Treatment of Anemia in Patients With Heart Disease: A Clinical Practice Guideline From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the treatment of anemia and iron deficiency in adult patients with heart disease.

Methods: This guideline is based on published literature in the English language on anemia and iron deficiency from 1947 to July 2012 that was identified using MEDLINE and the Cochrane Library. Literature was reassessed in April 2013, and additional studies were included. Outcomes evaluated for this guideline included mortality; hospitalization; exercise tolerance; quality of life; and cardiovascular events (defined as myocardial infarction, congestive heart failure exacerbation, arrhythmia, or cardiac death) and harms, including hypertension, venous thromboembolic events, and ischemic cerebrovascular events. The target audience for this guideline includes all clinicians, and the target patient population is anemic or iron-deficient adult patients with heart disease. This guideline grades the evidence and recommendations using the ACP's clinical practice guidelines grading system.

Recommendation 1: ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease. (Grade: weak recommendation; low-quality evidence)

Recommendation 2: ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure or coronary heart disease. (Grade: strong recommendation; moderate-quality evidence)

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Anemia is common in patients with heart disease. It is present in approximately one third of patients with congestive heart failure (CHF) and 10% to 20% of patients with coronary heart disease (CHD) (1–3). The cause of anemia in heart disease is not fully understood. Several factors probably contribute, including iron deficiency, comorbid chronic kidney disease, blunted erythropoietin production, hemodilution, aspirin-induced gastrointestinal blood loss, use of renin–angiotensin–aldosterone system blockers, cytokine-mediated inflammation (anemia of chronic disease), and gut malabsorption with consequent nutritional deficiency.

Anemia can worsen cardiac function and is associated with poor outcomes, including increased risk for hospitalization and death, decreased exercise capacity, and poor quality of life. However, it is not clear whether anemia directly and independently leads to these poor outcomes or whether it reflects more severe underlying illness (4–6). Treatments for anemia in patients with heart disease include erythropoiesis-stimulating agents (ESAs), red blood cell (RBC) transfusion, and iron replacement, although it is unclear whether these strategies improve outcomes.

The purpose of this American College of Physicians (ACP) guideline is to present current evidence on the treatment of anemia in patients with heart disease or iron deficiency. The target audience for this guideline includes all clinicians, and the target patient population is anemic or iron-deficient adult patients with heart disease. These recommendations are based on a background paper (7) and a systematic evidence review sponsored by the U.S. Department of Veterans Affairs (8).

METHODS

This guideline is based on a systematic evidence review and summary paper (7, 8) that addressed the following key questions related to the treatment of anemia in patients with heart disease:

1. In patients with CHF or CHD, what are the health benefits and harms of treating anemia with RBC transfusions?

Table 1. The American College of Physicians Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

2. In patients with CHF or CHD, what are the health benefits and harms of treating anemia with ESAs?

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

The systematic evidence review was conducted by the Evidence-based Synthesis Program Center at the Portland Veterans Affairs Medical Center. The literature search included English-language studies published from 1947 to July 2012 identified by using MEDLINE and the Cochrane Library. Additional information from the search came from systematic reviews; reference lists of pertinent studies, reviews, and editorials; by consulting experts and ClinicalTrials.gov; and by contacting pharmaceutical companies directly. In April 2013, the literature was reassessed, and 2 studies originally reported as in-progress were subsequently published and are included in this review (9, 10). Two reviewers assessed study quality according to a Cochrane protocol, and the Cochran Q test and I^2 statistic were used to assess statistical heterogeneity (11). The outcomes of interest included mortality (all-cause and disease-specific), hospitalization (all-cause and disease-specific), exercise tolerance (any metric, most commonly the New York Heart Association [NYHA] functional class and the 6-minute walk test), quality of life, and cardiovascular events (myocardial infarction [MI], exacerbation of heart failure, and need for revascularization). More details of the methods can be found in the article and full report (7, 8).

This guideline rates the evidence and recommendations by using ACP's guideline grading system (**Table 1**). Details of the ACP guideline development process can be found in the methods paper (12).

