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Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Mesgarpour B, Heidinger BH, Roth D, Schmitz S, Walsh CD, Herkner H

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	10
Figure 2.	14
Figure 3.	17
Figure 4.	20
Figure 5.	22
Figure 6.	23
Figure 7.	25
Figure 8.	26
DISCUSSION	28
AUTHORS' CONCLUSIONS	29
ACKNOWLEDGEMENTS	30
REFERENCES	31
CHARACTERISTICS OF STUDIES	41
DATA AND ANALYSES	107
Analysis 1.1. Comparison 1 ESAs versus placebo or no ESAs, Outcome 1 Any adverse event.	110
Analysis 1.2. Comparison 1 ESAs versus placebo or no ESAs, Outcome 2 Any serious adverse events_RCT.	111
Analysis 1.3. Comparison 1 ESAs versus placebo or no ESAs, Outcome 3 Venous thromboembolism (VTE).	111
Analysis 1.4. Comparison 1 ESAs versus placebo or no ESAs, Outcome 4 Deep Venous Thrombosis.	112
Analysis 1.5. Comparison 1 ESAs versus placebo or no ESAs, Outcome 5 Stroke _ RCT.	112
Analysis 1.6. Comparison 1 ESAs versus placebo or no ESAs, Outcome 6 Myocardial infarction_RCT.	113
Analysis 1.7. Comparison 1 ESAs versus placebo or no ESAs, Outcome 7 Pulmonary embolism.	113
Analysis 1.8. Comparison 1 ESAs versus placebo or no ESAs, Outcome 8 Sepsis.	114
Analysis 1.9. Comparison 1 ESAs versus placebo or no ESAs, Outcome 9 GI disorders_RCT.	114
Analysis 1.10. Comparison 1 ESAs versus placebo or no ESAs, Outcome 10 Cardiac arrest or ventricular fibrillation_RCT.	115
Analysis 1.11. Comparison 1 ESAs versus placebo or no ESAs, Outcome 11 Hypertension_RCT.	115
Analysis 1.12. Comparison 1 ESAs versus placebo or no ESAs, Outcome 12 Heart rate and rhythm disorders_RCT.	116
Analysis 1.13. Comparison 1 ESAs versus placebo or no ESAs, Outcome 13 Respiratory Distress or insufficiency.	116
Analysis 1.14. Comparison 1 ESAs versus placebo or no ESAs, Outcome 14 Pneumonia.	116
Analysis 1.15. Comparison 1 ESAs versus placebo or no ESAs, Outcome 15 Platelet, bleeding and clotting disorders.	117
Analysis 1.16. Comparison 1 ESAs versus placebo or no ESAs, Outcome 16 Seizure.	118
Analysis 1.17. Comparison 1 ESAs versus placebo or no ESAs, Outcome 17 Cardiovascular disorders, general_RCT.	118
Analysis 1.18. Comparison 1 ESAs versus placebo or no ESAs, Outcome 18 Renal failure.	119
Analysis 1.19. Comparison 1 ESAs versus placebo or no ESAs, Outcome 19 Infection_RCT.	119
Analysis 1.20. Comparison 1 ESAs versus placebo or no ESAs, Outcome 20 Heart Failure_RCT.	119
Analysis 1.21. Comparison 1 ESAs versus placebo or no ESAs, Outcome 21 Thrombocytosis.	120
Analysis 1.22. Comparison 1 ESAs versus placebo or no ESAs, Outcome 22 Stent thrombosis_RCT.	120
Analysis 1.23. Comparison 1 ESAs versus placebo or no ESAs, Outcome 23 Dyspnea_RCT.	121
Analysis 1.24. Comparison 1 ESAs versus placebo or no ESAs, Outcome 24 Abscess_RCT.	121
Analysis 1.25. Comparison 1 ESAs versus placebo or no ESAs, Outcome 25 Multiple-organ failure_RCT.	121
Analysis 1.26. Comparison 1 ESAs versus placebo or no ESAs, Outcome 26 Cerebrovascular event_RCT.	121
Analysis 1.27. Comparison 1 ESAs versus placebo or no ESAs, Outcome 27 Urinary tract infection_RCT.	122
Analysis 1.28. Comparison 1 ESAs versus placebo or no ESAs, Outcome 28 Vascular (extracardiac) disorders_RCT.	122

Analysis 1.29. Comparison 1 ESAs versus placebo or no ESAs, Outcome 29 Central and peripheral nervous system disorders_RCT.	122
Analysis 1.30. Comparison 1 ESAs versus placebo or no ESAs, Outcome 30 Musculoskeletal_RCT.	123
Analysis 1.31. Comparison 1 ESAs versus placebo or no ESAs, Outcome 31 IRA revascularization_RCT.	123
Analysis 1.32. Comparison 1 ESAs versus placebo or no ESAs, Outcome 32 CABG_RCT.	123
Analysis 1.33. Comparison 1 ESAs versus placebo or no ESAs, Outcome 33 LV thrombus_RCT.	124
Analysis 1.34. Comparison 1 ESAs versus placebo or no ESAs, Outcome 34 Hyperglycemia_RCT.	124
Analysis 1.35. Comparison 1 ESAs versus placebo or no ESAs, Outcome 35 Ventriculitis_RCT.	124
Analysis 1.36. Comparison 1 ESAs versus placebo or no ESAs, Outcome 36 Metabolic/laboratory_RCT.	124
Analysis 1.37. Comparison 1 ESAs versus placebo or no ESAs, Outcome 37 Hypokalemia_RCT.	125
Analysis 1.38. Comparison 1 ESAs versus placebo or no ESAs, Outcome 38 Hypotension_RCT.	125
Analysis 1.39. Comparison 1 ESAs versus placebo or no ESAs, Outcome 39 Neurology_RCT.	125
Analysis 2.1. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 1 mortality_trauma.	135
Analysis 2.2. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 2 Mortality_RCT_subgroup by ESAs type.	136
Analysis 2.3. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 3 Mortality_RCT_subgroup by dose. ..	137
Analysis 2.4. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 4 Mortality_Subgroup by ESAs effect. .	138
Analysis 2.5. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 5 Mortality_Subgroup by ESAs effect1.	139
Analysis 2.6. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 6 Mortality_Subgroup by anaemia. ...	140
Analysis 2.7. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 7 Mortality_Subgroup by anaemia1. .	142
Analysis 2.8. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 8 Any adverse event_Subgroup by type of EPO.	143
Analysis 2.9. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 9 Any adverse event_Subgroup by dose of ESAs.	144
Analysis 2.10. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 10 Any adverse event_Subgroup by effect of ESAs.	144
Analysis 2.11. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 11 Any adverse event_Subgroup by anaemia.	145
Analysis 2.12. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 12 Any SAEs_Subgroup by type of ESAs.	146
Analysis 2.13. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 13 Any SAEs_Subgroup by dose of ESAs.	147
Analysis 2.14. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 14 Any SAEs_Subgroup by effect of ESAs.	147
Analysis 2.15. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 15 Any SAEs_Subgroup by anaemia.	148
Analysis 2.16. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 16 VTE_Subgroup by type of ESAs. ..	149
Analysis 2.17. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 17 VTE_Subgroup by dose of ESAs_RCTs.	150
Analysis 2.18. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 18 VTE_Subgroup by effect of ESAs. .	150
Analysis 2.19. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 19 VTE_Subgroup by anaemia.	151
Analysis 2.20. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 20 Stroke _ Subgroup by type of ESAs.	152
Analysis 2.21. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 21 Stroke _ Subgroup by dose of ESAs.	153
Analysis 2.22. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 22 Stroke _ Subgroup by effect of ESAs.	153
Analysis 2.23. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 23 Stroke _ Subgroup by anaemia. ..	154
Analysis 2.24. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 24 MI_Subgroup by type of ESAs. ...	155
Analysis 2.25. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 25 MI_Subgroup by dose of ESAs. ...	156
Analysis 2.26. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 26 MI_Subgroup by effect of ESAs. ..	156
Analysis 2.27. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 27 MI_Subgroup by anaemia.	157
Analysis 2.28. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 28 DVT_Subgroup by type of ESAs. ..	158
Analysis 2.29. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 29 DVT_Subgroup by dose of ESAs. .	158

Analysis 2.30. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 30 DVT_Subgroup by effect of ESAs. .	159
Analysis 2.31. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 31 DVT_Subgroup by anaemia.	160
Analysis 2.32. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 32 PE_Subgroup by type of ESAs. ...	161
Analysis 2.33. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 33 PE_Subgroup by dose of ESAs. ...	162
Analysis 2.34. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 34 PE_Subgroup by effect of ESAs. ..	162
Analysis 2.35. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 35 PE_Subgroup by anaemia.	163
Analysis 2.36. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 36 Sepsis_Subgroup by type of ESAs.	164
Analysis 2.37. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 37 Sepsis_Subgroup by effect of ESAs.	164
Analysis 2.38. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 38 Sepsis_Subgroup by anaemia. ...	165
Analysis 2.39. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 39 GI disorders_Subgroup by type of ESAs.	166
Analysis 2.40. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 40 GI disorders_Subgroup by effect of ESAs.	166
Analysis 2.41. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 41 Cardiac arrest_Subgroup by type of ESAs.	167
Analysis 2.42. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 42 Hypertension_Subgroup by type of ESAs.	168
Analysis 2.43. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 43 Hypertension_Subgroup by dose of ESAs.	168
Analysis 2.44. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 44 Hypertension_Subgroup by effect of ESAs.	169
Analysis 2.45. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 45 Hypertension_Subgroup by anaemia.	169
Analysis 2.46. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 46 Heart rate_Subgroup by type of ESAs.	170
Analysis 2.47. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 47 Heart rate_Subgroup by effect of ESAs.	171
Analysis 2.48. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 48 Heart rate_Subgroup by anaemia.	171
Analysis 2.49. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 49 Respiratory Distress_Subgroup by anaemia.	172
Analysis 2.50. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 50 Seizure_Subgroup by type of ESAs.	172
Analysis 2.51. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 51 Seizure_Subgroup by dose of ESAs.	173
Analysis 2.52. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 52 Seizure_Subgroup by effect of ESAs.	174
Analysis 2.53. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 53 Seizure_Subgroup by anaemia. ..	174
Analysis 2.54. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 54 Cardiovascular disorders_Subgroup by dose of ESAs.	175
Analysis 2.55. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 55 Cardiovascular disorders_Subgroup by effect of ESAs.	175
Analysis 2.56. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 56 Cardiovascular disorders_Subgroup by anaemia.	176
Analysis 2.57. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 57 Heart Failure_Subgroup by type of ESAs.	177
Analysis 2.58. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 58 Heart Failure_Subgroup by dose of ESAs.	177
Analysis 2.59. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 59 Heart Failure_Subgroup by effect of ESAs.	178
Analysis 2.60. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 60 Heart Failure_Subgroup by anaemia.	178
ADDITIONAL TABLES	179
APPENDICES	183
WHAT'S NEW	191

CONTRIBUTIONS OF AUTHORS	191
DECLARATIONS OF INTEREST	192
SOURCES OF SUPPORT	192
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	192
INDEX TERMS	193

[Intervention Review]

Harms of off-label erythropoiesis-stimulating agents for critically ill people

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ABSTRACT

Background

Anaemia is a common problem experienced by critically-ill people. Treatment with erythropoiesis-stimulating agents (ESAs) has been used as a pharmacologic strategy when the blunted response of endogenous erythropoietin has been reported in critically-ill people. The use of ESAs becomes more important where adverse clinical outcomes of transfusing blood products is a limitation. However, this indication for ESAs is not licensed by regulatory authorities and is called off-label use. Recent studies concern the harm of ESAs in a critical care setting.

Objectives

To focus on harms in assessing the effects of erythropoiesis-stimulating agents (ESAs), alone or in combination, compared with placebo, no treatment or a different active treatment regimen when administered off-label to critically-ill people.

Search methods

We conducted a systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO via OvidSP, CINAHL, all evidence-based medicine (EBM) reviews including IPA and SCI-Expanded, Conference Proceedings Citation Index- Science, BIOSIS Previews and TOXLINE up to February 2017. We also searched trials registries, checked reference lists of relevant studies and tracked their citations by using SciVerse Scopus.

Selection criteria

We considered randomized controlled trials (RCTs) and controlled observational studies, which compared scheduled systemic administration of ESAs versus other effective interventions, placebo or no treatment in critically-ill people.

Data collection and analysis

Two review authors independently screened and evaluated the eligibility of retrieved records, extracted data and assessed the risks of bias and quality of the included studies. We resolved differences in opinion by consensus or by involving a third review author. We assessed the evidence using GRADE and created a 'Summary of findings' table. We used fixed-effect or random-effects models, depending on the heterogeneity between studies. We fitted three-level hierarchical Bayesian models to calculate overall treatment effect estimates.

Main results

Of the 27,865 records identified, 39 clinical trials and 14 observational studies, including a total of 945,240 participants, were eligible for inclusion. Five studies are awaiting classification. Overall, we found 114 adverse events in 33 studies (30 RCTs and three observational studies), and mortality was reported in 41 studies (32 RCTs and nine observational studies). Most studies were at low to moderate risk of bias for harms outcomes. However, overall harm assessment and reporting were of moderate to low quality in the RCTs, and of low quality in the observational studies. We downgraded the GRADE quality of evidence for venous thromboembolism and mortality to very low and low, respectively, because of risk of bias, high inconsistency, imprecision and limitations of study design.

It is unclear whether there is an increase in the risk of any adverse events (Bayesian risk ratio (RR) 1.05, 95% confidence interval (CI) 0.93 to 1.21; 3099 participants; 9 studies; low-quality evidence) or venous thromboembolism (Bayesian RR 1.04, 95% CI 0.70 to 1.41; 18,917 participants; 18 studies; very low-quality evidence).

There was a decreased risk of mortality with off-label use of ESAs in critically-ill people (Bayesian RR 0.76, 95% CI 0.61 to 0.92; 930,470 participants; 34 studies; low-quality evidence).

Authors' conclusions

Low quality of evidence suggests that off-label use of ESAs may reduce mortality in a critical care setting. There was a lack of high-quality evidence about the harm of ESAs in critically-ill people. The information for biosimilar ESAs is less conclusive. Most studies neither evaluated ESAs' harm as a primary outcome nor predefined adverse events. Any further studies of ESA should address the quality of evaluating, recording and reporting of adverse events.

PLAIN LANGUAGE SUMMARY

Harms of off-label erythropoiesis-stimulating agents for critically-ill people

Bottom line

Erythropoiesis-stimulating agents (ESAs) are medicines which stimulate red blood cell production. They can be given into a vein or under the skin. They are used in critically-ill people, despite not being licensed by marketing authorities for this indication (i.e. off-label). We were unable to find relevant harms associated with these medicines but found beneficial effects on the likelihood of dying, based on low- to moderate-quality evidence.

Background

Critically-ill people frequently suffer from a decrease in the amount of red blood cells or haemoglobin in their blood. If preventive measures do not work, transfusion of donor blood is an effective treatment but it carries known risks including allergic/immunologic reactions, volume and electrolyte overload, and infections. Alternatively, ESAs can be used to stimulate a person's own red blood cell production. However, this needs to be balanced against the risks associated with ESAs, which are not licensed by marketing authorities for most critically-ill people.

Study characteristics

We searched 10 databases for studies where ESAs were used to treat critically-ill people. The evidence is current to February 2017. We found 53 studies, involving 945,240 participants treated with epoetin-alfa, epoetin-beta, and darbepoetin-alfa or placebo. Five studies are awaiting classification.

Key results

Based on mainly low-quality evidence, we were unable to exclude relevant harms in terms of adverse effects of ESAs. 'Adverse effects' included any adverse events and problems from blood clotting in the veins. However, we found low-quality evidence for protective effects on the overall risk of dying in critically-ill people.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Risk of adverse events associated with ESAs use in RCTs and observational studies of critical-ill people

Patient or population: Critically-ill people

Settings: ICUs mainly in US, Europe and Middle East

Intervention: ESAs parenteral

Comparison: No ESAs (including no treatment, placebo, or other treatment)

Outcomes	Illustrative comparative risks* (95% CI)		Bayesian relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non ESAs	ESAs				
Any adverse event Follow-up: 28 days to 6 months	645 per 1000¹ 421 per 1000 ²	677 per 1000¹ (600 to 780) 442 per 1000² (391 to 509)	RR 1.05 (0.93 to 1.21)	3099 (8 RCTs and 1 observational)	⊕⊕⊕⊕ low³	There may be little or no effect on any adverse events.
Venous thromboembolism Follow-up: 5 days to 12 months	19 per 1000¹ 51 per 1000 ²	20 per 1000¹ (13 to 27) 53 per 1000² (36 to 72)	RR 1.04 (0.70 to 1.41)	18,917 (13 RCTs and 5 observational)	⊕⊕⊕⊕ very low⁴	There may be little or no effect on venous thromboembolism.
Mortality Follow-up: 5 to 30 days	68 per 1000¹ 150 per 1000 ²	52 per 1000¹ (41 to 62) 114 per 1000² (91 to 138)	RR 0.76 (0.61 to 0.92)	930,470 (25 trials and 9 observational)	⊕⊕⊕⊕ low⁵	There is possibly a decrease in mortality.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCTs:** randomized controlled trials; **RR:** Bayesian Risk Ratio combining both randomized and non-randomized studies;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

¹Mean baseline risk.

²Medium risk.

³Downgraded two levels due to high risk of bias in one study and study design limitation (one observational study).

⁴Downgraded three levels due to study design limitation (five observational studies), a high risk of bias in two studies, and high level of statistical heterogeneity.

⁵Downgraded two levels due to study design limitation (nine observational studies), a high risk of bias in four studies, and high level of heterogeneity.

BACKGROUND

Description of the condition

Patients requiring intensive care are defined as critically ill (Thomas 2006). These patients are susceptible to anaemia and are vulnerable to its adverse consequences. The prevalence of anaemia among those admitted to the intensive care unit (ICU) is about 67% (Corwin 2004); anaemia is frequently treated with allogeneic red blood cell (RBC) transfusions (Corwin 2006).

Allogeneic RBC transfusion has been found to be a risk factor for morbidity and mortality in critical-care patients (Clevenger 2014; Hopewell 2013; Marik 2008); there is therefore an urgent need for safe substitution. It is noteworthy that this evidence comes only from observational studies and is prone to confounding by indication. Even a restrictive RBC transfusion strategy (trigger for transfusion with low haemoglobin level of 7 g/dL or 8 g/dL) has no impact on the risk of 30-day mortality compared with a liberal transfusion strategy in critically-ill people (Carson 2016). Accordingly, anaemia might well constitute a therapeutic target, but also a prognostic factor, or even an adaptive beneficial response (Zarychanski 2008). Reduced endogenous production of the haematopoietic growth factor erythropoietin is observed in most ICU patients; consequently, administration of erythropoiesis-stimulating agents (ESAs) has been suggested as a therapeutic option (Zarychanski 2007). The application of ESAs has been further extended in acute cardiovascular and neuronal disorders because the biological role of human erythropoietin and its receptor in tissue outside of the haematopoietic system has been recognized (Maiese 2005).

Description of the intervention

A synthetic form of human erythropoietin, which is produced by recombinant DNA technology, became available in the 1980s (recombinant human erythropoietin (rHuEPO)). Several currently-available ESAs such as epoetin-alfa, epoetin-beta, epoetin-omega, epoetin-delta and darbepoetin-alfa are administered as intravenous or subcutaneous injections. These agents are analogues of recombinant erythropoietin with the same amino acid sequence, but their glycosylation pattern varies because of type- and host cell-specific differences in the production process. Darbepoetin-alfa is a novel erythropoiesis-stimulating protein that carries two additional glycosylation sites and produces a longer half-life and increased potency (Goldsmith 2010). ESAs are among the most widely manufactured recombinant biosimilar proteins in the world (Walsh 2010).

ESAs are approved for treatment of anaemia caused by end-stage renal disease, anaemia associated with HIV infection and anaemia that occurs with non-myeloid cancers in which anaemia is due to concomitantly-administered chemotherapy used to reduce the number of transfusions in patients scheduled for major surgery, except cardiac or vascular surgery (Fishbane 2010). Administration of ESAs to critically-ill people with none of the aforementioned conditions is outside the license of these agents and can be considered as an off-label indication.

Vekeman and co-workers conducted two retrospective analyses of data from participants admitted to more than 500 hospitals across the United States and treated with ESAs from July 2002 to March 2005. These investigators identified 72,903 hospitalized patients

(epoetin-alfa: 66,804; darbepoetin-alfa: 6099) treated with ESAs in the ICU setting (Vekeman 2006); 25,645 hospitalized patients with cancer (epoetin-alfa: 22,873; darbepoetin-alfa: 2772) and 66,822 hospitalized patients with chronic kidney disease (CKD) (epoetin-alfa: 60,079; darbepoetin-alfa: 6743) (Vekeman 2007). This study, which was conducted to evaluate erythropoiesis-stimulating protein use and clinical outcomes in hospitalized patients (ASSESS), used ESAs among a heterogeneous group of study participants with anaemia in the ICU at 19 sites across the United States in 2005 (Brophy 2008). On the basis of the overall cumulative dose per ICU stay, the costs of treatment of critically-ill people with erythropoietin-alfa and darbepoetin were estimated at approximately USD 576 and USD 841, respectively (Vekeman 2006).

How the intervention might work

Erythropoietin (EPO) is an endogenous glycoprotein hormone that is mainly produced in the kidneys under hypoxic conditions. EPO is well known for its role in the production and differentiation of erythroid progenitor cells. However, a variety of non-haematopoietic activities of EPO have been identified, including protection from apoptosis and inflammation (Chateauvieux 2011). Nonetheless, the potential efficacy of exogenous EPO and its therapeutic strategies including the onset, extent, and duration of treatment needs to be explored in clinical studies (Maiese 2016; Nguyen 2014). Increased risk of malignancy progression and reduced survival of people with anaemic cancer treated with ESAs suggested avoiding chronic use of ESAs in this setting (Debeljak 2014). Anaemia, which is common in critically-ill people, may be associated with a blunted EPO response (Corwin 2004; DeAngelo 2005; Hobisch-Hagen 2001; Krafte-Jacobs 1994; Rogiers 1997) and subsequently with inadequate stimulation of bone marrow erythropoiesis. Exogenous EPO therapy could therefore result in higher haemoglobin concentrations and less exposure to RBC transfusion.

The results of a growing body of controlled trials show that ESA treatment might not be as safe as was initially assumed. Systematic reviews of on-label use of ESAs have raised concerns about safety and increasing mortality (Bohlius 2009; Bohlius 2012; Phrommintikul 2007; Tonelli 2009). A meta-analysis of 27 randomized controlled trials (RCTs) involving 10,452 participants with CKD concluded that targeting higher haemoglobin concentration increases risks for fatal and non-fatal stroke, hypertension and vascular access thrombosis compared with targeting lower haemoglobin concentration (Palmer 2010). A meta-analysis that included 52 RCTs ($n = 12,006$) found that ESAs increased the risk of thrombotic events (risk ratio (RR) 1.69, 95% confidence interval (CI) 1.27 to 2.24) and serious adverse events (RR 1.16, 95% CI 1.08 to 1.25) in participants with cancer-related anaemia. However, ESAs improved some disease-specific measures of quality of life and decreased the use of blood transfusions. Routine use of ESAs in people with cancer-related anaemia as an alternative to blood transfusion is therefore not recommended (Tonelli 2009). A randomized, double-blind, placebo-controlled, multicentre trial ($N = 1460$) in anaemic critically-ill participants demonstrated an increased incidence of thrombotic vascular events among participants in the epoetin-alfa group compared with those in the placebo group (16.5% versus 11.5%; hazard ratio 1.41, 95% CI 1.06 to 1.86) (Corwin 2007b). Moreover, the US Food and Drug Administration (FDA) restricted the use and prescribing of ESAs under a risk management programme

known as a risk evaluation and mitigation strategy (REMS) following studies showing that ESAs can increase the risk of tumour growth and can shorten survival in people with cancer (FDA 2010).

Why it is important to do this review

Biological and pharmacological effects of drugs vary across several medical conditions. Beneficial and adverse effects of ESAs have been studied extensively in certain clinical settings (Aher 2012; Bohlius 2012; Cody 2016; Lambin 2009; Martí-Carvajal 2013; Ngo 2010; Tonia 2012), but we cannot necessarily extrapolate study results from one population to another. On the other hand, ESAs are frequently used beyond their label indications in critically-ill people (Vekeman 2006; Vekeman 2007), although not only drug cost but also the economic burden resulting from adverse drug reactions may substantially impact health systems. Therefore, in the absence of an unequivocal benefit, potential harm in this vulnerable population needs to be systematically assessed and analysed and the findings made readily available for evidence-based practice. We recently published a safety review in this field, but given that eight studies have been published since 2010 (Mesgarpour 2013a), and several studies are ongoing (Mesgarpour 2013b), a regularly-updated safety review within the Cochrane Library is an obvious measure.

OBJECTIVES

To focus on harms, in assessing the effects of erythropoiesis-stimulating agents (ESAs) alone or in combination, compared with placebo, no treatment or a different active treatment regimen when administered off-label to critically-ill people

METHODS

Criteria for considering studies for this review

Types of studies

We include randomized controlled trials (RCTs) and controlled observational studies (cohort or case-control) investigating the effects of ESAs given for the treatment of any kind of critical illness unless its indication was approved by the European Medicine Agency (EMA) or the FDA (see Background and Types of interventions).

Types of participants

We considered studies with acutely and critically-ill adults and children. We excluded studies looking at neonates and infants (one month to one year of age) because erythropoietin-beta is approved by the EMA for preventing anaemia in premature babies (NeoRecormon 2016). We excluded animal experiments. An expert in intensive care medicine (HH) assessed the setting of 'critical illness' in the absence of a stringent definition of the condition.

Types of interventions

The intervention was the scheduled systemic administration of ESAs versus placebo, no treatment or any alternative active treatment. We considered administration of ESAs as on-label if used to treat anaemia due to CKD, anaemia due to chemotherapy in people with cancer or anaemia due to zidovudine in HIV-infected people. Some discrepancy has been noted between the EMA and the FDA regarding the indication for ESAs to reduce allogeneic RBC transfusions in people undergoing surgery (Abseamed 2016;

Binocrit 2016; Epoetin Alfa Hexal 2016; Epogen 2016; Procrit 2016); we therefore considered this indication as off-label when a study was done in a critically-ill population.

Types of outcome measures

Primary outcomes

1. We identified adverse effects of ESAs in a broad sweep scope, as suggested by Loke 2007.
2. We reported all adverse events as reported by study authors and specifically included any adverse event, any serious adverse event (SAE), thrombotic events (such as venous thromboembolism (VTE), deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, myocardial infarction (MI), stent thrombosis and intracardiac thrombotic masses), bleeding, cardiovascular events including hypertension, infection and sepsis, respiratory events, neurological events, renal events, gastrointestinal events and musculoskeletal events. We accepted authors' definitions of outcome events. We selected outcomes for presentation in the 'Summary of findings' table based on clinical importance.

Secondary outcomes

1. We determined total mortality (in the ICU, in the hospital and three weeks after discharge). If mortality was assessed at several time points in a study, we used data from the closest follow-up time to 30 days.

Search methods for identification of studies

Electronic searches

We searched for eligible studies in the following databases, without language restrictions:

1. Ovid SP MEDLINE (from 1946 to February 2017);
2. Ovid SP Embase (from 1980 to February 2017);
3. Ovid SP All EBM Reviews;
4. Ovid SP International Pharmaceutical Abstracts (from 1966 to February 2017);
5. Ovid SP PsycINFO (from 1806 to February 2017);
6. CINAHL (from 1980 to February 2017);
7. BIOSIS Previews (from 2000 to February 2017);
8. Science Citation Index Expanded (from 1900 to February 2017);
9. Conference Proceedings Citation Index-Science (from 1995 to February 2017);
10. TOXLINE (from 1965 to date) (BM).

'All EBM reviews' consist of seven resources, including:

1. Cochrane Central Register of Controlled Trials (CENTRAL) to January 2017;
2. Cochrane Database of Systematic Reviews (CDSR) 2005 to February 2017;
3. ACP Journal Club (1991 to February 2017);
4. Database of Abstracts of Reviews of Effects (DARE) 1st Quarter 2016;
5. Cochrane Methodology Register (CMR) 3rd Quarter 2012;
6. Health Technology Assessment (HTA) 4th Quarter 2016;
7. NHS Economic Evaluation Database (NHSEED) 1st Quarter 2016.

Access to Ovid SP PASCAL, which we planned to search, was no longer available. We updated our search on 28 February 2017.

We searched for key words that describe the condition or the intervention. We expanded the common names of ESAs to trade names and chemical synonyms (Mesgarpour 2013b) to enhance the sensitivity of the search. To increase the objectivity of our search, we analysed the contents of our non-Cochrane systematic review on ESAs in critically-ill people and its 48 included studies (Mesgarpour 2013a), by using the AntConc freeware concordance program (www.antlab.sci.waseda.ac.jp/) (BM). We did not combine the search results with methodological search filters (RCT or observational studies) to obtain a highly sensitive search.

The full detailed search strategies based on the databases are given in [Appendix 1](#).

Searching other resources

We planned to search current controlled trials and unpublished studies via the Internet (www.controlledtrials.com), by using the multiple database search option (*metaRegister of Controlled Trials*), but during our search update we found this database changed its scope and our search did not retrieve some of the previous studies. We therefore searched the WHO International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch/) and ClinicalTrials.gov registry (BM). We updated our search in February 2017. We also contacted the four main manufacturers of ESAs (Amgen, Roche, Janssen-Cilag, Ortho Biotech) (BM). Furthermore, we undertook backward and forward track citations of relevant studies identified from the initial searches using SciVerse Scopus (BM).

Data collection and analysis

Selection of studies

We exported all search results into the bibliographic software EndNote X5 and removed duplicates (BM). Two review authors (BM and BHH or DR) independently screened the studies for exclusion, first by title and second by abstract, using a screening algorithm with inclusion and exclusion criteria. For all possibly relevant studies, we retrieved full papers, and two review authors independently assessed them for inclusion and exclusion criteria. We resolved any differences in opinion by consensus or by involving a third review author (HH).

Data extraction and management

Two review authors (BM and BHH or DR) summarized data independently onto a structured extraction form based on study design. We compared the forms, and resolved discrepancies in data extraction by discussion or if necessary by recourse to a third review author (HH). BM and DR entered data into [RevMan 5.3](#). We extracted the following data: study characteristics, verification of eligibility, study design, study population, screening and baseline characteristics of participants, details of intervention and control, outcome measures, adverse events and mortality.

Assessment of risk of bias in included studies

Two review authors (BM and BHH or DR) independently evaluated the risks of bias of included studies. We used Cochrane's tool (Higgins 2011) for assessing risk of bias in RCTs. We assessed whether adequate methods were used to generate a random

sequence, whether allocation before assignment was concealed, whether the clinical staff were blinded to the intervention, whether the assessor of the outcome was blinded to the intervention, whether the outcome description was adequate, whether the outcome reporting was selective, whether the data were analysed by intention-to-treat and whether the study has received funding support from companies manufacturing ESAs.

For assessing risk of bias in observational studies, we used the Newcastle-Ottawa Scale (NOS) (Wells 2009). For cohort studies, we assessed whether the exposed cohort was representative, the method of selecting the non-exposed cohort, the method of exposure ascertainment, whether the outcome of interest was not present at the start of the studies, whether cohorts were comparable on the basis of the design or analysis, the method of outcome assessment used and whether follow-up was adequate and was long enough for outcomes to occur. For case-control studies, we assessed whether the case definition was adequate, whether the cases were representative, the details on selection and definitions of controls, whether cases and controls were comparable on the basis of the design and analysis, the method of exposure ascertainment used, whether the same method was used for ascertainment of cases and controls and whether the non-response rate was the same for both groups.

In addition, two review authors (BM and BHH or DR) independently assessed the quality of harms assessment and reporting in included studies using the McMaster Quality Assessment Scale of Harms (McHarm) (Santaguida 2008). We assessed whether the harms were predefined using standardized or precise definitions, whether serious and severe events were precisely defined, whether the number of deaths in each study group was specified or whether the reason(s) for not specifying them were given, whether the mode of harms collection was specified as active or passive, whether the study specified who collected the harms, whether the study specified the training or background of those who ascertained the harms and the timing and frequency of collection of the harms, whether the study used standard scale(s) or checklist(s) for harms collection, whether the study authors specified if the harms reported encompassed all events collected or a selected sample, whether the number of participants who withdrew or were lost to follow-up was specified for each study group, whether the total number of participants affected by harms was specified for each study arm, whether the number of each type of harmful event was specified for each study group and whether the types of analyses undertaken for harms data were specified. We also created a MCHarm graph by using [RevMan 5.3](#). We compared the results from both review authors and resolved disagreements by consensus or by recourse to a third review author (HH). We completed a 'Risk of bias' table for each eligible study and outcome in [RevMan 5.3](#) and supplemented these with the 'Risk of bias' graph for RCTs as well as observational studies.

Measures of treatment effect

For dichotomous data presented as absolute counts or relative frequencies, we presented results as risk ratios (RRs) with 95% confidence intervals (CIs).

Unit of analysis issues

Generally, the unit of analysis was a single participant. If required and sufficient data were available, we incorporated properly analysed cross-over and cluster-randomized trials into the meta-

analyses, using the generic inverse variance method in [RevMan 5.3](#) ([Higgins 2011](#)). We checked for unit-of-analysis errors if cross-over trials or cluster-randomized trials were included, and yielded appropriate solutions. For included studies with more than two treatment groups, we grouped together all experimental groups if clinically sensible, and compared them collectively with the control group ([Higgins 2011](#)), or performed pair-wise comparisons against the control but refrained from a meta-analysis across all arms in this situation.

Dealing with missing data

We contacted authors of study reports to request information on missing data, if applicable. We analysed data as available, and used no statistical models for data imputation.

