found no benefit to transfusion in NSTE-ACS down to hemoglobin of ~7 g/dL, and a substantially increased risk of death with transfusion above hemoglobin of 10 g/dL.[52] One other study found a significantly reduced risk of death at six months in AMI patients transfused at hemoglobin < 8 g/dL,[58] and two noted non-significant trends toward improved survival in NSTE-ACS with transfusion at a hemoglobin below 8 – 9 g/dL.[54, 55] All three studies found higher adjusted mortality in patients transfused above the 8 – 9 g/dL hemoglobin threshold.

Why might the identified hemoglobin thresholds differ across studies? In particular, can we explain the outlier findings by Wu and Sabatine that transfusion may be beneficial above a hemoglobin of 10 g/dL? The patients in the Wu study were generally older than in other trials, with potentially greater comorbidities (having not been screened for a clinical trial), and had lower rates of exposure to red blood cells. In contrast to many of the other studies, the Wu study relied on claims data with limited granularity. For example, the study grouped patients according to baseline anemia and did not examine how the development of anemia during hospitalization or the timing of transfusion affected outcomes. Though they excluded patients with major bleeding, it is almost certain that mean hemoglobin fell over the course of hospitalization; thus, their results, stratified by admission hemoglobin, would seem to overestimate any potential nadir hemoglobin threshold below which transfusion may be beneficial. Wu also excluded patients who underwent CABG, and fewer patients in the Wu study had PCI or reperfusion therapy. In theory, revascularized/reperfused patients may be more tolerant of severe anemia than their conservatively managed counterparts, since they can increase myocardial oxygen delivery through augmentation of blood flow without the need for PRBCs.

The Sabatine study results suggest that STEMI patients, who suffer abrupt and complete occlusion of a coronary artery, may have a lower tolerance for anemia than NSTE-ACS patients

and thus benefit more from transfusion, even to a hemoglobin of 12 g/dL. However, like Wu et al., they used admission hemoglobin in their study, so their results likely inflate the threshold hemoglobin nadir. Moreover, several other studies that included STEMI patients primarily or exclusively did not find any evidence of benefit from transfusion.[50, 51, 56, 58] PCI rates were generally higher in these studies, however, which again might explain the difference.

As noted, aside from inconsistency of results, the major limitation of this body of observational studies is selection bias, namely, confounding by indication.[79] In other words, because of the observational nature of these studies, the decision to transfuse patients was based on clinical judgment which, in turn, would be naturally influenced by severity of illness, symptoms, and observation of bleeding. Indeed, the studies show that the groups who were transfused more aggressively were more severely ill. Additionally, bleeding rates did vary substantially across studies but were inconsistently reported; one might reasonably expect that the risk-benefit balance of red blood cell transfusion would change in the setting of bleeding compared to stable blood volume. Despite, in some cases, the very careful propensity adjustment, the possibility of residual confounding remains and renders this a fairly tenuous evidence base.

Perhaps in part because of the conflicting results, there is continued widespread variation in RBC transfusion practices, highlighting the need for more definitive guidance from large controlled clinical trials examining the comparative benefits of liberal and conservative transfusion strategies in patients with heart disease. Of note, the CRIT trial could not enroll their goal of 92 patients in over six years of active recruitment; it is not clear why there were difficulties with recruitment, but this raises concerns about the feasibility of a large scale trial. There is increasing evidence as well that freshly collected units may be safer and more effective than PRBCs stored for longer periods;[45, 80] future studies should also look specifically at the comparative benefits/risks of transfusion of fresh RBCs in the heart disease population.

CLINICAL APPLICATIONS

Clinicians encounter anemia in many different types of patients with heart disease, and may need to understand how the overall evidence base for anemia treatment pertains to the patient in front of them. Here we summarize how the data presented previously might apply to different common clinical scenarios:

1. Outpatient with stable NYHA class III congestive heart failure, ferritin of 50 µg/dL and a Hgb of 10g/dL

   Intravenous iron supplementation could be considered to improve symptoms, but there is no consistent good-quality evidence at this time to support the use of ESAs or blood transfusions in this patient. The use of iron could even be considered if this patient had a normal hemoglobin. Of note, the data supporting IV iron comes largely from one trial, albeit a well-conducted one, that reported only short-term quality of life and exercise tolerance outcomes.[33] Furthermore, the use of IV iron would be unsupported if this patient had milder heart failure symptoms or if the ferritin were normal given that there were few such patients included in the trial. Though a number of trials have examined the use of ESAs for patients similar to this, they do not convincingly show a consistent benefit and there may be important harms, especially if this patient had advanced kidney disease. A larger ongoing trial of

ESA use should better clarify their role in this type of patient. There are no trials of blood transfusions applicable to this patient.