BENEFITS OF TREATMENT OF ANEMIA WITH RBC TRANSFUSIONS
Medical and Surgical Patients Combined
Mortality

Low-quality evidence from 6 studies of medical and noncardiac surgical patients (10, 13–17) assessed the effect of RBC transfusions to treat anemia in patients with heart disease and showed no mortality benefit for liberal RBC transfusion (hemoglobin level >10 g/dL) compared with restrictive RBC transfusion (hemoglobin level <10 g/dL) (relative risk [RR], 0.94 [95% CI, 0.61 to 1.42]; $I^2 =$ 16.8%). A recent randomized pilot trial of patients with unstable and stable CHD having cardiac catheterization found that a liberal transfusion strategy was associated with fewer major cardiac events and deaths. The group assigned to the restrictive transfusion strategy was older and had more patients with unstable CHD, but inclusion of these results in the meta-analysis still did not result in a statistically significant improvement in outcomes (10).

Cardiovascular Events

Low-quality evidence (13–17) showed that liberal RBC transfusions were associated with reduced cardiovascular events (RR, 0.64 [CI, 0.38 to 1.09]; $I^2 = 0.0\%$), although the data were not statistically significant.

Exercise Tolerance and Duration

Evidence was insufficient to determine the effect of RBC transfusions on exercise tolerance and duration.

Quality of Life

Evidence was insufficient to determine the effect of RBC transfusions on quality of life.

Nonsurgical Patients
Mortality

Low-quality evidence from 3 trials (16, 18, 19) showed no mortality benefit with a higher RBC transfusion threshold in nonsurgical patients with acute MI or known ischemic heart disease. One study of 838 euvolemic, nonbleeding, critically ill patients with hemoglobin levels less than 9 g/dL defined restrictive transfusion as a hemoglobin threshold of 7 g/dL with goal hemoglobin levels of 7 to 9 g/dL and a liberal strategy threshold as 10 g/dL with a goal of 10 to 12 g/dL (19). The study did not find any statistically significant difference between the 2 groups in hospital mortality or at 30 days after treatment. Post hoc subgroup analysis of patients with ischemic heart disease showed a nonstatistically significant higher mortality in the restrictive transfusion group (30-day mortality of 21.2% vs. 26.1% for liberal vs. restrictive strategies, respectively; $P = 0.38$) (16). The other study (18) of 45 patients with acute MI and hematocrit less than 30 defined conservative transfusion as a trigger of 24 with a target hematocrit of 24 to 27, whereas the liberal strategy was defined as a trigger of 30 with a target hematocrit of 30 to 33. This study showed that the liberal strategy was associated with a higher rate of the composite outcome of in-hospital death, recurrent MI, or new or worsening heart failure (38% vs. 13%; $P = 0.046$). Pooled data from the 2 studies showed no mortality benefit for aggressive compared with conservative RBC transfusion protocols (RR, 1.00 [CI, 0.68 to 1.46]; $I^2 = 0.0\%$).

Exercise Tolerance and Duration

Evidence was insufficient to determine the effect of RBC transfusions on exercise tolerance and duration.

Quality of Life

Evidence was insufficient to determine the effect of RBC transfusions on quality of life.

Surgical Patients
Mortality

Low-quality evidence from 3 studies (13, 14, 20) assessed short-term mortality in hip fracture and vascular surgery patients treated with liberal RBC transfusion (hemoglobin trigger, 10 g/dL) compared with restrictive transfusion (hemoglobin trigger, 8 to 9 g/dL) and found no difference in outcomes between the 2 treatments (RR, 1.35 [CI, 0.80 to 2.25]; $I^2 = 0.0\%$). Observational studies also failed to find a mortality benefit with aggressive transfusion (14, 21, 22).

Cardiovascular Events

Subgroup analysis in 1 study in vascular surgery patients found an increase in MI in patients transfused at a hemoglobin level of 9 g/dL or more compared with those transfused at hemoglobin levels ranging from 7 to 9 g/dL (21). Low-quality evidence from 2 studies (10, 15) did not find a statistically significant difference between liberal and restrictive RBC transfusion protocols in cardiovascular complications of MI (RR, 0.60 [CI, 0.34 to 1.03]; $I^2 = 0.0\%$).

Exercise Tolerance and Duration

Evidence was insufficient to determine the effect of RBC transfusions on exercise tolerance and duration.

Quality of Life

Evidence was insufficient to determine the effect of RBC transfusions on quality of life.

Observational Studies of RBC Transfusions in Different Populations of Patients With Heart Disease

Because few randomized, controlled trials assessed RBC transfusions for treatment of anemia in patients with heart disease, the evidence review also included observational studies in various patient populations. For more information on the descriptions, quality, and outcomes of the individual studies, refer to the background evidence review (8).

