
Research

Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials

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Abstract

Introduction: Anemia and the need for red blood cell transfusions are common among patients admitted to intensive care units. Erythropoietin has been used to decrease the need for transfusions; however, its ability to improve clinical outcomes is unknown. We evaluated the effect of erythropoietin-receptor agonists on clinically important outcomes, including mortality, length of stay in hospital or intensive care unit, ventilator use, transfusion requirements and major adverse events.

Methods: To identify relevant studies, we searched electronic databases covering 1950 to 2007 (MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the Scopus database). We also searched conference proceedings and grey literature sources. We selected all randomized controlled trials involving critically ill patients that compared an erythropoietin-receptor agonist with a placebo or no intervention. No language restrictions were considered. Data were extracted using a standardized extraction template. We used a fixed effects model to calculate all summary measures of treatment effects.

Results: Of 673 identified records, 9 studies that investigated erythropoietin alpha met the eligibility criteria and were included in our analysis. Erythropoietin, compared with placebo or no intervention, had no statistically significant effect on overall mortality (odds ratio [OR] 0.86, 95% confidence interval [CI] 0.71–1.05, I² = 0%). The treatment and control groups did not differ in the length of stay in hospital or intensive care unit, or in the duration of mechanical ventilation, in the 3 studies that reported these outcomes. Erythropoietin, compared with placebo, significantly reduced the odds of a patient receiving at least 1 transfusion (OR 0.73, 95% CI 0.64–0.84, I² = 54.7%). The mean number of units of blood transfused per patient was decreased by 0.41 units in the erythropoietin group (95% CI 0.10–0.74, I² = 79.2%). Most of the included studies were performed before the widespread adoption of a restrictive transfusion strategy. Only 1 study provided detailed reports of adverse events, and none of the studies systematically evaluated all patients for venous thromboembolism.

Interpretation: At this time, we do not recommend the routine use of erythropoietin-receptor agonists in critically ill patients. The reduction in red blood cell transfusions per patient was very small, and there is insufficient evidence to determine whether this intervention results in clinically important benefits with acceptable risks.

Une version française de ce résumé est disponible à l’adresse www.cmaj.ca/cgi/content/full/177/7/725/DC1

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A
nemia and the need for allogeneic blood transfusion are common among patients who are critically ill. Observational studies have shown that anemia develops in 95% of patients admitted to intensive care units for 3 or more days.1–3 Studies in western Europe and North America have demonstrated that 42%–50% of patients admitted to intensive care units will require transfusion of packed red blood cells because of anemia.2,4 About 85% of patients admitted to an intensive care unit for more than 13 days will require such transfusions.2

Anemia can occur in critically ill patients for a variety of reasons, such as blood loss related to a surgical procedure, trauma and gastrointestinal bleeding. A less conspicuous, but equally important, cause of anemia is repetitive phlebotomy for surveillance and diagnosis. On average, 41 mL of blood is taken for laboratory testing per day of stay in an intensive care unit;6 however, this amount can exceed 240 mL per day in some surgical units.6 Anemia of inflammation, also known as anemia of chronic disease, is another important subtype of anemia in this patient population. About two-thirds of critically ill patients receive allogeneic blood because their hemoglobin level falls below a threshold value.7

Blood transfusions are known to have rare but serious adverse consequences, including transfusion-associated circulatory overload, transfusion-transmitted infections and transfusion-associated acute lung injury. Given the fre-
quent need for red blood cell transfusions in intensive care units and the risks associated with the administration of blood products, experimental studies of recombinant erythropoietin have been conducted.\textsuperscript{1,8–15} In an effort to overcome the relative erythropoietin deficiency observed in critically ill patients, recombinant erythropoietin has been used to stimulate erythropoiesis, mitigate anemia and reduce the need for blood transfusions. Early proof-of-concept studies were generally small and focused on hematologic response as an outcome measure. Larger trials have subsequently been conducted that permit the examination of clinical outcomes and safety.

The utility of erythropoietin-receptor agonists in the setting of critical illness is unclear despite the publication of several randomized controlled trials. We performed this systematic review to investigate the clinical benefits and harms associated with the use of erythropoietin-receptor agonists in critically ill patients.