2. Outpatient with stable NYHA class III congestive heart failure, end stage renal disease on hemodialysis, and Hgb 9 g/dL

   The decision to use ESAs would be based largely on this patient's comorbid kidney disease rather than the heart disease itself. The once common practice of using ESAs to raise hemoglobin in patients with advanced chronic kidney disease has been undermined by recent large-scale trials, and new FDA recommendations suggest use of ESAs only for patients with Hgb < 10 g/dL, and with as low a dose necessary to obviate blood transfusion. Three of these trials included substantial proportions of heart disease patients and found no benefit and possible serious harms from ESAs titrated to normal or near-normal hemoglobin.[13, 26, 30] The benefit of titrating ESAs to lower hemoglobin targets in patients with heart disease and advanced kidney disease remains unexplored. There are no studies of iron supplementation or blood transfusion that would apply to this patient.

3. Hospitalized patient with decompensated heart failure and Hgb 9 g/dL

   There is no data to guide the use of ESAs or iron in this patient. It is noteworthy that nearly all of the ESA and iron trials reviewed would have excluded patients like this with decompensated disease. Two observational studies of blood transfusions in patients hospitalized with CHF found conflicting results and do not convincingly support routine transfusion of patients like this, though the evidence base is very limited.

4. Patient with acute coronary syndrome and Hgb 9 g/dL

   There is very little good direct evidence to guide whether or not to administer blood transfusions in this patient. One older trial of critically ill patients with cardiovascular disease found that patients transfused more aggressively (Hgb threshold 10 g/dL) did no better than those transfused less aggressively (threshold 7 g/dL). A small recent trial suggested a more aggressive strategy may actually be harmful in patients with acute coronary syndrome. Many observational studies in patients with ACS have found conflicting results, though the majority of them suggest increased harms associated with transfusions certainly above Hgb 10g/dL and in some cases, above Hgb > 8 g/dL, especially in patients who have undergone PCI.

   No trials have evaluated iron in patients with ACS.

5. Outpatient with chronic stable angina and Hgb 8 g/dL

   There is no good evidence that directly applies to this patient. However, a large study of patients with ESRD and heart disease, many of whom had a history of angina, showed ESAs titrated to a normal hemoglobin did not reduce the incidence of angina requiring hospitalization and was associated with increased thrombotic events and higher mortality.[26] Though patients in this study also received IV iron, there are no studies of IV iron alone in patients with chronic stable angina, nor are there studies examining blood transfusions.

6. Patient admitted with a hip fracture awaiting surgery who has known, stable CHD and anemia with a Hgb of 9 g/dL

There is no evidence that transfusing such patients above a hemoglobin of 8 g/dL improves outcomes. Data from one large randomized controlled trial and a smaller pilot study found no benefit of transfusing patients to a target hemoglobin of 10 g/dL compared to 8 g/dL. There is no data which addresses the use of ESAs or iron in such patients.

LIMITATIONS

Because our review was focused on patient-centered health outcomes, we did not include physiologic surrogates of exercise tolerance such as Vo2 max. In excluding such outcomes, we could have missed evidence of benefit on proximal outcomes. The largest ESA trials by far are those of patients with advanced renal disease and comorbid heart disease. We felt it important to include these studies given the large proportion of heart disease patients with comorbid chronic kidney disease and the potential harms these studies underscore. However, we acknowledge the limited applicability of these results to many patients with heart failure. The inclusion of observational studies in our review of the efficacy of blood transfusions may risk overstating the depth of the evidence base when, in fact, there is little trial data to guide practice and the risk of bias in the observational studies is likely too high to make them a reliable source of evidence to guide decision-making. Nevertheless, we felt the inclusion of such studies would allow greater transparency of the types of studies that are, de facto, currently guiding practice.

FUTURE STUDIES

Ongoing studies such as RED-HF should be able to more clearly define whether or not there is a role for ESAs in the treatment of anemic heart failure patients. If the study results are positive, there may be a need for future studies comparing the relative benefits of ESAs and iron in heart failure patients. Given that most ESA studies were conducted in patients with systolic dysfunction but a large proportion of CHF patients have preserved systolic function, future studies should clarify the role of ESAs in patients with preserved systolic function. There should be more studies of anemic patients with ischemic heart disease. Future studies should better clarify the influence of chronic kidney disease on the effectiveness of various anemia treatments. Rather than the very high hemoglobin targets trials to date have examined in patients with advanced kidney disease, future studies may consider the value of more moderate hemoglobin targets given the remaining uncertainty for patients with moderate anemia. There is a pressing need for more trials examining the role of blood transfusions; treatment of patients with stable or decompensated heart failure, as well as patients with stable, asymptomatic or actively symptomatic ischemic heart disease, remains uncertain.

CONCLUSIONS

Anemia is common in patients with heart disease, but the evidence base to date does not convincingly support a role for ESAs for anemia correction. Iron treatment may help ameliorate symptoms over the short-term in patients with symptomatic heart failure. The role of blood transfusions remains understudied and unclear. Table 5 summarizes the evidence on the effectiveness of these therapies according to patient population and outcome.