Percutaneous Coronary Intervention

Nine observational studies (23–33) evaluated blood transfusion in patients having percutaneous coronary intervention. The mean nadir hemoglobin levels across the studies were 8 to 9 g/dL. Overall, most studies showed that transfusion was associated with a higher mortality risk in the percutaneous coronary intervention population and suggested that this risk may be higher in nonbleeding anemic patients.

The Acute Coronary Syndrome or MI

Twelve observational studies (25, 26, 32, 34–43) evaluated transfusion in patients with the acute coronary syndrome or MI. Overall, the data suggested that transfusion provides no benefit and may harm patients with heart disease and hemoglobin levels greater than 10 g/dL. Furthermore, patients with non–ST-segment elevation MI and hemoglobin levels ranging from 8 to 9 g/dL also do not have improved outcomes with transfusions.

Heart Failure

Evidence from 2 observational studies (44, 45) that assessed transfusion in patients with acute decompensated heart failure reported conflicting results on mortality.

HARMS OF TREATMENT OF ANEMIA WITH RBC TRANSFUSIONS

Adverse events potentially associated with RBC transfusions have been described in other patient populations and include CHF, fever, and transfusion-related acute lung injury. Reporting of harms for RBC transfusions for anemic patients with heart disease was sparse. No trials reported excess adverse events for liberal compared with restrictive transfusion.

BENEFITS OF TREATMENT OF ANEMIA WITH ESAs

Overall evidence from 16 randomized, controlled trials (9, 46–61) evaluating the effect of ESAs in patients with heart disease did not show that ESA use improved health outcomes (**Table 2**). The baseline hemoglobin levels for study patients ranged from 9 to 10 g/dL.

Mortality

High-quality evidence showed that ESA treatment did not improve mortality in anemic patients with stable CHF. Pooled data from 11 studies of patients with CHF or CHD (hemoglobin target levels, 12 to 15 g/dL) suggested an increased risk for mortality (RR, 1.07 [CI, 0.98 to 1.16]; $I^2 = 0.0\%$) for patients receiving ESA treatment compared with control patients (9, 46, 49, 50, 53–57, 60, 62).

Cardiovascular Events

High-quality evidence showed that ESAs do not affect cardiovascular events in patients with stable CHF. Pooled data from 7 studies (reported in 8 publications) (47, 48, 54–57, 60, 61) showed no difference in the risk for cardiovascular events when comparing ESA treatment with control (RR, 0.94 [CI, 0.82 to 1.08]; $I^2 = 41.5\%$). Hemoglobin target levels ranged from 9.0 to 15.0 g/dL in the studies.

Exercise Tolerance and Duration

Moderate-quality evidence showed that ESA treatment had no effect on exercise tolerance and duration in patients with stable CHF. Pooled data from 9 studies (46, 49, 50,

Table 2. **Evidence for the Effects of RBC Transfusions, ESAs and IV Iron for the Treatment of Anemia in Patients With Heart Disease**

Treatment	Patient Population	Outcome	Effect*	Data	Quality of Evidence
RBC transfusions	Stable CHD (all patients)	Mortality	(~)	RR, 0.86 (95% CI, 0.46 to 1.62)	Low
		Cardiovascular events	(~)	RR, 0.60 (CI, 0.34 to 1.03)	Low
	ACS	Mortality	(~)	RR, 0.23 (CI, 0.05 to 1.02)	Low
		Cardiovascular events	(~)	RR, 0.70 (CI, 0.24 to 2.07)	Low
	Noncardiac surgery	Mortality	(~)	RR, 1.44 (CI, 0.81 to 2.54)	Low
		Cardiovascular events	(~)	RR, 0.52 (CI, 0.27 to 1.01)	Low
ESAs	Stable CHF	Mortality	(~)	RR, 1.07 (CI, 0.98 to 1.16)	High
		Cardiovascular events	(~)	RR, 0.94 (CI, 0.82 to 1.08)	High
		Quality of life	(~)	No consistent differences	Moderate
		Exercise tolerance and duration	(~)	Mean difference in NYHA, −0.77 (CI, −1.21 to –0.32)	Moderate
		Hospitalizations	(~)	RR, 0.97 (CI, 0.87 to 1.10)	High
		Harms, including hypertension and cerebrovascular and thrombotic events	(−)	Hypertension: RR, 1.20 (CI, 0.90 to 1.59) Ischemic stroke: RR, 1.33 (CI, 0.93 to 1.89) VTE: RR, 1.36 (CI, 1.17 to 1.58)	Moderate
	Stable CHD†	Mortality	(−)	Increased mortality	Low
		Cardiovascular events	(~)	No effect	Low
		Quality of life	(~)	No effect	Low
		Venous thrombosis	(−)	Increased risk for venous thrombosis	Low
IV iron	Stable CHF	Mortality	(~)	NA	Insufficient
		Cardiovascular events	(+)	27.6% vs. 50.2% (P = 0.01)	Low
		Exercise tolerance and duration	(+)	Improvements in NYHA class and 6-min walk test	Moderate
		Quality of life	(+)	Improvement on various scales	Moderate
		Serious harms	(~)	No differences, although harms were sparsely reported	Moderate