Methods

We performed our meta-analysis using methods and analytic strategies designed and approved by 2 of us (A.F.T. and D.A.F.). This protocol is available online (Appendix 1, www.cmaj.ca/cgi/content/full/177/7/725/DC2).

Search

We developed a strategy to search OVID MEDLINE (1950–2007 February week 1). This search strategy was adapted to search EMBASE (1980–2007 February week 1) and the Cochrane Central Register of Controlled Trials (to first quarter 2007). The search strategy was developed with the help of an information specialist at The Ottawa Hospital. It underwent several iterations and was updated 1 month before publication. The complete MEDLINE search strategy is presented in Appendix 2 (available online at www.cmaj.ca/cgi/content/full/177/7/725/DC2). To identify ongoing or planned trials of erythropoietin-receptor agonists, we also searched the ClinicalTrial.gov database. We used the SIGLE (System for Information on Grey Literature) database and Google Scholar to assist in the identification of relevant grey literature. We contacted representatives from the manufacturers of erythropoietin-receptor agonists (Amgen, Ortho-Biotech, Roche), corresponding or first authors of all included trials and subject-area experts for information about ongoing studies. We searched the abstracts and conference proceedings from the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the International Symposium on Intensive Care Medicine (2002–2007 February). In addition, we canvassed the Scopus abstract and citation database, and we examined the individual bibliographies of all included trials and relevant reviews to minimize the omission of potentially relevant trials. No language restrictions were applied.

Selection

We included studies that met the following criteria: the treatment groups were randomly assigned; erythropoietin or darbepoietin was compared with a placebo, alternative therapy or no intervention; patients were admitted to an intensive care unit; enrolled patients were 1 year of age or older. Studies were excluded if there was exclusive enrollment of cardiac surgery patients or if erythropoietin-receptor agonists were administered preoperatively to decrease the need for perioperative transfusions.

Our primary outcome measure was death, regardless of the primary outcome of the included studies. Our secondary outcomes were length of stay in an intensive care unit or hospital, duration of mechanical ventilation and adverse events due to erythropoietin-receptor agonists (e.g., arterial and venous thrombosis, hypertension). Our secondary outcome measures also included transfusion-related outcomes, including transfusion independence (i.e., the ability of erythropoietin-receptor agonists to prevent the need for transfusion), units of blood transfused per patient and adverse events related to transfusion.

Quality assessment

The title, abstract and keywords of each identified record were screened for relevancy (level 1 screen) by 2 of us (R.Z. and A.F.T.) as the primary reviewers. Nonrelevant records agreed upon for exclusion by both reviewers were eliminated at this stage. Full-text articles were obtained for all remaining records. Non-English abstracts were translated as required. The same 2 reviewers independently assessed each full-text article, applying the inclusion and exclusion criteria (level 2 screen) to determine the studies to be included. Interrater agreement was calculated at each screening level with the use of Cohen’s kappa statistic. Discrepancies were resolved by means of consensus, and with input from the senior author (D.A.F.) if necessary.

The 2 primary reviewers independently assessed the methodologic quality of each of the included studies. We assessed allocation concealment using the method developed by Schultz and colleagues.\textsuperscript{17} We assessed allocation concealment using the method developed by Schultz and colleagues.\textsuperscript{17} The Jadad scale gives a score for methodologic quality based on the reported methods and description of randomization (0–2 points), blinding (0–2 points) and participant withdrawals (1 point). Possible scores varied from 0 to 5, with 5 representing the highest methodologic quality. Information about methodologic quality and potential risks of bias were used to guide sensitivity analyses and to explore sources of heterogeneity.

Data abstraction

The 2 primary reviewers extracted data from the included studies independently and without blinding using a standardized data extraction form. The form was initially piloted to ensure completeness and usability. If required data were ambiguous or missing, we contacted the authors of the study for clarification or additional data.