Assessment of heterogeneity

We deemed data synthesis appropriate if clinical heterogeneity and methodological heterogeneity were negligible. We assessed clinical heterogeneity by judging the comparability of populations, conditions and treatments. We assessed methodological heterogeneity by classifying study design types. We assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and a Chi² test. We regarded statistical heterogeneity as substantial if I^2 was greater than 50% or the P value was less than 0.1 in the Chi² test for heterogeneity ([Higgins 2011](#)).

Assessment of reporting biases

We used [RevMan 5.3](#), and the R package *meta* ([Schwarzer 2012](#)), to create funnel plots of standard errors versus effect estimates to assess reporting bias and small-study effects, provided that 10 or more studies were available for each outcome. We assessed asymmetry by visual inspection and formally tested for it using the arcsine test proposed by [Rucker 2008](#), for data from studies for which valid n/N data were available, and the Egger test ([Egger 1997](#)), in Stata (Stata 11, Stata Corp, College Station, TX) when effect estimates with their standard errors were available. We considered P values less than 0.05 as statistically significant.

Data synthesis

We excluded trials with zero reported events in both arms from the analysis; such trials therefore do not contribute information. We performed a zero-cell correction when we found zero events in one of the trial arms, by adding 0.5 to all cells. Assuming considerable heterogeneity, we used random-effects models to calculate summary estimates in a meta-analysis. If we detected no heterogeneity, we used a fixed-effect meta-analysis. Ideally, observational studies and randomized studies should not be different if confounding is handled appropriately. However, confounding could not be excluded in the observational studies. We therefore considered this a relevant source of methodological heterogeneity. To combine data from RCTs and observational studies, we fitted a three-level hierarchical Bayesian model ([Prevost 2000](#); [Schmitz 2013](#); [Sutton 2008](#)). This approach allows for between-study variability (in the same way as a classical random-effects model does), together with between-design variability. In this way, the overall estimate makes use of all available information ([Higgins 2012](#)). We conducted these analyses within [RevMan 5.3](#), and WinBUGs using R version 3.3.0 and the R2WinBUGs package. For very rare events, we had planned to use the Peto odds ratio method ([Higgins 2011](#)). We did not apply any measures to control

for type I error rate for the multiple harm outcomes, assuming that a type II error (overlooking important harm) matters more than falsely accepting a harm signal ([Loke 2011](#)).

The Bayesian approach models the number of events per treatment group using a binomial likelihood. We assume a normal distribution for the log risk ratios. We deemed a uniform prior on [0,2] for the random effects variance and a uniform [0,1] on the probability of response in the control group sufficiently vague for each trial type. We chose a flat normal prior (mean 0 and precision 0.001) for the combined log risk ratio. Each model discarded 50,000 burn-in iterations and was run with 100,000 iterations in each of two chains. We recorded every 100th iteration. We analysed chains for convergence, and checked the effective sample size for each parameter of interest. We summarize posterior distributions of parameters of interest as 95% credible intervals. We present details of the WinBUGs model code in the appendix ([Web Appendix](#)).

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses according to the type and dosage of ESAs. We also attempted subgroup analysis according to baseline anaemia or indication as a non-haematopoietic drug. Post hoc, we also tested for subgroup effects of trauma. We used the test for subgroup differences within [RevMan 5.3](#) ([Higgins 2011](#)), to formally test for subgroup differences.

Sensitivity analysis

We assessed the robustness of our estimates by comparing the effects from models that included all studies (possibly biased but with higher precision due to the use of all individuals) versus the effects from models that excluded studies with high risk of bias or of low quality (potentially lower risk of bias but also lower precision due to the exclusion of studies). We further assessed the sensitivity of our estimates by excluding studies on biosimilar ESAs.

We compared the estimates of fixed-effect and random-effects meta-analyses, to assess our assumptions on heterogeneity, where appropriate.

Acknowledging that observational evidence is of a different nature, we performed a sensitivity analysis down-weighting such evidence in the synthesis. This was done explicitly using a specified parameter that represents the weight given to observational evidence modelled as a multiplicative factor to the observational effect estimate precision. We applied different weights to inflate the variance in a sensitivity analysis. We also assessed whether funding sources influenced the estimates if data were available.

Summary of findings table and GRADE

We decided to include 'any adverse event', 'venous thromboembolism', and 'mortality' as the most important outcomes. We used the principles of the GRADE system ([Guyatt 2008](#)) to assess the quality of the body of evidence on frequent adverse events and mortality associated with off-label use of ESAs in critically-ill people, and constructed a 'Summary of findings' (SoF) table using the GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence reflects within-study risk of bias (methodological

quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

Description of studies

Results of the search

Searching electronic databases, reference lists and trial registers resulted in 30,743 records, which became 19,878 records after removing duplicates manually and by EndNote. Contact with manufacturers yielded no more data related to safety aspects beyond what we had already found through our search in bibliographic databases and other sources.

After screening the titles of 19,878 records, we were left with 2306 records; of those, we excluded 2163 irrelevant records and included

143 records. Then, from 143 potentially relevant documents, we excluded 24 studies for the reasons detailed in [Excluded studies](#).

We found two ongoing trials ([Günter 2015](#); [Minamino 2012](#)), and 9 trials in the recruitment phase by searching in trial registries and the references of two relevant papers ([Chen 2008](#); [Mocini 2008](#)), and through tracking reference list and citations of 36 out of 48 included studies in our non-Cochrane systematic review, which is indexed in Scopus (n = 4173) ([Mesgarpour 2013a](#)).

By searching Google, we found a full paper of one potentially relevant conference proceeding ([El Atroush 2005](#)). We also received further details of four studies by contacting the authors ([Alibai 2014](#); [Brophy 2007](#); [Gerasimov 2012](#); [Kashkouli 2011](#)). Finally, we analysed 53 studies out of 119 relevant documents. The reasons for not analysing 66 eligible records are detailed in [Figure 1](#).

Figure 1. Study flow diagram. ^a NCT02376881, NCT03061565, ChiCTR-TRC-12002576, IRCT201110267917N1, IRCT201204149462N1, IRCT2013072414138N1, IRCT2014041417272N1, IRCT2014071718517N1, KCT0000696. ^b NCT00375869. ^c NCT00451698, NCT00561067, NCT00626574. ^d NCT00149058, NCT01087450. ^e NCT01783847

Figure 1. (Continued)

Included studies

We included 53 studies, involving 945,240 participants (6678 in RCTs and 938,562 in observational studies), from 24 countries in our review.

Of the 53 studies, 39 were RCTs (Abrishamkar 2012; Alibai 2014; Aloizos 2015; Binbrek 2009; Chicella 2006; Corwin 1999; Corwin 2002; Corwin 2007a; De Seigneux 2012; El Atroush 2005; Endre 2010; Ferrario 2011; Gabriel 1998; Georgopoulos 2005; Gerasimov 2012; Gholamzadeh 2015; Kang 2012; Kateros 2010; Lakic 2010; Liem 2009; Lipsic 2006; Luchette 2012; Ludman 2011; Mattich 1993; Najjar 2011; Nichol 2015; Nirula 2010; Ott 2010; Prunier 2012; Robertson 2014; Silver 2006; Springborg 2007; Still 1995; Suh 2011; Taniguchi 2010; Tseng 2009; Van Iperen 2000; Vincent 2006; Voors 2010) a

One of the 39 RCTs was reported as a conference proceeding only (Chicella 2006), for which we acquired further details by contacting the authors. Twelve RCTs were designed as prospective, open-label studies (Binbrek 2009; El Atroush 2005; Gabriel 1998; Georgopoulos 2005; Kateros 2010; Lakic 2010; Lipsic 2006; Prunier 2012; Suh 2011; Taniguchi 2010; Van Iperen 2000; Voors 2010); endpoints were blinded in three of them (Prunier 2012; Taniguchi 2010; Voors 2010). All but one of the RCTs was reported in English (Gerasimov 2012 was in Russian).

Fourteen of the 53 included studies were observational studies (Brophy 2007; Bush 2008; Cariou 2008; Chen 2008; Ginger 2008; Grmec 2009; Hecht 2007; Kane-Gill 2007; Kashkouli 2011; Luh 2005; Lundy 2010; Shuman 2009; Talving 2010; Wittbrodt 2005).

We present full information on the characteristics of the 39 RCTs and 14 observational studies in the [Characteristics of included studies](#)

Randomized controlled studies

The summary of the included RCTs is presented in [Characteristics of included studies](#).

One RCT was reported as conference proceeding only (Chicella 2006), of which we received further details by contacting the authors. Twelve RCTs were designed as prospective, open-labelled studies (Binbrek 2009; El Atroush 2005; Gabriel 1998; Georgopoulos 2005; Kateros 2010; Lakic 2010; Lipsic 2006; Prunier 2012; Suh 2011; Taniguchi 2010; Van Iperen 2000; Voors 2010); endpoints were blinded in three of those RCTs (Prunier 2012; Taniguchi 2010; Voors 2010). All but one of the RCTs was reported in English (Gerasimov 2012 was in Russian).

Disease

Thirteen RCTs studied participants diagnosed with ST-segment elevation myocardial infarction (STEMI); among those, 12 (Ferrario 2011; Gholamzadeh 2015; Kang 2012; Lipsic 2006; Ludman 2011; Najjar 2011; Nirula 2010; Ott 2010; Prunier 2012; Suh 2011; Taniguchi 2010; Voors 2010) included primary percutaneous coronary intervention (PCI) and one (Binbrek 2009) included thrombolysis. Liem 2009 investigated the effect of EPO on myocardial damage in participants with non-ST segment elevation acute coronary syndrome (non-STE ACS). Lakic 2010 included participants who required surgical revascularization of the heart

with the use of a heart-lung machine. Participants within 48 to 72 hours of aneurysmal subarachnoid haemorrhage (aSAH) were randomized to receive epoetin (alfa or beta) or placebo in two studies (Springborg 2007; Tseng 2009). Ten studies enrolled critically-ill participants in the ICU (Chicella 2006; Corwin 1999; Corwin 2002; Corwin 2007a; El Atroush 2005; Endre 2010; Georgopoulos 2005; Silver 2006; Van Iperen 2000; Vincent 2006). Three studies included participants with traumatic brain injury (Abrishamkar 2012; Aloizos 2015; Nichol 2015). Kateros 2010 and Luchette 2012 included participants with orthopaedic trauma, Alibai 2014 recruited participants with acute spinal cord injury and Nirula 2010 enrolled people with blunt trauma. De Seigneux 2012 enrolled participants who were admitted to the ICU and at risk of acute kidney injury after elective cardiac surgery. Gabriel 1998 studied participants with multiple organ dysfunction syndromes who stayed in the ICU for at least three weeks. Mattich 1993 and Still 1995 studied people with burns.

Centres

Sixteen studies were conducted at multiple centres; Corwin 2007a in 115 centres, Corwin 2002 in 65, Nichol 2015 in 29, Najjar 2011 in 28, Georgopoulos 2005 in 13 centres and 11 studies in two to seven centres (Alibai 2014; Corwin 1999; Endre 2010; Ott 2010; Prunier 2012; Robertson 2014; Silver 2006; Still 1995; Taniguchi 2010; Vincent 2006; Voors 2010). Nineteen studies were performed in a single centre (Binbrek 2009; Chicella 2006; De Seigneux 2012; El Atroush 2005; Ferrario 2011; Gabriel 1998; Gerasimov 2012; Kateros 2010; Lakic 2010; Liem 2009; Lipsic 2006; Luchette 2012; Ludman 2011; Mattich 1993; Nirula 2010; Springborg 2007; Suh 2011; Tseng 2009; Van Iperen 2000) and Kang 2012 did not specify on this issue.

Route

Participants received epoetin-alfa intravenously in 16 studies, with dosage ranging from 6000 IU to 60,000 IU daily mostly for one to three doses (Alibai 2014; Aloizos 2015; Chicella 2006; De Seigneux 2012; Gabriel 1998; Gerasimov 2012; Gholamzadeh 2015; Lakic 2010; Liem 2009; Najjar 2011; Nirula 2010; Robertson 2014; Springborg 2007; Still 1995; Suh 2011; Voors 2010). Epoetin-beta was intravenously injected in seven studies ranging from 6000 IU to 50,000 IU daily for a maximum of three doses (Binbrek 2009; Endre 2010; Ludman 2011; Ott 2010; Prunier 2012; Taniguchi 2010; Tseng 2009) and 2000 IU subcutaneously in six doses in one study (Abrishamkar 2012). Two studies (Lipsic 2006; Kang 2012) administered an intravenous injection of darbepoetin (maximum 300 µg). In 11 studies, participants in the intervention group received subcutaneous injections of epoetin-alfa in dosages ranging from 10,000 IU to 40,000 IU daily at different time intervals (Corwin 1999; Corwin 2002; Corwin 2007a; El Atroush 2005; Georgopoulos 2005; Luchette 2012; Mattich 1993; Nichol 2015; Silver 2006; Van Iperen 2000; Vincent 2006). Two RCTs did not clearly specify the route of epoetin-alfa administration (Ferrario 2011; Kateros 2010). However, the delivery mode of epoetin-alfa in Kateros 2010 might be subcutaneous injection, because skin inflammatory response or bruising at the site of injection was reported as a complaint by five participants. We assume that EPO was administered intravenously in Ferrario 2011, since the participants received it in isotonic sodium chloride 50 ml over 30 minutes.

Manufacturer

The manufacturers of ESAs (mostly alongside their brand names) were reported in all but six studies (Chicella 2006; El Atroush 2005; Endre 2010; Ferrario 2011; Kateros 2010; Nirula 2010). We found four products biosimilar to ESA, including Epokine Prefilled®, CJ Pharm, Korea (Alibai 2014); Epocrin®, Sotex FarmFirm, Russia (Gerasimov 2012); PDpoetin®, Pooyesh Darou, Iran (Suh 2011); Epoetin-beta, Chugai Pharmaceutical, Tokyo, Japan (Taniguchi 2010)..

Study period

RCTs were conducted between July 1990 and November 2014; mostly during 2003 to 2009, and the longest one from May 2006 to August 2012 (Robertson 2014). Thirteen RCTs did not report the recruiting period of their studies (Abrishamkar 2012; Aloizos 2015; Binbrek 2009; Chicella 2006; Gabriel 1998; Gerasimov 2012; Lakic 2010; Liem 2009; Lipsic 2006; Luchette 2012; Still 1995; Suh 2011; Voors 2010). Epoetin-beta and darbepoetin have been assessed in included RCTs since 2005.

Setting

RCTs were carried out in 20 countries; 18 RCTs in European countries (Aloizos 2015; De Seigneux 2012; Ferrario 2011; Gabriel 1998; Georgopoulos 2005; Kateros 2010; Lakic 2010; Liem 2009; Lipsic 2006; Ludman 2011; Mattich 1993; Ott 2010; Prunier 2012; Springborg 2007; Tseng 2009; Van Iperen 2000; Vincent 2006; Voors 2010); 10 studies in the United States (Chicella 2006; Corwin 1999; Corwin 2002; Corwin 2007a; Luchette 2012; Najjar 2011; Nirula 2010; Robertson 2014; Silver 2006; Still 1995); four studies in the Middle East (Abrishamkar 2012; Alibai 2014; Binbrek 2009; Gholamzadeh 2015) and four studies in Asia (Gerasimov 2012; Kang 2012; Suh 2011; Taniguchi 2010). El Atroush 2005 was performed in Egypt, Endre 2010 in New Zealand, and Nichol 2015 in seven countries including Australia, New Zealand, France, Germany, Finland, Ireland, and Saudi Arabia.

Observational studies

We included 14 observational studies in our review. We have summarized the information from the included observational studies in the [Characteristics of included studies](#). Seven observational studies were reported as conference proceeding (Brophy 2007; Bush 2008; Ginger 2008; Hecht 2007; Luh 2005; Shuman 2009; Wittbrodt 2005) and we acquired more details on Brophy 2007 by contacting the author. All 14 observational studies were designed as cohort studies: five used local registries or data repositories (Bush 2008; Kane-Gill 2007; Luh 2005; Shuman 2009; Wittbrodt 2005), four of them used specific databases (Brophy 2007; Ginger 2008; Hecht 2007; Talving 2010), and five recruited cases before the ESAs intervention concurrently with non-exposed participants and followed them over a specified time period or compared them with a non-exposed population from past records (Cariou 2008; Chen 2008; Grmec 2009; Kashkouli 2011; Lundy 2010). All but one of the 14 observational studies was reported in English (Chen 2008 was published in Chinese).

Disease

Five studies were performed in critically-ill people admitted to the ICU (Brophy 2007; Kane-Gill 2007; Luh 2005; Shuman 2009; Wittbrodt 2005). Three studies were conducted in people with non-specific trauma (Bush 2008; Ginger 2008; Hecht 2007) and two in people with specific trauma (Talving 2010 on severe traumatic brain

injury and [Kashkouli 2011](#) on indirect traumatic optic neuropathy). Two studies were on out-of-hospital cardiac arrest ([Cariou 2008](#); [Grmec 2009](#)), one in critically-ill people with burns (more than 30% total body surface area (TBSA)) who stayed in the burns intensive care unit (BICU) for more than 15 days ([Lundy 2010](#)) and the other one in people with anaemic sepsis ([Chen 2008](#)).

Type, Route and Dosage

RHuEPO or epoetin-alfa was compared with non rHuEPO in six studies ([Ginger 2008](#); [Kane-Gill 2007](#); [Kashkouli 2011](#); [Luh 2005](#); [Lundy 2010](#); [Wittbrodt 2005](#)), with at least one dose of EPO (40,000 U) in [Ginger 2008](#) and [Wittbrodt 2005](#). Participants in [Lundy 2010](#) received subcutaneous injection of EPO (40,000 U) weekly, and cases in [Kashkouli 2011](#) were given an infusion of EPO (10,000) over three successive days. Five cohort studies did not report the ESA dosages in exposed groups ([Brophy 2007](#); [Bush 2008](#); [Hecht 2007](#); [Luh 2005](#); [Shuman 2009](#)) and [Kane-Gill 2007](#) indicated only the average number of doses.

ESAs versus non-ESAs were investigated in three cohort studies ([Brophy 2007](#); [Bush 2008](#); [Talving 2010](#)), with only [Talving 2010](#) reporting the dosage. Single IV bolus (90,000 IU) erythropoietin-beta was compared with placebo in [Grmec 2009](#) and darbepoetin with non-darbepoetin was investigated in [Shuman 2009](#). [Cariou 2008](#) conducted a study to compare standard care versus IV injection of four doses of epoetin-alfa (40,000 IU) beside the routine care. [Hecht 2007](#) studied the administration of ESAs with unfractionated heparin (UFH) or enoxaparin (ENOX) as prophylactic or treatment dose for venous thromboembolisms, compared with UFH or ENOX. Four observational studies reported the manufacturers of ESAs ([Cariou 2008](#); [Grmec 2009](#); [Kashkouli 2011](#); [Talving 2010](#)) and two of them also reported the brand names ([Kashkouli 2011](#); [Talving 2010](#)).

Study Period and Setting

The 14 observational studies were performed from January 1996 to March 2010. [Brophy 2007](#), [Ginger 2008](#) and [Wittbrodt 2005](#) did not report the dates of their studies. [Talving 2010](#) had the longest study period, from January 1996 to December 2007 and [Cariou](#)

[2008](#) had the shortest period, from November 2003 to May 2004. All observational studies were conducted in the United States, apart from [Chen 2008](#) in China, [Cariou 2008](#) in France, [Kashkouli 2011](#) in Iran and [Grmec 2009](#) in Slovenia.

Excluded studies

We excluded 24 full study reports ([Ahmed 2001](#); [Alibai 2015](#); [Andreotti 2008](#); [Avall 2003](#); [Ehrenreich 2002](#); [Ehrenreich 2009](#); [Kim 2013](#); [Mocini 2008](#); [Möllmann 1995](#); [Oriei 2015](#); [Ozawa 2010](#); [Pang 2013](#); [Poletes 1994](#); [Roubille 2013](#); [Shiehorteza 2011](#); [Shin 2006](#); [Sureshkumar 2012](#); [Swedberg 2013](#); [Tang 2009](#); [Vitale 2007](#); [Watanabe 1991](#); [Yip 2011](#); [Zhang 2009](#); [Zhu 2013](#)). The study populations were classified as not being critically ill in 15 studies ([Andreotti 2008](#); [Avall 2003](#); [Ehrenreich 2009](#); [Kim 2013](#); [Möllmann 1995](#); [Oriei 2015](#); [Ozawa 2010](#); [Pang 2013](#); [Shin 2006](#); [Swedberg 2013](#); [Tang 2009](#); [Vitale 2007](#); [Watanabe 1991](#); [Yip 2011](#); [Zhang 2009](#); [Characteristics of excluded studies](#)). In two studies ESAs were not scheduled for systemic administration ([Roubille 2013](#); [Sureshkumar 2012](#)). Seven studies fulfilled eligibility criteria for inclusion into our systematic review, but they did not report outcomes of interest, safety or mortality ([Ahmed 2001](#); [Alibai 2015](#); [Ehrenreich 2002](#); [Mocini 2008](#); [Poletes 1994](#); [Shiehorteza 2011](#); [Zhu 2013](#)).

Studies awaiting classification

Five studies are awaiting classification ([Cariou 2016](#); [Cheng 2016](#); [Costa 2015](#); [Günter 2015](#); [Li 2016](#)), which are outlined in the [Characteristics of studies awaiting classification](#).

Ongoing studies

There is one ongoing study ([Minamino 2012](#)), which is outlined in the [Characteristics of ongoing studies](#).

Risk of bias in included studies

Randomized controlled trials

The risk of bias in RCTs for safety outcomes (including death) is presented in [Figure 2](#), and also see [Web Appendix](#). We provide the details in the following sections.

Figure 2. Risk of bias summary for 39 RCTs: review authors' judgements about each risk of bias item for each included study [ordered by year of study]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abrishamkar 2012	?	?	+	+	+	?	?
Alibai 2014	+	?	+	+	+	?	?
Aloizos 2015	?	?	-	-	+	?	?
Binbrek 2009	+	+	-	?	?	?	?
Chicella 2003	?	?	+	?	?	?	?
Corwin 1999	+	?	+	?	?	+	?
Corwin 2002	+	+	+	+	+	+	?
Corwin 2007	+	+	+	?	?	+	?
de Seigneux 2012	+	+	+	+	+	+	?
El Atroush 2005	+	-	-	?	+	?	?
Endre 2010	+	+	+	+	?	+	+
Ferrario 2011	+	+	+	?	+	?	?
Gabriel 1998	?	?	?	+	+	?	?
Georgopoulos 2005	+	-	-	-	+	+	?
Gerasimov 2012	+	+	+	-	+	?	+
Gholamzadeh 2015	+	+	+	+	+	?	?
Kang 2012	?	+	+	+	+	+	+
Kateros 2010	+	-	-	?	+	?	?
Lakic 2010	-	-	-	+	+	?	?
Liem 2009	?	?	+	?	+	?	?

Figure 2. (Continued)

Liem 2009	?	?	+	?	+	?	?
Lipsic 2006	+	-	-	-	+	+	?
Luchette 2012	?	?	+	?	-	+	?
Ludman 2011	+	+	+	+	+	+	+
Mattich 1993	?	?	+	?	+	?	?
Najjar 2011	+	+	+	+	?	+	+
Nichol 2015	+	+	+	+	+	+	?
Nirula 2010	?	?	+	+	-	-	?
Ott 2010	+	+	+	+	+	+	+
Prunier 2012	+	+	-	+	+	?	+
Robertson 2014	+	?	+	+	+	+	-
Silver 2006	+	?	+	?	?	?	?
Springborg 2007	+	+	+	+	-	?	?
Still 1995	?	?	+	?	+	+	?
Suh 2011	+	-	-	+	+	+	+
Taniguchi 2010	+	-	-	+	+	+	?
Tseng 2009	+	+	+	+	+	+	?
van Iperen 2000	?	?	?	+	+	?	?
Vincent 2006	?	?	+	?	+	?	?
Voors 2010	+	+	-	+	+	+	+

Observational studies

Risk of bias in cohort studies for safety outcomes (including death) is presented in [Table 1](#) and see [Web Appendix](#). The median score (the number of stars awarded, with higher points meaning lower risk) was six (out of nine) for the 14 cohort studies, with an overall range of four to nine points ([Table 1](#)). Ten studies had low to moderate risk of bias and reached five or more star points ([Brophy 2007](#); [Cariou 2008](#); [Ginger 2008](#); [Grmec 2009](#); [Hecht 2007](#); [Kane-Gill 2007](#); [Kashkouli 2011](#); [Luh 2005](#); [Lundy 2010](#); [Talving 2010](#)). Among them, [Talving 2010](#) had the lowest risk of bias with nine star points. The remaining four studies had high risk of bias and reached four star points ([Bush 2008](#); [Chen 2008](#); [Shuman 2009](#); [Wittbrodt 2005](#)). All the observational studies were representative of exposed individuals in the community, with the non-exposed cohort selected from the same community as the exposed cohort. Ascertainment of exposure was unclear in five studies ([Bush 2008](#); [Grmec 2009](#); [Luh 2005](#); [Shuman 2009](#); [Wittbrodt 2005](#)). Cohorts were comparable on the basis of design or analysis in six studies ([Cariou 2008](#); [Ginger 2008](#); [Grmec 2009](#); [Kane-Gill 2007](#); [Luh 2005](#);

[Talving 2010](#)). Only five studies described the assessment of outcome, using record linkage ([Brophy 2007](#); [Ginger 2008](#); [Hecht 2007](#); [Kane-Gill 2007](#); [Talving 2010](#)). Five studies followed up outcomes for long enough ([Brophy 2007](#); [Cariou 2008](#); [Grmec 2009](#); [Luh 2005](#); [Talving 2010](#)) and follow-up of cohorts was adequate in all but [Chen 2008](#), where this was unclear. We detail the risk of bias in additional tables ([Table 1](#) and [Characteristics of included studies](#)).

Allocation

The risk of bias in the included RCTs was generally moderate to low. Random sequence generation was not reported in 12 studies ([Abrishamkar 2012](#); [Aloizos 2015](#); [Chicella 2006](#); [Gabriel 1998](#); [Kang 2012](#); [Liem 2009](#); [Luchette 2012](#); [Mattich 1993](#); [Nirula 2010](#); [Still 1995](#); [Van Iperen 2000](#); [Vincent 2006](#)), and inadequate in one trial ([Lakic 2010](#)). Allocation concealment was adequate in 17 studies ([Binbrek 2009](#); [Corwin 1999](#); [Corwin 2002](#); [Corwin 2007a](#); [De Seigneux 2012](#); [Endre 2010](#); [Ferrario 2011](#); [Gerasimov 2012](#); [Kang 2012](#); [Ludman 2011](#); [Najjar 2011](#); [Nichol 2015](#); [Ott 2010](#); [Prunier 2012](#); [Springborg 2007](#); [Tseng 2009](#); [Voors 2010](#)) and inadequate in

seven studies (El Atroush 2005; Georgopoulos 2005; Kateros 2010; Lakic 2010; Lipsic 2006; Suh 2011; Taniguchi 2010).

Blinding

Participants or personnel were not blinded for harms outcome in 11 studies (Aloizos 2015; Binbrek 2009; El Atroush 2005; Georgopoulos 2005; Kateros 2010; Lakic 2010; Lipsic 2006; Prunier 2012; Suh 2011; Taniguchi 2010; Voors 2010). Outcome assessors were blinded in 22 studies (Abrishamkar 2012; Alibai 2014; Corwin 2002; De Seigneux 2012; Endre 2010; Gabriel 1998; Gholamzadeh 2015; Kang 2012; Lakic 2010; Ludman 2011; Najjar 2011; Nichol 2015; Nirula 2010; Ott 2010; Prunier 2012; Robertson 2014; Springborg 2007; Suh 2011; Taniguchi 2010; Tseng 2009; Van Iperen 2000; Voors 2010).

Incomplete outcome data

Risk of attrition bias for harms outcomes was low in all but 10 studies (Binbrek 2009; Chicella 2006; Corwin 1999; Corwin 2007a; Endre 2010; Luchette 2012; Najjar 2011; Nirula 2010; Silver 2006; Springborg 2007).

Selective reporting

The study protocol was available for 16 studies (Corwin 2007a; De Seigneux 2012; Endre 2010; Georgopoulos 2005; Kang 2012; Luchette 2012; Ludman 2011; Najjar 2011; Nichol 2015; Ott 2010; Prunier 2012; Robertson 2014; Suh 2011; Taniguchi 2010; Tseng 2009; Voors 2010) and we found the study's prespecified harms outcomes to be reported accordingly in all but one study (Prunier 2012). This study reported the occurrence of major cardiac events or venous thrombotic events within three months following

administration of study medication, whereas the protocol specified 12 months follow-up.

Other potential sources of bias

Nine studies reported funding support from companies manufacturing ESAs (Corwin 1999; Corwin 2002; Corwin 2007a; Georgopoulos 2005; Luchette 2012; Silver 2006; Still 1995; Vincent 2006; Voors 2010) and Mattich 1993 expressed appreciation for the participation of Cilag AG, Schaffhausen, Switzerland. Study medication only was provided by ESA companies in six studies (De Seigneux 2012; Kateros 2010; Ludman 2011; Ott 2010; Tseng 2009; Van Iperen 2000). However, Hoffmann-La Roche and Roche Foundation of Anaemia Research (RoFAR, Switzerland) are named as sponsors and collaborators in the protocol for Tseng 2009. Furthermore, Janssen-Cilag provided the r-HuEPO in the active treatment arm and covered the cost of a urinary measurement in De Seigneux 2012, but had no role in study design, data collection, statistical analysis or writing up of the manuscript. Five studies declared no competing interest at all (Abrishamkar 2012; El Atroush 2005; Gabriel 1998; Lakic 2010; Liem 2009). The remaining studies reported that they were supported by non-industry resources. For details on funding see [Characteristics of included studies](#).

Quality of harm assessment and reporting in included studies

Randomized controlled trials

Quality of harm assessment and reporting for RCTs is presented in [Figure 3](#), and see also [Web Appendix](#). Harm assessment and reporting in the included RCTs were generally of medium to low quality.

Figure 3. Quality of harms assessment and reporting for 39 included RCTs

	Were the harms PREDEFINED using standardized or precise definitions	Were SERIOUS events precisely defined?	Were SEVERE events precisely defined?	Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?	Was the mode of harms collection specified as ACTIVE?	Was the mode of harms collection specified as PASSIVE?	Did the study specify WHO collected the harms?	Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?	Did the study specify the TIMING and FREQUENCY of collection of the harms?	Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Did the author(s) specify the type of analyses undertaken for harms data?
Abrishamkar 2012	-	-	-	+	?	?	-	-	-	-	-	-	-	-	-
Alibai 2014	-	-	-	-	?	?	-	-	+	-	?	+	-	+	+
Aloizos 2015	-	-	-	+	-	-	-	-	-	?	-	-	+	+	-
Binbrek 2009	-	-	-	+	?	?	-	-	-	-	-	-	-	+	+
Chicella 2003	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Corwin 1999	-	-	-	+	?	?	-	-	-	-	-	+	-	+	+
Corwin 2002	-	+	-	+	?	?	+	+	+	-	-	+	+	+	+
Corwin 2007	-	+	-	+	?	?	+	+	-	-	+	+	+	+	+
de Seigneux 2012	?	-	-	+	?	?	-	-	-	?	?	+	?	?	+
El Atroush 2005	-	-	-	+	?	?	-	-	-	-	-	+	-	-	+

+ Yes
 ? Unsure
 - No

Figure 3. (Continued)

El Atroush 2005	-	-	-	+	?	?	-	-	-	-	-	+	-	-	+
Endre 2010	+	+	+	+	?	?	?	?	-	?	+	+	+	+	+
Ferrario 2011	-	-	-	+	?	?	-	-	-	-	-	+	-	+	+
Gabriel 1998	-	-	-	+	?	?	-	-	-	-	-	+	-	-	+
Georgopoulos 2005	-	+	-	-	?	?	-	-	+	-	-	+	-	+	+
Gerasimov 2012	-	-	-	+	?	?	-	-	+	?	-	+	-	+	+
Gholamzadeh 2015	-	-	-	-	?	?	-	-	-	-	-	-	-	-	-
Kang 2012	-	-	-	-	?	+	-	-	+	-	?	?	-	+	+
Kateros 2010	-	-	-	-	?	?	-	-	-	-	-	-	-	+	+
Lakic 2010	-	-	-	+	?	?	-	-	-	-	-	+	-	-	-
Liem 2009	-	-	-	+	?	?	-	-	-	-	?	+	-	?	+
Lipsic 2006	-	-	-	-	?	?	-	-	+	-	+	+	-	+	+
Luchette 2012	-	+	-	+	?	?	-	-	-	-	-	+	+	+	+
Ludman 2011	-	-	-	+	?	?	-	-	-	-	-	+	-	+	+
Mattich 1993	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+
Najjar 2011	+	-	-	+	?	?	+	+	+	-	-	+	+	+	+
Nichol 2015	+	-	-	+	?	?	?	+	+	+	+	+	+	+	+
Nirula 2010	-	-	-	+	?	?	-	-	-	?	?	+	?	?	+
Ott 2010	?	+	-	+	+	?	-	-	+	-	-	+	+	+	+
Prunier 2012	-	-	-	+	?	?	-	-	?	-	-	+	+	+	+
Robertson 2014	+	-	-	+	?	?	-	-	+	-	+	+	+	+	+
Silver 2006	-	-	-	+	?	?	-	-	+	-	?	+	+	-	+
Springborg 2007	-	-	-	+	?	?	-	-	-	-	+	+	+	+	+
Still 1995	-	-	-	+	?	?	-	-	+	-	+	+	+	+	+
Suh 2011	+	-	-	+	+	+	?	-	+	-	-	+	-	+	+
Taniguchi 2010	-	+	-	+	+	?	-	-	+	-	-	+	+	+	+
Tseng 2009	-	-	-	+	?	+	-	-	?	-	-	+	-	+	+
van Iperen 2000	-	-	-	+	?	?	-	-	-	-	-	+	-	-	+
Vincent 2002	-	-	-	-	?	?	-	-	-	-	?	-	+	+	+
Voors 2010	+	-	-	+	?	+	+	+	+	-	-	+	+	+	+

Harms were defined in five papers (Endre 2010; Nichol 2015; Robertson 2014; Suh 2011; Voors 2010) and in the published trial design of Najjar 2011 only. Eight studies defined serious adverse

events (SAEs) or major adverse events of EPO (Corwin 2002; Corwin 2007a; Endre 2010; Georgopoulos 2005; Luchette 2012; Ott 2010; Robertson 2014; Taniguchi 2010), which are detailed in Appendix

2. [Endre 2010](#) was the only study which graded the severity of adverse events by using the Common Terminology Criteria for Adverse Events (CTCAE) coding system. The number of deaths in each study group was not specified, or the reason(s) for not specifying them were not given, for nine studies ([Alibai 2014](#); [Chicella 2006](#); [Georgopoulos 2005](#); [Gholamzadeh 2015](#); [Kang 2012](#); [Kateros 2010](#); [Lipsic 2006](#); [Mattich 1993](#); [Vincent 2006](#)). Active and passive ascertainment of harms can be assumed in three ([Ott 2010](#); [Suh 2011](#); [Taniguchi 2010](#)) and four studies, respectively ([Kang 2012](#); [Suh 2011](#); [Tseng 2009](#); [Voors 2010](#)).