Table 5. Summary of the Evidence for the Effects of ESAs, Iron and Blood Transfusions for Anemia, by Patient Population and Outcome

Treatment	Outcome	Effect*	GRADE Classification†	Comment
Stable CHF, and no worse than stage 3 CKD				
ESAs	Exercise tolerance and duration	(~)	Moderate	Inconsistent results and methodologic weaknesses in some studies limit the evidence base. Overall, studies with low risk of bias found no significant effect.
	Quality of life	(~)	Low	Infrequent reporting, inconsistent results, the variety of instruments used, and methodologic weaknesses in some studies greatly limit the evidence base.
	Mortality	(~)	Low	Based on mainly small, single center trials with limited power and low event rates.
	Hospitalizations	(~)	Low	Inconsistent results and methodologic weaknesses in some studies limit the evidence base. The two studies with low risk of bias found no significant effect.
	Harms including hypertension, cerebrovascular and thrombotic events	(~)	Low	Based on mainly small, single-center trials with low event rates.
Iron	Exercise tolerance and duration	(+)	Moderate/High	One well-conducted large multicenter trial and two smaller trials found benefit.
	Quality of life	(+)	Moderate/High	One well-conducted large multicenter trial and two smaller trials found benefit.
	Mortality	(~)/(+)	Low	The one large trial showed a trend towards benefit, but was, like the two smaller trials, not powered for this outcome.
	Cardiovascular events	(+)	Moderate	One large multicenter trial found benefit, but follow-up was relatively short.
	Serious harms	(~)	Moderate	Based on one large and two small trials.
Blood transfusions	All outcomes	(0)		No evidence.
Stable CHF, and stage 4 or 5 CKD				
ESAs	Exercise tolerance and duration	(0)		No evidence. Trials including subgroups of CHF patients did not report this outcome separately.
	Quality of life	(~)	Low	One large trial of heart disease patients including large subgroup of CHF patients, but subgroup specific data not available.
	Mortality	(–)	Moderate	Based on two large trials including large numbers with CHF; in one trial the increased risk of mortality was not significant; type and severity of CHF not reported.
	Cardiovascular events	(~)	High	Based on three large trials including large numbers with CHF; type and severity of CHF not reported.
	Venous thrombosis	(–)	Moderate	Based on two large trials including large numbers with CHF; type and severity of CHF not reported; effects of more moderate hemoglobin targets not tested.

Treatment	Outcome	Effect*	GRADE Classification†	Comment
	Hypertension, cerebrovascular events	(–)	Low	Based on one large trial including large numbers with CHF, but CHF subgroup data not separately reported for this outcome.
Iron	All outcomes	(0)		No evidence.
Blood transfusions	All outcomes	(0)		No evidence.
Decompensated CHF				
ESAs	All outcomes	(0)		No evidence.
Iron	All outcomes	(0)		No evidence.
Blood transfusions	Mortality	(–)	Very low	Two observational studies found conflicting results – one showed harm, one a possible benefit.
Stable CHD				
ESAs	Mortality	(–)	Low	One large trial of heart disease patients including large subgroup of CHD patients, but subgroup specific data not available. Patients with ESRD, unclear application to other populations.
	Quality of life	(~)	Low	One large trial of heart disease patients including large subgroup of CHD patients, but subgroup specific data not available. Patients with ESRD, unclear application to other populations.
	Venous thrombosis	(–)	Low	One large trial of heart disease patients including large subgroup of CHD patients, but subgroup specific data not available. Patients with ESRD, unclear application to other populations.
	All other outcomes	(0)		No evidence.
Iron	All outcomes	(0)		No evidence.
Blood transfusions	All outcomes	(0)		No evidence.
Acute coronary syndrome				
ESAs	All outcomes	(0)		No evidence.
Iron	All outcomes	(0)		No evidence.
Blood transfusions	Mortality	(~)	Moderate	Two RCTs, one with limited applicability to non ICU population, showed no benefit from transfusing above Hgb > 10 g/dL. Observational studies in PCI patients consistently showed no benefit and possible harm.
	Cardiovascular events	(~)	Low	Two RCTs found conflicting results: one found harm, a larger trial found no effect. Observational studies did not commonly report this as a separate outcome.
Non-cardiac surgery				
ESAs	All outcomes	(0)		No evidence.
Iron	All outcomes	(0)		No evidence.

Treatment	Outcome	Effect*	GRADE Classification†	Comment
Blood transfusions	Mortality	(~)	Low	One large RCT, but reported only in abstract form and only applicable to hip fracture patients.
Cardiac surgery				
ESAs	All outcomes	(0)		No evidence.
Iron	All outcomes	(0)		No evidence.
Blood transfusions	Mortality	(~)	Moderate	Two large and two small RCTs with some methodologic weaknesses.

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; ICU = intensive care unit; RCT = randomized controlled trial.

*Effect: (+) benefit; (–) harm; (~) mixed findings/no effect; (0) no evidence.

† 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 impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

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