Data synthesis

We analyzed discrete and continuous data using the Cochrane Review Manager (version 4.2.10). We used an electronic double-data entry system to minimize transcription errors. We employed a fixed-effects model using inverse vari-
Of the 673 records identified, 618 were excluded after level 1 screening: 216 were duplicate records, 402 were excluded for other reasons (Figure 1). The agreement between the 2 primary reviewers at this level of screening was substantial (estimated kappa = 0.77). The full-text articles for 56 studies were retrieved, and after level 2 screening, 10 articles were selected for inclusion in the meta-analysis. Agreement between the 2 reviewers at the second level of screening was almost perfect (estimated kappa = 0.94), and the single discrepancy was resolved by consensus. The reasons for excluding studies at both level 1 and 2 screening are listed in Figure 1. We did not identify any records from grey literature sources. During the process of data extraction, it became apparent that 2 publications were separate analyses of the same study; thus, we included the article that was most informative for the purpose of this review.

**Study characteristics**

A total of 3326 participants were enrolled in the 9 included studies. All of the studies were published in peer-reviewed, English-language journals and were sponsored by the same parent company. Five of the studies were conducted in North America, and 4 were conducted in Europe. Of the 9 studies, 4 enrolled more than 100 patients. All 9 studies appeared to enrol only adults, but the explicit age criteria were not stated in 2 of the articles. Seven studies included patients admitted to mixed medical and surgical intensive care units, and 1 included patients admitted to a long-term acute care facility, and 1 included patients admitted to a burn unit (Table 1).

All of the trials compared erythropoietin alpha with either a placebo or no therapy. No eligible studies of darbepoietin were identified. In 8 of the included studies, all of the participants received iron supplementation as a co-intervention. In the remaining study, iron was administered to 42% of patients who received erythropoietin and 24% of patients in the control group. Iron was administered either enterally or intravenously depending on the patient’s gut function and the study protocol.

The mean hemoglobin concentration before transfusion was between 75 (standard deviation [SD] 9) g/L and 93 (SD 13) g/L (Table 1). A liberal transfusion strategy (target hemoglobin ≥ 90 g/L) was used in 4 studies, and a restrictive transfusion strategy (hemoglobin ≤ 80 g/L) was practised in 3 studies. A mandated transfusion protocol was reported in 2 of the trials and was inferred from 2 other studies (Table 1). The remaining studies either had no stated transfusion criteria or offered practice suggestions that were not mandated within the context of a study protocol. The transfusion practice adopted by each study (liberal or restrictive) was inferred from the mean hemoglobin concentration before transfusion.