Harm events were monitored by an independent data and safety monitoring board (DSMB) in six studies ([Corwin 2002](#); [Corwin 2007a](#); [Najjar 2011](#); [Nichol 2015](#); [Robertson 2014](#); [Voors 2010](#)) and probably by an internal DSMB in [Endre 2010](#). The time interval when harms were collected was specified in 15 studies ([Alibai 2014](#); [Corwin 2002](#); [Georgopoulos 2005](#); [Gerasimov 2012](#); [Kang 2012](#); [Lipsic 2006](#); [Najjar 2011](#); [Nichol 2015](#); [Ott 2010](#); [Robertson 2014](#); [Silver 2006](#); [Still 1995](#); [Suh 2011](#); [Taniguchi 2010](#); [Voors 2010](#)).

None of the included RCTs used standard scales or checklists for harm collection. All but seven studies failed to specify if the harms reported encompassed all the events collected or a selected sample ([Corwin 2007a](#); [Endre 2010](#); [Lipsic 2006](#); [Nichol 2015](#); [Robertson 2014](#); [Springborg 2007](#); [Still 1995](#)).

The number of participants who withdrew or were lost to follow-up was specified for each study group in all but eight studies

([Abrishamkar 2012](#); [Aloizos 2015](#); [Binbrek 2009](#); [Chicella 2006](#); [Gholamzadeh 2015](#); [Kang 2012](#); [Kateros 2010](#); [Vincent 2006](#)).

Seventeen studies specified the total number of participants affected by harms for each study arm ([Aloizos 2015](#); [Corwin 2002](#); [Corwin 2007a](#); [Endre 2010](#); [Luchette 2012](#); [Mattich 1993](#); [Najjar 2011](#); [Nichol 2015](#); [Ott 2010](#); [Prunier 2012](#); [Robertson 2014](#); [Silver 2006](#); [Springborg 2007](#); [Still 1995](#); [Taniguchi 2010](#); [Vincent 2006](#); [Voors 2010](#)). However, [Voors 2010](#) reported overall SAEs only. Only 11 studies indicated the number for each type of harmful event in each study group ([Abrishamkar 2012](#); [Chicella 2006](#); [De Seigneux 2012](#); [El Atroush 2005](#); [Gabriel 1998](#); [Gholamzadeh 2015](#); [Lakic 2010](#); [Liem 2009](#); [Nirula 2010](#); [Silver 2006](#); [Van Iperen 2000](#)).

Only five studies specified the type of analysis undertaken for harms data ([Abrishamkar 2012](#); [Aloizos 2015](#); [Chicella 2006](#); [Gholamzadeh 2015](#); [Lakic 2010](#)).

Observational studies

We present the quality of harm assessment and reporting for observational studies in [Figure 4](#), and see also [Web Appendix](#). Observational studies had low quality of harm assessment and reporting overall. None of the studies either predefined harms and serious/severe events or specified the mode of harms collection, the person who collected the harms, professional designation of this person, frequency of harms collection, using standard scale for harms collection, or indicated if the harms reported encompass all the events collected or a selected sample.

Figure 4. Quality of harms assessment and reporting for 14 included observational studies

	Were the harms PREDEFINED using standardized or precise definitions	Were SERIOUS events precisely defined?	Were SEVERE events precisely defined?	Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?	Was the mode of harms collection specified as ACTIVE?	Was the mode of harms collection specified as PASSIVE?	Did the study specify WHO collected the harms?	Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?	Did the study specify the TIMING and FREQUENCY of collection of the harms?	Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Did the author(s) specify the type of analyses undertaken for harms data?
Brophy 2007	+	+	+	+	?	?	?	?	?	?	+	?	?	?	+
Bush 2008	?	?	?	?	?	?	?	?	?	?	?	?	+	+	?
Cariou 2008	?	+	+	+	?	?	+	+	?	+	?	?	?	+	+
Chen 2008	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Ginger 2008	?	?	?	?	?	?	?	?	?	?	?	?	?	?	+
Grmec 2009	+	+	+	+	?	?	+	+	+	+	+	+	+	+	+
Hecht 2007	?	?	?	?	?	?	?	?	?	?	?	?	+	+	+
Kane-Gill 2007	+	+	+	+	?	?	+	+	+	+	+	+	+	+	+
Kashkouli 2011	+	+	+	+	?	?	+	+	+	+	+	+	+	+	+
Luh 2005	?	?	?	+	?	?	?	?	?	?	?	?	?	?	?

+ Yes
 ? Unsure
 + No

Figure 4. (Continued)

Luh 2005	?	?	?	+	?	?	?	?	?	?	?	?	?	?
Lundy 2010	?	-	-	+	?	?	-	-	-	-	?	?	+	-
Shuman 2009	?	?	?	?	?	?	?	?	?	?	?	?	+	+
Talving 2010	-	?	?	-	?	?	-	-	-	-	?	?	+	+
Wittbrodt 2005	?	?	?	+	?	?	?	?	?	?	?	?	?	?

Only two studies reported the number of participants who withdrew or were lost to follow-up for each study group (Grmec 2009; Kashkouli 2011). The number of participants affected by harms for each study arm was specified in seven studies (Bush 2008; Grmec 2009; Hecht 2007; Kane-Gill 2007; Lundy 2010; Shuman 2009; Talving 2010). Only six studies gave the number of each type of harmful event for each study group (Brophy 2007; Chen 2008; Ginger 2008; Luh 2005; Lundy 2010; Wittbrodt 2005).

All but four studies (Bush 2008; Chen 2008; Luh 2005; Wittbrodt 2005) mentioned the type of analysis undertaken for harms data.

Effects of interventions

See: [Summary of findings for the main comparison](#)

Primary outcomes

1. Effects of ESAs on adverse events (AEs)

Combined effects: We found 114 adverse events (including combinations of events) in 33 studies; 74 AEs were reported in one study only (Table 2), 18 AEs in two studies, two AEs in three studies and 20 AEs in at least four studies (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 1.20; Analysis 1.21; Analysis 1.22; Analysis 1.23; Analysis 1.24; Analysis 1.25; Analysis 1.26; Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.30; Analysis 1.31; Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.35; Analysis 1.36; Analysis 1.37; Analysis 1.38; Analysis 1.39).

Randomized controlled trials

All randomized controlled trials reported adverse effects from treatment with ESAs except for five studies (Abrishamkar 2012; El Atroush 2005; Gabriel 1998; Lakic 2010; Van Iperen 2000). From these five studies, Lakic 2010 followed up the study participants for five days and the four remaining studies investigated for a minimum of 21 days. Twenty-one out of 39 RCTs reported safety endpoints as prespecified secondary or additional outcomes of interest (Alibai 2014; Binbrek 2009; Corwin 2007a; Endre 2010; Ferrario 2011; Georgopoulos 2005; Gerasimov 2012; Kang 2012; Liem 2009; Lipsic 2006; Luchette 2012; Najjar 2011; Nichol 2015; Nirula 2010; Ott 2010; Prunier 2012; Robertson 2014; Springborg 2007; Suh 2011; Taniguchi 2010; Voors 2010). The remaining studies did not prespecify safety as an outcome.

No adverse effects of treatment were observed in seven studies (Aloizos 2015; De Seigneux 2012; Ferrario 2011; Kateros 2010;

Mattich 1993; Springborg 2007; Taniguchi 2010) and no difference was noted between the rHuEPO group and the placebo group in the frequency of adverse events in Chicella 2006. Aloizos 2015 recorded no side effects or complications such as hypertension, thromboembolic episodes, or raised blood levels of urea or creatinine from EPO administration in 24 participants with severe closed traumatic brain injury compared to 18 participants in the control group. No thrombotic event or other secondary effects attributed to r-HuEPO injection was recorded in 80 participants admitted to the ICU after cardiac surgery, who received a single dose of Epoetin-alpha or placebo (De Seigneux 2012). Mattich 1993 reported no adverse effects observed in participants with superficial and deep burns (20% to 55% of TBSA) treated with epoetin for 21 days. A study of people with orthopaedic trauma reported that none of the participants had to stop receiving epoetin-alfa because of its possible adverse effects, such as gastrointestinal, cardiovascular, respiratory, and central or peripheral nervous system disorders (Kateros 2010). However, the authors did not indicate whether any of these adverse effects had occurred. Low-dose EPO (6000 IU, IV injection) or placebo (saline) in 35 participants with STEMI administered immediately, two days and four days after PCI did not cause any major cardiovascular events including stent thrombosis or cancer after six months follow-up (Taniguchi 2010). In Ferrario 2011, 30 participants with their first STEMI undergoing primary PCI within six hours of symptom onset who received EPO (33,000 IU) in isotonic sodium-chloride 50 ml over 30 minutes or placebo (isotonic sodium chloride 50 ml) starting before and continuing during PCI, and 24 and 48 hours later (for a total EPO dose of $\sim 1 \times 10^5$ IU) did not experience any major cardiovascular events or cancer during 12-month follow-up. Nevertheless, one EPO-treated participant suffered from in-stent thrombosis seven days after PCI and underwent successful emergency re-PCI without further cardiac enzyme release. He was the only participant who received ticlopidine rather than the scheduled double anti-platelet treatment because of a history of aspirin allergy. During a six-month follow-up period, no adverse effects of treatment were observed in 73 participants with aSAH who were randomized to treatment with EPO (500 IU/kg/day for three days) or placebo (Springborg 2007). Allergy was assessed in two studies (Endre 2010; Nichol 2015), with no event reported.

Observational studies

Seven out of 14 observational studies reported 14 adverse effects of ESAs, with a range of one to seven adverse effects (Bush 2008; Cariou 2008; Hecht 2007; Kashkouli 2011; Lundy 2010; Shuman 2009; Talving 2010). Among these studies, the risk of venous thromboembolisms (VTEs) was specified as a primary outcome in Hecht 2007 and Bush 2008.

Kashkouli 2011 reported no significant adverse effect following intravenous injection of erythropoietin, including hypertension, polycythaemia, thrombocytosis, thrombotic phenomena, and flu-like syndrome. However, they observed mild transient hypotension during injection in two cases that subsided after a holding injection for 30 minutes and continuing with slow reinfusion.

1.1. Effects of ESAs on any adverse events

Based on nine studies that included 3099 participants (Corwin 2007a; Georgopoulos 2005; Luchette 2012; Najjar 2011; Nichol 2015; Prunier 2012; Still 1995; Talving 2010; Vincent 2006), ESAs treatment did not significantly increase the risk of any adverse event (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.93 to 1.21; combining both RCTs and observational studies, Bayesian estimates) (see Figure 5). Using GRADE, we downgraded the quality of this evidence to low, as we noted a high level of bias in Georgopoulos 2005 and one observational study identified (Talving 2010).

Figure 5. Forest plot of comparison: 1 ESAs versus placebo or no ESAs, outcome: 1.1 any adverse event

1.2. Effects of ESAs on any serious adverse events

Based on 10 studies that included 4183 participants (Corwin 2002; Corwin 2007a; Endre 2010; Luchette 2012; Najjar 2011; Ott 2010; Silver 2006; Taniguchi 2010; Vincent 2006; Voors 2010), ESAs treatment did not significantly increase the risk of any serious adverse event (RR 1.00, 95% CI 0.87 to 1.16, Bayesian estimates) (see Web Appendix). Using GRADE, we downgraded the quality of this evidence to moderate, as some studies reported very wide confidence intervals (Najjar 2011; Ott 2010) and wide confidence intervals (Luchette 2012; Silver 2006; Vincent 2006).

1.3. Effects of ESAs on venous thromboembolism (VTE)

Based on 18 studies that included 18,917 participants (Bush 2008; Corwin 1999; Corwin 2002; Corwin 2007a; Endre 2010; Georgopoulos 2005; Gerasimov 2012; Hecht 2007; Luchette 2012; Lundy 2010; Nichol 2015; Nirula 2010; Robertson 2014; Shuman 2009; Still 1995; Talving 2010; Tseng 2009; Voors 2010), ESAs treatment did not significantly increase the risk of VTE (RR 1.04, 95% CI 0.70 to 1.41; combining both RCTs and observational studies, Bayesian estimates) (see Figure 6). Using GRADE, we downgraded the quality of this evidence to very low, as we identified five observational studies (Bush 2008; Hecht 2007; Lundy 2010; Shuman

2009; Talving 2010), a high level of bias in Georgopoulos 2005 and Nirula 2010, and we noted a high level of statistical heterogeneity for this effect estimate ($I^2 = 84\%$). Furthermore, six studies reported

very wide confidence intervals (Georgopoulos 2005; Lundy 2010; Nirula 2010; Shuman 2009; Still 1995; Voors 2010).

Figure 6. Forest plot of comparison: 1 ESAs versus placebo or no ESAs, outcome: 1.3 venous thromboembolism

1.4. Effects of ESAs on deep vein thrombosis (DVT)

Based on 13 studies that included 5141 participants (Corwin 1999; Corwin 2002; Corwin 2007a; Endre 2010; Georgopoulos 2005; Gerasimov 2012; Luchette 2012; Nichol 2015; Nirula 2010; Robertson 2014; Still 1995; Voors 2010; Talving 2010), ESAs treatment did not significantly increase the risk of DVT (RR 1.15,

95% CI 0.93 to 1.41; combining both RCTs and observational studies (see Analysis 1.4; Web Appendix). Using GRADE, we downgraded the quality of this evidence to low, as one was an observational study (Talving 2010), some studies reported wide confidence intervals and there was a high level of bias in Georgopoulos 2005 and Nirula

2010, as well as moderate risk of bias in three RCTs (Gerasimov 2012; Luchette 2012; Voors 2010).

1.5. Effects of ESAs on stroke

Based on 11 studies that included 2229 participants (Endre 2010; Gerasimov 2012; Kateros 2010; Ludman 2011; Najjar 2011; Nichol 2015; Ott 2010; Prunier 2012; Robertson 2014; Suh 2011; Voors 2010), ESAs treatment did not significantly increase the risk of stroke (RR 1.57, 95% CI 0.58 to 4.29) (see Analysis 1.5; Web Appendix). Using GRADE, we downgraded the quality of this evidence to moderate, as all studies reported very wide confidence interval.

1.6. Effects of ESAs on myocardial infarction (MI)

Based on 10 studies that included 3254 participants (Binbrek 2009; Corwin 2007a; Endre 2010; Gerasimov 2012; Najjar 2011; Nichol 2015; Ott 2010; Prunier 2012; Robertson 2014; Suh 2011), ESAs treatment did not significantly increase the risk of MI (RR 1.58, 95% CI 0.84 to 2.97) (see Analysis 1.6; Web Appendix). Using GRADE, we downgraded the quality of this evidence to low, as all studies reported very wide confidence intervals and we noted moderate risk of bias in three studies (Binbrek 2009; Prunier 2012; Suh 2011).

1.7. Effects of ESAs on pulmonary embolism (PE)

Based on eight studies that included 3475 participants (Corwin 2007a; Endre 2010; Gerasimov 2012; Luchette 2012; Nichol 2015; Robertson 2014; Talving 2010; Voors 2010), ESAs treatment did not significantly increase the risk of PE (RR 0.87, 95% CI 0.36 to 2.08; combining both RCTs and observational studies) (see Analysis 1.7; Web Appendix). Using GRADE, we downgraded the quality of this evidence to very low, as one was an observational study (Talving 2010), all studies but two (Corwin 2007a; Nichol 2015) reported very wide confidence intervals and there was moderate risk of bias in three studies (Gerasimov 2012; Luchette 2012; Voors 2010). Furthermore, we noted a high level of statistical heterogeneity for this effect estimate ($I^2 = 67\%$).

1.8. Effects of ESAs on sepsis

Based on seven studies that included 3973 participants (Corwin 2002; Corwin 2007a; Nichol 2015; Robertson 2014; Talving 2010; Tseng 2009; Vincent 2006), ESAs treatment did not significantly increase the risk of sepsis (RR 1.06, 95% CI 0.84 to 1.35; combining both RCTs and observational studies) (Analysis 1.8). Using GRADE, we downgraded the quality of this evidence to moderate, as one was an observational study (Talving 2010) and two studies reported wide confidence intervals (Robertson 2014; Vincent 2006).

1.9. Effects of ESAs on gastrointestinal system disorders

Based on six studies that included 2475 participants (Corwin 2002; Endre 2010; Lipsic 2006; Luchette 2012; Nichol 2015; Robertson 2014), ESAs treatment did not significantly increase the risk of gastrointestinal system disorders (RR 0.98, 95% CI 0.63 to 1.52) (Analysis 1.9). Using GRADE, we downgraded the quality of this evidence to low, as all studies but one (Corwin 2002) reported wide confidence intervals and Lipsic 2006 was at high risk of bias.

1.10. Effects of ESAs on cardiac arrest or ventricular fibrillation

Based on six studies that included 3755 participants (Corwin 2002; Corwin 2007a; Endre 2010; Nichol 2015; Robertson 2014; Still 1995), ESAs treatment did not significantly increase the risk of cardiac arrest or ventricular fibrillation (RR 0.96, 95% CI 0.67 to 1.38) (Analysis 1.10). Using GRADE, we downgraded the quality of this evidence to moderate, as all studies but one (Corwin 2002) reported wide confidence intervals.

1.11. Effects of ESAs on other AEs

ESAs treatment did not significantly increase the risk of other frequently-reported adverse events in critically-ill people. See Analyses 1.11 to 1.39, apart from Analysis 1.29 where they decreased the risk of central and peripheral nervous system disorders by 63% ($P = 0.03$). There was no effect on AEs reported in the single studies except for two AEs: a clinically-relevant thrombotic vascular event (RR 1.43, 95% CI 1.10 to 1.85) (Corwin 2007a) and upper limb thrombosis (RR 0.51, 95% CI 0.26 to 0.97) (Endre 2010) (See Table 2).

Subgroup effects

The adverse effects of ESAs on critically-ill people were similar in all four subgroups (at the 5% significance level). For detailed subgroup analyses according to harm outcomes see Analysis 2.8; Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14; Analysis 2.15; Analysis 2.16; Analysis 2.17; Analysis 2.18; Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.22; Analysis 2.23; Analysis 2.24; Analysis 2.25; Analysis 2.26; Analysis 2.27; Analysis 2.28; Analysis 2.29; Analysis 2.30; Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36; Analysis 2.37; Analysis 2.38; Analysis 2.39; Analysis 2.40; Analysis 2.41; Analysis 2.42; Analysis 2.43; Analysis 2.44; Analysis 2.45; Analysis 2.46; Analysis 2.47; Analysis 2.48; Analysis 2.49; Analysis 2.50; Analysis 2.51; Analysis 2.52; Analysis 2.53; Analysis 2.54; Analysis 2.55; Analysis 2.56; Analysis 2.57; Analysis 2.58; Analysis 2.59; Analysis 2.60. These findings are supported by the Bayesian analysis. It is noteworthy that a number of subgroups included very few trials, resulting in increased variation of the effect estimates.

Sensitivity analyses

Excluding studies judged as having high risk of bias or the studies with biosimilar ESAs left the estimates of adverse effects of ESAs virtually unchanged. The estimates appeared robust against risk of bias within studies.

Reporting bias

We had too few studies for all adverse events but VTE and DVT to sensibly perform a formal test for funnel plot asymmetry. The funnel plot of VTE indicated some asymmetry on visual inspection (Figure 7), concordant with significance at formal testing for funnel plot asymmetry (arcsine transformation regression, $t = -2.3$, $df = 15$, P value = 0.04). However, the small-study effect was rejected in Egger's test (P value = 0.42). There was no funnel plot asymmetry for DVT on visual inspection (see Web Appendix), nor on formal testing (arcsine transformation regression, $t = -0.05$, $df = 10$, P value = 0.6; Egger's test for small-study effects, P value = 0.77).

Figure 7. Funnel plot of comparison: 1 rHuEPO versus placebo or no rHuEPO, outcome: 1.3 venous thromboembolism.

Secondary outcomes

Effects of ESAs on mortality

Mortality was reported in 41 studies (32 RCTs and nine observational studies). Overall 68,045 mortality outcomes (734 in RCTs and 67,311 in observational studies) were observed in 931,369 participants (6416 in RCTs and 924,953 in observational studies). Seven RCTs had zero outcomes and did not contribute information to the meta-analyses, so the estimates refer to 34 studies. If mortality was assessed at several time points in a study, we used data from the closest follow-up time to 30 days. Mortality was assessed at an undetermined time point or linked to a setting (like ICU mortality) in [Chen 2008](#), [Kateros 2010](#) and [Wittbrodt 2005](#); at 50 days and also six months in [Nichol 2015](#); and at six months in [Aloizos 2015](#) and [Robertson 2014](#). The risk for mortality in participants treated with ESAs was lower compared to those treated with non-ESAs (RR 0.76, 95% CI 0.61 to 0.92; combining both

RCTs and observational studies, Bayesian estimates) (see [Figure 8](#)). Using GRADE, we downgraded the quality of this evidence to low, as nine were observational studies ([Brophy 2007](#); [Cariou 2008](#); [Ginger 2008](#); [Grmec 2009](#); [Kane-Gill 2007](#); [Luh 2005](#); [Lundy 2010](#); [Talving 2010](#); [Wittbrodt 2005](#)), there was a high risk of bias in four studies ([Aloizos 2015](#); [El Atroush 2005](#); [Georgopoulos 2005](#); [Nirula 2010](#)), and we noted the large heterogeneity ($I^2 = 91\%$) between studies. There was also some discrepancy between the frequentist (RR 0.84, 95% CI 0.62 to 1.12) and the Bayesian estimate (RR 0.76, 95% CI 0.61 to 0.92) which is attributable to the lower importance of the observational studies in the Bayesian analysis. This is probably caused by the lack of adjusting for trial design, resulting in a different weighting of the studies in the Bayesian analysis. Furthermore we noted very wide confidence intervals in nine studies ([Abrishamkar 2012](#); [Aloizos 2015](#); [Binbrek 2009](#); [De Seigneux 2012](#); [Ludman 2011](#); [Najjar 2011](#); [Nirula 2010](#); [Ott 2010](#); [Prunier 2012](#)).

Figure 8. Forest plot of comparison: 1 ESAs versus placebo or no ESAs, outcome: mortality

Figure 8. (Continued)

0.001 0.01 0.1 1 10 100
Favours Experimental Favours Control

Randomized controlled studies

Thirty-two RCTs reported mortality, with 734 deaths observed in 6416 participants. Sixteen out of 39 RCTs reported mortality as a prespecified secondary or additional outcome of interest (Aloizos 2015; Binbrek 2009; Corwin 2007a; El Atroush 2005; Endre 2010; Georgopoulos 2005; Gerasimov 2012; Najjar 2011; Nichol 2015; Nirula 2010; Ott 2010; Prunier 2012; Silver 2006; Suh 2011; Taniguchi 2010; Voors 2010). Studies were performed in critically-ill people in the ICU (Corwin 1999; Corwin 2002; Corwin 2007a; El Atroush 2005; Endre 2010; Georgopoulos 2005; Silver 2006; Van Iperen 2000), people admitted to the ICU and at risk for acute kidney injury after elective cardiac surgery (De Seigneux 2012), people diagnosed with STEMI undergoing PCI (Ferrario 2011; Ludman 2011; Najjar 2011; Ott 2010; Prunier 2012; Suh 2011; Taniguchi 2010; Voors 2010) and thrombolysis (Binbrek 2009), people with trauma (Abrishamkar 2012; Aloizos 2015; Gerasimov 2012; Kateros 2010; Luchette 2012; Nichol 2015; Nirula 2010; Robertson 2014), people with non-STE ACS (Liem 2009), with aneurysmal subarachnoid haemorrhage (Springborg 2007; Tseng 2009), people who required surgical revascularization of the heart with the use of the heart-lung machine (Lakic 2010), people with burns (Still 1995) and people with multiple organ dysfunction syndromes (Gabriel 1998). Seven RCTs did not report mortality (Alibai 2014; Chicella 2006; Gholamzadeh 2015; Kang 2012; Lipsic 2006; Mattich 1993; Vincent 2006) and eight randomized trials reported no deaths in a total of 660 participants (333 in intervention groups and 327 in control groups) over a specified time period (Ferrario 2011; Kateros 2010; Lakic 2010; Liem 2009; Luchette 2012; Robertson 2014; Suh 2011; Taniguchi 2010). A study on the use of epoetin-alfa in people with intertrochanteric fracture reported eight deaths during mean follow-up of 34 months, but for causes that were not directly related to medication administration (Kateros 2010); the report therefore did not provide further information about the causes of death and causality assessment. Another study of people with major blunt trauma orthopaedic injuries reported an adverse event of peritoneal haemorrhage resulting in death in one participant in the epoetin-alfa group, but the event was not considered to be related to study medication (Luchette 2012). Meta-analysis of 25 RCTs that contributed effect size information (i.e. excluding the seven RCTs with zero events) revealed that ESAs use was associated with a significant reduction in mortality (RR 0.75, 95% CI 0.63 to 0.87; Bayesian estimates) in critically-ill people (see Figure 8).

Observational studies

Nine observational studies reported mortality, with 67,311 deaths observed in 924,953 participants. Studies were performed in critically-ill people who were admitted to the ICU (Brophy 2007; Kane-Gill 2007; Luh 2005; Wittbrodt 2005), people with trauma (Ginger 2008; Talving 2010), out-of-hospital cardiac arrest (Cariou 2008; Grmec 2009) and critically-ill people with burns (Lundy 2010). Among these studies, Ginger 2008 and Talving 2010 reported mortality as a primary outcome of their studies. Four observational studies did not report mortality (Bush 2008; Hecht 2007; Kashkouli 2011; Shuman 2009). However, we received confirmation from Kashkouli 2011 that no deaths occurred during the follow-up in

their study. The abstract of Chen 2008 reported no significant difference in mortality between rHuEPO and control groups ($P > 0.05$) but no number of events. The forest plot of nine cohort studies is shown in Figure 8, with no significant association between ESAs use and mortality (RR 1.00, 95% CI 0.44 to 1.94; Bayesian estimates).

Sensitivity Analysis

Excluding studies judged as having a high risk of bias left the estimates virtually unchanged in the subset of RCTs (RR 0.81, 95% CI 0.70 to 0.93), but somewhat more pronounced in the observational studies (RR 0.80 95% CI 0.45 to 1.44). The estimates appeared robust against risk of bias within studies. Furthermore, excluding Gerasimov 2012, which studied a biosimilar EPO, did not change the estimates.

Subgroup Analysis:

Type of ESAs

There was no heterogeneity explained by ESA type detected, and the test for subgroup differences was not significant ($P = 0.47$; Analysis 2.2).

Dosage of ESAs

There was no heterogeneity explained by ESA dosage detected, and the test for subgroup differences was not significant ($P = 0.26$; Analysis 2.3).

Indication as a haematopoietic drug:

Some heterogeneity was explained by non-haematopoietic indications, although the test for subgroup difference was not significant ($P = 0.18$; Analysis 2.5).

Baseline anaemia

Some heterogeneity was explained by anaemia, although the test for subgroup difference was not significant ($P = 0.42$; Analysis 2.7).

Trauma

Some heterogeneity was explained by trauma. In the subgroup of trauma participants the I^2 value was 0%. The effect of ESAs on mortality was more pronounced in people with trauma compared to those without trauma (RR 0.57, 95% CI 0.46 to 0.71 versus RR 0.95, 95% CI 0.69 to 1.3), P for subgroup differences = 0.01 (Analysis 2.1).

Subgroup findings are supported by the Bayesian analysis, where credible intervals for subgroups were overlapping, indicating no difference in the 95% credible level.

Reporting bias

For the outcome of mortality there was no indication of funnel plot asymmetry on visual inspection, either for RCTs alone or for RCTs with observational studies, except for the one disproportionately large study by Brophy 2007, which had very small standard errors (0.01) as a result of the study design (see Web Appendix). Formally, there was no funnel plot asymmetry (arcsine transformation

regression, $t = -1.106$, $df = 30$, P value = 0.28; Egger's test for small-study effects: $P = 0.88$, for RCTs only, and $P = 0.28$ for RCTs and observational studies), suggesting no small-study effect or reporting bias.

DISCUSSION

Summary of main results

We found 39 RCTs and 14 cohort studies fulfilling our inclusion criteria. We found overall 20,429 participants with 7602 adverse event (AE) outcomes and 930,470 participants with 67,931 mortality outcomes. Information on adverse events is mainly derived from three RCTs (Corwin 2002; Corwin 2007a; Robertson 2014), with 4922 adverse events (69.65% of total AEs) reported in 2962 participants (0.3% of total).

Information on mortality is mainly derived from one observational database study (Brophy 2007). This cohort study reported on 923,043 participants (99.1% of total) and 66,884 mortality outcomes (98.4% of total mortality outcomes).

Approximately 72% of the studies (29 RCTs and nine cohort studies) compared epoetin-alfa alone or with other treatments. Epoetin-beta was compared with placebo in seven RCTs (Abrishamkar 2012; Endre 2010; Ludman 2011; Ott 2010; Prunier 2012; Taniguchi 2010; Tseng 2009), and one cohort study (Grmec 2009), as well as in addition to tenecteplase in Binbrek 2009.

Darbepoetin was compared with non-DARB in two studies (Shuman 2009; Talving 2010), with routine care in Lipsic 2006 and in combination with granulocyte-colony stimulating factor (G-CSF) in Kang 2012. The type of ESA was not clarified in Bush 2008.

In summary, it is unclear whether ESAs are associated with increased risk of adverse events, and there is uncertainty related to the low quality of reporting harms. There is low-quality evidence for a benefit of ESAs in preventing death in some people with critical illness.

Overall completeness and applicability of evidence

Even though 53 studies met our inclusion criteria, most distinct adverse events were reported in three RCTs only (Corwin 2002; Corwin 2007a; Robertson 2014). Except for a few studies (Corwin 2002; Corwin 2007a; Endre 2010; Nichol 2015; Robertson 2014), the number of participants was small (fewer than 100) for most of the adverse events. Furthermore, safety was measured as the primary outcome in only two of the cohort studies (Bush 2008; Hecht 2007). Some of the analyses may therefore lack power to detect elevated rates of such events, despite the reasonably large overall numbers of participants. Studies were performed in a wide range of conditions in several countries, and included RCTs, cohort studies and 'daily life' observational cohorts. Given these characteristics and the average mortality in the included population of between 7% and 17%, the results may be applicable to most circumstances of critical-care medicine.

Quality of the evidence

Only two RCTs (Ludman 2011; Ott 2010), and one cohort study (Talving 2010), fulfilled all criteria for low risk of bias (Figure 2 and Table 1). However, we rated 30 RCTs and 10 cohort studies at low to moderate risk of bias for safety outcomes. None of the included

studies fulfilled all criteria in the quality of harm assessment and reporting evaluation. Harm assessment and reporting evaluation were of medium to low quality in the included RCTs and of low quality in the observational studies overall. Only six RCTs monitored adverse events by an independent data and safety monitoring board (DSMB) (Corwin 2002; Corwin 2007a; Najjar 2011; Nichol 2015; Robertson 2014; Voors 2010). The ability of the observer to accurately and consistently assess the participant and collect the adverse events is crucial in safety studies.

Most of the included studies did not define 'harms' in their report. For example, the incidence of major adverse cardiovascular events was specified as an outcome in Ferrario 2011. This study reported that, "all of the patients were alive and had not experienced any major cardiovascular events or cancer", without defining what they meant by major cardiovascular events. Variability, and overlap of terms used to describe each adverse event across studies, was apparent. This was also an issue for considering adverse events as serious. Only one study graded the severity of adverse events by using the CTCAE coding system (Endre 2010). Definitions for expected adverse events were detailed in only one study's supplemental information (Robertson 2014).

Potential biases in the review process

We minimized the biases in the review process by performing an exhaustive search strategy, which included the 10 most important bibliographic databases and the two main trials registries, without date or language limitation. We also performed backward and forward citation chasing of 48 included studies in a non-Cochrane systematic review of ESAs in critically-ill patients (Mesgarpour 2013a). Furthermore, we contacted the four main manufacturers of ESAs. We were able to obtain all the published papers of the trials and all available data. However, seven observational studies were published only as abstracts, and we received no reply to our enquiries from their corresponding authors (Bush 2008; Chen 2008; Ginger 2008; Hecht 2007; Luh 2005; Shuman 2009; Wittbrodt 2005). Anglemeyer 2014 has recently reported that conclusions from randomized and observational evidence were similar for a broad range of conditions. However, this increase in statistical power by pooling randomized and observational studies comes with costs in methodological complexity, and remains a challenging exercise.

There are a large number of subgroup analyses with no adjustment for multiple testing. We decided not to perform multiplicity adjustments with the aim of mainly focusing on estimating treatment effects, rather than seeing our analysis from a strict decision-making perspective.

Agreements and disagreements with other studies or reviews

The results of our review are consistent with a Cochrane Review of RCTs comparing the benefits and risks of ESA for chronic heart failure patients with anaemia (Ngo 2010). Moderate-quality evidence in our review showed a lower risk of all-cause mortality and no increased risk of adverse events with ESA therapy.