ACS = acute coronary syndrome; CHD = coronary heart disease; CHF = congestive heart failure; ESA = erythropoiesis-stimulating agent; IV = intravenous; NA = not applicable; NYHA = New York Heart Association; RBC = red blood cell; RR = relative risk; VTE = venous thromboembolism.
*Effect: (+) indicates that treatment provided benefit; (−) indicates that treatment resulted in harm; (~) indicates mixed findings or no effect.
† Patients included in these studies had advanced kidney disease and/or end-stage renal disease, so the application to other patient populations is unclear.

52, 53, 55–57, 59) showed that treatment with ESAs in patients with CHF (hemoglobin target levels, 12.0 to 15.0 g/dL) resulted in improved NYHA functional class scores compared with control patients (mean difference, −0.77 [CI, −1.12 to −0.32]; I^2 = 96%). However, the results were generally inconsistent and the studies were highly heterogeneous. Limiting the analysis to the 4 methodologically rigorous studies (50, 53, 56, 57) showed no statistically significant difference in NYHA scores (NYHA score, −0.15 [CI, −0.36 to 0.06]; I^2 = 62.1%). Pooled data from 4 studies (51, 52, 56, 58) (hemoglobin target levels, 12.5 to 15.0 g/dL) showed that ESA treatment resulted in a nonstatistically significant increase in the 6-minute walk test, and the studies were heterogeneous (mean change in distance walked, 74.4 m [CI, −0.16 to 149.0 m]; I^2 = 88.7%). Reported clinically important differences in the 6-minute walk test range from 43 to 54 m (63). Two studies used the Naughton protocol to assess change in exercise treadmill time. The smaller trial showed a slight increase in exercise duration with ESA treatment (62); however, the larger trial showed no difference (53).

Quality of Life

Moderate-quality evidence from 6 studies (51, 53, 56–58) showed that treatment with ESAs did not improve quality of life in anemic patients with stable CHF (hemoglobin target levels, 13.0 to 15.0 g/dL in the studies). The variability of tools used to assess quality of life and inconsistencies in the results limited analysis of this outcome. Two of the 4 trials (53, 56–58) that used the Patient Global Assessment scale showed that ESA treatment improved scores. One trial (58) had methodological flaws, and 1 study (57) found no significant differences in the Kansas City Cardiomyopathy Questionnaire and Minnesota Living With Heart Failure Questionnaire scores. One of the 4 trials (53, 56–58) that evaluated the Minnesota Living With Heart Failure Questionnaire scores showed improvement with treatment, although this study had a high risk of bias (58). Of the 3 studies (51, 56, 57) that evaluated patients by using the Kansas City Cardiomyopathy Questionnaire, 1 study reported an improvement from baseline "total symptom score" (56), whereas another study reported improvements in "functional score" and "summary score" (51). Low-quality evidence from 1 study of patients with CHD and end-stage renal disease showed no improvement in quality of life (60).

Hospitalization

High-quality evidence showed that hospitalizations were not statistically significantly different for patients with stable CHF. Limiting the analysis to the 3 trials with a low risk of bias (53, 54, 57, 60) showed no difference in hospitalizations (RR, 0.97 [CI, 0.87 to 1.10]; I^2 = 0.0%). Pooling data from all 8 studies showed that ESA treatment was associated with a reduction in hospitalizations compared with control (RR, 0.69 [CI, 0.52 to 0.93]; I^2 =

37.7%); however, pooling data from only the larger and higher-quality studies showed no effect. Hemoglobin target levels in the studies ranged from 13.0 to 15.0 g/dL.