Erythropoietin dosing varied between the studies, as did the maximum duration of therapy (Table 1). In 5 of the 9 studies, a fixed dose of erythropoietin was administered, and in 4 studies dosing was based on patient weight (units/kg). The most frequent (89.9% of patients) dosing regimen was 40 000 units per week; however, the dose of erythropoietin per week (based on 70 kg) varied from 36 750 to 160 000 units.
Table 1: Characteristics of the 9 studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>No. of patients, EPO/control</th>
<th>APACHE II score, EPO/control, mean</th>
<th>Study population</th>
<th>EPO dose*</th>
<th>Control</th>
<th>Transfusion protocol</th>
<th>Pre-transfusion hemoglobin, g/L (SD), mean</th>
<th>Duration of intervention</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still et al13</td>
<td>40</td>
<td>19/21</td>
<td>NR</td>
<td>Burn unit</td>
<td>300 U/kg for 7 d, then 150 U/kg every other day for 23 d</td>
<td>Placebo</td>
<td>Yes (maintain Hct &gt; 30%)</td>
<td>NR</td>
<td>Max 30 d</td>
<td>36 d (mean)</td>
</tr>
<tr>
<td>Gabriel et al10</td>
<td>21</td>
<td>11/10</td>
<td>10/11</td>
<td>Mixed (medical and surgical ICU)</td>
<td>600 U/kg intravenous, 3 times/wk + iron, folic acid and vitamin B12</td>
<td>Placebo and iron, folic acid, vitamin B12</td>
<td>Yes (maintain Hct &gt; 30%)</td>
<td>NR</td>
<td>Max 3 wk</td>
<td>21 d</td>
</tr>
<tr>
<td>Corwin et al1</td>
<td>160</td>
<td>80/80</td>
<td>18/18</td>
<td>Mixed (medical and surgical ICU)</td>
<td>300 U/kg/d for 5 d, then every other day + iron</td>
<td>Placebo and iron</td>
<td>No</td>
<td>EPO: 93 (13)† Control: 92 (14)†</td>
<td>Max 42 d</td>
<td>42 d</td>
</tr>
<tr>
<td>Van Iperen et al14</td>
<td>36</td>
<td>12/12</td>
<td>28/24</td>
<td>Mixed (medical and surgical ICU)</td>
<td>300 U/kg/d for every other day (max 5 doses) + iron and folic acid</td>
<td>A: folic acid B: iron and folic acid</td>
<td>Yes (transfuse at Hb 89 g/L or 97 g/L if cardiac history)</td>
<td>NR</td>
<td>Max 5 doses</td>
<td>21 d</td>
</tr>
<tr>
<td>Corwin et al9</td>
<td>1302</td>
<td>652/650</td>
<td>20/20</td>
<td>Mixed (medical and surgical ICU)</td>
<td>40 000 U/wk + iron</td>
<td>Placebo and iron</td>
<td>Suggested (no transfusion if Hb ≥ 90 g/L)</td>
<td>EPO: 85 (11) Control: 86 (10)</td>
<td>Max 3 wk</td>
<td>28 d</td>
</tr>
<tr>
<td>Georgopoulous et al15</td>
<td>148</td>
<td>A: 51/B:49/48</td>
<td>A:14/B:15/14</td>
<td>Mixed (medical and surgical ICU)</td>
<td>A: 40 000 U/wk + iron B: 40 000 U, 3 times/wk + iron</td>
<td>Iron</td>
<td>Yes (transfuse at Hb 70 g/L) A: EPO: 76 (8) B: EPO: 77 (9) Control: 79 (11)</td>
<td>Min-max, 2.3 wk</td>
<td>28 d</td>
<td></td>
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<tr>
<td>Silver et al12</td>
<td>86</td>
<td>42/44</td>
<td>17/16 (median)</td>
<td>Long-term acute care hospital</td>
<td>40 000 U/wk + iron</td>
<td>Placebo and iron</td>
<td>Suggested (no transfusion if Hct ≥ 24%)</td>
<td>EPO: 80 (5) Control: 75 (8)</td>
<td>Max 12 wk</td>
<td>42, 84 d</td>
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<tr>
<td>Vincent et al10</td>
<td>73</td>
<td>48/25</td>
<td>17/14</td>
<td>Mixed (medical and surgical ICU)</td>
<td>40 000 U/wk + iron</td>
<td>Placebo and iron</td>
<td>No</td>
<td>EPO: 82 Control: 80</td>
<td>Max 4 wk</td>
<td>28 d (mean)</td>
</tr>
<tr>
<td>Corwin et al9</td>
<td>1460</td>
<td>733/727</td>
<td>20/20</td>
<td>Mixed (medical and surgical ICU)</td>
<td>40 000 U/wk + iron</td>
<td>Placebo and iron</td>
<td>Suggested (no transfusion if Hb ≥ 90 g/L)</td>
<td>EPO: 82 (9) Control: 80 (9)</td>
<td>Max 3 wk</td>
<td>29, 42, 140 d</td>
</tr>
</tbody>
</table>

Note: APACHE = Acute Physiology and Chronic Health Evaluation, EPO = erythropoietin, ICU = intensive care unit, Hb = hemoglobin, Hct = hematocrit, SD = standard deviation, NR = not reported.

*EPO was delivered subcutaneously unless otherwise specified.
†Estimated Hemoglobin (g/L) = hematocrit (decimal fraction) × 34.
The study by Georgopoulos and colleagues had 2 treatment groups, each with different erythropoietin dosing schedules. Data for patients in the 2 groups were pooled for the purposes of this meta-analysis. The study by Van Iperen and colleagues included 2 control groups, and for the purpose of our meta-analysis, we considered the group that received iron as the comparator group.

The maximum duration of the intervention period (period when erythropoietin or placebo was administered) varied from 3 to 12 weeks. The length of follow-up varied from 21 to 140 days, and the length of follow-up was not always the same as the length of the intervention period (Table 1). The follow-up periods that were used to determine the summary effect measures of mortality and the transfusion differences were between 21 and 42 days. Reporting of adverse events and the related analyses were adjudicated at the study closeout, which varied from 21 to 140 days.