Our findings were not in full agreement with a review of RCTs comparing the efficacy and safety of ESAs (epoetin-alfa, epoetin-beta, darbepoetin-alfa, methoxy polyethylene glycol-epoetin-beta, or biosimilar ESA) with placebo or no treatment in adults with chronic kidney disease (CKD) (Palmer 2014). The odds in the Palmer

review of all-cause mortality for ESAs treatment compared to placebo or no treatment in people with CKD were uncertain. The odds of harm outcomes including cardiovascular mortality, fatal or nonfatal MI, fatal or nonfatal stroke, vascular access thrombosis, major adverse cardiovascular event and end-stage kidney disease were also uncertain. However, the odds of hypertension were increased with epoetin-alfa, epoetin-beta and darbepoetin-alfa when compared to placebo and also epoetin-beta compared to no treatment (Palmer 2014).

Furthermore, our findings were not in agreement with a Cochrane Review of RCTs comparing the effects of ESAs either on prevention or treatment of anaemia in people with cancer (Tonia 2012). This review found evidence that ESAs increase mortality, thromboembolic complications, hypertension and thrombocytopenia or haemorrhage in people with cancer receiving ESAs compared to controls. Another Cochrane Review of RCTs comparing epoetin or darbepoetin plus red blood cell (RBC) transfusions versus RBC transfusions alone, to prevent or treat anaemia in adults or children with cancer, with or without concurrent antineoplastic therapy, provided evidence that ESAs increased mortality (Bohlius 2012).

The survival benefit of epoetin-alfa in critically-ill people with trauma, a subgroup of critically-ill people, was demonstrated in post-trial analysis of two RCTs by Corwin 2002 (day 29, adjusted hazard ratio (aHR) for baseline and trauma variables 0.50, 95% CI 0.26 to 0.97) and Corwin 2007a (day 29, aHR 0.38, 95% CI 0.19 to 0.74; day 140 aHR 0.39, 95% CI 0.21 to 0.72). A Canadian economic analysis of epoetin-alfa in surgical trauma patients in an ICU setting showed an incremental cost-effectiveness ratio of CAD 89,958 per quality-adjusted life year (QALY) using epoetin-alfa compared with standard care, using a one-year time horizon (Chui 2012). However, this study revealed that there is significant uncertainty about the true cost effectiveness of epoetin-alfa in people with trauma, driven by uncertainty about its mortality benefits and the lack of long-term costs and outcomes data (Chui 2012). Our post hoc subgroup analysis in people with trauma was in agreement with Corwin 2002 and Corwin 2007a. Moreover, we cannot exclude other relevant subgroup differences in our effect estimates, given the wide definition of 'off-label' use in critical illness.

None of the included studies reported pure red cell aplasia (PRCA), which is the consequence of developing antibodies against the EPO protein. Most of this uncommon severe anaemia was caused by a preparation of epoetin-alfa marketed outside the United States (Eprex/Erypo) and peaked during 2002 to 2003 (exposed-adjusted peaked incidence rate: 45 per 100,000 patient-years) (McKoy 2008). Several factors have been identified as possible causes of increasing the immunogenicity of erythropoietin-alfa or other ESAs: product-related factors such as sequence variations in proteins, the degree and nature of protein glycosylation, the manufacturing process, handling and storage, components and properties of the product formulation; patient-related factors including skin reactions, immune status and treatment history (Macdougall 2005). Consequently, the UK Department of Health called for a change in the route of epoetin-alfa administration to intravenous (IV) (Ng 2003), and subcutaneous administration of epoetin-alfa in people with CKD was contraindicated in the European Union between 2002 and 2006. A prospective immunogenicity surveillance registry was conducted from June 2006 to December 2010 to estimate the incidence of antibody-

mediated PRCA with subcutaneous administration of Eprex® (epoetin-alfa) compared to NeoRecormon® (epoetin-beta) and Aranesp® (darbepoetin alfa). This cohort study, which enrolled 15,333 participants with CKD in parallel groups across 751 sites in Europe and Australia confirmed only five cases of PRCA (Eprex®, n = 3; NeoRecormon®, n = 1; Aranesp®, n = 1). The exposed incidence rate of PRCA was 35.8/100,000 patient-years (95% CI 7.4 to 104.7) for Eprex® versus 14.0/100,000 patient-years (95% CI 1.7 to 50.6) for NeoRecormon®/Aranesp®. The PRCA incidence rate ratio with Eprex® versus comparator ESAs was not statistically significant (2.56; 95% CI 0.43 to 15.31) (Macdougall 2015).

Allergic responses were recorded in two studies as zero in both experimental and control groups (Endre 2010; Nichol 2015). However, five out of 38 participants complained of a skin inflammatory response or bruising at the site of epoetin-alfa injection in Kateros 2010 (absolute risk increase 13.2%).

One of the included randomized trials (Alibai 2014) reported sexual dysfunction as an adverse event during six months follow-up. Thirty participants with spinal cord injury were assigned to receive rHuEPO plus methyl prednisolone sodium succinate (MPSS) or MPSS plus placebo. However, the incidence of sexual dysfunction was not statistically significant between erythropoietin (47%) and control groups (60%), but it is in contrast to the erectile function recovery of rHuEPO or darbepoetin in the experimental model of cavernous nerve injury (Allaf 2005).

AUTHORS' CONCLUSIONS

Implications for practice

It is unclear whether ESAs are associated with increased risk of adverse events, and there is uncertainty related to the low quality of reporting harms. There is low-quality evidence of the benefit of ESAs in preventing death in some people with critical illness.

The benefits and harms of ESAs in critically-ill people need also to be considered in the light of the licensing status of the medicinal products.

Implications for research

The evidence (current to January 2016) for adverse events of ESAs in people in a critical care setting is of low to medium quality, and we are uncertain about the estimates.

The quality of the reporting of harms was a major concern. However, it may be attributable to the low quality of the recording of adverse events in the included studies. Very few studies defined 'harm', 'SAEs' or 'major adverse events' of ESAs.

Future RCTs and observational comparative studies should use prespecified and consistent harm outcomes, and should adhere to reporting guidelines, such as CONSORT and STROBE, so that results can be compared across studies. The development of a predefined set of harm outcomes, or serious adverse event outcomes, for ESAs will facilitate this process.

The use of a standardized coding system for grading the severity of major adverse events of ESAs and monitoring of harm events in trials by an independent or even an internal DSMB is highly desirable. The time interval of harm monitoring, as well as a

reliable, valid, and unbiased manner of harm assessment is required for high-quality evidence.

Given the variation in content, isoform profiles, and potency of biological products from different manufacturers or in different batches of the same product, the details about the manufacture of original or biosimilar ESAs should be reported. The physiochemical characterization and biological assay of biosimilar ESAs demonstrate the attributes of products. This should be evaluated as part of the comparative clinical studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abrishamkar 2012

Methods	Randomized, double-blinded controlled trial The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences and all patients gave written, informed consent.
Participants	54 patients with post traumatic diffuse axonal injury (PTDAI) admitted within less than 6 h after the trauma Age: 20-47 years old Male: 54 (100%) Location: Isfahan, Iran Setting: University affiliated Medical Centre
Interventions	rhEPO or placebo; Subcutaneous injection of 2000U open-label rhEPO erythropoietin (erythropoietin- β) for six doses in two weeks (on admission, days 2, 4, 6, 8 and 10) or saline (0.9% NaCl), Length of follow-up: 10 days
Outcomes	The study's endpoints were Glasgow Coma Scale (GCS) during study and at the end. Additional clinical variables were collected on days 2, 4, 6, 8 and 10 including serum EPO, haematocrit, haemoglobin, leukocyte and thrombocyte counts, partial prothrombin time (PTT), C-reactive protein (CRP), ferritin, transferrin, iron, electrolytes, glucose, blood urea nitrogen (BUN) and creatinine
Notes	Study duration: No detail Sponsorship source: No detail Conflict of Interests: Authors have no conflict of interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Insufficient information
Allocation concealment (selection bias)	Unclear risk	Quote: "The vials were randomly assigned to patients upon enrolment and the contents of each vial were known only by the pharmacist." Comment: Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For blinding, a pharmacist prepared and numbered identical vials containing either saline (0.9% NaCl) or rhEPO reconstituted in saline. The vials were randomly assigned to patients upon enrolment and the contents of each vial were known only by the pharmacist" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "None of the clinicians who performed neurologic or imaging analyses had access to any of the serum laboratory data (platelet or reticulocyte counts) during the study. Serum EPO levels were analysed only after unbinding" Comment: Probably done

Abrishamkar 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available
Other bias	Unclear risk	Comment: Insufficient information about source of funding; However, authors declared no conflict of interests. Erythropoietin- β were from Roche, Grenzach-Wyhlen, Germany

Alibai 2014

Methods	Randomized, double-blinded controlled trial The study protocol was approved by the institutional ethics committee and all the enrolled participants completed a written informed consent
Participants	30 adults with acute spinal cord injury (SCI) admitted within less than 6 hours after the trauma Age: 18 - 65 years old Male: 23 (76.6%) Location: Shiraz, Iran Setting: 2 university-affiliated hospitals
Interventions	rHuEPO + methyl prednisolone sodium succinate (MPSS) or placebo + MPSS; IV injection of EPO (500 unit/kg) on admission and 24 hours later, MPSS 30 mg/kg initially and 5.4 mg/kg every hour till 23 hours if admitted within 3 hours and till 47 hours if recruited within 3 - 6 hours after injury Length of follow-up: 10 days
Outcomes	- Primary outcomes: Neurological function assessed by American Spinal Injury Association (ASIA) score at 24 hours, 48 hours, 1 week, 1 month and 6 months after symptoms - Secondary outcomes: Sphincter dysfunction on 1st day and 1 month after, sexual dysfunction at 6 months after SCI, clinically significant venous thromboembolism
Notes	Study duration: 2005 - 2006 Sponsorship source: Shiraz University of Medical Sciences; rHuEPO was provided by Pooyesh Darou pharmaceutical company (local EPO producer) Conflict of Interests: Authors declare no conflict of interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done by drawing of cards with pre-written numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients with odd numbers were assigned to control group (MPSS + placebo; group M) and even numbers to intervention group (MPSS + erythropoietin; Epo group)"

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Alibai 2014 (Continued)

All outcomes

Comment: Blinding of participants and personnel was probably done

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neurologic examinations were performed only by an approved and blinded physician un-aware of the patients' group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement
Other bias	Unclear risk	Comment: The study is supported by Shiraz University of Medical Sciences and rHuEPO was provided by Pooyesh Darou pharmaceutical company (local EPO producer)

Aloizos 2015

Methods	Randomized controlled trial All human studies were approved by the appropriate ethics committees of the 2 hospitals included in this study. The studies were performed according to the ethical standards determined in the 1964 Declaration of Helsinki. All the persons included in the studies gave their informed consent
Participants	42 adults with severe closed traumatic brain injury (TBI) admitted within the 1st 6 hours after the trauma Age: ≥ 18 to ≤ 65 years old Male: 39 (92.8%) Location: Athens, Greece Setting: ICU of the 401 General Army Hospital of Athens and the Athens University School of Nursing at KAT General Hospital
Interventions	rhEPO or routine care; injection of EPO (10,000 IU) within 6 hours from the time of the initial injury and for 6 consecutive days Length of follow-up: 6 months
Outcomes	- Primary outcomes: Combined proportion of unfavourable neurological outcomes at 6 months: severe disability (defined as GOS-E scores 2 - 4) or death (GOS-E score 1) - Secondary outcomes: Probability of an equal or greater GOS-E level at 6 months compared to the probability of a lesser GOS-E level; Proportion of surviving participants with unfavourable neurological outcome (GOS-E 2 - 4) at 6 months; Mortality at 6 months
Notes	Study duration: no detail Sponsorship source: no detail; No industrial funding was provided for the study Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
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Aloizos 2015 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "Our model examined the influence of the outcome and neurological recovery in 42 adults with TBI who were admitted to ICU within 6 hours of their injury and were recruited into a randomised controlled study of two groups" Comment: Insufficient information
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: It was not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: It was not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available
Other bias	Unclear risk	Comment: Small study group; No industrial funding was provided for the study

Binbrek 2009

Methods	Randomized, open, prospective trial Participants were studied after the acquisition of written informed consent and in accordance with a protocol approved by the institutional review board at Rashid Hospital
Participants	236 adults, admitted < 6 hours after the onset of chest pain indicative of acute coronary syndromes confirmed to be STEMI who were treated with tenecteplase to induce coronary thrombolysis Age: ≥ 18 years old Male: 234 (99%) Location: Dubai, United Arab Emirates Setting: Rashid Hospital
Interventions	Single IV bolus of epoetin beta (30,000 IU) plus tenecteplase (TNK) or tenecteplase only (EPO immediately before the onset of treatment with TNK) Length of follow-up: 30 day
Outcomes	- Primary outcomes: Enzymatic estimation of infarct size index (with the correction for body surface area made using the Dubois formula) - Secondary outcomes: Infarct size (uncorrected for body surface area), changes in platelet counts, concentrations of EPO in plasma, haematocrit, haemoglobin, estimated time to reperfusion on the basis of the time of an increase in the concentration in blood of the tissue form of the MM isoform of CK, echocardiographic measurements before discharge, the incidence of cerebrovascular accidents and major adverse coronary events within 30 days of hospital admission, and overall 30-day mortality

Binbrek 2009 (Continued)

Notes	Study duration: no detail
	Sponsorship source: partly supported by a Shaikh Hamdan Bin Rashed Al Maktoum Award (Dubai, United Arab Emirates)
	Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed as previously described." (p: 1035) Comment: Probably done, since earlier report from the same investigators clearly describe use of random sequences (Binbrek 2004)
Allocation concealment (selection bias)	Low risk	Quote: "The investigators were blinded to the assignments to groups" (p: 1035) Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: The EPO group received standard care plus treatment with a single IV bolus of EPO while control group received standard care only. Participants and personnel was very likely aware of performance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Authors did not clearly describe whether all study population completed the study
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available but it seems that the report should not limit the safety outcomes to the incidence of cerebrovascular accidents and major adverse coronary events or give the reason for not specifying other AEs
Other bias	Unclear risk	Comment: Study included exclusively male participants due to sample population; Study was partly supported by a Shaikh Hamdan Bin Rashed Al Maktoum Award (United Arab Emirates)

Brophy 2007

Methods	Cohort (a multicentre, retrospective database study)
Participants	923,043 adults admitted to the ICU and remained for ≥ 3 days Age: ≥ 18 years old Male: 474,571 (51.4%) Location: United States Setting: ICU admission for ≥ 3 days

Brophy 2007 (Continued)

Interventions	Having filled in a prescription for 1st dose of darbepoetin alfa or epoetin alfa between January 2003 and December 2005
Outcomes	Participant characteristics, mortality, RBC transfusion patterns
Notes	Type of report: Conference proceeding (further information is obtained by contacting the 1st author) Length of follow-up: 30 days Study duration: January 2003 - December 2005 Sponsorship source: funded by Amgen Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: All critically-ill people admitted to the ICU for ≥ 3 days were included
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Low risk	Comment: Information on medication orders for people admitted to the hospital/ICU was obtained from Solucient® ACTracker® database
Demonstration that the outcome of interest was not present at start of study?	Unclear risk	Comment: Insufficient information
Comparability of cohorts on the basis of the design or analysis?	High risk	Comment: No matching; Not controlled for potential confounders
Assessment of outcome?	Low risk	Comment: Record linkage using the discharge data abstracted from Solucient® ACTracker® database
Was the follow-up long enough for the outcomes to occur?	Low risk	Comment: 30-day outcome data are reported
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

Bush 2008

Methods	Cohort (a retrospective review)
Participants	687 high-risk trauma adults who received enoxaparin for VTE prophylaxis; Exclusion criteria were an Injury Severity Score (ISS) < 9 ; people discharged within 2 days of admission; need for therapeutic anticoagulation for an indication other than development of VTE; receipt of > 1 pharmacologic agent and/or dosing regimen for VTE prophylaxis during hospitalization; active gastrointestinal bleeding on admission; development of a VTE within 24 hours of admission; intracranial bleeding on computed tomography on admission; systemic coagulopathy; pregnancy; and renal failure

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Bush 2008 (Continued)

Age: ≥ 18 years

Location: United States

Setting: Health Shands hospital at the University of Florida

Interventions	ESAs and non-ESAs
Outcomes	<p>- Primary outcome: Development of VTE, defined as a PE or DVT</p> <p>- Secondary outcome: The incidence of clinically significant bleeding</p>
Notes	<p>Type of report: Conference proceeding</p> <p>Length of follow-up: no detail</p> <p>Study duration: 1 January 2005 - 31 December 2007</p> <p>Sponsorship source: no detail</p> <p>Conflict of Interests: no detail</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: A retrospective review of all people with trauma who were admitted to Shands at the University of Florida over a certain time period
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Unclear risk	Comment: Insufficient information
Demonstration that the outcome of interest was not present at start of study?	Low risk	Comment: People who developed a VTE within 24 hours of admission were excluded
Comparability of cohorts on the basis of the design or analysis?	Unclear risk	Comment: Insufficient information
Assessment of outcome?	Unclear risk	Comment: Insufficient information
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

Cariou 2008

Methods	Cohort (prospective with case-matched historical controls)
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Cariou 2008 (Continued)

Protocol and consent procedures were approved by the ethics review committee of the Cochin University Hospital, in accordance with the European Guidelines for Good Clinical Practice. In accordance with French law, the next of kin were verbally informed about the trial by the pre-hospital emergency team at the time of inclusion, and written consent was systematically obtained from participants' next of kin within 24 hours. Written consent was obtained from all survivors

Participants	58 adults with witnessed out-of-hospital cardiac arrest (OHCA) of presumed cardiac origin who had been successfully resuscitated with mild hypothermia Age: 18 - 75 years old Location: Paris, France Setting: Cochin University Hospital ICU
Interventions	IV injection of Epo-alpha (40,000 IU) as soon as possible after stable ROSC (return of spontaneous circulation) followed by 4 additional injections every 12 hours during the 1st 48 hours after ICU admission + mild hypothermia or mild hypothermia only
Outcomes	Neurological performance according to the Glasgow- Pittsburgh Cerebral Performance Category (CPC) scale, haematological outcomes, pharmacokinetics and safety of Epo-alpha, mortality
Notes	Length of follow-up: 28 days Study duration: November 2003 - May 2004 Sponsorship source: no detail Conflict of Interests: Cariou received honoraria from OrthoBiotech France when engaged as a speaker, and Hababou was previously an employee of OrthoBiotech France (a manufacturer of erythropoietin). No other potential conflict of interest has occurred since this work was initiated

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Quote: "We studied the effects of high-dose Epo-alpha for 20 consecutive patients who had been successfully resuscitated by the emergency medical service (EMS)." (p: 398)
Selection of the non-exposed cohort?	Low risk	Quote: "These controls, all treated by mild hypothermia, were selected from our local cardiac arrest database by an independent investigator blinded to patient outcome." (p: 398)
Ascertainment of exposure?	Low risk	Comment: Cases were prospectively treated with Epo-alpha and controls were selected from their local cardiac arrest database
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Low risk	Quote: "The investigator selected matched control patients admitted to our ICU after OHCA during the same time period (2003—2004), using the following criteria: age, SAPS 2, no flow and low flow intervals, number of electric shocks and total adrenaline (epinephrine) dosage required during initial resuscitation" (p: 398)
Assessment of outcome?	Unclear risk	Comment: Insufficient information

Cariou 2008 (Continued)

Was the follow-up long enough for the outcomes to occur?	Low risk	Comment: 28 days
Adequacy of follow-up of the cohorts?	Low risk	Comment: No information has been provided

Chen 2008

Methods	Cohort (prospective control)
Participants	60 people with sepsis and anaemia Location: Tianjin, China Setting: Second Affiliated Hospital of Tianjin Medical University
Interventions	SC injection of rHuEPO (6000 U) at 48 hours after admission and every other day for 2 weeks versus control group
Outcomes	Change in Hgb concentration from baseline, the number of RBC units transfused, and mortality
Notes	Type of report: Abstract (insufficient information is provided in the abstract. We received no reply to our contact with the authors for further information and full paper Length of follow-up: no detail Study duration: June 2005 - December 2006 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: People with sepsis and anaemia who were admitted to a university-based hospital over a certain time period
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same source as the exposed cohort
Ascertainment of exposure?	Low risk	-
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Unclear risk	Comment: Insufficient information
Assessment of outcome?	Unclear risk	Comment: Insufficient information

Chen 2008 (Continued)

Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Unclear risk	Comment: Insufficient information

Chicella 2006

Methods	Randomized, double-blind, placebo-controlled trial This research was approved by the Institutional Review Board of the University of South Alabama
Participants	27 anaemic children in paediatric intensive care (PICU) Age: 1 month to 13 years Male: 17 (62.9%) Location: Alabama, United States Setting: PICU at the University of South Alabama Children's and Women's Hospital
Interventions	IV injection of rHuEPO (300 units/kg/day) and oral ferrous sulfate 6 mg (elemental iron)/kg/day or normal saline in a volume equivalent to the volume of rHuEPO the child would receive based on weight and oral ferrous sulfate 6 mg (elemental iron)/kg/day
Outcomes	Number of RBC transfusions
Notes	Type of report: Conference proceeding Length of follow-up: 30 day Study duration: May 2000 and May 2002 Sponsorship source: no detail Conflict of Interests: Authors declared no conflict of interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised, double-blind, placebo-controlled trial..." Comment: Insufficient information
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomised, double-blind, placebo-controlled trial..." Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Chicella 2006 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information
Other bias	Unclear risk	Comment: Insufficient information

Corwin 1999

Methods	Randomized, double-blind, placebo-controlled, multicentre trial Approval of the study was obtained from the Institutional Review Committee at each participating institution, and informed consent was obtained from each participant (or their surrogate). The Food and Drug Administration via an investigator-sponsored investigational new drug application also approved the study	
Participants	160 critically-ill participants admitted to ICU and remaining ≤ 3 day Age: ≥ 18 years Male: 82 (51.3%) Location: United States Setting: multidisciplinary ICU at Dartmouth-Hitchcock Medical Center, the multidisciplinary ICU at Stanford University Medical Center, and the surgical ICU at the Naval Medical Center San Diego	
Interventions	SC injection of rHuEPO (300 units/kg) or placebo by beginning ICU day 3 and continuing daily for 5 days (until ICU day 7), then every other day to achieve an Hct $> 38\%$ (minimum of 2 weeks or until ICU discharge for participants with ICU LOS > 2 weeks) up to a total of 6 weeks (42 days); the study drug was given IV if the platelet count was $< 20,000$.	
Outcomes	The cumulative blood transfusion requirement from study day 1, transfusion independence between study days 8 and 42	
Notes	Length of follow-up: 42 days Study duration: November 1993 - July 1997 Sponsorship source: Supported in part by Ortho Biotech, Raritan, NJ Conflict of Interests: no detail	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised using computer-generated random numbers" Comment: Insufficient description
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement

Corwin 1999 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was a prospective, randomised, double-blind, placebo, controlled ..." Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient reporting of attrition/exclusion
Selective reporting (reporting bias)	Low risk	Comment: The study protocol was not available but it seems authors reported all prespecified outcomes. However, adverse events reported if they were observed in more than 4 individuals
Other bias	Unclear risk	Comment: Supported in part by Ortho Biotech, Raritan, NJ; Analysis was based on intention-to-treat assessment

Corwin 2002

Methods	Randomized, double-blind, placebo-controlled, multicentre trial Approval of the study was obtained from the institutional review committee at each participating institution and written informed consent was obtained from each participant (or surrogate). Each institutional review committee determined who could qualify as a participant surrogate for the purpose of giving consent at their institution
Participants	1302 critically-ill people who remained in the medical, surgical, or a medical/surgical ICU for ≥ 2 days Age: ≥ 18 years Male: 806 (61.9%) Location: United States Setting: 65 US medical centres
Interventions	SC injection of rHuEPO (40,000 UI) or placebo on ICU day 3 and continued once weekly for participants who remained in the hospital, for 3 doses (study days 1, 7, and 14). Participants who remained in the ICU on study day 21 received a 4th dose.
Outcomes	<p>- Primary outcomes: Transfusion independence, assessed by comparing the percentage of participants in each treatment group who received any RBC transfusion between study days 1 and 28</p> <p>- Secondary outcomes: Cumulative RBC units transfused per participant through study day 28; cumulative mortality through study day 28; change in haemoglobin from baseline; and time to 1st transfusion or death</p> <p>- Additional outcomes: ICU length of stay, hospital length of stay, and days receiving mechanical ventilation</p>
Notes	<p>Study duration: December 1998 - June 2001</p> <p>Sponsorship source: Ortho Biotech Products LP, manufacturer of rHuEPO</p> <p>Conflict of Interests: Drs H. Corwin, Gettinger, and Pearl have received honoraria from Ortho Biotech; Drs H. Corwin and Gettinger have received research funding from Ortho Biotech; Drs H. Corwin, Get-</p>

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Corwin 2002 (Continued)

tinger, Fink, Levy, Shapiro, and Pearl have been paid consultants to Ortho Biotech; and Drs Colton and M. Corwin are partners in CareStat Inc, the study contract research organization

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was stratified by site and entailed use of computer-generated random numbers". (p: 2828)
Allocation concealment (selection bias)	Low risk	Comment: Participant enrolment was done at each site and supervised by the data coordinating centre, which also did the randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This study was a prospective, randomised, double-blind, placebo-controlled, multicenter trial conducted at 65 US medical centres". (p: 2828) Comments: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The principal investigators and manuscript committee, with assistance from the data coordinating centre, interpreted the data and were responsible for the manuscript". (p: 2828)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Attrition was 5.5% in the EPO group (19 discontinued (1 due to AEs, 6 physician choice, 3 protocol deviation, 9 participant choice) and 17 lost to follow-up) and 4.7% in the control group (12 discontinued (5 due to physician choice, 7 participant choice) and 19 lost to follow-up)
Selective reporting (reporting bias)	Low risk	Comment: The study protocol was not available but it seems the authors assessed and reported AEs beyond the prespecified outcomes
Other bias	Unclear risk	Comment: Study was supported by Ortho Biotech Products LP, manufacturer of rHuEPO; Analysis was based on intention-to-treat assessment

Corwin 2007a

Methods	Randomized, double-blind, placebo-controlled, multicenter trial The study was approved by the institutional review committee at each participating institution, and written informed consent was obtained from each participant (or his or her surrogate). If a surrogate provided consent, participants were approached for written informed consent when it was medically appropriate. An independent data and safety monitoring board monitored the safety of the study
Participants	1460 critically-ill people, who were admitted to medical, surgical, or medical-surgical ICUs and remained for ≥ 2 days Age: ≥ 18 years Male: 922 (63.1%) Location: United States Setting: 115 medical centres
Interventions	SC injection of epoetin alfa (40,000 U) or placebo on study day 1 and weekly thereafter, for 3 doses (on days 1, 8, and 15), in participants remaining in the hospital. The study drug was withheld from people with Hgb ≥ 12 g/dL at the time at which the 2nd or 3rd dose would have been given.

Corwin 2007a (Continued)

Outcomes	<p>- Primary outcomes: Percentage of participants who received a RBC transfusion between days 1 and 29</p> <p>- Secondary outcomes: N of RBC units transfused between days 1 and 42, mortality at days 29 and 140, change in Hgb concentration from baseline to day 29</p> <p>- Additional outcome: All adverse events through day 140</p>	
Notes	<p>Study duration : December 2003 - June 2006</p> <p>Sponsorship source: Johnson & Johnson Pharmaceutical R&D</p> <p>Conflict of Interests: Dr. H. Corwin reports receiving consulting and lecture fees from Ortho Biotech and Johnson & Johnson Pharmaceutical Research and Development; Drs. Fabian and May receiving consulting fees from Ortho Biotech; Dr. Pearl receiving lecture fees from Ortho Biotech; Drs. An, Bowers, Burton, and Klausner being employees of Johnson & Johnson Pharmaceutical Research and Development; and Dr. M. Corwin being an employee of BattelleCRO, which is a paid contractor to Johnson & Johnson Pharmaceutical Research and Development. No other potential conflict of interest relevant to this article was reported</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation was achieved with the use of computer-generated random numbers and was stratified according to site and three mutually exclusive admission groups” (p: 966)
Allocation concealment (selection bias)	Low risk	Quote: “Patient enrolment and data collection were done at each site and supervised by the clinical research organization, which provided randomisation and initial data analysis.” (p: 967)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “We conducted this prospective, randomised, double-blind, placebo-controlled trial” (p: 966) Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Initial data analysis and also randomization were provided by the clinical research organization which supervised participant enrolment and data collection
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Attrition was 115/733 (16%) in the EPO group (54 due to loss to follow-up and 61 due to discontinuing the drug) and 134/727 (18%) in the placebo group (55 due to lost to follow-up and 79 due to discontinuing the drug)
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00091910)
Other bias	Unclear risk	Comment: Analysis based on intention-to-treat assessment; Study supported by Johnson & Johnson (J&J) Pharmaceutical R&D. The 1st author reported receiving consulting (plus two other authors) and lecture fees (plus another author) from Ortho Biotech and J&J. Four authors were employees of J&J

De Seigneux 2012

Methods	Randomized double-blind, placebo-controlled trial
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De Seigneux 2012 (Continued)

The study was approved by the ethical committee from Geneva University Hospital and registered at ClinicalTrials.gov (NCT00676234).