HARMS OF TREATMENT OF ANEMIA WITH ESAS

Hypertension

Moderate-quality evidence pooled from 7 studies of patients with CHF (48, 50–53, 56, 57) showed that ESA treatment was associated with a nonstatistically significant increased risk for hypertension compared with control (RR, 1.20 [CI, 0.90 to 1.59]; $I^2 = 0.0\%$) (hemoglobin target levels, 9.0 to 15.0 g/dL).

Cerebrovascular Events

Moderate-quality evidence from 4 studies (51–53, 57) reported on cerebrovascular events in patients with CHF. However, few events were reported, and no difference between ESA and control groups was shown (RR, 1.33 [CI, 0.93 to 1.89]; $I^2 = 15.9\%$) (hemoglobin target levels, 12.5 to 14.0 g/dL).

Venous Thrombosis

Moderate-quality evidence from 4 studies in patients with CHF showed that ESAs (hemoglobin target levels, 12.5 to 15.0 g/dL) increased the risk for venous thrombosis, with 1 trial reporting on patients with chronic kidney disease and diabetes (RR, 1.36 [CI, 1.17 to 1.58]). A recent randomized, double-blind trial of patients with systolic heart failure and anemia found a significant increase in thromboembolic events in those treated with darbepoetin-α to a goal hemoglobin level greater than 13 mg/dL (9).

INFLUENCE OF HEMOGLOBIN TARGET LEVELS ON OUTCOMES

No studies assessed the effects of moderate compared with lower hemoglobin target levels on outcomes in patients with heart disease. All of the small trials comparing ESAs with placebo in patients with heart failure included patients with moderate anemia and a mean baseline hemoglobin level within the narrow range (10 to 12 g/dL). In all case patients, ESA use was associated with a statistically significant increase in hemoglobin level (mean range, 1.6 to 2.8 g/dL).

Three studies (47, 48, 54) evaluated the titration of ESAs to target normal hemoglobin levels compared with lower targets (9 to 11.3 g/dL) in patients with comorbid chronic kidney disease and heart disease and found no benefit from aggressive ESA use. Two of the studies (48, 54) showed that aggressive ESA use to normalize hemoglobin level increased the risk for venous thromboembolic events and suggested increased mortality rates (48, 54).

BENEFITS OF USING INTRAVENOUS IRON TO TREAT IRON DEFICIENCY WITH OR WITHOUT ANEMIA

Three studies (64–66) assessed the effect of intravenous (IV) iron in patients with heart failure. Data were primarily derived from 1 large study, which included patients with and without anemia and found similar results for both groups (64) (**Table 2**).

Mortality

Evidence was insufficient to determine the effect of IV iron treatment on mortality.

Cardiovascular Events

Low-quality evidence from 1 study (64) found that 27.6% of patients treated with IV iron carboxymaltose had cardiovascular events compared with 50.2% of patients receiving placebo ($P = 0.01$). However, this end point was not prespecified in the study, and the definition of the outcome was unclear.

Exercise Tolerance and Duration

Moderate-quality evidence showed that IV iron administration increased exercise tolerance and duration in patients with stable CHF and chronic kidney disease no worse than stage 3. The largest trial, FAIR-HF (Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure) included anemic and nonanemic patients, with most patients having ferritin levels less than 100 μg/L (64). This trial showed that 200 mg of IV ferric carboxymaltose increased 6-minute walk distance (313 m vs. 277 m) compared with IV saline (64). A second study found that among patients with iron deficiency, anemia, chronic heart failure, and chronic kidney disease, treatment with 200 mg of IV iron sucrose weekly for 5 weeks increased 6-minute walk distance compared with saline (66). The FERRIC-HF (Ferric Iron Sucrose in Heart Failure) (65) study showed that patients who received 200 mg of IV iron sucrose had improved exercise duration compared with placebo. However, this trial had a high risk of bias due to lack of patient blinding.

Quality of Life

Moderate-quality evidence showed that IV iron improved quality of life in patients with anemia or iron deficiency, stable CHF, and chronic kidney disease no worse than stage 3. The FAIR-HF study showed that IV iron treatment improved Patient Global Assessment scores compared with control patients (50% vs. 28%; odds ratio, 2.51 [CI, 1.75 to 3.61]) and improved NYHA functional class (odds ratio for improvement by 1 class, 2.40 [CI, 1.55 to 3.71]), regardless of anemia status (hemoglobin level ≤12 g/dL) (64). This trial also showed improved quality-of-life scores as assessed by the European Quality of Life–5 Dimensions (EQ-5D) (63 vs. 67) (64). Two other studies showed that patients who received 200 mg of IV iron sucrose had improved Minnesota Living With Heart Failure Questionnaire and NYHA scores (65, 66).