The primary outcomes in 6 of the included studies were transfusion related (decreased amount of blood transfused or facilitation of transfusion independence). In 4 studies, laboratory results were included as primary end points, including reticulocyte counts or levels of circulating early peripheral blood erythroid progenitors, hemoglobin and hematocrit levels, indices of cytokine production, serum erythropoietin concentration and serum iron indices. Several studies reported or inferred both transfusion-related end points and laboratory results as primary outcomes. None of the studies included death, length of stay, measures of organ dysfunction or quality of life as primary outcomes.

Assessment of methodologic quality
Of the 9 included studies, 3 were of high methodologic quality (Table 2). Adequate allocation concealment was reported in 3 of the studies. Two studies were not blinded, and 1 did not use intention-to-treat analysis of all randomized patients when performing statistical analyses. Six of the studies reported losses to follow-up that varied from 5.1% to 27% (Table 2).

Data synthesis
Death
We pooled the data from the 9 included studies (n = 3314) to generate a summary odds ratio (OR) for mortality (Figure 2). We found that the use of erythropoietin, compared with placebo or no intervention, was not associated with a statistically significant reduction in the overall rate of death from all causes (OR 0.86, 95% CI 0.71–1.05, I² = 0%).

No statistical evidence of heterogeneity was detected.

We performed sensitivity analyses to evaluate mortality among the different patient subgroups (Figure 3). Among patients admitted to mixed medical and surgical units (the 2 trials that enrolled patients with burns or patients admitted to a long-term acute care hospital were excluded), the reduction in death remained nonsignificant (OR 0.88, 95% CI 0.72–1.07, I² = 0%). Among patients who received 40 000 units of erythropoietin per week, the OR for death was 0.82 (95% CI 0.66–1.02, I² = 0%). Among patients who received more than 40 000 units weekly, there was a trend toward harm (OR 1.26, 95% CI 0.74–2.15, I² = 0%). The pooled OR for death was of borderline significance among studies that used a restrictive (hemoglobin ≥ 90 g/L) transfusion practice that was either mandated or in keeping with current practice patterns (OR 0.73, 95% CI 0.53–1.00, I² = 0%), but it was nonsignificant among studies that adopted a liberal (hemoglobin ≥ 90 g/L) transfusion practice (OR 1.18, 95% CI 0.66–2.11, I² = 0%). A nonsignificant reduction in death was observed among the studies of high methodologic quality (OR 0.81, 95% CI 0.65–1.01, I² = 2.8%).

No significant reduction in mortality was observed among the unblinded studies (OR 1.03, 95% CI 0.42–2.53, I² = 0%). In the 3 studies that reported ade-

<table>
<thead>
<tr>
<th>Study</th>
<th>RCT type</th>
<th>Sponsor</th>
<th>Total</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Attrition information</th>
<th>Allocation concealment</th>
<th>Intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still et al</td>
<td>Multicentre</td>
<td>Johnson and Johnson</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Unclear</td>
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</tr>
<tr>
<td>Gabriel et al</td>
<td>Single centre</td>
<td>Janssen-Cilag</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>Unclear</td>
<td>No</td>
</tr>
<tr>
<td>Corwin et al</td>
<td>Multicentre</td>
<td>Ortho-Biotech</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>Unclear</td>
<td>Yes</td>
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<td>Van Iperen et al</td>
<td>Multicentre</td>
<td>Janssen-Cilag</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
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<td>Multicentre</td>
<td>Ortho-Biotech</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Adequate</td>
<td>Yes</td>
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<td>Georgopoulos et al</td>
<td>Multicentre</td>
<td>Janssen-Cilag</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Adequate</td>
<td>Yes</td>
</tr>
<tr>
<td>Silver et al</td>
<td>Multicentre</td>
<td>Ortho-Biotech</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Vincent et al</td>
<td>Multicentre</td>
<td>Janssen-Cilag</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Corwin et al</td>
<td>Multicentre</td>
<td>Ortho-Biotech</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Adequate</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*The Jadad scale gives a score for methodologic quality based on the reported methods and description of randomization (0–2 points), blinding (0–2 points) and participant withdrawals (0–1 point). Possible scores vary from 0 to 5, with a score of 5 indicating high methodologic quality.
Research