Participants	<p>80 people admitted to the ICU and at risk for acute kidney injury (mechanical ventilation, sepsis, post-operative state, haemodynamic impairment, previous chronic kidney disease) after an elective cardiac surgery</p> <p>Age: ≥ 18 years</p> <p>Male: 56 (70%)</p> <p>Location: Geneva, Switzerland</p> <p>Setting: ICU at Geneva University Hospital</p>
Interventions	<p>Group 1: α-Epoetin: 20,000 UI, group 2 α-Epoetin: 40,000 UI and group 3 (control group) isotonic sodium chloride (all administered IV and as a single dose on arrival in the ICU between 1 and 4 hours after surgery)</p> <p>Length of follow-up: 28 days</p>
Outcomes	<p>- Primary outcome: mean change (%) in urinary NGAL concentration from baseline and 48 hours after r-HuEPO injection</p> <p>- Secondary outcomes: mean change (%) in traditional renal function markers (serum creatinine and cystatin C) and in cytokines levels from baseline and 48 hours and 96 hours after r-HuEPO injection</p>
Notes	<p>Location: Switzerland, Geneva (Geneva University Hospital)</p> <p>Study duration: 2008 - 2009</p> <p>Sponsorship source: Janssen-Cilag provided the r-HuEPO in the active treatment arm and covered the cost for NGAL measurements. They had no role in study design, data collection, statistical analysis or writing of the manuscript. The authors had full access to all data and had final responsibility to submit for publication.</p> <p>Conflict of Interests: The authors declare that they have no competing interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to 2 treatment groups or a control group after cardiac surgery"
Allocation concealment (selection bias)	Low risk	Quote: "A randomization code was generated by a computer 1:1:2 and envelopes with allocation were prepared by the quality of care unit"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: Investigators and participants were blinded to the treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcomes were lab values, death, length of stay. Not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 participant was lost to follow-up due to transfer after 48 hours. Analysed as ITT

De Seigneux 2012 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: Primary and secondary outcomes in the protocol and the report are the same
Other bias	Unclear risk	Comment: Janssen-Cilag provided the r-HuEPO in the active treatment arm and covered the cost for NGAL measurements. They had no role in study design, data collection, statistical analysis or writing of the manuscript. The authors had full access to all data and had final responsibility to submit for publication

El Atroush 2005

Methods	Randomized, controlled trial
Participants	60 critically-ill people with anaemia and sepsis Male: 33 (55%) Location: Cairo, Egypt Setting: ICU at Cairo University Hospital, Egypt
Interventions	SC injection of rHuEPO (40,000 U) starting on ICU day 2 and continued once weekly for minimum of 2 doses or until ICU discharge (max. 4 doses) Length of follow-up: 28 days
Outcomes	The need for RBC transfusion, erythropoietic response, length of ICU stay, severity of illness during ICU stay (APACHE II and SOFA scoring system), final outcome (recovery, mortality and morbidity)
Notes	Date: September 2003- September 2004 Study duration: September 2003 - September 2004 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were divided into 2 equal groups on a randomisation pattern" (p: 86) Comment: Probably done
Allocation concealment (selection bias)	High risk	Comment: Participants or investigators enrolling participants could possibly foresee assignments
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: In this study, 1 group received SC injection of rHuEPO plus oral or parenteral iron and the other group received iron only. Blinding was probably not done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided

El Atroush 2005 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All outcome data for mortality are provided
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available but it seems that the report should specify expected safety outcomes at 4-week follow-up or give the reason for not specifying them
Other bias	Unclear risk	Comment: No competing interests are declared

Endre 2010

Methods	Randomized, double-blind, placebo-controlled trial The study was approved by the multi-regional ethics committee of New Zealand (MEC/050020029) and registered under the Australian Clinical Trials Registry (ACTRN012606000058572; www.actr.org.au). Screening on entry to ICU was by presumed consent, followed by written consent from the participant or family
Participants	162 people admitted consecutively to the general ICU, or high-risk patients scheduled for cardiothoracic surgery with cardiopulmonary bypass surgery Age: ≥ 18 years Male: 71 (43.8%) Location: New Zealand Setting: ICU of either Christchurch or Dunedin Hospital
Interventions	IV injection of erythropoietin-beta (500 U/kg to a maximum of 50,000U) within 6 hours of the time of collection of the sample with increased GGT $\times$ AP- indicated for kidney injury, and a 2nd dose 24 hours later Length of follow-up: 30 days
Outcomes	- Primary outcome: Relative average plasma creatinine (RAVC) - Secondary outcomes: RIFLE ($\geq 50\%$ increase in pCr within 7 days and sustained for 24 hours) and AKIN (≥ 0.3 mg/dl or 50% increase in pCr within 48 hours) categorical definitions of AKI, plasma cystatin-C, urine output, need for dialysis, death within 7, 30 or 90 days - Additional outcome: Safety endpoints
Notes	Study duration: 5 March 2006 - 8 July 2008 Sponsorship source: Health Research Council of New Zealand grant 05/131 Conflict of Interests: ZHE received non-directed research funding from Roche Pharmaceuticals. All the other authors declared no competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were allocated to EPO or placebo (normal saline) groups in a 1:1 ratio, using a predefined computer-generated randomisation sequence with permuted blocks stratified on centre." (p: 1027)

Endre 2010 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Concealment was by pharmacist; pairs of identical 5-ml syringes containing EPO (50 000U in 3 ml) or normal saline were prepared and stored." (p: 1027)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, all medical staff, and investigators were masked to treatment." (p: 1027)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, all medical staff, and investigators were masked to treatment." (p: 1027)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Attrition was 14/84 (17%) in the EPO group (1 due to death before 2nd dose, 4 deaths before 96 hours, 1 due to rhabdomyolysis) and 15/78 (19%) in the control group (4 due to death before 2nd dose, 3 deaths before 96 hours, 1 due to anuria and 1 due to rhabdomyolysis)
Selective reporting (reporting bias)	Low risk	Comment: Safety endpoints are not specified in the protocol (AC-TRN012606000058572)
Other bias	Low risk	Comment: Negative trial; Analysis based on intention-to-treat assessment; Study was supported by Health Research Council of New Zealand grant 05/131

Ferrario 2011

Methods	Pilot, randomized, double-blind, placebo-controlled, single-centre study The study was approved by the Institution's Ethics Committee and all of the participants gave their written informed consent to participate in the study	
Participants	30 people with a 1st STEMI undergoing primary PCI within 6 hours of symptom onset Age: ≤ 70 years Male: 30 (100%) Location: Pavia, Italy Setting: single centre; no more detail	
Interventions	EPO (33 × 10 ³ IU) in isotonic sodium-chloride (50 ml) over 30 minutes or placebo (isotonic sodium-chloride 50 ml) starting before and continuing during PCI, and 24 and 48 hours later (for a total EPO dose of ~1 × 10 ⁵ IU) Length of follow-up: 12 months	
Outcomes	- Primary outcome: CD34+ cell mobilization 72 hours after admission - Additional outcomes: 1) safety-oriented investigations based on the measurement of short-term haematometric, coagulation and blood pressure responses to EPO, and the incidence of major adverse cardio-circulatory events during the 12-month follow-up; and 2) efficacy-oriented investigations of the differential PBC expression of the genes involved in apoptotic, angiogenic and inflammatory pathways, and an evaluation of the effect of EPO on the enzymatic (CK, CK-MB), echocardiographic and CMR findings	
Notes	Study duration: April 2005 - March 2006	

Ferrario 2011 (Continued)

Sponsorship source: a grant from the Italian Ministry of Health

Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After coronary angiography, the patients were randomly assigned (1:1 in blocks of six stratified for the site of infarction by means of sequentially numbered sealed envelopes)" (p: 125)
Allocation concealment (selection bias)	Low risk	Comment: Participants and investigators enrolling participants could not foresee assignment because the participants were randomly assigned by means of sequentially-numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a pilot, single-centre, randomised, placebo-controlled, double-blind study." (p: 125) Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on safety outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available but for 12-month follow-up the report should state the definition of "the major cardiovascular events" which none of the participants had experienced and specify whether it encompassed all the events collected
Other bias	Unclear risk	Comment: Small study group; Study was supported by a grant from the Italian Ministry of Health

Gabriel 1998

Methods	Prospective, randomized, placebo-controlled trial The study was approved by the institutional review board.
Participants	19 adults with multiple organ dysfunction syndrome admitted to the ICU after major abdominal surgery or major trauma and stayed for ≥ 3 weeks Male: 13 (68.4%) Location: Vienna, Austria Setting: ICU at General Hospital of the University of Vienna
Interventions	IV injection of rHuEPO (600 IU/kg) or saline 3 times weekly for 3 weeks Length of follow-up: three weeks

Gabriel 1998 (Continued)

Outcomes	Reticulocyte blood levels, erythropoietin serum concentrations, circulating cytokine levels, red cell indices, iron metabolic indices and peripheral progenitor cells
Notes	Study duration: no detail Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After baseline measurements, patients were assigned randomly to receive..." Comment: Insufficient description
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No blinding; Since the study reported mortality only, participants will not have been aware. However, it is unclear who was informed about the treatment allocation within the team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: No blinding but mortality is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available but for 3 weeks follow-up the report should specify expected safety outcomes or give the reason for not specifying them
Other bias	Unclear risk	Comment: Small study group; No competing interests are declared

Georgopoulos 2005

Methods	Randomized, controlled, multicentre trial Approval of the study was given by the institutional review committee at each participation centre and written informed consent was obtained from each participant or next of kin
Participants	148 critically-ill people with anaemia (Hgb < 12 g/dl) and an expected ICU stay ≥ 7 days Age: ≥ 18 years Male: 113 (76.3%) Location: Greece Setting: ICU in 13 participating centres
Interventions	Group A: SC injection of rHuEPO (40,000 IU) + IV injection of iron saccharate once a week;

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Georgopoulos 2005 (Continued)

Group B: SC injection of rHuEPO (40,000 IU) + IV injection of iron saccharate 3 times a week; **Control group:** IV injection of iron saccharate alone

Length of follow-up: 28 days

Outcomes	<p>- Primary outcomes: Differences in Hct and Hgb between groups and transfusion independence between study days 1 and 28</p> <p>- Secondary outcomes: ICU length of stay, cumulative mortality through day 28, adverse effects (daily) and nosocomial infections</p>
Notes	<p>Study duration: November 2000 - December 2003</p> <p>Sponsorship source: a grant from Janssen-Cilag</p> <p>Conflict of Interests: The author(s) declared that they have no competing interests</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation and data analysis were done by the data coordinating centre. A stratified random sampling scheme was employed as the selection method for randomisation." (p: R509)
Allocation concealment (selection bias)	High risk	Comment: Since the study was not blinded, allocation concealment was not performed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was not blinded and this might be a limitation." (p: R513)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: It was not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Attrition was 5.9% and 6.2% in EPO groups A and B (3 lost to follow-up after hospital discharge in each group) and 4.2% in control group (2 lost to follow-up after hospital discharge in each group)
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ISRCTN48523317)
Other bias	Unclear risk	Comment: Study was supported by grant from Janssen-Cilag. Analysis was based on intention-to-treat assessment

Gerasimov 2012

Methods	<p>Randomized, double-blind, controlled trial</p> <p>Participants included with written informed consent</p>
Participants	<p>78 adults with trauma and blood loss</p> <p>Male: 48 (61.5%)</p> <p>Location: Moscow, Russia</p>

Gerasimov 2012 (Continued)

Setting: Single-centre mixed ICU

Interventions	Single IV bolus of epoetin alfa (40,000 U) + IV Iron (100 mg) on the 2nd day of admission or IV iron (100 mg) only Length of follow-up: 28 days
Outcomes	- Primary outcomes: Number of participants requiring RBC transfusion and volume of RBC per participant on day 18 - Secondary outcomes: Number of thrombotic events (developed before and after 3 weeks of treatment), ICU-free days and mortality on day 28
Notes	Study duration: no detail Sponsorship source: mixed (funding from 2 institutes - V.A. Negovsky Research Institute of General Reanimatology, Moscow and Research Institute of Pure Biological Products, St. Petersburg) Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Random sequence is done by coin-tossing
Allocation concealment (selection bias)	Low risk	Comment: Participants and investigators enrolling participants could not foresee assignment because the process of coin-tossing was independent of them
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and key study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: No blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information
Other bias	Low risk	Comment: Study was supported by V.A. Negovsky Research Institute of General Reanimatology, Moscow and Research Institute of Pure Biological Products, St. Petersburg

Gholamzadeh 2015

Methods	Randomized, double-blind, placebo-controlled study This study was approved by the Ethics Review Boards of Mashhad University of Medical Science. All participants entered the study after signing a written informed consent
Participants	40 people undergoing PCI for STEMI within 6 hours from symptom onset

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

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Gholamzadeh 2015 (Continued)

Age: 18 - 76 year

Male: 29 (72.5%)

Location: Mashhad, Iran

Setting: Cardiology Department of Ghaem Educational, Research and Treatment Centre

Interventions	IV injection of rh-EPO (33,000 units within 50 mL isotonic solution of sodium chloride) in the intervention group or 50 mL sodium chloride in the placebo group for 30 minutes immediately after PCI Length of follow-up: 14 days
Outcomes	Occurrence of arrhythmias in 24 hours after PCI; creatine kinase-MB, haematologic and haemodynamic data within 2 weeks after MI
Notes	Study duration: October 2013 - March 2014 Sponsorship source: Mashhad University of Medical Science (MUMS), Mashhad, Iran Conflict of Interests: The authors reported no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by www.randomizer.org to receive either placebo (n = 20) or EPO (n = 20) and entered this double blind, placebo-controlled randomised trial"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised by www.randomizer.org to receive either placebo or EPO" Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomised by www.randomizer.org to receive either placebo (n = 20) or EPO (n = 20) and entered this double blind, placebo-controlled randomised trial" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Arrhythmias were blindly documented by full 12-lead configuration 24 hours after PCI by a cardiologist who judged arrhythmia development, and diagnosis was unaware of the patient's clinical information"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available
Other bias	Unclear risk	Comment: Insufficient information about study's funding

Ginger 2008

Methods	Cohort (trauma and pharmacy registry)
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Ginger 2008 (Continued)

Participants	<p>Critically-ill trauma population admitted to the ICU for ≥ 2 days</p> <p>Age: ≥ 18 years old</p> <p>Male: (%)</p> <p>Location: Virginia, United States</p> <p>Setting: ICU at Carilion Clinic</p>
Interventions	<p>Epoetin alfa or non-epoetin alfa</p> <p>Length of follow-up: 30 days</p>
Outcomes	- Primary outcome: 30-day mortality
Notes	<p>Type of report: Conference proceeding</p> <p>Sponsorship source: no detail</p> <p>Conflict of Interests: no detail</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: Participants identified by using the institution's trauma and pharmacy registry
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same source as the exposed cohort
Ascertainment of exposure?	Low risk	Comment: Record linkage using the registry database
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Low risk	Comment: Controlled for potential confounders including age and injury severity score (ISS)
Assessment of outcome?	Low risk	Comment: Record linkage using the registry database
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

Grmec 2009

Methods	Cohort: 1) A non-randomized controlled trial; 2) Post hoc: A retrospective matched control*
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Grmec 2009 (Continued)

The study was approved by the Ethical Board of the Ministry of Health, granting waiver of the informed consent. Participants who regained consciousness, or their relatives, were informed after enrolment

Participants	<p>54 people with non-traumatic out-of-hospital cardiac arrest</p> <p>Age: 18 - 80 years</p> <p>Male: 36 (66.6%)</p> <p>Location: Maribor, Slovenia</p> <p>Setting: ICU</p>
Interventions	A 90,000 IU bolus of beta-epoetin or 0.9% NaCl within 1 or 2 minutes of physician-led chest compressions followed by a 10-ml bolus of 0.9% NaCl
Outcomes	<p>- Primary outcome: ICU admission</p> <p>- Secondary outcomes: Return of spontaneous circulation (ROSC) in the field, survival at 24 hours, and survival at hospital discharge</p>
Notes	<p>Study duration: April 2007– May 2008</p> <p>Sponsorship source: no detail</p> <p>Conflict of Interests: None of the authors had a conflict of interest</p> <p>* We analysed the data of prospective controls only</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: Restricted to people with non-traumatic out-of-hospital cardiac arrest
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population both concurrently and historically
Ascertainment of exposure?	Unclear risk	Comment: Insufficient information
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Low risk	Comment: Odds ratios adjusted for age, male sex, witnessed arrest, time from call to start CPR, PEA, asystole, and bystander CPR as the pre-treatment co-variables
Assessment of outcome?	Unclear risk	Quote: "The present study is limited primarily by its lack of randomisation and blinding". (p: 636)
Was the follow-up long enough for the outcomes to occur?	Low risk	Comment: 24-hour and also hospital survival is reported
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Hecht 2007

Methods	Cohort (a retrospective pharmacy database study)
Participants	12,834 people admitted to the trauma service for trauma-related injuries Location: United States Setting: no detail
Interventions	ESAs or non ESA with unfractionated heparin (> 5000 units twice or three times daily) or enoxaparin (> 30 mg twice or 40 mg once daily)
Outcomes	Risk of venous thromboembolisms (VTEs)
Notes	Type of report: Conference proceeding Study duration: 8 January 2002 - 8 January 2007 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Quote: "We searched a database for all patients admitted for trauma-related injuries between 8/1/2002 and 8/1/2007"
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Low risk	Comment: Record linkage using the pharmacy database
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Unclear risk	Comment: Insufficient information
Assessment of outcome?	Low risk	Comment: High doses of unfractionated heparin or enoxaparin were considered to be treatment for VTEs. It was assessed by record linkage using the pharmacy database
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

Kane-Gill 2007

Methods	Cohort (a retrospective, case-matched study) The study is approved by Institutional Review Board of University of Pittsburgh-Presbyterian
Participants	1173 adults with an ICU length of stay ≥ 3 days Age: ≥ 18 years Male: 645 (55%) Location: United States Setting: University of Pittsburgh-Presbyterian (UPMC-P) ICU
Interventions	rHuEPO or non- rHuEPO
Outcomes	Participant demographics and variables that estimated severity of illness (SAPS II and need for renal replacement therapy), number of RBC transfusions, Hgb concentrations, LOS (ICU, hospital, post-ICU), mortality (ICU, hospital), number of mechanical ventilation days, ICU resource use
Notes	Study duration: January 2000 - July 2002 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: Participants identified by an electronic data repository
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Low risk	Quote: "Patients were identified using the UPMC Medical Archival Retrieval System (MARS), a data repository containing clinical and financial data." (p: 54)
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Low risk	Comment: Participants were matched by age (± 5 years), sex, admission year and ICU type. The study controlled for potential confounders including age, sex, race, SAPS II, 1st Hgb and 1st serum creatinine concentration
Assessment of outcome?	Low risk	Comment: Record linkage using MARS and the ICU-specific computer system (Eclipsys/EMTEK)
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

Kang 2012

Methods	Randomized, double-blind controlled, multicentre trial The study protocol was approved by the institutional review board of Seoul National University Hospital.
Participants	60 adults with STEMI undergoing successful revascularization of culprit vessel Male: 52 (86.6%) Location: Seoul, Republic of Korea Setting: Seoul National University Hospital
Interventions	(1) Combicytokine group: SC injection of G-CSF (5 mg/kg) twice a day for 3 days + an IV bolus of darbepoetin (4.5 µg/kg, maximum: 300 µg) just after revascularization; (2) G-CSF group: SC injection of G-CSF (5 mg/kg) twice a day for 3 days + a bolus infusion of placebo Length of follow-up: one month
Outcomes	- Primary outcome: The peripheral blood stem/progenitor cells (PBSCs) mobilizing effects of G-CSF with or without darbepoetin - Secondary outcomes: Safety of G-CSF with or without darbepoetin
Notes	Study duration: June 2007 - April 2009 Sponsorship source: a grant from Stem Cell Research Center (SC4210), and the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A062260) Conflict of Interests: The authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We prospectively collected peripheral blood and apheresis products from patients who were randomised to either treatment of G-CSF alone (the G-CSF group) or of combination cytokine with G-CSF and darbepoetin (the combi-cytokine group) with randomisation ratio of 1: 2." (p: 4) Comment: Insufficient information
Allocation concealment (selection bias)	Low risk	Quote: "patients will be randomly allocated by means of sealed envelope." (Trial design: <i>Trials</i> 2011, 12:33)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Infusion of darbepoetin or placebo will be performed by double blind manners." (Trial design: <i>Trials</i> 2011, 12:33)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "with blind evaluation of endpoints." (<i>Trials</i> 2011, 12:33)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data

Kang 2012 (Continued)

Selective reporting (reporting bias)	Low risk	Quote: "This study was performed as a sub-study of MAGIC Cell-5- combicytokine trial in two participating centres."(p: 4) Comment: The detail of this phase of study is not specified in the protocol (ClinicalTrials.gov with identifier NCT00501917) or trial design which is published in <i>Trials</i> 2011, 12:33. However, it might not influenced the safety outcome
Other bias	Low risk	Comment: The study is supported by a grant from Stem Cell Research Centre (SC4210), and the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A062260)

Kashkouli 2011

Methods	Cohort (prospective with historical controls) All participants signed a written informed consent form in accordance with the tenets of the Declaration of Helsinki and the Iranian Declaration of Patients Rights. Ethic committee approval of the Iran University Eye Research Center was obtained
Participants	15 participants with indirect traumatic optic neuropathy (TON) Male: 12 (80%) Location: Tehran, Iran Setting: University-based hospital
Interventions	IV infusion of rHuEPO (10,000 IU) with 200 ml NS in 2 hours
Outcomes	Visual function of study participants and side effects of EPO
Notes	Study duration: December 2008 - March 2010 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: Participants with indirect TON who were admitted to a university-based hospital over a certain time were included
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Low risk	-
Demonstration that the outcome of interest was not present at start of study?	Low risk	-

Kashkouli 2011 (Continued)

Comparability of cohorts on the basis of the design or analysis?	Unclear risk	Comment: Insufficient information
Assessment of outcome?	Unclear risk	Comment: Insufficient information.
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Both cases and controls had a large range of follow-up (1 - 13 and 3 - 14 months, respectively)

Kateros 2010

Methods	Randomized, prospective, placebo-controlled trial The study protocol was approved by the institutional review board.
Participants	79 people who sustained an intertrochanteric fracture Age: 67 - 96 years Male: 21 (26.6%) Location: Greece Setting: Department of Orthopaedics
Interventions	10 daily doses of epoetin alfa (20,000 IU) or placebo beginning from the day of trauma Length of follow-up: 72 month
Outcomes	Full blood count, including Hct, Hgb, white blood cells, red blood cells, platelets count, and evaluation of renal and liver biochemistry (daily from the day of admission until discharge); blood count, coagulation, and biochemistry tests at 15 and 30 days post-discharge and then at 3, 6, and 12 months, and annually thereafter
Notes	Study duration: December 2002 - January 2007 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients meeting the inclusion criteria were randomly divided into 2 groups using randomisation tables." (p:349)
Allocation concealment (selection bias)	High risk	Comment: Participants or investigators enrolling participants could possibly foresee assignments
Blinding of participants and personnel (performance bias)	High risk	Comment: The authors did not specify any performance relevant to blinding. It seems an open-label study

Kateros 2010 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients were lost to follow-up at 24, 36, and 48 months, respectively, doing well at their latest examination." (p:349)
Selective reporting (reporting bias)	Unclear risk	Quote: "None of the patients had to stop receiving medication because of possible adverse effects from the use of epoetin alfa, such as gastro-intestinal, cardiovascular, respiratory, and central or peripheral nervous system disorders." (p: 350) "Eight patients died at 24, 24, 36, 48, 60, 60, 60, and 72 months, respectively, of causes that were not directly related to the hip fracture or to epoetin alfa administration." (p: 349) Comment: The authors have not explicitly reported whether these AEs had happened. In addition, the number of deaths in each study group was not specified, or the causes of deaths which the authors deemed irrelevant to intervention
Other bias	Unclear risk	Comment: The authors reported that company provided the medication (p: 352) but with no further detail of company name or competing interest of investigators

Lakic 2010

Methods	Pilot, open, prospective controlled trial All of the participants signed a written consent form approved by the State Ethical Committee
Participants	20 people who required surgical revascularization of the heart with the use of the heart-lung machine (HLM) Age: ≥ 18 year Male: 12 (60%) Location: Ljubljana, Slovenia Setting: University Medical Centre Ljubljana
Interventions	IV injection of rHuEPO consisting of 3 consecutive doses (24,000 IU): 1 day before the procedure, on the day of operation, and 1 day after completion of the surgery Length of follow-up: 5 days
Outcomes	The number of coronary artery bypass grafts, anaesthesia duration, blood pressure, and transfusion volume
Notes	Study duration: no detail Sponsorship source: no detail Conflict of Interests: no detail

Lakic 2010 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: This is a pilot trial with no randomization
Allocation concealment (selection bias)	High risk	Comment: Participants or investigators enrolling participants could possibly foresee assignments
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This is a pilot study of EPO compared to standard care. Blinding was probably not done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: No information but death is unlikely to be influenced by not blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available
Other bias	Unclear risk	Comment: Small study group; No competing interests are declared

Liem 2009

Methods	<p>Pilot, randomized, placebo-controlled trial</p> <p>Written informed consent was obtained from all participants before inclusion in the study. The protocol was approved by the Medical Ethics Committee of the Medical Centre Rijnmond-Zuid. The study was conducted in full accordance with the principles of the Declaration of Helsinki, with ICH-GCP, and with the laws and regulations of The Netherlands</p>
Participants	<p>51 people with non-ST segment elevation acute coronary syndrome (non-STE ACS) and a troponin I value ≥ 0.20 $\mu\text{g/L}$</p> <p>Location: The Netherlands</p> <p>Setting: Medical Centre Rijnmond-Zuid</p>
Interventions	<p>Single IV bolus of epoietin-alpha (40,000 IU) or placebo within a maximum time window of 8 hours after the elevated troponin I value was available</p> <p>Length of follow-up: 1½ years</p>
Outcomes	<p>Myocardial infarct size based on the CK and CK-MB_{mass} levels and in terms of troponin I values, major adverse coronary events, strokes and other reasons for hospitalization, blood pressure</p>
Notes	<p>Study duration: no detail</p> <p>Sponsorship source: no detail</p> <p>Conflict of Interests: no detail</p>

Liem 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Within a maximal time window of 8 h after the elevated troponin I value was available, patients were randomly assigned to a single intravenous dose of 40,000 IU Epoietin-alpha or a matching placebo (saline)." (p: 285) Comment: No further information on randomization
Allocation concealment (selection bias)	Unclear risk	Comment: No information has been provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Blinding was not specifically mentioned, but considering the quote "During hospitalization, three patients turned out not to have a clinically significant ACS and were excluded from the analysis before debinding the data." (p: 286), it was probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: No information on number of patients with high systolic blood pressure. This complication is reported as mean $\pm$ SD only
Other bias	Unclear risk	Comment: Negative trial; Small study group; No competing interests are declared

Lipsic 2006

Methods	Pilot, randomized, no-treatment-controlled study Written informed consent was obtained from all participants before the study, and the institutional review board of the University Hospital of Groningen approved the study protocol. The study was consistent with the principles outlined in the Declaration of Helsinki
Participants	22 adults undergoing primary coronary intervention (PCI) for a 1st acute ST-elevation myocardial infarction (STEMI) within 6 hours from symptom onset Age: 18 - 76 year Male: 22 (100%) Location: Groningen, The Netherlands Setting: University Hospital of Groningen
Interventions	Single IV bolus of darbepoetin alfa (300 μ g) or no additional medication before PCI Length of follow-up: 30 days
Outcomes	Adverse events, complete blood cell count, standard CK and CK-MB monitoring, serum erythropoietin levels, No. of circulating blood CD34+/CD45-cells, LV function

Lipsic 2006 (Continued)

Notes

Study duration: no detail

Sponsorship source: Although previous experimental studies were supported by an unrestricted educational grant from Amgen Inc. (Thousand Oaks, CA, USA), no industrial funding was provided for the present study.

Conflict of Interests: Dr. Lipsic is being supported by GUIDE, Dr. Van derMeer is being supported by Zon-MW. Dr. Van Veldhuisen is an Established Investigator of the Netherlands Heart Foundation (grant D97-017). Dr. De Boer is supported in part by Netherlands Heart Foundation (grant NHS 2002B157)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by Trial Co-ordination Centre of the Academic Hospital Groningen, based on a computer-generated randomisation list." (p: 136)
Allocation concealment (selection bias)	High risk	Comment: Since the study was not blinded, allocation concealment should not be performed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: It was not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: It was not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Low risk	Comment: The study protocol was not available but the authors reported all safety outcomes over 30 days follow-up
Other bias	Unclear risk	Comment: Small study group; No industrial funding was provided for the study

Luchette 2012

Methods

Phase 2, randomized, double-blind, placebo-controlled, multicentre trial

This study was conducted in accordance with the ethical principles set forth by the Declaration of Helsinki and reviewed by an institutional review board, consistent with good clinical practices. Participants or their legal representative provided informed consent at screening, after admission to the critical care area, and before study entry (Protocol PR04-15-001, [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00210626): NCT00210626)

Participants

192 adults with major blunt trauma orthopaedic injuries

Age: 18 - 55 years

Male: 121 (63.0%)

Location: United States

Setting: ICUs in 21 centres

Luchette 2012 (Continued)

Interventions	<p>SC injection of epoetin alfa or placebo weekly up to 12 weeks after discharge or until Hgb > 12.0 g/dL (EPO)</p> <p>dosing algorithm: (1) Hgb < 9.0 g/dL: 40,000 IU; (2) Hgb 9.0 to < 10.0 g/dL: 30,000 IU; (3) Hgb 10.0 to < 11.0 g/dL: 20,000 IU; and (4) Hgb 11.0 to ≤ 12.0 g/dL: 10,000 IU)</p> <p>Length of follow-up: 24 weeks</p>
Outcomes	<p>- Primary outcomes: Average of all SF-36 PF scores obtained between hospital discharge and the end of week 24 post-hospital discharge</p> <p>- Secondary outcomes: FACIT - anaemia and fatigue sub-scales, Functional Independence Measure (FIM) total and motor sub-score, haemoglobin</p> <p>- Additional endpoints: APACHE II, SOFA, Cognitive Function Scale (COG) scores and safety evaluation</p>
Notes	<p>Study duration: no detail</p> <p>Sponsorship source: Supported by Janssen Services, LLC</p> <p>Conflict of Interests: no detail</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "This study ... was a phase 2, prospective, randomised, double-blind, multicenter trial." (p: 509)</p> <p>Comment: No further information</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: Insufficient information is provided to make a judgement</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "This was a blinded study, however, in order to optimize acute care, during the in-hospital treatment phase only, study personnel were not blinded to complete blood count or other laboratory results." (p: 509)</p> <p>Comment: Probably done</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Comment: No information on outcome assessment has been provided</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Comment: In minimum 24 weeks, 47/97 (48%) did not complete the study in the EPO group (29 voluntarily withdrew, 11 due to 'lost to follow-up' and 1 due to 'adverse event'); 45/95 (47%) did not complete the study in the control group (20 voluntarily withdrew, 11 due to 'lost to follow-up' and 2 due to 'adverse event')</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: Authors reported all pre-specified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00210626)</p>
Other bias	Unclear risk	<p>Comment: Analysis based on intention-to-treat assessment; Supported by Janssen Services, LLC</p>

Ludman 2011

Methods	Randomized, double-blinded, placebo-controlled trial This study received local Ethics Committee approval and was carried out in accordance with the University College London Hospital Trust guidelines
Participants	51 adults with STEMI undergoing PPCI within 12 hours from onset of symptoms Male: 44 (86.3%) Location: London, UK Setting: single tertiary cardiac centre
Interventions	An IV bolus of rHuEPO beta (50,000 IU) or placebo prior to PPCI with a further bolus given 24 hours later Length of follow-up: 4 months
Outcomes	- Primary outcome: MI size as determined by late gadolinium enhancement (LGE) CMR - Secondary outcomes: 24-hour AUC serum CK-MB and troponin T, myocardial salvage index and CMR-determined LV volumes, mass and ejection fraction and the presence of micro-vascular obstruction (MVO)
Notes	Study duration: July 2007 - August 2009 Sponsorship source: The work was supported by Roche Ltd. which kindly supplied the rhEPOβ (NeoRecormon), but it played no role in conception, conduct or analysis of this study. This work was undertaken at University College London Hospital/University College London which received a proportion of funding from the Department of Health's National Institute of Health Research Biomedical Research Centres funding scheme; This study has been also funded and supported by British Heart Foundation (Program Grant RG/03/007)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated blocked randomisation list was prepared in advance of the trial." (p: 1561)
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was undertaken by a Clinical Research Fellow (not involved with assessing clinical outcomes or the PPCI procedure) using sealed opaque envelopes." (p: 1561)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patient, the PPCI operator and the assessor of clinical outcomes were blinded to the treatment allocation." (p: 1561)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patient, the PPCI operator and the assessor of clinical outcomes were blinded to the treatment allocation." (p: 1561)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Low risk	Comment: Primary and secondary outcomes, as well as inclusion criteria, intervention and design of study in the report were performed as defined in

Ludman 2011 (Continued)

formed the protocol (Controlled-trials.com with identifier ISRCTN49989273). However, the safety outcome was not prespecified in the protocol

Other bias	Low risk	Comment: Small study group; Negative result for primary outcome; Supported by British Heart Foundation and Roche Ltd. supplied the study medication, but authors addressed that it played no role in conception, conduct or analysis of this study
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Luh 2005

Methods	Cohort (a retrospective review)
Participants	All critically-ill adults (N = 200) admitted to the SICU) over a certain time period and remained for at least five days Location: United States Setting: SICU at Los Angeles County and USC Medical Center
Interventions	rHuEPO or non-rHuEPO
Outcomes	- Primary outcome: Amount of packed RBC transfused per participant after day 7 of SICU stay - Secondary outcomes: Mortality
Notes	Type of report: Conference proceeding Study duration: January 2001 - December 2003 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Quote: "all adult patients admitted to the SICU of the LAC + USC Medical Centre between January, 2001 and December, 2003, who remained in the SICU for at least five days"
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Unclear risk	Comment: Insufficient information
Demonstration that the outcome of interest was not present at start of study?	Unclear risk	Comment: Insufficient information
Comparability of cohorts on the basis of the design or analysis?	Low risk	Quote: "Multivariate stepwise logistic regression analyses were conducted to determine the significant covariates which were associated with rHuEPO administration. Selection bias was adjusted by matching subjects using propensity score methods"

Luh 2005 (Continued)

Assessment of outcome?	Unclear risk	Comment: Insufficient information
Was the follow-up long enough for the outcomes to occur?	Low risk	Comment: Long enough follow-up because SICU mortality was determined
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

Lundy 2010

Methods	Cohort (contemporaneous and historical controls*) This study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board and in accordance with good clinical practices	
Participants	52 critically-ill people with burns (> 30% total body surface area and > 15 ICU days) Location: Texas, United States Setting: BICU	
Interventions	SC injection of rHuEPO (40,000 U) weekly starting within 72 hours of BICU admission, or non-rHuEPO	
Outcomes	Haemoglobin at admission and discharge, total packed RBC transfusion requirement (mL pRBC/hospital stay), complications and mortality	
Notes	Study duration: 1 January 2007 - 31 December 2008 Sponsorship source: no detail Conflict of Interests: no detail * We analysed the data for contemporaneous controls only because of higher level of evidence	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: severely-burned people who received rHuEPO over a certain period of time identified by a retrospective chart review
Selection of the non-exposed cohort?	Low risk	Comment: Controls were drawn from the same population, both contemporaneously and historically
Ascertainment of exposure?	Low risk	-
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Unclear risk	Quote: "We choose not to match on severity because this would significantly reduce our sample size and we were trying to capture real-world practices." (p: 57)

Lundy 2010 (Continued)

Assessment of outcome?	Unclear risk	Comment: Insufficient information.
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study population was retrospectively reviewed

Mattich 1993

Methods	Pilot, randomized, double-blind, placebo-controlled trial The study was approved by the ethical committee of the institution and informed consent has been obtained	
Participants	12 people with superficial and deep burns of 20% - 55% total body surface area (TBSA) Age: 15 - 65 years Male: 9 (75%) Location: Lausanne, Switzerland Setting: Burn unit at the Centre Hospitalier Universitaire Vaudois	
Interventions	SC injection of epoietin (10,000 IU) or placebo (albumin/NaCl 0,9%) within 48 hours of admission and daily up to 21 days Length of follow-up: 50 days	
Outcomes	Levels of haemoglobin, reticulocytes, serum erythropoietin, ferritin, serum iron, transferrin and side effects of epoetin	
Notes	Study duration: July 1990 - September 1991 Sponsorship source: no detail Conflict of Interests: No detailed information on the role of Cilag AG, Schaffhausen, Switzerland was outlined but its participation was appreciated	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were double blind randomised into two groups." (p: 298) Comment: Insufficient description
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients were double blind randomised into two groups." (p: 298) Comment: Probably done

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Mattich 1993 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Quote: "There were no side effects observed which could be attributed to epoetin administration throughout the study. One patient developed a deep venous thrombosis six weeks after the Eprex® medication had been stopped." (p: 301) Comment: The authors did not report the observed adverse events which they considered as not attributable to intervention
Other bias	Unclear risk	Comment: The study was too small and non-homogeneous; No detail information on the role of Cilag AG, Schaffhausen, Switzerland was outlined but its participation was appreciated

Najjar 2011

Methods	Phase 2, randomized, double-blind, placebo-controlled, multicentre trial The REVEAL study was reviewed and approved by the MedStar Research Institute's institutional review board and by the respective institutional review boards of the participating sites. Written informed consent was obtained from all participants or their legally-authorized representatives (clinicaltrials.gov Identifier: NCT00378352).
Participants	222 people (131 in efficacy phase and 91 in dose-escalation safety phase) with STEMI who underwent successful PCI as a primary or rescue reperfusion strategy within 8 hours of onset of ischaemic symptoms Age: > 21 year Male: 178 (80.2%) Location: United States Setting: 22 sites
Interventions	Dose-escalation safety phase: 3 doses of IV epoetin alfa (15,000 U, 30,000 U, and 60,000 U) or placebo within 4 hours of successful reperfusion Efficacy phase: Single IV bolus of epoetin alfa (60,000 U) or placebo within 4 hours of successful reperfusion Length of follow-up: 14 weeks
Outcomes	- Primary outcomes: Infarct size in the territory of the infarct-related artery, expressed as percentage of LV mass and measured by CMR - Secondary outcomes: Infarct size, 3 LV remodeling parameters (LVESV, LVEDV, and LV mass, each indexed to BSA) and LVEF measured by CMR - Safety endpoints: vital signs, haemoglobin level, reticulocyte count, markers of cardiac injury, and clinical events including death, recurrent MI, unplanned PCI, arterial thrombotic events (stent throm-