HARMS OF USING INTRAVENOUS IRON TO TREAT IRON DEFICIENCY WITH OR WITHOUT ANEMIA

Moderate-quality evidence from 3 studies (64–66) found no statistically significant difference in serious harms between IV iron treatment and control. However, harms were sparsely reported, and there is no available evidence on long-term outcomes.

SUMMARY

Management of patients with heart disease and anemia might appropriately differ from that of the general population. Hence, understanding the evidence base and using clinical judgment are critical when managing these patients. Anemia is associated with worse outcomes in patients with CHF or CHD. However, it is uncertain if anemia is the cause of poorer outcomes or if it is a marker of poor outcomes and reflects advanced cardiovascular disease. See **Table 2** for a summary of the evidence reviewed in this guideline.

Low-quality evidence found that RBC transfusion using restrictive compared with liberal transfusion protocols had no effect on mortality in patients with CHD. Observational studies suggested that transfusion is not beneficial and may be harmful among patients with heart disease and hemoglobin levels greater than 10 g/dL. A recently published trial indicated a trend toward improved cardiovascular outcomes in patients with anemia and unstable or stable CHD (10). However, differences in the baseline characteristics of the study groups and the small size of this pilot study do not answer the key clinical questions above, even after inclusion in the meta-analysis.

Overall, moderate-quality evidence showed no benefit from ESAs for improving exercise tolerance and duration or quality of life, and high-quality evidence showed no mortality benefit. Serious harms associated with the treatment include mortality and vascular thrombosis. A recently published trial showed no benefit across all subgroups studied and showed increased harms among those treated to a goal hemoglobin level greater than 13 g/dL (9). The evidence for ESA use is most applicable to patients with CHF and systolic dysfunction.

Few studies addressed IV iron therapy for patients with heart disease, and data on long-term harms were unavailable. One good-quality study among patients with chronic stable systolic heart failure showed that IV iron carboxymaltose improved exercise tolerance, quality of life, and exercise duration. Overall, moderate-quality evidence showed that IV iron therapy reduced cardiovascular events, and low-quality evidence found a mortality benefit. The evidence for IV iron therapy is most applicable to patients with NYHA class III heart failure and low ferritin levels. Refer to the **Figure** for a summary of the recommendations and clinical considerations.

Recommendation 1: ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease. (Grade: weak recommendation; low-quality evidence)

Low-quality evidence showed no mortality benefit of liberal compared with restrictive transfusion strategies across the patient populations studied. Most evidence did not show a substantial difference in benefit between liberal and restrictive RBC transfusions. In addition, low-quality evidence showed conflicting results for cardiovascular events. Low-quality evidence showed no mortality benefit of a higher (liberal) transfusion threshold (hemoglobin levels >10 g/dL) and fewer cardiovascular events with a lower (restrictive) transfusion threshold (hemoglobin levels of 7 to 8 g/dL) in noncardiac surgery patients. Studies showed no short-term mortality benefit in hip fracture and vascular surgery patients treated with liberal RBC transfusion compared with restrictive transfusion and found no difference in outcomes. Observational studies also failed to find a mortality benefit with aggressive liberal transfusion. For noncardiac surgeries other than hip fracture surgery, data are inconclusive. Low-quality evidence showed that patients with the acute coronary syndrome who received liberal RBC transfusions (hemoglobin threshold of 10 g/dL) had a mortality benefit compared with those who received more restrictive transfusion thresholds. However, this result was from a small study that included patients with stable and unstable CHD, and the difference was not statistically significant. Harms were sparsely reported, and no trials reported a difference in adverse events for liberal compared with restrictive transfusions.
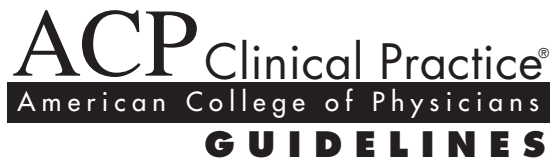
Recommendation 2: ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure or coronary heart disease. (Grade: strong recommendation; moderate-quality evidence)

The harms outweigh the benefits for treating patients with mild to moderate anemia using ESAs. The potential harms associated with ESA therapy include increased risk for thromboembolic events shown in 3 studies and a suggestion of increased stroke rates in 1 study. Although anemia is common in patients with CHF and CHD, high-quality evidence showed that treatment with ESAs did not improve mortality or affect cardiovascular events or hospitalizations, and moderate-quality evidence showed no improvement for quality of life. Baseline hemoglobin levels for study patients ranged from 9 to 10 g/dL.

