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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are erythropoiesis-stimulating agents beneficial for anemia in chronic heart failure patients?

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Abstract

Anemia is a common comorbidity among patients with chronic health failure and appears to be associated with increased mortality and morbidity. However, it is unclear whether correcting it with erythropoiesis stimulating agents improves clinical outcomes. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified 11 systematic reviews including 17 trials overall addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded the use of erythropoiesis stimulating agents in patients with chronic heart failure and anemia does not decrease mortality, and it is not clear if they decrease the risk of hospitalization or if they improve functional status because the certainty of the evidence is very low. The risk of thromboembolic events probably increases.

Problem

Anemia is a common comorbidity among patients with chronic heart failure. Multiple mechanisms may contribute to anemia, including hemodilution, activation of pro-inflammatory cytokines, chronic kidney disease and impaired erythropoiesis. Anemia in people with chronic heart failure is associated with a higher risk of hospitalization, increased mortality, and poor functional status [1].

Erythropoiesis-stimulating agents, such as the two forms of recombinant human erythropoietin (epoetin-alfa and epoetin-beta) and its analogue darbepoetin alfa, share the same mechanism of endogenous erythropoietin, and are the first-line treatment for non-iron-deficiency anemia in patients with cancer or chronic kidney disease. However, its use has been associated with increased thromboembolic events, hypertension and mortality when high hemoglobin targets are used. There is controversy about their role in patients with heart failure and anemia.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- The use of erythropoiesis stimulating agents in patients with chronic heart failure and anemia does not decrease mortality.
- It is uncertain whether erythropoiesis-stimulating agents decrease hospitalization risk or improve functional status because the certainty of the evidence is very low.
- The use of erythropoiesis stimulating agents in patients with chronic heart failure and anemia probably increases the risk of total thromboembolic events.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 11 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11] including 17 randomized controlled trials overall, reported in 18 references [12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29]. One trial was reported in two articles [15],[16].
What types of patients were included	All of the trials included chronic heart failure patients with representation of all etiologies. All of the trials included patients with symptomatic chronic heart failure and anemia. Regarding NYHA functional class, three trials included NYHA I [14],[26],[29] eight included NYHA II [12], [14],[15],[23],[24],[26],[28],[29], all included NYHA III, 13 trials included NYHA IV [12],[13],[14],[17],[18],[19],[20],[21], [22],[23],[27],[28],[29], and one trial did not report NYHA functional class [25]. Most trials included participants with low ejection fraction (<40%), with the exception of two trials; one reported a mean ejection fraction of 58% [18], and the other did not report this variable [25]. Different hemoglobin levels were used to define anemia among the trials. Two of them considered hemoglobin level < 11g/dl [20], [25], four <11.5 g/dl [21],[22],[23],[27], six <12 g/dl [13],[14],[18],[26],[28],[29], four < 12.5 g/dl [12], [15], [23],[24]and one defined anemia by hematocrit <35% [17].
What types of interventions were included	Eight trials used alfa or beta recombinant human erythropoietin [13],[17],[18],[19],[20],[21],[22],[27]), and nine used darbepoetin alfa [12],[14],[15],[23],[24],[25],[26],[28],[29]. Most trials compared against placebo, with the exception of two that compared against no treatment [13],[27]. All trials except three [12],[13],[25] associated iron supplementation to the treatment. Regarding hemoglobin targets, one trial considered a target > 11.5 g/dl [20], one >12 g/dl [22], two >12.5 g/dl [15], [27], five >13 g/dl [14], [25], [26], [28], [29], one >14 g/dl [24], one considered a hematocrit target > 45% [17], and six did not report a target [12], [13], [18], [19], [21], [23].

What types of outcomes were measured	The different systematic reviews grouped the outcomes as follows: All-cause mortality, all-cause hospitalization, exercise tolerance, hemoglobin level, quality of life (measured in KCCQ, MLHFQ and PGA scales), NYHA functional class, B-type natriuretic peptide levels, left ventricular ejection fraction, total thromboembolic events, myocardial infarction, deep vein thrombosis, ischemic stroke, pulmonary embolism.