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> 40 000 U/wk

Restrictive (hemoglobin \( \leq 80 \text{ g/L} \))

Liberal (hemoglobin \( \geq 90 \text{ g/L} \))

High

Unblinded

Adequate allocation concealment

Erythropoietin Transfusion practice Methodologic quality

Odds ratio (95% CI)

Subgroup

Erythropoietin

40 000 U/wk

> 40 000 U/wk

Transfusion practice

Restrictive (hemoglobin \( \leq 80 \text{ g/L} \))

Liberal (hemoglobin \( \geq 90 \text{ g/L} \))

Methodologic quality

High

Unblinded

Adequate allocation concealment

Figure 2: Analysis of mortality in selected trials of erythropoietin use in critically ill patients. Note: EPO = erythropoietin, CI = confidence interval.

Figure 3: Mortality sensitivity analysis of studies included in the meta-analysis of erythropoietin use in critically ill patients. Note: CI = confidence interval.
quate allocation concealment, the pooled OR for death was 0.84 (95% CI 0.68–1.04, I² = 0%).8,11

Length of stay and ventilator use
Of the 9 included studies, 3 reported a similar median length of hospital stay for the erythropoietin and control groups (19 and 21 days;4 15 and 15 days;6 68 and 62 days7). These studies included 84.0% (2794/3326) of the randomized study population.8,9,12 No measures of variation were provided. Outcomes that reflected the length of time spent in an intensive care unit were reported in 4 studies as the median or mean length of stay in an intensive care unit, and 1 study reported “intensive care unit-free days.”8–10 Regardless of this difference in reporting, the amount of time spent in an intensive care unit was similar in all studies. Four of the studies reported outcomes pertaining to ventilator use.8,9,11,12 None of the studies found a statistically significant difference in the duration of mechanical ventilation, the number of ventilator-free days or successful weaning.8,9,11,12 Length of stay and ventilator use were not suitable for pooled analyses owing to variation in the reporting methods.

Adverse events
Six of the studies included information about adverse events (Table 3); however, most adverse events, diagnostic procedures and surveillance mechanisms were not clearly or reproducibly defined. One study reported the acquired incidence of myocardial infarction to be 2.1% (15/728) among patients who received erythropoietin, compared with 0.8% (6/720) in the control group (OR 2.50, 95% CI 0.97–6.49).9 Only 1 study reported data on the development of hypertension (Table 3).10

Five of the studies reported deep vein thrombosis as an adverse event.1,8,9,11,13 No study reported systematic screening methods for venous thrombosis. The pooled OR for the occurrence of deep vein thrombosis associated with erythropoietin use was 1.32 (95% CI 0.95–1.84, I² = 0%).

Given that the presumed benefit of erythropoietin is a reduced need for transfusion, we would expect that there would be parallel reductions in blood use and transfusion-related adverse events, such as transfusion-associated circulatory overload, transfusion-related acute lung injury and bloodstream infections. None of the studies reported transfusion reactions, pulmonary edema or acute lung injury. Bloodstream infections were not reported, but the proportion of patients with an acquired diagnosis of sepsis was reported in 3 studies and was not significantly different between the treatment and control groups (OR 0.95, 95% CI 0.69–1.30, I² = 0%).8,9,15

Transfusion-related outcomes
The ability of erythropoietin to prevent the need for at least 1 red blood cell transfusion (i.e., transfusion independence) was evaluated in 7 studies.1,8–12,15 Erythropoietin, compared with placebo, significantly reduced the odds of a patient receiving at least 1 transfusion (OR 0.73, 95% CI 0.64–0.84, I² = 54.7%) (Figure 4). Significant heterogeneity was evident in the pooled estimate, which could not be explained by variations in drug dosing, transfusion strategy (restrictive v. liberal), patient population or methodologic quality. The baseline transfusion rate did not correlate with individual study effect sizes.