INCONCLUSIVE AREAS OF EVIDENCE

Emerging evidence shows a short-term benefit from IV iron carboxymaltose in patients with CHF and ferritin levels less than 100 μg/L. However, evidence is lacking on long-term outcomes, and evidence on harms was sparsely reported. The effect of oral administration of iron and how it compares with IV iron for treating anemic patients with heart disease is unknown. Current evidence suggests that IV iron treatment improves exercise tolerance and quality

Figure. **Summary of the American College of Physicians guideline on treatment of anemia in patients with heart disease.**

ACP Clinical Practice®
American College of Physicians
GUIDELINES

Summary of the American College of Physicians Guideline on Treatment of Anemia in Patients With Heart Disease

Disease/Condition	Anemia and heart disease
Target Audience	Internists, family physicians, and other clinicians
Target Patient Population	Adult patients with symptomatic CHF (with or without reduced systolic function) or CHD (acute coronary syndrome, postacute coronary syndrome, or a history of MI or angina) and anemia or iron deficiency
Interventions	Red blood cell transfusion, ESAs with or without iron (including erythropoietin and darbepoetin), and intravenous iron
Outcomes	Mortality (all-cause and disease-specific); cardiovascular events (MI, CHF exacerbation, arrhythmia, or cardiac death); exercise tolerance (any metric, most commonly NYHA class, 6-min walk test); quality of life; hospitalization (all-cause and disease-specific); and harms, including hypertension, venous thromboembolic events, and ischemic cerebrovascular events
Benefits of Treatment	Red blood cell transfusion: no benefits shown when comparing liberal to restrictive transfusion ESAs: no benefit Intravenous iron: increased exercise tolerance, improved quality of life
Harms of Treatment	Red blood cell transfusion: adverse events potentially associated with red blood cell transfusions, such as fever, transfusion-related acute lung injury, and congestive heart failure ESAs: hypertension and venous thrombosis Intravenous iron: no harms identified but sparsely reported
Recommendations	*Recommendation 1: ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7–8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease. (Grade: weak recommendation; low-quality evidence)* *Recommendation 2: ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure or coronary heart disease. (Grade: strong recommendation; moderate-quality evidence)*
High Value Care	Current evidence does not support the benefit of liberal blood transfusions in patients with asymptomatic anemia and heart disease. Therefore, the ACP does not support the liberal use of blood transfusions in the management of mild to moderate anemia in patients with cardiovascular disease. The probability that transfusion may be beneficial is higher in patients with lower hemoglobin levels (<7 g/dL) and lower in less anemic patients (hemoglobin >10 g/dL) (67). The ACP does not support the use of ESAs for treating patients with mild to moderate anemia and heart disease because the harms outweigh the benefits for these patients.
Clinical Considerations	Patients with heart disease may have anemia because of iron deficiency, use of ACE inhibitors, renal insufficiency, and poor nutrition. Presence of anemia is associated with increased mortality and morbidity. However, it is uncertain if anemia is an independent risk factor for poor outcomes or if it is a marker of more severe illness. The impact of oral administration of iron and how it compares with IV iron for treating anemic patients with heart disease is unknown.

ACE = angiotensin-converting enzyme; CHD = coronary heart disease; CHF = congestive heart failure; ESA = erythropoiesis-stimulating agent; MI = myocardial infarction; NYHA = New York Heart Association.

of life and reduces mortality and hospitalizations. Although the evidence is intriguing and positive, it is limited to only 3 studies at this time, and the data were primarily derived from 1 large trial that included patients with and without anemia. Note that at the time of writing of this guideline, ferrous carboxymaltose was not yet approved for IV treatment of anemic patients in the United States.