Summary of findings

The information on the effects of erythropoiesis-stimulating agents is based on 17 randomized trials including 4617 patients. Sixteen trials reported mortality (4587 patients) [12],[14],[15],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29]. Fourteen trials reported hospitalizations by any cause (3210 patients) [12],[14],[15],[17],[18],[19],[20],[21],[22],[24],[26],[27],[28],[29], and 11 trials reported NYHA functional capacity (857 patients) [13],[14],[19],[20],[21],[22],[23],[24],[25],[26], [27], [29]. Data from thromboembolic events were reported in a way that precluded meta-analysis, therefore we present data from one review [4].

The summary of findings is the following:

- The use of erythropoiesis stimulating agents in patients with chronic heart failure and anemia does not decrease mortality. The certainty of the evidence is high.
- It is not clear whether erythropoiesis-stimulating agents decrease hospitalization in patients with chronic heart failure and anemia because the certainty of the evidence is very low.
- It is not clear whether erythropoiesis-stimulating agents improve functional status in patients with chronic heart failure and anemia because the certainty of the evidence is very low.
- The use of erythropoiesis stimulating agents in patients with chronic heart failure and anemia probably increases the risk of total thromboembolic events. The certainty of the evidence is moderate.

Erythropoiesis-stimulating agents for anemia in heart failure

Patients Chronic heart failure and anemia
Intervention Erythropoiesis-stimulating agents (ESA)
Comparison Placebo or no treatment

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT Erythropoiesis-stimulating agents	**WITH Erythropoiesis-stimulating agents**		
	Difference: patients per 1000			
All-cause mortality	310 per 1000	317 per 1000	RR 1.02 (0.94 to 1.11)	⨁⨁⨁⨁[1] High
	Difference: 7 patients more per 1000 (Margin of error: 19 less to 34 more)			
Heart failure-associated hospitalization	269 per 1000	239 per 1000	RR 0.89 (0.79 to 1.0)	⨁◯◯◯[1,2,3] Very low
	Difference: 30 patients less per 1000 (Margin of error: 0 to 57 less)			
NHYA functional capacity	3.0 points	2.7 points	--	⨁◯◯◯[1,4] Very low
	MD: 0.3 points better (Margin of error: 0.23 to 0.38 better)			
Thromboembolic events	An increased risk of total thromboembolic events was observed. However, when considering only severe thromboembolic events (such as myocardial infarction, deep vein thrombosis, pulmonary embolism and ischemic stroke) there was no evidence of an increased risk.		Total: RR 1.28 (1.03 to 1.58) Severe: RR 1.08 (0.6 to 1.34)	⨁⨁⨁◯[4] Moderate

RR= Risk ratio.
MD= Mean difference.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT erythropoiesis-stimulating agents** is based on the risk in the control group of the trials. The risk **WITH erythropoiesis-stimulating agents** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] Most trials have limitations, being the more frequent absence of allocation concealment and blinding. However, one study (RED-HF) weighing 57% in the meta-analysis has low risk of bias, so we did not downgrade the certainty of the evidence for mortality. Additionally, bias would probably strengthen the conclusion.
[2] We downgraded the certainty of the evidence due to imprecision, since the confidence interval is wide and included both the possibility of increase or decrease in hospitalization.
[3] The publication bias analysis (funnel plot) suggests there might be small undetected studies.
[4] We downgraded the certainty of the evidence due to inconsistency between studies; in the case of functional capacity we downgraded de certainty of the evidence by two levels (I=96%).