Najjar 2011 (Continued)

bosis), venous thrombotic events (deep venous thrombus, pulmonary embolus), heart failure and neurological events (stroke, transient ischaemic attack)

Notes

Study duration: October 2006 - November 2009

Sponsorship source: Intramural Research Program contract HHS-N-260-2005-00010- C from the National Institute on Aging

Conflict of Interests: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Najjar reported receiving research funding from HeartWare. Dr Rao reported receiving research funding from Novartis, Cordis Corporation, and Ikaria; and being a consultant for Sanofi-aventis, Bristol-Meyers Squibb, Astra- Zeneca, Daiichi Sankyo-Lilly, and Terumo USA. Dr Raman reported receiving grant support from the National Institutes of Health and from Siemens Corporation. Dr Povsic reported receiving grants from Baxter International, Regado Biosciences, and Theragen. Dr Barsness reported being a consultant for Gilead Sciences Inc and receiving travel compensation from Novartis Pharmaceuticals Corporation. Dr Heitner reported that New York Methodist Hospital received compensation for his work as a principal investigator for a study; receiving compensation for his expert testimony in an individual malpractice case; receiving grant support from the Empire Clinical Research Investigator Program; and receiving compensation for serving on a steering committee for a trial. Dr Hasselblad reported receiving salary support via grants from Eli Lilly and Medtronic Inc administered through Duke University. Dr Greenbaum reported receiving compensation from various law firms for expert testimony; compensation for serving on speakers bureaus for various companies; and owning stock or stock options in various other device and health care companies. Dr Patel reported being a board member for Genzyme's advisory board and Bayer Healthcare; and serving as a consultant for Ikaria. Dr Kim reported being an inventor on a US patent for Delayed Enhancement MRI, which is owned by Northwestern University. Dr Harrington reported that a complete listing of disclosure information is available at dcric.org/about-us/conflict-of-interest/Harrington-COI_2010.pdf. None of the other authors reported disclosures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with a fixed-block randomisation scheme using a Web-based application." (p: 1864)
Allocation concealment (selection bias)	Low risk	Comment: Since web-based randomization is a central form of allocation, participants or investigators enrolling participants could not possibly foresee assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled." (p: 1864) Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Assessments will be performed blinded to patient identity, treatment assignment, and clinical outcomes." (<i>American Heart Journal</i> 2010;160: 803.e1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Attrition bias in total cohort was 22/125 (18%) in the EPO group (8 due to withdrawn consent, 2 lost to follow-up and 1 unwilling to travel) and 11/97 (11%) in the control group (12 due to withdrawn consent, 8 lost to follow-up and 2 unwilling to travel)
Selective reporting (reporting bias)	Low risk	Comment: "change in numbers of circulating endothelial progenitor cells" which is specified in the protocol (ClinicalTrials.gov with identifier NCT00378352) and trial design (<i>American Heart Journal</i> 2010; 160: 795-803) as secondary outcome is not reported. However, it might not influence safety outcome. Duration of study or maximum follow-up was not provided

Najjar 2011 (Continued)

Other bias	Low risk	Comment: Large study group with negative result of primary outcome; Safety data were analysed on an as-treated basis; Supported by Intramural Research Program contract HHS-N-260-2005-00010- C from the National Institute on Aging
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Nichol 2015

Methods	Prospective, multicentre, multinational, double-blind, parallel group, placebo-controlled trial Clinical research ethics approvals were obtained at all participating institutions. A detailed study protocol was published before completion of the study. Site medical teams retained full independent control of management of every participant's traumatic brain injury, although all sites agreed to adhere to the Brain Trauma Foundation guidelines for the management of traumatic brain injury
Participants	603 people admitted < 24 hours since primary traumatic brain injury and expected to stay ≥ 48 hours, and had a haemoglobin not exceeding the upper limit of the applicable normal (ULN) reference range in clinical use at the treating institution Age: 15 - 65 year Male: 502 (83.2%) Location: Australia (Australian Capital Territory, New South Wales, Queensland, South Australia, Tasmania, Victoria, Western Australia), Finland, New Zealand, Saudi Arabia Setting: 29 hospitals in 7 countries
Interventions	Epoetin alfa (40,000 IU) or sodium chloride (placebo) given as SC injection weekly up to 3 doses Length of follow-up: 6 months
Outcomes	- Primary outcomes: Combined proportion of unfavourable neurological outcomes at 6 months: severe disability (defined as GOSE scores 2 - 4) or death (GOSE score 1) - Secondary outcomes: Probability of an equal or greater GOSE level at 6 months compared to the probability of a lesser GOSE level, using a proportional odds model; Proportion of surviving participants with unfavourable neurological outcome (GOSE 2 - 4) at 6 months; Quality of life assessment (SF-12 and EQ-5D) at 6 months; Mortality at 6 months; Rate of proximal DVT detected during screening by compression Doppler ultrasound; Proportion of participants with composite thrombotic vascular events (DVT, PE, myocardial infarction, cardiac arrest and cerebrovascular events) at 6 months; cost effectiveness analysis at 6 months (based on EQ-5D)
Notes	Study duration: 3 May 2010 to 6 May 2015 Sponsorship source: EPO-TBI was supported by grants from the National Health and Medical Research Council of Australia (grant 545902) and the Transport Accident Commission of Victoria (grant D162). The members of the writing committee assume responsibility for the overall content and integrity of the article. Conflict of Interests: AN, CF, LL, SH, JP, YA, MB, DJC, JD, OH, AM, CM, VP, MS, MV, DV, JW, and RB received funding from the National Health and Medical Research Council and the Transport Accident Commission during the conduct of the study. The other authors declare no competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
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Nichol 2015 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned 1:1 to receive erythropoietin or placebo"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned 1:1 to receive erythropoietin or placebo with the use of permuted blocks of varying sizes of 2, 4, and 6 by a concealed web based centralised computer-generated randomisation schedule"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Designated site pharmacists, the site dosing nurses at all sites, and the pharmacists at the central pharmacy in France (Clinical Trial Department of the Pharmaceutical Establishment of Assistance Publique-Hôpitaux de Paris, Paris, France) were not masked to treatment assignment. All other site personnel and patients were masked to treatment allocation. After randomisation, a designated unmasked trial pharmacist dispensed the trial drug in a tamper-proof sealed opaque box"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "With the exception of designated site pharmacists, the site dosing nurses at all sites, and the pharmacists at the central pharmacy in France, all study personnel, patients, and patients' relatives were masked to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Safety follow-up might be completed in all participants
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00987454)
Other bias	Unclear risk	Comment: This study was supported by grants from the National Health and Medical Research Council of Australia (grant 545902) and the Transport Accident Commission of Victoria (grant D162)

Nirula 2010

Methods	Randomized, double-blind, placebo-controlled single-centre trial The study is approved by the institutional review board and informed consent has been obtained from the family of participants.
Participants	16 people with blunt trauma with an admission GCS < 13 and evidence of traumatic brain injury (TBI) on CT Age: ≥ 18 year Male: 11 (68.7%) Location: United States Setting: Division of Trauma and Critical Care
Interventions	Single IV bolus of EPO (40,000 Units) or placebo administered within 6 hours of the time of injury Length of follow-up: 5 days
Outcomes	- Primary outcome: S-100B and NSE levels - Secondary outcomes: ICU length of stay, GCS at ICU discharge, and in-hospital mortality

Nirula 2010 (Continued)

Notes

Study duration: no detail

Sponsorship source: This research was funded by the American Association for the Surgery of Trauma Research and Education Foundation Scholarship Award

Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: No information on randomization has been provided.
Allocation concealment (selection bias)	Unclear risk	Comment: No information on allocation concealment has been provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This was a randomised, double-blind, placebo-controlled single-center trial", "randomised to receive EPO (40,000 Units IV) or placebo", CT scans were independently reviewed by a radiologist (blinded to the randomisation)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Lab values are unlikely to be influenced by lack of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "23 patients were initially randomised with 7 patients dropping out before receiving the study agent leaving 16 patients (EPO n = 11, placebo n = 5) for subsequent analysis. The 7 dropouts were patients who were initially randomised but never received the study agent or placebo because they were found to be outside of the six hour inclusion criteria by the time the agent was available" Comment: Analysed per protocol. High number of exclusions
Selective reporting (reporting bias)	High risk	Comment: Registering a trial is mandatory for RCTs in US but it was not referred to in the report and was not retrieved by searches in ClinicalTrials.gov. It is the only trial with Nirula R as principle investigator entitled "Erythropoietin effects after traumatic brain injury" (NCT00260052) which has been withdrawn prior to enrolment
Other bias	Unclear risk	Comment: insufficient information The study has been funded by American Association for the Surgery of Trauma Research and Education Foundation Scholarship Award

Ott 2010

Methods	Randomized, double-blind, placebo-controlled study The study protocol was approved by the institutional ethics committee responsible for both participating centres, and all participants gave written informed consent for participation in the study
Participants	138 adults undergoing PCI for a 1st acute STEMI $\leq$ 24 h from symptom onset Age: 18 - 80 year Male: 108 (78.3%)

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

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Ott 2010 (Continued)

Location: Munich, Germany

Setting: Deutsches Herzzentrum and 1st Medizinische Klinik rechts der Isar

Interventions	IV injection of epoetin- beta (3.33×10^4 IU) or placebo immediately, 24 and 48 hours after PCI Length of follow-up: 6 months
Outcomes	<p>- Primary outcome: LVEF 6 months after random assignment measured by MRI</p> <p>- Secondary outcomes: changes in LVEF and infarct size between 5 days to 6 months after random assignment, measured by MRI</p> <p>- Additional outcomes: LV volumes and infarct size in MRI, LVEF, and number of hypokinetic chords in angiography and major adverse cardiac and cerebrovascular events at 30 days and 6 months (composite of death, recurrent MI, revascularization of the infarct-related artery, and stroke)</p>
Notes	<p>Study duration: January 2007 - November 2008</p> <p>Sponsorship source: no detail</p> <p>Conflict of Interests: The study drug was provided by F. Hoffmann-La Roche, Basel, Switzerland</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Sealed envelopes containing blinded treatment code were used for random assignment." (p: 409)
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes containing blinded treatment code were used for random assignment." (p: 409)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo controlled study" (p: 408) Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All events were adjudicated and classified by an event adjudication committee blinded to the assigned treatment group." (p: 409)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Clinical follow-up was complete in all patients." (p: 410)
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00390832)
Other bias	Low risk	Comment: Negative trial; Study protocol described in detail; No funding support but study drug was provided by manufacturer

Prunier 2012

Methods	Randomized, open-label and multicentre with blind evaluation of endpoints
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Prunier 2012 (Continued)

The ethics committee of the Angers University Hospital approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki and French legislation. All participants gave informed consent before being included in the study

Participants	<p>110 adults undergoing successful PCI for a 1st STEMI within 6 hours from symptom onset</p> <p>Age: > 18 years</p> <p>Male: 90 (82%)</p> <p>Location: France (Angers, Brest, Lille, Paris, Poitiers, and Tours)</p> <p>Setting: French University Hospitals</p>
Interventions	<p>Single IV bolus of epoetin beta (1000 IU/kg) immediately after reperfusion or standard care</p> <p>Length of follow-up: 3 months</p>
Outcomes	<p>- Primary outcome: Infarct size expressed as total LGE mass at 3 months</p> <p>- Secondary outcomes: LVEF, LV volumes 5 days and 3 months after PCI</p> <p>- Additional outcomes: peak CK release, kinetics of blood haemoglobin and haematocrit levels as well as platelet and reticulocyte counts in the follow-up, blood pressure level after epoetin-beta administration, and major adverse cardiac events at 3 months (including death, recurrent MI, revascularization of the infarct related artery, and stroke)</p>
Notes	<p>Study duration: April 2008 - September 2010</p> <p>Sponsorship source: academic grants from the Fédération Française de Cardiologie, the Société Française de Cardiologie, and Programme Hospitalier de Recherche Clinique (PHRC) from the French Department of Health</p> <p>Conflict of Interests: no detail</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Web-based randomisation was performed using a computer-generated sequence." (p: 201)
Allocation concealment (selection bias)	Low risk	Comment: Since web-based randomization is a central form of allocation, participants or investigators enrolling participants could not possibly foresee assignments
Blinding of participants and personnel (performance bias) All outcomes	High risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "De-identified records were reanalysed in a core laboratory in a blinded fashion." "All de-identified images were analysed at the central core laboratory by an experienced observer who was blinded to all patient data" (p: 201)
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Other bias	Low risk	

Robertson 2014

Methods	<p>Randomized trial using a factorial design</p> <p>The protocol was approved by the Food and Drug Administration and institutional review boards at all clinical sites. Participants in the 1st year of the study were enrolled after obtaining written informed consent from their legally-authorized representative. In August 2007 after approval of the requirements for emergency research, the study was conducted under regulations for the Exception From Informed Consent for Emergency Research (21 CFR 50.24). When families were subsequently located and/or the participant recovered sufficiently to consent, they were asked to sign a consent form to permit continued participation in the study</p>
Participants	<p>200 adults admitted to the trauma centres with a closed head injury who were not able to follow commands after resuscitation and could be enrolled within 6 hours of injury</p> <p>Male: 174 (87%)</p> <p>Location: United States (Houston, Texas)</p> <p>Setting: Ben Taub General Hospital and Memorial Hermann Hospital</p>
Interventions	<p>Epo (500 IU/kg) or an equal volume of saline intravenous bolus infusion over 2 minutes for each dose of the study drug; Participants received an initial dosage regimen of the assigned study drug followed by 2 additional doses, 1 per week for the next 2 weeks provided that the participant remained in ICU and haemoglobin concentration remained below 12 g/dl. For the 1st 74 participants, the initial dosage regimen was 1 dose given within 6 hours of injury followed by 2 additional doses given every 24 hours (Epo 1 regimen). In 2009, the initial dosage regimen was changed for the subsequent 126 participants to 1 dose given within 6 hours of injury (Epo 2 regimen)</p> <p>Length of follow-up: 6 months</p>
Outcomes	<p>- Primary outcome: the Glasgow Outcome Scale (GOS)</p> <p>- Primary safety outcomes for the transfusion threshold comparison: mortality, the incidence of Adult Respiratory Distress Syndrome (ARDS), and the incidence of infections (total incidences of pneumonia, bacteraemia, urinary tract infection, and ventriculitis)</p> <p>- Secondary transfusion threshold outcome: Disability Rating Scale (DRS)</p> <p>- Secondary Epo/placebo outcome: mortality</p>
Notes	<p>Study duration: May 2006 - August 2012</p> <p>Sponsorship source: This study was supported by National Institute of Neurological Disorders and Stroke (grant #P01-NS38660), which had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript</p> <p>Conflict of Interests: Dr. Robertson, Dr. Doshi, and Jace Wagaspack report receiving grants from NIH NINDS during the conduct of the study. None of the other authors report any disclosures</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list, stratified by site and using one randomization event to both factors in blocks of 4,..."
Allocation concealment (selection bias)	Unclear risk	Quote: "A randomization list... was prepared by the study statisticians and kept in each hospital's research pharmacy. When a new patient was enrolled, the research pharmacist prepared the study drug based on the patient's weight

Robertson 2014 (Continued)

		and treatment assignment from the randomization list and informed the investigators of the transfusion threshold assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators and clinical personnel caring for the patient were blinded to the patients treatment with study drug (Epo or placebo)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Personnel conducting outcome assessments were blinded to both treatment assignment and transfusion threshold"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Safety follow-up might be completed in all participants
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00313716)
Other bias	High risk	Comment: Study intervention was changed within course of study This study was supported by National Institute of Neurological Disorders and Stroke (grant #P01-NS38660), which had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript

Shuman 2009

Methods	Cohort (chart review)
Participants	73 critically-ill people with a Hgb < 12 g/dL at admission to the medical or surgical ICU Age: ≥ 18 year Location: United States Setting: Medical or surgical ICU
Interventions	Darbepoetin alfa (DARB) or non-DARB
Outcomes	Need for RBC transfusion, changes in haemoglobin from baseline to ICU discharge and the incidence of thrombotic events
Notes	Type of report: Conference proceeding Study duration: January 2004 - August 2008 Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: Critically-ill adults with anaemia (not due to chronic renal failure or chemotherapy) admitted to the ICU over a certain period of time were includ-

Shuman 2009 (Continued)

		ed. People with pregnancy, refusal of RBC transfusion, or thrombotic events within 6 months of ICU admission were excluded
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Unclear risk	Comment: Insufficient information
Demonstration that the outcome of interest was not present at start of study?	Low risk	-
Comparability of cohorts on the basis of the design or analysis?	Unclear risk	Quote: "There were no statistically significant differences in any demographic or baseline characteristics"
Assessment of outcome?	Unclear risk	Comment: Insufficient information
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study population was retrospectively reviewed

Silver 2006

Methods	Randomized, double-blind, placebo-controlled, multicentre trial Approval of the study was obtained from a central Institutional Review Board, Shulman Associates, and informed consent was obtained from each participant (or his or her surrogate). The Institutional Review Board determined who could qualify as a participant surrogate for the purpose of giving consent
Participants	86 critically-ill adults with haematocrit < 38 admitted to the long-term acute care hospitals (LTAC) ≤ 7 days Age: ≥ 18 years Male: 43 (50%) Location: United States Setting: LTAC
Interventions	SC injection of rHuEPO (40,000 U) or placebo during the 1st week of LTAC admission and continued weekly for participants who remained in the LTAC, for a maximum of 12 doses (study days 1, 8, 15, etc.) Length of follow-up: 84 days
Outcomes	- Primary outcomes: Cumulative RBC units transfused - Secondary outcomes: The % of participants receiving any RBC transfusion, the % of participants alive and transfusion-independent, cumulative mortality, and change in haematologic variables from baseline
Notes	Study duration: April 2000 - May 2002

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Silver 2006 (Continued)

Sponsorship source: Supported in part by Ortho Biotech Products, L.P.

Conflict of Interests: Drs. Silver, HL Corwin, and Gettinger have received research support and served as consultants for Ortho Biotech Products, L.P. Mr. Enny is employed by Ortho Biotech Products, L.P., and is a stock shareholder for Johnson and Johnson. Dr. MJ Corwin is employed by Battelle CRO, which has been a paid contractor to Ortho Biotech Products, L.P. Dr. Bazan has not disclosed any potential conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation entailed use of computer-generated random numbers." (p: 2311)
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was a prospective, randomised, double-blind, placebo-controlled, multiple-centre trial". (p: 2311) Comment: Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: "Randomisation, study monitoring, and data analysis were done by a contract research organization (Battelle CRO)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Attrition was 12/42 (28.6%) in the EPO group (2 discontinued intervention (2 adverse events, 1 convulsion, and 1 pulmonary embolus) and 10 lost to follow-up after hospital discharge) and 11/44 (25%) in the control group (1 discontinued intervention (1 participant choice) and 10 lost to follow-up after hospital discharge)
Selective reporting (reporting bias)	Unclear risk	Comment: Participants were not followed following discharge from the LTAC
Other bias	Unclear risk	Comment: Study was supported, in part, by Ortho Biotech Products, L.P. Three authors (1 st , 4 th and the last one) have received research support and served as consultants for Ortho Biotech Products, L.P. The 5 th author is employed by Ortho Biotech Products, L.P., and is a stock shareholder for Johnson and Johnson. The 2 nd author is employed by Battelle CRO, which has been a paid contractor to Ortho Biotech Products, L.P.

Springborg 2007

Methods	Randomized, double-blind, placebo-controlled clinical trial The Regional Committee for Biomedical Research Ethics (KF 01-087/02) and the Danish Medicines Agency (2612-1415) approved the study protocol
Participants	73 people admitted to the neuro-intensive care unit with aneurysmal subarachnoid haemorrhage (aSAH), occurring not more than 48 hours previously Age: 18 - 80 year Male: 15 (20.5%) Location: Copenhagen, Denmark

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

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Springborg 2007 (Continued)

Setting: Neuro-intensive Care Unit at Copenhagen University Hospital

Interventions	IV injection of rHuEPO (500 IU/kg/day) or placebo for 3 days (the 1st dose immediately after randomization and the 2nd and 3rd doses after 24 and 48 hours) Length of follow-up: 6 months
Outcomes	Glasgow Outcome Scale (GOS) score, vasospasm (TCD and symptomatic), cerebral infarction, cerebral metabolism, jugular venous oximetry, markers of brain damage, blood–brain barrier integrity and drug safety
Notes	Study duration: 1 April 2002 - September 2004 Sponsorship source: This study was supported by grants from the University of Copenhagen, the H:S foundation, Copenhagen University Hospital (Rigshospitalet) and HjerneSagen Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “An independent investigator (NVO) generated a restricted randomisation list with blocks of 10 using a computer program” (p: 1090)
Allocation concealment (selection bias)	Low risk	Quote: “After patient inclusion NVO opened a sealed opaque envelope containing the treatment code and prepared the medication” (p:1090)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “A single blinded investigator (JBS) enrolled the patients.” ... “Project medication was administered intravenously as bolus injections by a blinded investigator (JBS)” (p: 1090)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: “Selection of patients for analysis was done before code breaking, and data analysis was performed by a blinded investigator (JBS) with treatment groups coded as A and B.” (p: 1092)
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Attrition was 12/36 (33%) in the EPO group (3 due to perimesencephalic haemorrhage and 1 due to arterio-venous malformation (AVM)) and 7/37 (19%) in the placebo group (4 due to perimesencephalic haemorrhage and 1 due to AVM)
Selective reporting (reporting bias)	Unclear risk	Comment: Due to low inclusion rate and high withdrawals, they had to stop participant enrolment after 30 months. They therefore conceded that their primary research questions were impossible to answer due to the limited sample size and the significant heterogeneity of the groups
Other bias	Unclear risk	Comment: Analysis based on per-protocol assessment; Study was supported by grants from the University of Copenhagen, the H:S foundation, Copenhagen University Hospital (Rigshospitalet) and HjerneSagen (Stroke Association)

Still 1995

Methods	Randomized, double-blind, placebo-controlled, multicentre trial No detail on ethics committee approval
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Still 1995 (Continued)

Participants	40 acutely burned adults(25% - 65% of TBSA) Age: 18 - 70 years Location: United States Setting: 7 medical centres
Interventions	IV injection of rHuEPO (300 U/kg) within 72 hours of admission and daily for 7 days, then 150 U/kg every other day for 23 days (in total for 30 days) Length of follow-up: 30 days
Outcomes	Blood transfusion requirement, change in anaemia parameters
Notes	Study duration: no detail Sponsorship source: supported by the RW Johnson Pharmaceutical Research Institute Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Prospective double-blind randomised study of 40 patients" (p: 233) Comment: Insufficient description
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This was a double-blind, placebo-controlled, parallel group, multicenter study" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No information on outcome assessment has been provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Low risk	Comment: The study protocol was not available but it seems that the published report includes all expected safety outcomes (including death)
Other bias	Unclear risk	Comment: Negative trial; Supported by the RW Johnson Pharmaceutical Research Institute

Suh 2011

Methods	Randomized, open-label, placebo-controlled, single-centre trial The trial was performed in accordance with the Declaration of Helsinki (revised version, 1996) and relevant Korean laws. In accordance with relevant Korean laws, the study protocol was approved by the
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Suh 2011 (Continued)

	ethics committee of the institution of Seoul National University Bundang Hospital. All participants were given a written informed consent before being included in the study
Participants	<p>57 people with acute, anterior wall STEMI who were presented ≤ 12 hours after the onset of chest pain, and clinical decision was made to treat with PCI</p> <p>Age: ≥ 18 year</p> <p>Male: 43 (75.4%)</p> <p>Location: Seoul, Korea</p> <p>Setting: Cardiovascular Centre, Seoul National University Bundang Hospital</p>
Interventions	<p>Single IV bolus of rHuEPO (50 U/kg) immediately before PCI or usual care</p> <p>Length of follow-up: 6 months</p>
Outcomes	<p>- Primary outcome: The size of the infarct, assessed by measurements of cardiac biomarkers (CK, CK-MB) at baseline and 3 days after PCI</p> <p>- Secondary outcomes: The size of the infarct as measured by cardiac MRI, at day 4 after infarction</p> <p>- Additional outcomes: Clinical outcomes: death, MI, ischaemic stroke and composite of atherothrombotic events (cardiac death, MI and non-haemorrhagic cerebral infarction) at 1 and 6 months after PCI</p>
Notes	<p>Study duration: no detail</p> <p>Sponsorship source: This study was supported by the grants from the Innovative Research Institute for Cell Therapy (IRICT: A062260)</p> <p>Conflict of Interests: The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of randomisation table" (p: 217)
Allocation concealment (selection bias)	High risk	<p>Quote: "randomised, open-label" (p: 217)</p> <p>Comment: Participants or investigators enrolling participants could possibly foresee assignments</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "randomised, open-label" (p: 217)</p> <p>Comment: Blinding of participants and personnel were not done</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigators who evaluated the clinical outcomes were blinded to the status of randomisation" (p: 217)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data

Suh 2011 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00882466)
Other bias	Low risk	Comment: Negative result of primary and secondary outcomes; Supported by the grants from the Innovative Research Institute for Cell Therapy

Talving 2010

Methods	Cohort (review of the trauma registry) The study is approved by the Institutional Review Board, the trauma registry of the Los Angeles County + University of Southern California Medical Center	
Participants	267 adults (> 16 years) admitted to SICU with severe traumatic brain injury (sTBI) (head Abbreviated Injury Scale (AIS) ≥ 3) Age: > 16 years Male: 186 (69.7%) Location: California, United States Setting: SICU	
Interventions	SC injection of ESAs consisted of rHuEPO (100 U/kg) or darbepoetin (0.45 mcg/kg) weekly or non- ESAs within the 1st 30 days after hospital admission Length of follow-up: 30 days	
Outcomes	- Primary outcome: In-hospital mortality - Secondary outcomes: Incidence of ARDS, pneumonia, sepsis, acute renal failure, DVT, and PE	
Notes	Study duration: 1 January 1996 - 31 December 2007 Sponsorship source: no detail Conflict of Interests: no detail	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: Identified by review of all adults admitted to the SICU with sTBI over a certain period of time
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Low risk	Comment: Record linkage by using the trauma registry
Demonstration that the outcome of interest was not present at start of study?	Low risk	-

Talving 2010 (Continued)

Comparability of cohorts on the basis of the design or analysis?	Low risk	Comment: For each case, 2 controls were matched for gender, age, mechanism of injury, AIS for each body region, Injury Severity Score, hypotension on admission, Glasgow Coma Scale score on admission, and the presence of anaemia during the hospital stay
Assessment of outcome?	Low risk	Comment: Record linkage by using the trauma registry
Was the follow-up long enough for the outcomes to occur?	Low risk	Comment: 30 days
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study population was retrospectively reviewed

Taniguchi 2010

Methods	Pilot, randomized, open-labelled, placebo-controlled, blinded endpoints (PROBE), multicentre study The study is approved by the ethics review boards of Takahashi Hospital, Kyoto City Hospital, Shiga Saiseikai Hospital and Kyoto Prefectural University Hospital. Written informed consent was obtained from all participants before the study	
Participants	35 people with a 1st ST-elevated AMI, who underwent successful PCI within 12 hours from the onset Age: 20 - 80 years Male: 32 (91.4%) Location: Japan Setting: Takahashi Hospital, Kyoto City Hospital, Shiga Saiseikai Hospital and Kyoto Prefectural University Hospital	
Interventions	IV injection of epoetin-beta (6000 IU) or saline immediately, 2 and 4 days after PCI Length of follow-up: 6 months	
Outcomes	- Primary outcomes: neointimal volume (assessed by intravascular ultrasound), late lumen loss (by quantitative coronary angiography; QCA) and infarct size (defect score by ECG-gated Tc99m-tetrofosmin SPECT) - Secondary outcomes: LV function and volume (LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF), % diameter stenosis (% DS by QCA) and major adverse cardiac events	
Notes	Study duration: October 2006 - March 2008 Sponsorship source: no detail Conflict of Interests: no detail	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patients were randomised in accordance with the computer-assisted minimization method."(p: 2366)

Taniguchi 2010 (Continued)

Allocation concealment (selection bias)	High risk	Quote: "Randomised, Open-labelled" (p: 2366) Comment: Participants or investigators enrolling participants could possibly foresee assignments
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Randomised, Open-labelled" (p: 2366) Comment: Blinding of participants and personnel was not done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded Endpoints study" (p: 2366)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All outcome data are provided
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00423020)
Other bias	Unclear risk	Comment: Small study group; Changed the prespecified design in protocol from "Masking: Double-Blind" to "Open-labelled, Blinded Endpoints" in report; Supported by Kyoto Prefectural University of Medicine

Tseng 2009

Methods	Phase 2 randomized, double-blind, placebo-controlled trial The trial was approved by Cambridge Local Research Ethics Committee (04/Q0108/87) and Medicines and Healthcare Products Regulatory Agency (EudraCT 2004-001141-15), registered with ClinicalTrials.org (NCT00140010)
Participants	80 people with aSAH within 72 hours after the ictus Age: 24 – 82 year Male: 24 (30%) Location: Cambridge, UK Setting: Addenbrooke's Hospital, a tertiary referral centre
Interventions	IV injection of epoetin-beta (30,000 U) or placebo on the day of recruitment and then every 48 hours for a total of 3 doses (90,000 U) Length of follow-up: 6 months
Outcomes	- Primary outcomes: Incidence, duration, and severity of vasospasm on TCD ultrasound; duration of impaired auto-regulation on THRT - Secondary outcomes: Incidence of DIDs; outcome at discharge and at 6 months
Notes	Study duration: April 2005 - April 2006 Sponsorship source: no detail Conflict of Interests: The EPO (Epoetin-beta, NeoRecormon) was donated by Roche Products (Welwyn Garden City, UK). Dr. Tseng was supported by a research grant from the Roche Foundation for Ane-

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Tseng 2009 (Continued)

mia Research (Meggen, Switzerland, I.D. No. 6294470694) from December 2005 to November 2006. Dr. Hutchinson is supported by a UK Academy of Medical Sciences/Health Foundation Senior Surgical Specialist Fellowship. Dr. Czosnyka is on unpaid leave from Warsaw University of Technology in Poland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed according to a computer generated randomisation list" (p: 172)
Allocation concealment (selection bias)	Low risk	Quote: "Each set was sequentially numbered and assigned to a patient with the content only known by the Ipswich Pharmacy" (p: 172)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both patients and investigators were blinded to the treatment allocation, and the randomisation code was not broken until the last recruited patient was assessed at 6 months" (p: 172)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcomes at discharge and at 6 months were assessed by an independent neurosurgeon" (p: 173)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00140010)
Other bias	Unclear risk	Comment: Hoffmann-La Roche and Roche Foundation of Anaemia Research (RoFAR, Switzerland) are specified as sponsors and collaborators in the protocol (ClinicalTrials.gov with identifier NCT00140010) but they reported only that epoetin-beta (Neo-Recormon) was donated by Roche Products

Van Iperen 2000

Methods	Open, prospective, randomized study The study was approved by the Medical Ethical Committee of the Eemland Hospital, Amersfoort, The Netherlands
Participants	36 critically-ill people admitted to the ICU and stayed for ≥ 7 days who became anaemic (Hgb < 11.2 g/dL or < 12.1 g/dL in case of cardiac disease) Age: > 18 year Male: 20 (55.5%) Location: Amersfoort, The Netherlands Setting: ICU of the Eemland Hospital
Interventions	EPO group: IV folic acid (1 mg daily) + IV iron saccharate (20 mg daily for 14 days) + SC epoetin alfa (300 IU/kg) on days 1, 3, 5, 7, and 9; Iron group: IV folic acid (1 mg daily) + iv iron saccharate (20 mg daily for 14 days); Control group: IV folic acid (1 mg daily). Follow-up time: 22 days

Van Iperen 2000 (Continued)

Length of follow-up: 22 days

Outcomes	APACHE II score, blood loss and red cell transfusions, total blood count, reticulocyte count, serum EPO concentrations, serum transferrin receptor, iron metabolism, vitamin B12 and folic acid concentrations, serum concentrations of creatinine, haptoglobin, and C-reactive protein
Notes	<p>Study duration: 1996 - 1997</p> <p>Sponsorship source: no detail</p> <p>Conflict of Interests: "The epoetin alfa used in this study was graciously provided by Janssen-Cilag (Tilburg, The Netherlands) and the VAMP system was provided by Baxter Healthcare (Utrecht, The Netherlands)"</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "Study participants were randomly assigned to receive ..." (p: 2774)</p> <p>Comment: Insufficient description</p>
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information is provided to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No blinding; Since the study reported mortality only, participants will not have been aware of this outcome. However, it is unclear who was informed about the treatment allocation within the team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: It was an open study but mortality outcome is unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available but for 22 days follow-up, the report should specify expected safety outcomes or give the reason for not specifying them
Other bias	Unclear risk	Comment: The study drug (epoetin alfa) was provided by Janssen-Cilag, The Netherlands

Vincent 2006

Methods	<p>Randomized, double-blind, placebo-controlled study</p> <p>The study was approved by the ethics committee of each institution, and participants or their next of kin provided written informed consent</p>
Participants	<p>68 anaemic critically-ill people with expected ICU and hospital stays of > 3 and ≥ 7 days, respectively, and a haematocrit value of < 38%</p> <p>Age: ≥ 18 years</p> <p>Male: 49 (72%)</p>

Vincent 2006 (Continued)