ACP HIGH-VALUE CARE

Current evidence does not support the benefit of liberal blood transfusions in patients with asymptomatic anemia and heart disease. Therefore, ACP does not support this practice for management of mild to moderate anemia in patients with cardiovascular disease. The probability that transfusion may be beneficial is greater in patients with lower hemoglobin levels (<7 g/dL) and lower in less anemic patients (hemoglobin levels >10 g/dL) (67). The ACP does not support use of ESAs in cases of mild to moderate anemia and heart disease because the harms outweigh the benefits for these patients.

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are con-

sidered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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AD LIBITUM

He Lectures at the Heritage Association Dinner

After dessert, the women
arranged themselves upstairs
in a private room. He began
by presenting the usual
distinction between letting
a patient die and killing.
His examples generated
a spark that ignited
tiny firecrackers behind
a dozen faces and waving
hands rose, *Doctor! Doctor!*
A husband suffering torture
long after his body
gave out—a physician's
hubris. An injured brother
severed from machines too soon
by doctors who had stolen
his wife's consent. Passion
took hold of the group.
Anger and urgency tore
great hunks of experience
from the women's hearts
and grief uncovered its roots.
Having sprung the hinges
of ethics, he sampled
the best dose in his cabinet—
silence. When passion subsided,
the president praised the talk
that had not been given
and thanked him profusely
for sharing his wisdom.

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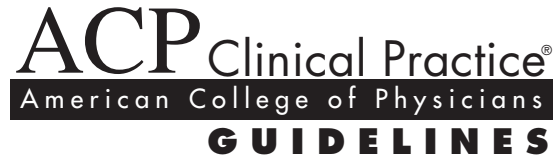Statistical expertise: A. Qaseem.
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Collection and assembly of data: A. Qaseem.

Correction: Treatment of Anemia in Patients With Heart Disease

The figure in a recent guideline (1) was incorrect. The correct version appears below.

ACP Clinical Practice®
American College of Physicians
GUIDELINES

Summary of the American College of Physicians Guideline on Treatment of Anemia in Patients With Heart Disease

Disease/Condition	Anemia and heart disease
Target Audience	Internists, family physicians, and other clinicians
Target Patient Population	Adult patients with symptomatic CHF (with or without reduced systolic function) or CHD (acute coronary syndrome, postacute coronary syndrome, or a history of MI or angina) and anemia or iron deficiency
Interventions	Red blood cell transfusion, ESAs with or without iron (including erythropoietin and darbepoetin), and intravenous iron
Outcomes	Mortality (all-cause and disease-specific); cardiovascular events (MI, CHF exacerbation, arrhythmia, or cardiac death); exercise tolerance (any metric, most commonly NYHA class, 6-min walk test); quality of life; hospitalization (all-cause and disease-specific); and harms, including hypertension, venous thromboembolic events, and ischemic cerebrovascular events
Benefits of Treatment	Red blood cell transfusion: no benefits shown when comparing liberal to restrictive transfusion ESAs: no benefit Intravenous iron: increased exercise tolerance, improved quality of life
Harms of Treatment	Red blood cell transfusion: adverse events potentially associated with red blood cell transfusions, such as fever, transfusion-related acute lung injury, and congestive heart failure ESAs: hypertension and venous thrombosis Intravenous iron: no harms identified but sparsely reported
Recommendations	*Recommendation 1: ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7–8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease. (Grade: weak recommendation; low-quality evidence)* *Recommendation 2: ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure or coronary heart disease. (Grade: strong recommendation; moderate-quality evidence)*
High Value Care	Current evidence does not support the benefit of liberal blood transfusions in patients with asymptomatic anemia and heart disease. Therefore, the ACP does not support the liberal use of blood transfusions in the management of mild to moderate anemia in patients with cardiovascular disease. The probability that transfusion may be beneficial is higher in patients with lower hemoglobin levels (<7 g/dL) and lower in less anemic patients (hemoglobin >10 g/dL) (67). The ACP does not support the use of ESAs for treating patients with mild to moderate anemia and heart disease because the harms outweigh the benefits for these patients.
Clinical Considerations	Patients with heart disease may have anemia because of iron deficiency, use of ACE inhibitors, renal insufficiency, and poor nutrition. Presence of anemia is associated with increased mortality and morbidity. However, it is uncertain if anemia is an independent risk factor for poor outcomes or if it is a marker of more severe illness. The impact of oral administration of iron and how it compares with IV iron for treating anemic patients with heart disease is unknown.

This has been corrected in the online version.

Reference

1. Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P, for the Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013;159:770-9.