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to patients with symptomatic chronic heart failure and anemia, not requiring erythropoiesis-stimulating agents for other reason.
- It does not apply to patients who have chronic kidney disease or cancer as comorbidity, because depending on their hemoglobin level and in absence of iron deficiency, erythropoiesis-stimulating agents might be indicated.
- Most trials used high hemoglobin targets, and the study with higher weight on mortality targetted an hemoglobin level of 13 g/dl, which might have led to an increased risk for total thromboembolic events [28].

About the outcomes included in this summary

- The outcomes presented in this summary are those considered critical for decision making in the main guidelines and by the authors of this summary.
- We did not include hypertension in the summary of findings table, because this outcome is not directly important to patients. However, its consideration does not make a diference in the conclusions (11 patients more per 1000 [5 less to 32 more]; RR 1.20, CI 95% 0.91 to 1.59).

Balance between benefits and risks, and certainty of the evidence

- The use of erythropoiesis-stimulating agents does not decrease mortality with a high level of certainty. There is uncertainty regarding any other benefit, an there is an increased risk of thromboembolic events.
- The balance between benefits and harms is probably not favorable.

What would patients and their doctors think about this intervention

- There is uncertainty about the balance between benefits and risks, which probably leads to different decisions depending on what patients and physicians value the most.
- Patients putting a higher value in an uncertain benefit might consider its use, especially if there are no resource constraints.

Resource considerations

- Erythropoiesis-stimulating agents constitute a relatively expensive intervention. Only in settings without resource constraints, their use could be admissible in selected cases.

Differences between this summary and other sources

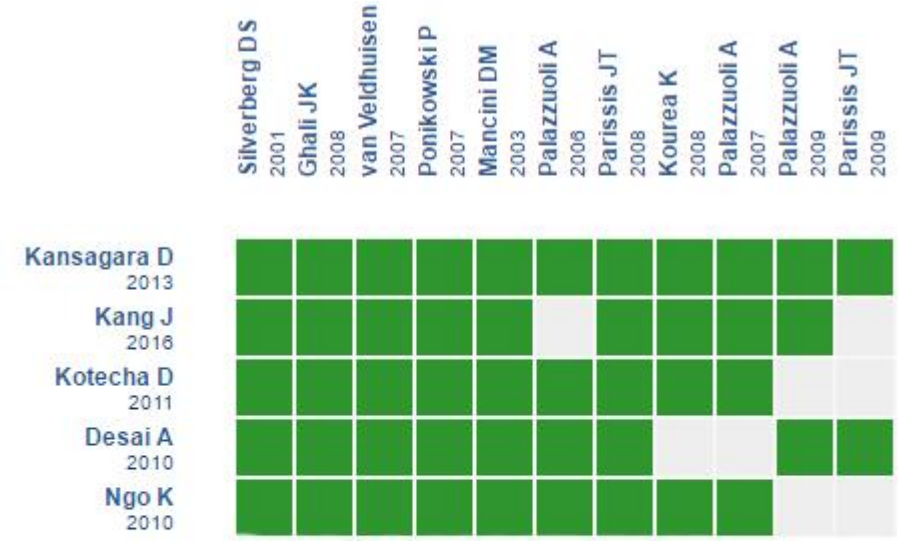
- The systematic reviews differ in their conclusions, and some even state there is a clear benefit on mortality and hospitalization risk. It is important to notice the change in conclusions given the incorporation of RED-HF [28] on the more recent systematic reviews.
- This summary is in agreement with the recommendations given by the Canadian Cardiovascular Society Heart Failure Management Guidelines [30], which does not recommend the use of erythropoiesis-stimulating agents given the neutral effect on mortality and hospitalization risk reported by the two largest studies [14], [28].

Could this evidence change in the future?

- The probability that the information on the effect of erythropoiesis-stimulating agents on mortality change in the future is very low.
- We did not identify any ongoing trial answering this question, and given the lack of effect on mortality and the increased risk of thromboembolic events reported in RED-HF [28], it is unlikely that another morbidity or mortality study will be undertaken.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Erythropoiesis-stimulating agents for anemia in chronic heart failure

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).
These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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