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

EXECUTIVE REPORT

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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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EXECUTIVE SUMMARY

BACKGROUND

Anemia is very common in congestive heart failure (CHF) and coronary heart disease (CHD) patients. Anemia in CHF and CHD patients is associated with poorer outcomes, including an increased risk of hospitalization, decreased exercise capacity, and poor quality of life. Despite the association with poorer outcomes, it is unclear whether treating anemia or iron deficiency will improve outcomes. Anemia treatment strategies in heart failure and CHD patients include erythropoiesis-stimulating agents (ESAs) and red blood cell transfusions. Iron replacement in iron deficient patients with or without anemia has also been investigated. The objective of this evidence review is to evaluate the balance of benefit and harms of these treatments. We conducted a systematic review to address the following key questions:

In patients with CHF or CHD,

Key Question #1. What are the health outcome benefits and harms of treating anemia with 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?

METHODS

We conducted searches in Medline® and the Cochrane database of systematic reviews of literature published from 1947 to November 2010, and 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 and by contacting pharmaceutical companies directly. Reviewers trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literatures searches. Full-text articles of potentially relevant abstracts were retrieved for further review. We assessed the internal validity of each study using the Cochrane Risk of Bias tool. We assessed the overall quality of the body of evidence for each outcome by considering the consistency, coherence, and applicability across studies, as well as the internal validity of individual studies, using a method developed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. We performed meta-analyses of the effects of ESAs on health outcomes and we conducted additional analyses according to study quality, and according to baseline and change in hemoglobin. We qualitatively reviewed the much smaller number of trials evaluating iron and blood transfusion effects.

RESULTS

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. Of the full-text articles, we rejected 266 that did not meet our inclusion criteria.

ESAs

Sixteen randomized, controlled trials evaluated the impact of ESAs in patients with heart disease. Most of these studies included patients with CHF and reduced systolic function. Though the group of studies as a whole showed ESA use may improve exercise tolerance, this benefit diminished substantially when we included only trials with low risk of bias. 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.

Iron

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.

Blood Transfusions

Nine controlled trials have compared outcomes with the use of a restrictive versus more liberal strategy of red blood cell transfusion among patients with heart disease. In each, conservative use of blood products, guided by a transfusion trigger of hemoglobin 7-9 g/dL, was found to be as safe as transfusion to a higher hemoglobin threshold (most often 10 g/dL). However, the large majority of these studies were quite small, substantially underpowered for detecting important differences in clinical outcomes, and most were conducted in the perioperative setting. Nevertheless, the consistency of the results in the perioperative setting suggests conservative use of transfusion should be the default strategy.

Twenty-one additional observational studies have examined transfusion 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; 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.

DISCUSSION/CONCLUSION

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 erythropoiesis-stimulating agents or blood transfusions improves 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. The application of the evidence to different patient subsets is described in the main report and is summarized in the following table.

EXECUTIVE SUMMARY TABLE

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.

Treatment	Outcome	Effect*	GRADE Classification†	Comment
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.
	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.

Treatment	Outcome	Effect*	GRADE Classification†	Comment
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.
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.