Location: Brussels, Belgium

Setting: 3 medical, surgical, or mixed medical/surgical ICUs

Interventions	SC injection of epoetin alfa (40,000 IU) or matching placebo once weekly for up to 4 doses (on days 1, 8, 15, and 22) Length of follow-up: 42 days
Outcomes	- Primary outcomes: Pharmacokinetic profile of erythropoietin (C _{max} , T _{max} , C _{min} on days 1 and 8, AUC _(0-Tlast) , T _{last} , t _{1/2} , CL/F) - Secondary outcomes: Pharmacodynamics profiles (reticulocytes, total RBCs, and haemoglobin vs time)
Notes	Study duration: 14 March 2001 - 8 October 2001 Sponsorship source: Supported in part by a research grant from Johnson and Johnson Pharmaceutical Research and Development, Raritan, NJ Conflict of Interests: Dr. Vincent has consulted for Johnson and Johnson and received grants and honoraria from the company. Drs. Vercammen and Beaver are employed by Johnson and Johnson, and Dr. Beaver owns stock and stock options in the company. The remaining authors do not have any financial interests to disclose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised 2:1 to receive either epoetin alfa or placebo, respectively." (p:1662) Comment: Insufficient information
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In this double-blind, randomised, placebo- controlled multicenter study". (p: 1662) Comment: Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: In pharmacokinetic analysis 17/73 (23%) did not complete the study (5 due to insufficient blood, 4 due to adverse events, 4 chose to withdraw, and 4 were either lost to follow-up or withdrew for other reasons). However, for the assessment of adverse events all participants were included
Selective reporting (reporting bias)	Unclear risk	Comment: The study protocol was not available but it was expected that the authors report death outcomes or the reason for not specifying them
Other bias	Unclear risk	Comment: Analysis based on Intention-to-treat assessment; Study was supported, in part, by a research grant from Johnson and Johnson (J&J) Pharmaceutical Research and Development, Raritan, NJ. The 1st author has consulted for J&J and received grants and honoraria from the company. The last and penultimate authors were employed by J&J, and the former owned stock and stock options in the company

Voors 2010

Methods	<p>Randomized, open-label and multicentre with blind evaluation of endpoints</p> <p>The research protocol was approved by the central Ethics Committee of the University Medical Centre Groningen, and by the local Ethics Committees of each participating centre</p>
Participants	<p>529 adults undergoing successful PCI for a 1st STEMI, symptom onset 12 hours before hospital admission or 24 hours in case of ongoing ischaemia</p> <p>Age: 60.9 ± 11.1 year (Mean+ SD)</p> <p>Male: 411 (77.7%)</p> <p>Location: The Netherlands</p> <p>Setting: 7 cardiac catheterization laboratories</p>
Interventions	<p>Single IV bolus of epoetin alfa (60,000 IU) within 3 hours after PCI or standard care</p> <p>Length of follow-up: 12 months</p>
Outcomes	<p>- Primary outcomes: LVEF assessed at 6 weeks after the primary PCI procedure by planar radionuclide ventriculography</p> <p>- Secondary outcomes: Myocardial infarct size: determined by area under the marker curves and peak values of serial computerized measurements of CK, CK-MB and troponin-T; Incidence of a cardiovascular event within 6 weeks after PCI: defined as cardiovascular death, re-infarction (any STEMI or non-STEMI), emergency re-PCI or coronary artery bypass grafting, stroke, and clear symptoms of heart failure</p>
Notes	<p>Study duration: no detail</p> <p>Sponsorship source: The study was funded by the Interuniversity Cardiology Institute of the Netherlands (ICIN). Additional unrestricted grants were received from Janssen-Cilag, Tilburg, the Netherlands, and B.R.A.H.M.S. AG, Hennigsdorf, Germany. DJvV and AAV are clinical established investigators of the Netherlands Heart Foundation (D97-017 and 2006T37). AMSB is supported by the Netherlands Heart Foundation (grant 2007T20)</p> <p>Conflict of Interests: SDA received consultancy fees and honoraria for speaking from Amgen Inc, Vifor Pharma, BRAHMS AG and consultancy fees from Nanosphere. DJvV received consultancy fees from Amgen Inc</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were immediately randomised by means of a computerized program." (p: 2594)
Allocation concealment (selection bias)	Low risk	Comment: Since they used a computerized programme for randomization, participants or investigators enrolling participants could not possibly foresee assignments
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "randomised, open-label study" (p: 2594)</p> <p>Comment: Blinding of participants and personnel was not done</p>

Voors 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All endpoints were assessed in a blinded manner." "Safety data were periodically reviewed by an independent data- safety- monitoring committee." (p: 2594)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were included in the safety assessment." (p: 2596)
Selective reporting (reporting bias)	Low risk	Comment: Authors reported all prespecified outcomes in the protocol (ClinicalTrials.gov with identifier NCT00449488) and trial design which is published in <i>American Heart Journal</i> 2008; 155:817 - 22
Other bias	Low risk	Comment: Study was funded by Interuniversity Cardiology Institute of the Netherlands (ICIN). Additional unrestricted grants were received from Janssen-Cilag, the Netherlands, and B.R.A.H.M.S. AG, Germany. 2 authors are clinical established investigators of the Netherlands Heart Foundation and 1 author received a grant from this Foundation (grant 2007T20)

Wittbrodt 2005

Methods	Cohort (a retrospective review)
Participants	56 critically-ill adults with anaemia admitted to the Medical or Surgical ICU Location: United States Setting: Medical or Surgical ICU
Interventions	rHuEPO or non- rHuEPO
Outcomes	RBCs transfused, length of stay, organ failure (SOFA) scores and mortality
Notes	Type of report: Conference proceeding Study duration: no detail Sponsorship source: no detail Conflict of Interests: no detail

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of the exposed cohort?	Low risk	Comment: All critically-ill people with anaemia admitted to the Medical or Surgical ICU were included
Selection of the non-exposed cohort?	Low risk	Comment: Drawn from the same population
Ascertainment of exposure?	Unclear risk	Comment: Insufficient information
Demonstration that the outcome of interest was	Low risk	-

Wittbrodt 2005 (Continued)

not present at start of study?

Comparability of cohorts on the basis of the design or analysis?	High risk	Quote: "Unadjusted mortality was compared using chi-square"
Assessment of outcome?	Unclear risk	Comment: Insufficient information
Was the follow-up long enough for the outcomes to occur?	Unclear risk	Comment: Insufficient information
Adequacy of follow-up of the cohorts?	Low risk	Comment: Complete follow-up because the study was retrospective

ACS: acute coronary syndrome; AE: adverse event; AIS: abbreviated injury scale; AKI: acute kidney injury; AKIN: acute kidney injury network; AMI: acute myocardial infarction; AP: alkaline phosphatase; APACHE: Acute physiology and chronic health evaluation; ARDS: acute respiratory distress syndrome; aSAH: aneurysmal subarachnoid haemorrhage; ASIA: American Spinal Injury Association; AUC: area under the curve; AVM: arterio-venous malformation; BICU: burn intensive care unit; BSA: body surface area; BUN: blood urea nitrogen; CK: creatine kinase; CK-MB: creatine kinase, muscle and brain; CMR: cardiovascular magnetic resonance; COG: cognitive function scale; CPC: cerebral performance category; CPR: cardiopulmonary resuscitation; CRP: C-reactive protein; CT: computed tomography; DARB: darbepoetin; DIDs: delayed ischaemic deficits; DRS: disability rating scale; DVT: deep venous thrombosis; EPO: epoetin-alpha ; EQ-5D: European quality of life-5 dimensions; FACIT: functional assessment of chronic illness therapy; G-CSF: granulocyte colony stimulating factor; GCS: Glasgow coma scale; GGT: gamma-glutamyl transferase; GOS: Glasgow outcome scale; GOS-E: Glasgow outcome scale-extended; h: hour; Hct: haematocrit; Hgb: haemoglobin; HLM: heart-lung machine; ICU: intensive care unit; ISS: injury severity score; ITT: intention-to-treat; IU: international unit; IV: intravenous; LGE: late gadolinium enhancement; LOS: length of stay; LTAC: long-term acute care hospitals; LV: Left ventricular; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; MARS: medical archival retrieval system; Mg: milligram; MI: myocardial infarction; MM: muscle isoform of creatine kinase; MPSS: methyl prednisolone sodium succinate; MRI: magnetic resonance imaging; MVO: micro-vascular obstruction; NGAL: neutrophil gelatinase-associated lipocalin; NS: normal saline; NSE: neuron-specific enolase; OHCA: out-of-hospital cardiac arrest; PBC: peripheral blood cells; PBSC: peripheral blood stem/progenitor cells; PCI: percutaneous coronary intervention; pCr: plasma creatinine; PE: pulmonary embolism; PEA: pulseless electrical activity; PICU: prenatal intensive care unit; PPCI: primary percutaneous coronary intervention; PROBE: Pilot, randomized, open-labelled, blinded endpoints; PTDAL: post-traumatic diffuse axonal injury; PTT: prothrombin time; QCA: quantitative coronary angiography; RAVC: relative average plasma creatinine; RBC: Red Blood Cell; rhEPO: recombinant human erythropoietin; rHuEPO: recombinant human erythropoietin; RIFLE: risk injury failure loss end-stage kidney disease; ROSC: return of spontaneous circulation; SAPS: simplified acute physiologic score; SC: subcutaneous; SCI: spinal cord injury; SD: standard deviation; SF-12: short form with 12 questions; SICU: surgical intensive care unit; SOFA: sequential organ failure assessment; STE: segment elevation; STEMI: ST-elevation myocardial infarction; TBI: traumatic brain injury; TBSA: total body surface area; TCD: transcranial Doppler; THRT: transient hyperaemic response test; TNK: tenecteplase; TON: traumatic optic neuropathy; ULN: Upper limit of normal; VTE: venous thromboembolism

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahmed 2001	The EPO safety or mortality was not reported
Alibai 2015	The EPO safety or mortality was not reported
Andreotti 2008	Study population was not critically ill
Avall 2003	Study population was not critically ill
Ehrenreich 2002	The EPO safety or mortality was not reported for the control arm of this study
Ehrenreich 2009	Not all of study population was critically ill

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

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Study	Reason for exclusion
Kim 2013	Some critically-ill people were excluded
Mocini 2008	The EPO safety or mortality was not reported
Möllmann 1995	Study population was not critically ill
Orii 2015	Study population was not critically ill
Ozawa 2010	Study population had all undergone successful percutaneous coronary intervention. They were therefore not critically ill
Pang 2013	Not all of study population was critically ill
Poletes 1994	The EPO safety or mortality was not reported
Roubille 2013	Darbepoetin-alpha was administered intracoronary at the onset of reflow obtained by primary percutaneous coronary intervention
Shiehorteza 2011	The EPO safety or mortality was not reported
Shin 2006	Study population was not critically ill
Sureshkumar 2012	EPO- α given intra-arterially during the early reperfusion phase in deceased-donor kidney transplant recipients
Swedberg 2013	Study population was not critically ill
Tang 2009	Study population was people with acute MI undergone successful percutaneous coronary intervention. They were therefore not critically ill
Vitale 2007	Study population was not critically ill
Watanabe 1991	Study population was not critically ill
Yip 2011	Not all of study population was critically ill
Zhang 2009	Not all of study population was critically ill
Zhu 2013	The EPO safety was not considered as an outcome and no adverse events or mortality were reported

EPO: epoetin alfa; MI: myocardial infarction

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Cariou 2016](#)

Methods	Single-blind, placebo-controlled, randomized, multicentre clinical trial
	The study received ethics committee approval by CPP Ile de France III, Paris-Tarnier Cochin, Paris (France). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and adhered to French regulatory requirements. When possible, written informed consent was obtained from participant surrogates before study enrolment

Cariou 2016 (Continued)

	The study was registered under the name of "High dose of erythropoietin analogue after cardiac arrest" (Epo-ACR-02) ClinicalTrials.gov: NCT00999583
Participants	<p>476 adults with witnessed out-of-hospital cardiac arrest (OHCA) of presumed cardiac origin; time from cardiac arrest and recovery of circulatory activity < 60 minutes; persistent coma after ROSC (GCS < 7)</p> <p>Age: 18 - 80 years old</p> <p>Location: France</p> <p>Setting: 20 French hospitals</p>
Interventions	<p>Intravenous Epo as soon as possible after ROSC followed by 4 injections every 12 hours during the 1st 48 hours or standard care without any Epo medication. Each Epo injection was 40,000 units, resulting in a maximum total dose of 200,000 units. Each dose of Epo was conditioned in ready-prepared syringes that were stocked and transported at constant temperature (i.e. between 4° C and 8° C)</p> <p>Length of follow-up: 60 days</p>
Outcomes	<p>- Primary outcome: Neurological performance according to the Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale</p> <p>- Secondary outcome: Distribution of participants in each CPC level at day 30 and day 60; the all-cause mortality rate at ICU discharge, at hospital discharge, at day 30, and at day 60; and all adverse events</p>
Notes	<p>Study duration: October 2009 - July 2013</p> <p>Sponsorship source: Research grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique PHRC-AOM P 071217)</p> <p>Conflict of Interests: Dr. Kimmoun has received a grant from Baxter for the Esmosepsis clinical trial (NCT02068287) and fees for a consultancy activity. All the other authors declared no competing interests.</p>

Cheng 2016

Methods	<p>Cohort (a retrospective study)</p> <p>The study was approved by the Ethics Committee of The Second Affiliated Hospital, School of Medicine, Zhejiang University</p>
Participants	<p>60 adults with acute spinal cord injury (ASCI) admitted 10 ~ 60 hours after the trauma with blood haemoglobin (Hb) ≤ 15.0 g/dL</p> <p>Age: ≥ 18 years</p> <p>Male: 34 (56.7%)</p> <p>Location: Zhejiang, China</p> <p>Setting: Department of Orthopaedic Surgery</p>
Interventions	<p>IV injection of rhEPO (4000 unit) and IV infusion (intravenously guttae) of rhEPO at 12,000 IU/day (in 100 ml normal saline during 30 minutes) or IV injection of rhEPO (4000 unit) and IV infusion of 100 ml normal saline during 30 minutes for 10 days</p> <p>Length of follow-up: 2 to 3 years (average of 2.4 years)</p>

Cheng 2016 (Continued)

Outcomes	Injuries graded with ASIA Impairment Scale (AIS) at admission, 1-year and 2-year follow-up; blood routine examination on admission and after treatment for 14 days, side effects
Notes	<p>Study duration: December 2009 - December 2011</p> <p>Sponsorship source: Huangyan Science and Technology Bureau (Science and Technology Project 2010060 to Cheng)</p> <p>Conflict of Interests: Authors declared no conflict of interests</p>

Costa 2015

Methods	<p>Single-blind, randomized, multicentre clinical trial</p> <p>All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committees of the participating institutions</p>
Participants	<p>19 people with TSCI and AIS grade A or B consecutively admitted within 8 hours of the traumatic event with haemodynamic stability at treatment start (systolic blood pressure (90 mmHg) for at least 1 hour without massive infusion or vasopressor support) and neurological level between C5 and T12</p> <p>Age: 18 - 65 years old</p> <p>Male: 18 (94.7%)</p> <p>Location: Italy</p> <p>Setting: Italian Spinal Units</p>
Interventions	<p>IV injection of EPO (500 IU/Kg diluted in 50 ml saline) in 30 minutes started within 8 hours after injury, repeated at 24 and 48 hours afterward or IV injection of methylprednisolone (30 mg/Kg) in the 1st hour, followed by 5.4 mg/kg/h for 23 hours if treatment was started within 3 hours after the spinal injury, or for 48 hours if treatment was started between 3 and 8 hours</p> <p>Length of follow-up: 90 days</p>
Outcomes	ASIA motor/sensory level, AIS score and grade, Spinal Cord Independence Measure (SCIM) version II, Ashworth measure, Penn Spasm Frequency and VAS scores, MRI findings, somatosensory-evoked potentials (SSEP) from the pudendal and tibial nerve, and laboratory values at days 3, 7, 14, 30, 60 and 90; adverse events included drug-related events and disease-related events
Notes	<p>Study duration: 15 May 2008 - 19 July 2010</p> <p>Sponsorship source: Italian Drug Agency (Agenzia Italiana del Farmaco), contract number FAR-M6Y35XMI.</p> <p>Conflict of Interests: EB has received personal fees for board membership by VIROPHARMA and GSK; has received funding for travel and speaker honoraria from UCB-Pharma and GSK, for educational presentations from GSK; has received Grants for research activities from the Italian Drug Agency, Italian Ministry of Health, EISAI and the American ALS Association. EP has received funding from the American ALS Association and Italian Ministry of Health for data management and data monitoring of an observational study protocol. She is receiving funding from Italian Drug Agency (AIFA) for data monitoring and study management of randomized clinical trial. PM has received funding from Sanofi-Aventis, EISAI, Lombardy Region, and the American ALS Association for the data analysis and data management of RCT and observational study protocol. PC, DDC, FF, AG, CP and TR: nothing to disclose.</p>

Günter 2015

Methods	Double-blind, placebo-controlled, randomized, multicentre clinical trial
Participants	84 people with 2° and 3° burn and scald thermal injuries, which require operations including split skin harvesting and grafting, admitted earlier than 24 hours after injury Age: 18 - 75 years old Location: Germany Setting: German burn care centres
Interventions	Subcutaneous erythropoietin (150 IU/kg) or placebo every other day for 3 weeks Length of follow-up: 1 year
Outcomes	- Primary outcome: The complete re-epithelialization of a defined split skin graft donor area - Secondary outcomes: cellular and molecular regenerative effects, quality of scar formation, quality of life, gender differences, and organ dysfunction parameters (SOFA Score), adverse events and serious adverse events
Notes	Type of report: Conference proceeding Sponsorship source: No detail Conflict of Interests: No detail

Li 2016

Methods	Double-blind, placebo-controlled, randomized, clinical trial This study was approved by the institutional review board of Liaocheng People's Hospital, a major trauma centre in the southwest of Shandong province, China (approval number 2010031)
Participants	159 people with severe traumatic brain injury (head trauma plus the worst initial GCS of 8 or less on arrival) within 6 hours after injury Age: 15 - 71 years old Male: 90 (61.6%) Location: South-west of Shandong province, China Setting: Neurosurgery Department
Interventions	Subcutaneous injection of EPO (100 units/kg, average 6000 units) or the same volumes of subcutaneous normal saline on days 1 (within 2 hours of admission), 3, 6, 9 and 12 following the brain injury Length of follow-up: 3 months
Outcomes	Levels of 2 serum biomarkers for traumatic brain injuries, neuron specific enolase (NSE) and S-100 β protein day 1 (before EPO administration), day 4, 7, 10 and 14, and 3 months after treatment; GOS scores at 3 months after the treatment
Notes	Study duration: July 2010 - July 2014 Sponsorship source: No external funding

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

Li 2016 (Continued)

Conflict of Interests: No detail

AIFA: Italian Drug Agency; AIS: ASIA Impairment Scale; ALS: amyotrophic lateral sclerosis; ASCI: acute spinal cord injury; CPC: cerebral performance category; EPC: endothelial progenitor cell; EPO: epoetin alfa; GOS: Glasgow outcome scale; Hb: blood haemoglobin; IV: intravenous; MRI: magnetic resonance imaging; NSE: neuron specific enolase; OHCA: out-of-hospital cardiac arrest; RCT: randomized clinical trial; rhEPO: recombinant human erythropoietin; ROSC: return of spontaneous circulation; SCIM: spinal cord independence measure; SOFA: sequential organ failure assessment; SSPE: somatosensory-evoked potentials; SDW: second-degree wounds; TSCI: traumatic spinal cord injury; VAS: visual analogue scale

Characteristics of ongoing studies [ordered by study ID]

Minamino 2012

Trial name or title	EPO-AMI-II Study
Methods	Double-blind, placebo-controlled, randomized, multicentre clinical trial
Participants	People with acute ST-segment elevation myocardial infarction (STEMI) and a low LVEF (< 50%)
Interventions	IV bolus dose of epoetin-beta (6000 or 12,000 IU) or placebo within 6 hours after successful percutaneous coronary intervention (PCI)
Outcomes	<p>- Primary endpoint: The improvement of left ventricular ejection fraction at the chronic phase (the mean of differences between LVEF value at 4 – 7 days and that at 6 months after administration)</p> <p>- Secondary endpoint</p> <p>Efficacy: 1. Indices of cardiac function 6 months after administration of epoetin-beta, which are calculated with cardiac scintigraphy (LVEDV, LVESV, LVEDVI, LVESVI, regional wall motion score, ischaemia and defect size (SRS, SDS, % Defect Size, % uptake at resting)); 2. Survival ratio; 3. Cardiac event ratio (Cardiac death, stroke, non-lethal myocardial infarction, admission due to worsening of heart failure or unstable angina, revascularization, onset of heart failure symptoms (typical dyspnoea at rest or during exercise, pulmonary congestion or pretibial oedema); 4. NT-ProBNP 6 months after administration</p> <p>Safety: 1. Adverse events; 2. Laboratory test data; 3. Vital signs (blood pressure, pulse rate)</p>
Starting date	December 2011
Contact information	Issei Komuro: Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan e-mail: komuro-tky@umin.ac.jp
Notes	<p>Location: Japan</p> <p>This trial was registered at the UMIN Clinical Trials Registry as UMIN000005721</p>

IV: intravenous; LVEDV: left ventricular end-diastolic volume; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVESVI: left ventricular end-systolic volume index; NT-ProBNP: N-terminal prohormone of brain natriuretic peptide; PCI: percutaneous coronary intervention; SDS: Summed difference score; SRS: Summed rest score; STEMI: ST-elevation myocardial infarction

DATA AND ANALYSES

Comparison 1. ESAs versus placebo or no ESAs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event	9		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 RCT	8		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Observational	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Any serious adverse events_RCT	10	4183	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]
3 Venous thromboembolism (VTE)	18		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 RCTs	13		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Observational studies	5		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Deep Venous Thrombosis	13	5141	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
4.1 RCT	12	4874	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.92, 1.41]
4.2 Observational	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.34, 6.56]
5 Stroke _ RCT	11	2229	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.58, 4.29]
6 Myocardial infarction_RCT	10	3254	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.84, 2.97]
7 Pulmonary embolism	8	3475	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.08]
7.1 RCT	7	3208	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.29, 1.64]
7.2 Observational	1	267	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.75, 21.42]
8 Sepsis	7	3973	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.35]
8.1 RCT	6	3706	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.82, 1.34]
8.2 Observational	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.49, 3.63]
9 GI disorders_RCT	6	2475	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.63, 1.52]
10 Cardiac arrest or ventricular fibrillation_RCT	6	3755	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.38]
11 Hypertension_RCT	5	884	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
12 Heart rate and rhythm disorders_RCT	5	1672	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.20]
13 Respiratory Distress or insufficiency	5	3257	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 RCT	4	2990	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 0.99]
13.2 Observational	1	267	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.43, 1.89]
14 Pneumonia	5	1882	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.96, 1.80]
14.1 RCT	4	1615	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.96, 2.30]
14.2 Observational	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.72, 1.75]
15 Platelet, bleeding and clotting disorders	5	2794	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.71, 2.12]
15.1 RCT	4	2107	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.56, 1.98]
15.2 Observational	1	687	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.77, 7.06]
16 Seizure	5	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.01]
16.1 RCT	4	1494	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 0.98]
16.2 Observational	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.38, 2.24]
17 Cardiovascular disorders, general_RCT	4	2596	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.59]
18 Renal failure	4	1809	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.66, 1.59]
18.1 RCT	3	1542	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.52, 1.52]
18.2 Observational	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.66, 3.09]
19 Infection_RCT	4	698	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.74, 1.53]
20 Heart Failure_RCT	4	852	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.46]
21 Thrombocytosis	3	366	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.85, 6.48]
21.1 RCT	2	308	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.55, 7.10]
21.2 Observational	1	58	Risk Ratio (M-H, Fixed, 95% CI)	3.33 [0.61, 18.26]
22 Stent thrombosis_RCT	3	470	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.48, 4.96]
23 Dyspnea_RCT	2	2750	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.64, 1.56]
24 Abscess_RCT	3	2950	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.86, 2.36]
25 Multiple-organ failure_RCT	2	2750	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.52, 1.39]
26 Cerebrovascular event_RCT	2	1684	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.47, 1.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27 Urinary tract infection_RCT	2	240	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.02]
28 Vascular (extracardiac) disorders_RCT	2	1464	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.21]
29 Central and peripheral nervous system disorders_RCT	2	1490	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.15, 0.91]
30 Musculoskeletal_RCT	2	350	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.05, 1.98]
31 IRA revascularization_RCT	2	248	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [0.80, 7.63]
32 CABG_RCT	2	242	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.03, 1.92]
33 LV thrombus_RCT	2	273	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.33, 6.74]
34 Hyperglycemia_RCT	2	240	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.28, 3.54]
35 Ventriculitis_RCT	2	280	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.36, 2.71]
36 Metabolic/laboratory_RCT	2	362	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.51, 4.90]
37 Hypokalemia_RCT	2	235	Risk Ratio (M-H, Random, 95% CI)	3.40 [0.36, 32.04]
38 Hypotension_RCT	2	803	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.77, 1.80]
39 Neurology_RCT	2	765	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.42, 1.46]

Analysis 1.1. Comparison 1 ESAs versus placebo or no ESAs, Outcome 1 Any adverse event.

Analysis 1.2. Comparison 1 ESAs versus placebo or no ESAs, Outcome 2 Any serious adverse events_RCT.

Analysis 1.3. Comparison 1 ESAs versus placebo or no ESAs, Outcome 3 Venous thromboembolism (VTE).

Analysis 1.4. Comparison 1 ESAs versus placebo or no ESAs, Outcome 4 Deep Venous Thromboembolism.

Analysis 1.5. Comparison 1 ESAs versus placebo or no ESAs, Outcome 5 Stroke _ RCT.

Analysis 1.6. Comparison 1 ESAs versus placebo or no ESAs, Outcome 6 Myocardial infarction_RCT.

Analysis 1.7. Comparison 1 ESAs versus placebo or no ESAs, Outcome 7 Pulmonary embolism.

Analysis 1.8. Comparison 1 ESAs versus placebo or no ESAs, Outcome 8 Sepsis.

Analysis 1.9. Comparison 1 ESAs versus placebo or no ESAs, Outcome 9 GI disorders_RCT.

Analysis 1.10. Comparison 1 ESAs versus placebo or no ESAs, Outcome 10 Cardiac arrest or ventricular fibrillation_RCT.

Analysis 1.11. Comparison 1 ESAs versus placebo or no ESAs, Outcome 11 Hypertension_RCT.

Analysis 1.12. Comparison 1 ESAs versus placebo or no ESAs, Outcome 12 Heart rate and rhythm disorders_RCT.

Analysis 1.13. Comparison 1 ESAs versus placebo or no ESAs, Outcome 13 Respiratory Distress or insufficiency.

Analysis 1.14. Comparison 1 ESAs versus placebo or no ESAs, Outcome 14 Pneumonia.

Analysis 1.15. Comparison 1 ESAs versus placebo or no ESAs, Outcome 15 Platelet, bleeding and clotting disorders.

Analysis 1.16. Comparison 1 ESAs versus placebo or no ESAs, Outcome 16 Seizure.

Analysis 1.17. Comparison 1 ESAs versus placebo or no ESAs, Outcome 17 Cardiovascular disorders, general_RCT.

Analysis 1.18. Comparison 1 ESAs versus placebo or no ESAs, Outcome 18 Renal failure.

Analysis 1.19. Comparison 1 ESAs versus placebo or no ESAs, Outcome 19 Infection_RCT.

Analysis 1.20. Comparison 1 ESAs versus placebo or no ESAs, Outcome 20 Heart Failure_RCT.

Analysis 1.21. Comparison 1 ESAs versus placebo or no ESAs, Outcome 21 Thrombocytosis.

Analysis 1.22. Comparison 1 ESAs versus placebo or no ESAs, Outcome 22 Stent thrombosis_RCT.

Analysis 1.23. Comparison 1 ESAs versus placebo or no ESAs, Outcome 23 Dyspnea_RCT.

Analysis 1.24. Comparison 1 ESAs versus placebo or no ESAs, Outcome 24 Abscess_RCT.

Analysis 1.25. Comparison 1 ESAs versus placebo or no ESAs, Outcome 25 Multiple-organ failure_RCT.

Analysis 1.26. Comparison 1 ESAs versus placebo or no ESAs, Outcome 26 Cerebrovascular event_RCT.

Analysis 1.27. Comparison 1 ESAs versus placebo or no ESAs, Outcome 27 Urinary tract infection_RCT.

Analysis 1.28. Comparison 1 ESAs versus placebo or no ESAs, Outcome 28 Vascular (extracardiac) disorders_RCT.

Analysis 1.29. Comparison 1 ESAs versus placebo or no ESAs, Outcome 29 Central and peripheral nervous system disorders_RCT.

Analysis 1.30. Comparison 1 ESAs versus placebo or no ESAs, Outcome 30 Musculoskeletal_RCT.

Analysis 1.31. Comparison 1 ESAs versus placebo or no ESAs, Outcome 31 IRA revascularization_RCT.

Analysis 1.32. Comparison 1 ESAs versus placebo or no ESAs, Outcome 32 CABG_RCT.

Analysis 1.33. Comparison 1 ESAs versus placebo or no ESAs, Outcome 33 LV thrombus_RCT.

Analysis 1.34. Comparison 1 ESAs versus placebo or no ESAs, Outcome 34 Hyperglycemia_RCT.

Analysis 1.35. Comparison 1 ESAs versus placebo or no ESAs, Outcome 35 Ventriculitis_RCT.

Analysis 1.36. Comparison 1 ESAs versus placebo or no ESAs, Outcome 36 Metabolic/laboratory_RCT.

Analysis 1.37. Comparison 1 ESAs versus placebo or no ESAs, Outcome 37 Hypokalemia_RCT.

Analysis 1.38. Comparison 1 ESAs versus placebo or no ESAs, Outcome 38 Hypotension_RCT.

Analysis 1.39. Comparison 1 ESAs versus placebo or no ESAs, Outcome 39 Neurology_RCT.