The impact of erythropoietin therapy on the mean number

Table 3: Erythropoietin- and transfusion-related adverse events reported in the 9 studies included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
<th>Hypertension</th>
<th>Deep venous thrombosis</th>
<th>Blood-stream infection or sepsis</th>
<th>Transfusion reaction</th>
<th>Pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still et al13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>EPO: 3 (15.8) Control: 2 (9.5)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gabriel et al10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Corwin et al11</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>EPO: 4 (5.0) Control: 4 (5.0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Van Iperen et al14</td>
<td>NR</td>
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<td>Corwin et al8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>EPO: 14 (2.1) Control: 15 (2.3)</td>
<td>EPO: 31 (4.7) Control: 30 (4.6)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Georgopoulos et al11</td>
<td>NR</td>
<td>EPO: 4 (4.0) Control: 3 (6.2)</td>
<td>NR</td>
<td>EPO: 1 (1.0) Control: 2 (4.2)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Silver et al12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
</tr>
<tr>
<td>Vincent et al15</td>
<td>NR</td>
<td>EPO: 1 (4.0) Control: 2 (4.2)</td>
<td>NR</td>
<td>EPO: 3 (6.2) Control: 3 (12)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Corwin et al8</td>
<td>EPO: 15 (2.1) Control: 6 (0.8)</td>
<td>EPO: 14 (1.9) Control: 16 (2.2)</td>
<td>NR</td>
<td>EPO: 63 (8.7) Control: 42 (5.8)</td>
<td>EPO: 47 (6.5) Control: 50 (6.9)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: EPO = erythropoietin, NR = not reported.
of units of red blood cells transfused per patient was evaluated in 5 of the 9 studies.\textsuperscript{8,9,11,12,14} Erythropoietin use, compared with a placebo or no therapy, was associated with a decrease in the number of units transfused per patient (weighted mean difference $-0.41$ units per patient, 95% CI $-0.74$ to $-0.10$, $I^2 = 79.2\%$). This decrease represents a transfusion savings of less than 0.5 units per patient.

The most recent study reported the widespread adoption of a restrictive transfusion practice (hemoglobin $\leq 80$ g/L).\textsuperscript{9} Erythropoietin did not reduce the proportion of patients who required transfusion of at least 1 unit of red blood cells in the context of a restrictive transfusion strategy.

**Publication bias**

We minimized the potential for publication bias by conducting a thorough literature search that included searching grey literature and consulting with content experts. We also generated funnel plots for the outcomes of death and transfusion independence. No obvious patterns in these plots suggested publication bias; however, the inclusion of only 9 studies limits possible inferences.\textsuperscript{21} Variation observed in these plots may have been because of differences in methodologic quality, target populations or treatment regimens.

**Interpretation**

We found insufficient evidence to infer that erythropoietin decreases mortality or improves other clinically important outcomes among patients who are critically ill. Overall, the risk of death was decreased by 14% with erythropoietin use; however, the boundaries of the 95% confidence interval could not exclude an increase in all-cause mortality as high as 5%. There is no evidence to suggest erythropoietin shortens the length of stay in intensive care units or hospitals or shortens the duration of mechanical ventilation. Erythropoietin reduced the proportion of patients who required red blood cell transfusions; however, this reduction all but disappeared in the latest trial,\textsuperscript{9} which adopted a restrictive transfusion practice. Moreover, about 46% of patients required a transfusion despite receiving erythropoietin. The number of transfusions saved by use of erythropoietin was less than 1 unit per patient.

Many of the included trials had limited or discrepant reports of adverse events; thus, it is difficult to ascertain whether erythropoietin use was associated with an increase or a decrease in the occurrence of major adverse events, including myocardial infarction, hypertension, blood-stream infections or transfusion reactions. In the largest and most recent clinical study,\textsuperscript{9} the occurrence of clinically relevant thrombotic vascular events, including deep vein thrombosis, was higher among patients receiving erythropoietin than among those in the control group. Although the pooled OR for deep vein thrombosis did not reach statistical significance, underdetection and underreporting of adverse events probably influenced this analysis.

Erythropoietin did not reduce mortality in the overall intensive care unit population; however, 2 separate studies by Corwin and colleagues reported a significant reduction in mortality among patients with multiple trauma admitted to intensive care units in the United States.\textsuperscript{8,9} In this subgroup, the pooled OR for death was 0.42 (95% CI 0.29–0.73). Al-

![Figure 4: Analysis of transfusion independence among critically ill patients who received erythropoietin or control (placebo or no intervention). EPO = erythropoietin, CI = confidence interval.](image-url)
Though this analysis is intriguing, it can be interpreted only as hypothesis-generating because pooled analysis of subgroups could amplify systemic bias. Low event rates in the trauma subgroup (29 deaths among 716 with trauma in the erythropoietin group v. 59 deaths among 797 with trauma in the control group) also provide for unstable estimates of the treatment effect. Lastly, as shown in the most recent study, the apparent reduction in mortality in the trauma group occurred in absence of any measurable reduction in transfusions. The current scientific understanding of the transfusion-independent roles of erythropoietin is limited. This finding must be confirmed through future basic science investigations and prospective clinical studies. Cook and Crowther, commenting on the lastest erythropoietin trial, urge caution and the need for a large rigorous randomized trial to evaluate whether erythropoietin is beneficial in patients with multiple trauma.

The use of erythropoietin in patients with chronic kidney disease and cancer is known to be associated with specific adverse events, including cardiovascular events and thrombosis. Despite this knowledge, only 1 study reported adverse events due to myocardial infarction, and only 1 study reported events due to hypertension. Of the 9 included studies, 5 reported events due to deep vein thrombosis. The largest study reported significantly increased rates of deep vein thrombosis and other clinically relevant vascular events associated with erythropoietin use (OR 1.55, 95% CI 1.15–2.10), despite the exclusion of high-risk patients (history of pulmonary embolus, deep venous thrombosis, ischemic stroke, other arterial or venous thrombotic event or chronic hypercoagulable disorders) with a history of arterial or venous thrombotic events. We hypothesize that the generalized use of erythropoietin outside the context of a clinical trial in patients who are at high risk of arterial or venous thrombosis will be associated with an even greater risk of adverse thrombotic events and a higher risk-to-benefit ratio. Given the known adverse thrombotic consequences of erythropoietin, future trials must include mechanisms for systematic surveillance to ensure adequate detection of relevant adverse events.

The main limitation of our study is the methodologic limitations of the primary studies. Erythropoietin-dosing regimens and the duration of follow-up varied substantially between the studies. The total dose of erythropoietin administered could not be abstracted for each trial. This limitation is minimized since all dosing regimens were “high” based on the standard indication for this drug. Furthermore, subgroup analysis demonstrated consistent effects among patients receiving more or less than 40,000 units of erythropoietin per week. Another limitation of our systematic review is that we did not contact industry representatives to find additional relevant, yet unpublished, studies.

Several measures of study quality have been developed, including the Jadad score and the Schulz criteria. The limitations of these empiric techniques are demonstrated in this review. Although 3 studies received the highest Jadad score attainable, 1 of the 3 studies had a lost-to-follow-up rate of 27% and the hemoglobin concentration before transfusion was significantly lower among patients in the control group than among those in the treatment group. The risk for bias within this trial highlights the need to carefully consider each aspect of the trials included in a systematic review.

Maintaining adequate blinding throughout the duration of a study is essential. Should a study become unblinded, the introduction of systematic error, or bias, threatens its validity. Lower degrees of blinding are associated with greater apparent treatment effects. Given the availability of hemoglobin measurements in the intensive care unit, blinding procedures could have been compromised in any of the 7 blinded studies included in this review. Formal testing of the blinding strategy was not reported in any of the included studies, and the adequacy of the blinding procedures used is therefore unknown.

In summary, at this time we do not recommend the routine use of erythropoietin-receptor agonists in critically ill patients because of a very small decrease in the use of red blood cell transfusions and insufficient evidence to determine whether treatment results in clinically important benefits. Before widespread use of this product, we recommend further research to better explore potential benefits and harms of erythropoietin-receptor agonists in patients with multiple trauma. We also encourage researchers to conduct and report more detailed evaluations of anticipated and relevant adverse events within clinical trials.

This article has been peer reviewed.

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