Comparison 2. Subgroup analyses ESAs versus placebo or no ESAs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 mortality_trauma	34		Risk Ratio (Random, 95% CI)	0.80 [0.59, 1.09]
1.1 Trauma patients	10		Risk Ratio (Random, 95% CI)	0.57 [0.46, 0.71]
1.2 Non trauma patients	24		Risk Ratio (Random, 95% CI)	0.95 [0.69, 1.31]
2 Mortality_RCT_subgroup by ESAs type	32	6416	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.70, 0.92]
2.1 Epoetin alpha	24	5550	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.71, 0.93]
2.2 Epoetin beta	8	866	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.37, 1.15]
2.3 Darb	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Mortality_RCT_subgroup by dose	32	6416	Risk Ratio (IV, Random, 95% CI)	0.80 [0.70, 0.92]
3.1 More than 60,000 IU	20	4928	Risk Ratio (IV, Random, 95% CI)	0.82 [0.72, 0.94]
3.2 less or equivalent to 60,000 IU	12	1488	Risk Ratio (IV, Random, 95% CI)	0.63 [0.40, 0.98]
4 Mortality_Subgroup by ESAs effect	34		Risk Ratio (Random, 95% CI)	0.84 [0.62, 1.12]
4.1 observational studies_Hematopoietic effect of EPO	7		Risk Ratio (Random, 95% CI)	1.07 [0.65, 1.77]
4.2 Observational studies_Non-hematopoietic effect of EPO	2		Risk Ratio (Random, 95% CI)	0.66 [0.44, 0.99]
4.3 RCTs_Hematopoietic effect of EPO	17		Risk Ratio (Random, 95% CI)	0.81 [0.71, 0.93]
4.4 RCTs_Non-hematopoietic effect of EPO	8		Risk Ratio (Random, 95% CI)	0.64 [0.37, 1.10]
5 Mortality_Subgroup by ESAs effect1	34		Risk Ratio (Random, 95% CI)	0.84 [0.62, 1.12]
5.1 Hematopoietic effect of EPO	24		Risk Ratio (Random, 95% CI)	0.88 [0.64, 1.21]
5.2 Non-Hematopoietic effect of EPO	10		Risk Ratio (Random, 95% CI)	0.65 [0.48, 0.88]
6 Mortality_Subgroup by anaemia	34		Risk Ratio (Random, 95% CI)	0.84 [0.62, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 observational studies_patients with anemia	2		Risk Ratio (Random, 95% CI)	0.59 [0.17, 2.11]
6.2 Observational studies_patients without anemia	7		Risk Ratio (Random, 95% CI)	1.08 [0.66, 1.77]
6.3 RCTs_patients with anemia	16		Risk Ratio (Random, 95% CI)	0.81 [0.71, 0.93]
6.4 RCTs_patients without anemia	9		Risk Ratio (Random, 95% CI)	0.66 [0.39, 1.13]
7 Mortality_Subgroup by anaemia1	34		Risk Ratio (Random, 95% CI)	0.84 [0.62, 1.12]
7.1 patients with anemia	18		Risk Ratio (Random, 95% CI)	0.80 [0.70, 0.91]
7.2 patients without anemia	16		Risk Ratio (Random, 95% CI)	0.96 [0.63, 1.46]
8 Any adverse event_Subgroup by type of EPO	9	3099	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.05]
8.1 EPO alpha	7	2722	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.03]
8.2 EPO beta	1	110	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.51, 1.71]
8.3 DARB + EPO alpha	1	267	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.94, 1.60]
9 Any adverse event_Subgroup by dose of ESAs	9	3099	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.05]
9.1 More than 60,000IU	7	2767	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.98, 1.03]
9.2 Less or equivalent to 60,000 IU	2	332	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.92, 1.66]
10 Any adverse event_Subgroup by effect of ESAs	9	3099	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.05]
10.1 Haematopoietic effect of EPO	7	2767	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.98, 1.03]
10.2 Non-Haematopoietic effect of EPO	2	332	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.92, 1.66]
11 Any adverse event_Subgroup by anaemia	9	3099	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.05]
11.1 Patients with anemia	6	2727	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.98, 1.03]
11.2 Patients without anemia	3	372	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.97, 1.59]
12 Any SAEs_Subgroup by type of ESAs	10	4183	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.11]
12.1 EPO alpha	7	3848	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 EPO beta	3	335	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.56, 2.95]
13 Any SAEs_Subgroup by dose of ESAs	10	4183	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.11]
13.1 More than 60,000 IU	7	3397	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.08]
13.2 Less or equivalent to 60,000	3	786	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.44, 2.98]
14 Any SAEs_Subgroup by effect of ESAs	10	4183	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.11]
14.1 Haematopoietic effect of EPO	6	3259	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]
14.2 Non- haematopoietic effect of EPO	4	924	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.62, 3.00]
15 Any SAEs_Subgroup by anaemia	10	4183	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.11]
15.1 Patients with anemia	6	3259	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]
15.2 Patients without anemia	4	924	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.62, 3.00]
16 VTE_Subgroup by type of ESAs	18	18917	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.75, 2.11]
16.1 EPO alpha	14	18335	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.73, 2.32]
16.2 EPO beta	2	242	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.18, 2.11]
16.3 DARB + EPO alpha	2	340	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.35, 6.20]
17 VTE_Subgroup by dose of ESAs_RCTs	13	4954	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.90, 1.40]
17.1 More than 60,000 IU	10	4331	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.87, 1.45]
17.2 Less or equivalent to 60,000 IU	3	623	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.30, 2.82]
18 VTE_Subgroup by effect of ESAs	18	18917	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.75, 2.11]
18.1 Haematopoietic effect of EPO	16	18308	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.77, 2.18]
18.2 Non- Haematopoietic effect of EPO	2	609	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.24]
19 VTE_Subgroup by anaemia	18	18917	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.75, 2.11]
19.1 Patients with anemia	12	4645	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.90, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Patients without anemia	6	14272	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.52, 7.24]
20 Stroke _ Subgroup by type of ESAs	11	2229	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.58, 4.29]
20.1 EPO alpha	8	1930	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.50, 4.18]
20.2 EPO beta	3	299	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 74.48]
21 Stroke _ Subgroup by dose of ESAs	11	2229	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.58, 4.29]
21.1 More than 60,000 IU	6	1233	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.41, 5.01]
21.2 Less or equivalent to 60,000 IU	5	996	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.34, 10.06]
22 Stroke _ Subgroup by effect of ESAs	11	2229	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.46, 4.71]
22.1 Haematopoietic effect of EPO	6	1260	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.21, 10.56]
22.2 Non-Haematopoietic effect of EPO	5	969	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.31, 10.22]
23 Stroke _ Subgroup by anaemia	11	2229	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.46, 4.71]
23.1 Patients with anemia	4	1043	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.06, 25.96]
23.2 Patients without anemia	7	1186	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.44, 9.36]
24 MI_Subgroup by type of ESAs	10	3254	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.84, 2.97]
24.1 EPO alpha	6	2608	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.97, 4.44]
24.2 EPO beta	4	646	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.26, 2.71]
25 MI_Subgroup by dose of ESAs	10	3254	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.84, 2.97]
25.1 More than 60,000 IU	6	2629	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.73, 3.67]
25.2 Less or equivalent to 60,000 IU	4	625	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.36, 4.23]
26 MI_Subgroup by effect of ESAs	10	3254	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.84, 2.97]
26.1 Haematopoietic effect of EPO	5	2491	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.44, 3.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 Non- Haematopoietic effect of EPO	5	763	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.51, 4.50]
27 MI_Subgroup by anaemia	10	3254	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.84, 2.97]
27.1 Patients with anemia	5	2491	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.44, 3.70]
27.2 Patients without anemia	5	763	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.51, 4.50]
28 DVT_Subgroup by type of ESAs	13	5141	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
28.1 EPO alpha	11	4712	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.94, 1.45]
28.2 EPO beta	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.07, 1.86]
28.3 DARB + EPO alpha	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.34, 6.56]
29 DVT_Subgroup by dose of ESAs	13	5141	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
29.1 More than 60,000 IU	10	4518	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.92, 1.43]
29.2 Less or equivalent to 60,000 IU	3	623	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.59]
30 DVT_Subgroup by effect of ESAs	13	5141	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
30.1 Haematopoietic effect of EPO	12	4612	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
30.2 Non- haematopoietic effect of EPO	1	529	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 DVT_Subgroup by anaemia	12	5125	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.94, 1.43]
31.1 Patients with anemia	10	4556	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.42]
31.2 Patients without anemia	2	569	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [0.38, 29.23]
32 PE_Subgroup by type of ESAs	8	3475	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.08]
32.1 EPO alpha	6	3046	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.27, 1.73]
32.2 EPO beta	1	162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.06, 14.59]
32.3 DARB + EPO alpha	1	267	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.75, 21.42]
33 PE_Subgroup by dose of ESAs	8	3475	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.08]
33.1 More than 60,000 IU	6	2868	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.32, 2.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.2 Less or equivalent to 60,000 IU	2	607	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.21, 4.35]
34 PE_Subgroup by effect of ESAs	8	3475	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.08]
34.1 Haematopoietic effect of EPO	7	2946	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.33]
34.2 Non- Haematopoietic effect of EPO	1	529	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.24]
35 PE_Subgroup by anaemia	8	3475	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.08]
35.1 Patients with anemia	7	2946	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.33]
35.2 Patients without anemia	1	529	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.24]
36 Sepsis_Subgroup by type of ESAs	7	3973	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.35]
36.1 EPO alpha	5	3626	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.76, 1.30]
36.2 EPO beta	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.84, 2.69]
36.3 DARB + EPO alpha	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.49, 3.63]
37 Sepsis_Subgroup by effect of ESAs	7	3973	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.35]
37.1 Haematopoietic effect of EPO	6	3893	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.32]
37.2 Non-Haematopoietic effect of EPO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.84, 2.69]
38 Sepsis_Subgroup by anaemia	7	3973	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.35]
38.1 Patients with anemia	6	3893	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.32]
38.2 Patients without anemia	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.84, 2.69]
39 GI disorders_Subgroup by type of ESAs	6	2475	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.60, 1.80]
39.1 EPO alpha	4	2293	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.46, 1.70]
39.2 EPO beta	1	162	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.58, 5.92]
39.3 DARB	1	20	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.14, 65.90]
40 GI disorders_Subgroup by effect of ESAs	6	2475	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.60, 1.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Haematopoietic effect of EPO	5	2455	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.56, 1.86]
40.2 Non- Haematopoietic effect of EPO	1	20	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.14, 65.90]
41 Cardiac arrest_Subgroup by type of ESAs	6	3755	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.38]
41.1 EPO alpha	5	3593	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.70, 1.48]
41.2 EPO beta	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.53]
42 Hypertension_Subgroup by type of ESAs	5	884	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
42.1 EPO alpha	4	722	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.18, 6.29]
42.2 EPO beta	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.13, 6.43]
43 Hypertension_Subgroup by dose of ESAs	5	884	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
43.1 More than 60,000 IU	4	355	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
43.2 Less or equivalent to 60,000 IU	1	529	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
44 Hypertension_Subgroup by effect of ESAs	5	884	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
44.1 Haematopoietic effect of EPO	3	275	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
44.2 Non- Haematopoietic effect of EPO	2	609	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
45 Hypertension_Subgroup by anaemia	5	884	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
45.1 Patients with anemia	2	235	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.22, 4.33]
45.2 Patients without anemia	3	649	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.07, 16.47]
46 Heart rate_Subgroup by type of ESAs	5	1672	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.20]
46.1 EPO alpha	4	1510	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.42]
46.2 EPO beta	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.14, 1.05]
47 Heart rate_Subgroup by effect of ESAs	5	1672	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.1 Haematopoietic effect of EPO	4	1652	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.16]
47.2 Non- Haematopoietic effect of EPO	1	20	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.27, 92.62]
48 Heart rate_Subgroup by anaemia	5	1672	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.20]
48.1 Patients with anemia	3	1612	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.52, 1.11]
48.2 Patients without anemia	2	60	Risk Ratio (M-H, Fixed, 95% CI)	5.24 [0.65, 42.12]
49 Respiratory Distress_Subgroup by anaemia	5	3257	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 1.00]
49.1 Patients with anemia	4	3217	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.99]
49.2 Patients without anemia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.3 [0.14, 76.46]
50 Seizure_Subgroup by type of ESAs	5	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.01]
50.1 EPO alpha	4	1390	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.43, 1.09]
50.2 EPO beta	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.03, 2.03]
51 Seizure_Subgroup by dose of ESAs	5	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.01]
51.1 More than 60,000 IU	4	1023	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.01]
51.2 Less or equivalent to 60,000 IU	1	529	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
52 Seizure_Subgroup by effect of ESAs	5	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.01]
52.1 Haematopoietic effect of EPO	3	965	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 0.98]
52.2 Non-Haematopoietic effect of EPO	2	587	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.38, 2.24]
53 Seizure_Subgroup by anaemia	5	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.01]
53.1 Patients with anemia	3	965	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 0.98]
53.2 Patients without anemia	2	587	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.38, 2.24]
54 Cardiovascular disorders_Subgroup by dose of ESAs	4	2596	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.59]
54.1 More than 60,000 IU	3	2067	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.59, 2.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54.2 Less or equivalent to 60,000 IU	1	529	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.19, 0.96]
55 Cardiovascular disorders_Subgroup by effect of ESAs	4	2596	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.59]
55.1 Haematopoietic effect of EPO	3	2067	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.59, 2.03]
55.2 Non- Haematopoietic effect of EPO	1	529	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.19, 0.96]
56 Cardiovascular disorders_Subgroup by anaemia	4	2596	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.59]
56.1 Patients with anemia	3	2067	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.59, 2.03]
56.2 Patients without anemia	1	529	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.19, 0.96]
57 Heart Failure_Subgroup by type of ESAs	4	852	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.46]
57.1 EPO alpha	2	580	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.03, 0.78]
57.2 EPO beta	2	272	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.19, 11.89]
58 Heart Failure_Subgroup by dose of ESAs	4	852	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.46]
58.1 More than 60,000 IU	1	162	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.12, 67.45]
58.2 Less or equivalent to 60,000 IU	3	690	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.06, 1.01]
59 Heart Failure_Subgroup by effect of ESAs	4	852	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.46]
59.1 Haematopoietic effect of EPO	1	162	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.12, 67.45]
59.2 Non-Haematopoietic effect of EPO	3	690	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.06, 1.01]
60 Heart Failure_Subgroup by anaemia	4	852	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.46]
60.1 Patients with anemia	1	162	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.12, 67.45]
60.2 Patients without anemia	3	690	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.06, 1.01]

Analysis 2.1. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 1 mortality_trauma.

Analysis 2.2. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 2 Mortality_RCT_subgroup by ESAs type.

Analysis 2.3. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 3 Mortality_RCT_subgroup by dose.

Analysis 2.4. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 4 Mortality_Subgroup by ESAs effect.

Analysis 2.5. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 5 Mortality_Subgroup by ESAs effect1.

Analysis 2.6. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 6 Mortality_Subgroup by anaemia.

Analysis 2.7. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 7 Mortality_Subgroup by anaemia1.

Analysis 2.8. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 8 Any adverse event_Subgroup by type of EPO.

Analysis 2.9. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 9 Any adverse event_Subgroup by dose of ESAs.

Analysis 2.10. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 10 Any adverse event_Subgroup by effect of ESAs.

Analysis 2.11. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 11 Any adverse event_Subgroup by anaemia.

Analysis 2.12. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 12 Any SAEs_Subgroup by type of ESAs.

Analysis 2.13. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 13 Any SAEs_Subgroup by dose of ESAs.

Analysis 2.14. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 14 Any SAEs_Subgroup by effect of ESAs.

Analysis 2.15. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 15 Any SAEs_Subgroup by anaemia.

Analysis 2.16. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 16 VTE_Subgroup by type of ESAs.

Analysis 2.17. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 17 VTE_Subgroup by dose of ESAs_RCTs.

Analysis 2.18. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 18 VTE_Subgroup by effect of ESAs.

Analysis 2.19. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 19 VTE_Subgroup by anaemia.

Analysis 2.20. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 20 Stroke _ Subgroup by type of ESAs.

Analysis 2.21. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 21 Stroke _ Subgroup by dose of ESAs.

Analysis 2.22. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 22 Stroke _ Subgroup by effect of ESAs.

Analysis 2.23. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 23 Stroke _ Subgroup by anaemia.

Analysis 2.24. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 24 MI_Subgroup by type of ESAs.

Analysis 2.25. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 25 MI_Subgroup by dose of ESAs.

Analysis 2.26. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 26 MI_Subgroup by effect of ESAs.

Analysis 2.27. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 27 MI_Subgroup by anaemia.

Analysis 2.28. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 28 DVT_Subgroup by type of ESAs.

Analysis 2.29. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 29 DVT_Subgroup by dose of ESAs.

Analysis 2.30. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 30 DVT_Subgroup by effect of ESAs.

Analysis 2.31. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 31 DVT_Subgroup by anaemia.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI			
Heterogeneity: Tau²=0; Chi²=10.39, df=10(P=0.41); I²=3.74%								
Test for overall effect: Z=1.38(P=0.17)								
Test for subgroup differences: Chi²=0.91, df=1 (P=0.34), I²=0%								
		Favours ESAs	0.01	0.1	1	10	100	Favours control

Analysis 2.32. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 32 PE_Subgroup by type of ESAs.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI				
2.32.1 EPO alpha									
Corwin 2007a	16/728	12/720		19.75%	1.32[0.63,2.77]				
Gerasimov 2012	3/42	2/36		12.04%	1.29[0.23,7.27]				
Luchette 2012	1/96	2/92		8.44%	0.48[0.04,5.19]				
Nichol 2015	13/305	54/298		20.89%	0.24[0.13,0.42]				
Robertson 2014	4/102	3/98		13.9%	1.28[0.29,5.58]				
Voors 2010	0/263	1/266		5.61%	0.34[0.01,8.24]				
Subtotal (95% CI)	1536	1510		80.63%	0.68[0.27,1.73]				
Total events: 37 (ESAs), 74 (Control)									
Heterogeneity: Tau ² =0.76; Chi ² =15.8, df=5(P=0.01); I ² =68.36%									
Test for overall effect: Z=0.81(P=0.42)									
2.32.2 EPO beta									
Endre 2010	1/84	1/78		6.96%	0.93[0.06,14.59]				
Subtotal (95% CI)	84	78		6.96%	0.93[0.06,14.59]				
Total events: 1 (ESAs), 1 (Control)									
Heterogeneity: Not applicable									
Test for overall effect: Z=0.05(P=0.96)									
2.32.3 DARB + EPO alpha									
Talving 2010	4/89	2/178		12.41%	4[0.75,21.42]				
Subtotal (95% CI)	89	178		12.41%	4[0.75,21.42]				
Total events: 4 (ESAs), 2 (Control)									
Heterogeneity: Not applicable									
Test for overall effect: Z=1.62(P=0.11)									
Total (95% CI)	1709	1766		100%	0.87[0.36,2.08]				
Total events: 42 (ESAs), 77 (Control)									
Heterogeneity: Tau ² =0.85; Chi ² =21.24, df=7(P=0); I ² =67.04%									
Test for overall effect: Z=0.31(P=0.75)									
Test for subgroup differences: Chi ² =3.27, df=1 (P=0.19), I ² =38.86%									
			Favours ESAs	0.01	0.1	1	10	100	Favours control

Analysis 2.33. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 33 PE_Subgroup by dose of ESAs.

Analysis 2.34. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 34 PE_Subgroup by effect of ESAs.

Analysis 2.35. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 35 PE_Subgroup by anaemia.

Analysis 2.36. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 36 Sepsis_Subgroup by type of ESAs.

Analysis 2.37. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 37 Sepsis_Subgroup by effect of ESAs.

Analysis 2.38. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 38 Sepsis_Subgroup by anaemia.

Analysis 2.39. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 39 GI disorders_Subgroup by type of ESAs.

Analysis 2.40. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 40 GI disorders_Subgroup by effect of ESAs.

Analysis 2.41. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 41 Cardiac arrest _Subgroup by type of ESAs.

Analysis 2.42. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 42 Hypertension_Subgroup by type of ESAs.

Analysis 2.43. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 43 Hypertension_Subgroup by dose of ESAs.

Analysis 2.44. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 44 Hypertension_Subgroup by effect of ESAs.

Analysis 2.45. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 45 Hypertension_Subgroup by anaemia.

Analysis 2.46. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 46 Heart rate_Subgroup by type of ESAs.

Analysis 2.47. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 47 Heart rate_Subgroup by effect of ESAs.

Analysis 2.48. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 48 Heart rate_Subgroup by anaemia.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI					Weight	Risk Ratio M-H, Fixed, 95% CI	
Total events: 49 (ESAs), 56 (Control)										
Heterogeneity: Tau²=0; Chi²=5.45, df=4(P=0.24); I²=26.67%										
Test for overall effect: Z=0.98(P=0.32)										
Test for subgroup differences: Chi²=3.21, df=1 (P=0.07), I²=68.84%										
			Favours ESAs	0.01	0.1	1	10	100	Favours control	

Analysis 2.49. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 49 Respiratory Distress_Subgroup by anaemia.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI				
2.49.1 Patients with anemia									
Corwin 2002	28/650	39/652		35.62%	0.72[0.45,1.16]				
Corwin 2007a	20/728	37/720		34.03%	0.53[0.31,0.91]				
Robertson 2014	22/102	19/98		17.73%	1.11[0.64,1.92]				
Talving 2010	9/89	20/178		12.2%	0.9[0.43,1.89]				
Subtotal (95% CI)	1569	1648		99.56%	0.75[0.57,0.99]				
Total events: 79 (ESAs), 115 (Control)									
Heterogeneity: Tau ² =0; Chi ² =3.8, df=3(P=0.28); I ² =20.99%									
Test for overall effect: Z=2.07(P=0.04)									
2.49.2 Patients without anemia									
Still 1995	1/19	0/21		0.44%	3.3[0.14,76.46]				
Subtotal (95% CI)	19	21		0.44%	3.3[0.14,76.46]				
Total events: 1 (ESAs), 0 (Control)									
Heterogeneity: Not applicable									
Test for overall effect: Z=0.74(P=0.46)									
Total (95% CI)	1588	1669		100%	0.76[0.58,1]				
Total events: 80 (ESAs), 115 (Control)									
Heterogeneity: Tau ² =0; Chi ² =4.61, df=4(P=0.33); I ² =13.29%									
Test for overall effect: Z=1.97(P=0.05)									
Test for subgroup differences: Chi ² =0.85, df=1 (P=0.36), I ² =0%									
			Favours ESAs	0.01	0.1	1	10	100	Favours control

Analysis 2.50. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 50 Seizure_Subgroup by type of ESAs.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI				
2.50.1 EPO alpha									
Cariou 2008	5/18	12/40		17.32%	0.93[0.38,2.24]				
Nichol 2015	14/305	26/298		61.17%	0.53[0.28,0.99]				
Robertson 2014	6/102	5/98		11.86%	1.15[0.36,3.66]				
Voors 2010	0/263	0/266			Not estimable				
Subtotal (95% CI)	688	702		90.35%	0.69[0.43,1.09]				
Total events: 25 (ESAs), 43 (Control)									
			Favours ESAs	0.01	0.1	1	10	100	Favours control

Analysis 2.51. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 51 Seizure_Subgroup by dose of ESAs.

Analysis 2.52. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 52 Seizure_Subgroup by effect of ESAs.

Analysis 2.53. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 53 Seizure_Subgroup by anaemia.

Analysis 2.54. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 54 Cardiovascular disorders_Subgroup by dose of ESAs.

Analysis 2.55. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 55 Cardiovascular disorders_Subgroup by effect of ESAs.

Analysis 2.56. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 56 Cardiovascular disorders_Subgroup by anaemia.

Analysis 2.57. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 57 Heart Failure_Subgroup by type of ESAs.

Analysis 2.58. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 58 Heart Failure_Subgroup by dose of ESAs.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=1.42(P=0.16)$					
Test for subgroup differences: $\text{Chi}^2=1.9, \text{df}=1 (P=0.17), I^2=47.26\%$					
Favours ESAs 0.01 0.1 1 10 100 Favours control					

Analysis 2.59. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 59 Heart Failure_Subgroup by effect of ESAs.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.59.1 Haematopoietic effect of EPO					
Endre 2010	1/84	0/78		17.59%	2.79[0.12,67.45]
Subtotal (95% CI)	84	78		17.59%	2.79[0.12,67.45]
Total events: 1 (ESAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.63(P=0.53)$					
2.59.2 Non-Haematopoietic effect of EPO					
Liem 2009	0/26	3/25		20.82%	0.14[0.01,2.53]
Prunier 2012	1/57	1/53		23.26%	0.93[0.06,14.49]
Voors 2010	1/263	7/266		38.34%	0.14[0.02,1.17]
Subtotal (95% CI)	346	344		82.41%	0.24[0.06,1.01]
Total events: 2 (ESAs), 11 (Control)					
Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=1.33, \text{df}=2(P=0.52); I^2=0\%$					
Test for overall effect: $Z=1.94(P=0.05)$					
Total (95% CI)	430	422		100%	0.37[0.09,1.46]
Total events: 3 (ESAs), 11 (Control)					
Heterogeneity: $\text{Tau}^2=0.14; \text{Chi}^2=3.23, \text{df}=3(P=0.36); I^2=7.04\%$					
Test for overall effect: $Z=1.42(P=0.16)$					
Test for subgroup differences: $\text{Chi}^2=1.9, \text{df}=1 (P=0.17), I^2=47.26\%$					
Favours ESAs 0.01 0.1 1 10 100 Favours control					

Analysis 2.60. Comparison 2 Subgroup analyses ESAs versus placebo or no ESAs, Outcome 60 Heart Failure_Subgroup by anaemia.

Study or subgroup	ESAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.60.1 Patients with anemia					
Endre 2010	1/84	0/78		17.59%	2.79[0.12,67.45]
Subtotal (95% CI)	84	78		17.59%	2.79[0.12,67.45]
Total events: 1 (ESAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.63(P=0.53)$					
2.60.2 Patients without anemia					
Liem 2009	0/26	3/25		20.82%	0.14[0.01,2.53]
Prunier 2012	1/57	1/53		23.26%	0.93[0.06,14.49]
Favours ESAs 0.01 0.1 1 10 100 Favours control

ADDITIONAL TABLES

Table 1. Risk of bias assessment for 14 cohort studies

Study	Selection	Comparability	Outcome
Brophy 2007	***	-	***
Bush 2008	***	-	*
Cariou 2008	****	*	**
Chen 2008	****	-	-
Ginger 2008	****	*	**
Grmec 2009	***	**	**
Hecht 2007	****	-	**
Kane-Gill 2007	****	**	**
Kashkouli 2011	****	-	*
Luh 2005	**	**	**
Lundy 2010	****	-	*
Shuman 2009	***	-	*
Talving 2010	****	**	***
Wittbrodt 2005	***	-	*

Note: A study can be rated a maximum of four, three and two stars for “Selection”, “Outcome” and “Comparability” categories, respectively.

Table 2. Risk of adverse events associated with ESAs use in critical ill patients reported in single studies

Adverse events	No. of participants	Control group risk (%)	Risk Ratio (95% CI) ^a
Constipation (Vincent 2006)	73	0.0	13.27 (0.82 to 215.20)
Reaction at the site of injection (Kateros 2010)	79	0.0	11.85 (0.68 to 207.28)
Diarrhoea (Vincent 2006)	73	0.0	12.20 (0.75 to 198.93)
Dermatology/skin ^b (Endre 2010)	162	0.0	6.51 (0.34 to 123.97)
Pneumocephalus (Robertson 2014)	200	0.0	4.81 (0.23 to 98.85)
Chronic subdural haematoma (Robertson 2014)	200	0.0	4.81 (0.23 to 98.85)
Ischaemic (Endre 2010)	162	0.0	4.65 (0.23 to 95.31)
Unstaged PCI (Najjar 2011)	222	0.0	3.89 (0.19 to 80.08)
Transfusion reaction (Kateros 2010)	79	0.0	3.23 (0.14 to 76.98)
Confusion (Still 1995)	40	0.0	3.30 (0.14 to 76.46)
Oedema (Still 1995)	40	0.0	3.30 (0.14 to 76.46)
Rash (Still 1995)	40	0.0	3.30 (0.14 to 76.46)
Blood in stool (Still 1995)	40	0.0	3.30 (0.14 to 76.46)
Decreased urine output (Still 1995)	40	0.0	3.30 (0.14 to 76.46)
Carotid cavernous fistula (Robertson 2014)	200	0.0	2.88 (0.12 to 69.94)
Haemothorax (Robertson 2014)	200	0.0	2.88 (0.12 to 69.94)
Unplanned revascularization (Ludman 2011)	51	0.0	2.89 (0.12 to 67.75)
Emergency admission to hospital (Ludman 2011)	51	4.0	4.81 (0.60 to 38.32)
Airway obstruction requiring re-intubation (Robertson 2014)	200	1.0	3.84 (0.44 to 33.78)
Subgaleal fluid collection (Robertson 2014)	200	1.0	0.96 (0.06 to 15.15)
Additional elective PCI (Lipsic 2006)	20	10.0	1.00 (0.07 to 13.87)
Thrombocytopenia (Corwin 1999)	160	3.8	3.00 (0.84 to 10.68)
Cardiovascular complications (Robertson 2014)	200	3.1	2.88 (0.80 to 10.33)
Hydrocephalus (Robertson 2014)	200	2.0	1.92 (0.36 to 10.25)
New or worsening CHF (Najjar 2011)	222	2.1	1.94 (0.38 to 9.79)
Emergency re-PCI for unstable angina (Voors 2010)	529	0.8	1.52 (0.26 to 9.01)

Table 2. Risk of adverse events associated with ESAs use in critical ill patients reported in single studies (Continued)

Dizziness (Kang 2012)	60	5.3	0.93 (0.09 to 9.60)
Headache (Kang 2012)	60	5.3	0.93 (0.09 to 9.60)
Fever (Kang 2012)	60	5.3	0.93 (0.09 to 9.60)
CSF leak (Robertson 2014)	200	2.0	1.44 (0.25 to 8.44)
Vaginal infection/thrush (Still 1995)	40	4.8	0.37 (0.02 to 8.50)
Agitation (Still 1995)	40	4.8	0.37 (0.02 to 8.50)
Syndromes ^b (Endre 2010)	162	1.3	0.31 (0.01 to 7.49)
Respiratory failure (Luchette 2012)	188	2.2	0.96 (0.14 to 6.66)
Planned revascularization (Ludman 2011)	51	8.0	0.96 (0.15 to 6.31)
Recurrent acute coronary syndrome (re-ACS) (Liem 2009)	51	8.0	0.96 (0.15 to 6.31)
Other (Nichol 2015)	603	1.3	1.22 (0.33 to 4.50)
Metabolic complications (excluding Diabetes insipidus and severe hyperglycaemia) (Robertson 2014)	200	3.1	0.96 (0.20 to 4.65)
Blood/bone marrow ^b (Endre 2010)	162	15.4	1.39 (0.72 to 2.70)
Death (other) ^b (Endre 2010)	162	9.0	1.19 (0.47 to 3.05)
Immediate postoperative deficits (Tseng 2009)	80	20.0	1.25 (0.55 to 2.84)
Myalgia or bone pain (Kang 2012)	60	15.8	0.93 (0.26 to 3.32)
Clinically relevant thrombotic vascular event ^c (Corwin 2007a)	1448	11.5	1.43 (1.10 to 1.85)
Atelectasis (Robertson 2014)	200	20.4	1.35 (0.81 to 2.22)
Renal/genitourinary ^b (Endre 2010)	162	3.8	0.62 (0.11 to 3.61)
Pulmonary/upper respiratory ^b (Endre 2010)	162	14.1	1.18 (0.57 to 2.45)
Postprocedural haemorrhage (Luchette 2012)	188	2.2	0.19 (0.01 to 3.94)
Urinary system disorders (Corwin 2002)	1302	3.2	1.19 (0.68 to 2.11)
CNS disorders (new ischaemics or haemorrhagic stroke) (Georgopoulos 2005)	148	6.3	0.63 (0.13 to 2.91)
Acid-base abnormalities (Robertson 2014)	200	8.2	0.84 (0.32 to 2.23)
Bacteraemia (Robertson 2014)	200	3.1	0.32 (0.03 to 3.03)

Table 2. Risk of adverse events associated with ESAs use in critical ill patients reported in single studies (Continued)

Delayed/recurrent intracranial haematoma (Robertson 2014)	200	29.6	1.06 (0.70 to 1.61)
Resistance mechanism disorders (Corwin 2002)	1302	6.6	1.05 (0.70 to 1.57)
Pain ^b (Endre 2010)	162	3.8	0.31 (0.03 to 2.91)
Respiratory system disorders (Corwin 2002)	1302	14.0	1.05 (0.80 to 1.37)
Respiratory, thoracic, and mediastinal disorders (Luchette 2012)	188	5.4	0.57 (0.14 to 2.34)
Brain tissue hypoxia (Robertson 2014)	200	29.6	0.93 (0.60 to 1.44)
Anaemia (Robertson 2014)	200	44.9	0.93 (0.74 to 1.17)
Electrolyte disturbances (Robertson 2014)	200	4.7	0.88 (0.61 to 1.28)
Sexual dysfunction (Alibai 2014)	30	60.0	0.78 (0.39 to 1.54)
Intracranial hypertension requiring second or third tier therapy (Robertson 2014)	200	43.9	0.87 (0.62 to 1.22)
Superficial venous thrombosis (Endre 2010)	162	3.8	0.13 (0.01 to 2.53)
Sphincter dysfunction (Alibai 2014)	30	93.3	0.86 (0.64 to 1.14)
Pneumothorax (Robertson 2014)	200	7.1	0.55 (0.17 to 1.82)
Injury, poisoning, and procedural complications (Luchette 2012)	188	6.5	0.48 (0.12 to 1.86)
Haematological complications (excluding anaemia) (Robertson 2014)	200	44.9	0.79 (0.56 to 1.11)
General disorders (Corwin 2002)	1302	4.0	0.73 (0.41 to 1.31)
Atrial fibrillation (Endre 2010)	162	7.7	0.46 (0.12 to 1.79)
Upper limb thrombosis (Nichol 2015)	603	8.4	0.51 (0.26 to 0.97)
Emergency re-PCI for In-stent thrombosis/re-infarction (Voors 2010)	529	2.6	0.29 (0.06 to 1.38)
Pleural effusion (Robertson 2014)	200	7.1	0.27 (0.06 to 1.29)
Diabetes insipidus (Robertson 2014)	200	9.2	0.32 (0.09 to 1.15)
Major cardiovascular event (Ferrario 2011)	30	0.0	Not estimable
Cancer (Ferrario 2011)	30	0.0	Not estimable

^aIf number of events in one group was zero, 0.5 was added to each cell of 2×2 table to calculate RR and a 95% CI.

^bA category described in CTCAE v3.0 ([Endre 2010](#)).

^c"Clinically relevant thrombotic vascular event" refers to PE, DVT, Cerebrovascular events, MI, Cardiac arrest or ventricular fibrillation ([Corwin 2007a](#)).

APPENDICES

Appendix 1. Detailed search strategy in databases

Search strategy in OvidSP MEDLINE

1 critical care. kw,tw,ti,ot.

2 life support care*.af.

3 (critical* adj ill*).af.

4 (icu or icus).kw,tw,ti,ot.

5 intensive care*.kw,tw,ti,ot,sh.

6 (ventilat*or Respirat* or Artificial).af.

7 exp Respiration, Artificial/

8 acute care facilit*.af.

9 (thermal injur* or burn* or trauma or resuscitation*).kw,tw,ti,ot,sh.

10 ((APACHE or intensive) adj2 score*).af.

11 exp Heart Arrest/dt, th or exp Acute Coronary Syndrome/dt, th or *Myocardial Infarction/dt, th or exp Brain Injuries/dt, th or exp Ventricular Dysfunction, Left/dt, th or exp Ischemia/dt, th or exp Brain Infarction/dt, th or exp Vasospasm, Intracranial/dt, th or exp Intracranial Aneurysm /dt, th or exp Brain Ischemia/dt, th or exp Subarachnoid Hemorrhage/dt, th or exp Myocardial Ischemia/dt, th or exp Cerebral Hemorrhage/dt, th or exp Stroke/dt, th

12 (erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*).af.

13 (r adj HuEPO).af.

14 (Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoade or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop).kw,tw,nm,ti,ot.

15 (Receptors, Erythropoietin or Erythropoiesis).sh.

16 (HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697).af.

17 (113427-24-0 or 11096-26-7 or 209810-58-2 or 122312-54-3 or 261356-80-3 or 604802-70-2 or 130455-76-4 or 148363-16-0 or 154725-65-2 or 879555-13-2).rn.

18 or/1-11

19 or/12-17

20 18 and 19

Search strategy in OvidSP Embase

1 critical care. kw,tw,ti,ot.

2 life support care*.af.

3 (critical* adj ill*).af.

4 (icu or icus).kw,tw,ti,ot.

5 (intensive adj2 care*).kw,tw,ti,ot.

6 intensive care*. sh.

7 exp artificial ventilation/

8 acute care facilit*.af.

9 (thermal injur* or burn* or trauma or resuscitation*).kw,tw,ti,ot,sh.

10 ((APACHE or intensive) adj2 score*).af.

11 exp heart arrest/dt, th or exp ST segment elevation myocardial infarction/dt, th or exp acute heart infarction/dt, th or exp brain infarction/dt, th or exp brain vasospasm/dt, th or exp brain artery aneurysm/dt, th or exp brain ischemia/dt, th or exp subarachnoid hemorrhage/dt, th or exp brain injury/dt, th or exp cerebrovascular accident/dt, th or exp stroke patient/

12 (erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*).af.

13 (r adj HuEPO).af.

14 (Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoad or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop).kw,tw,tn,ti,ot.

15 exp erythropoietin/ or exp recombinant erythropoietin/ or exp erythropoietin receptor/ or exp novel erythropoiesis stimulating protein/

16 (HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697).af.

17 (113427-24-0 or 11096-26-7 or 209810-58-2 or 122312-54-3 or 261356-80-3 or 604802-70-2 or 130455-76-4 or 148363-16-0 or 154725-65-2 or 879555-13-2).rn.

18 or/1-11

19 or/12-17

20 19 and 20

Search strategy in OvidSP All EBM reviews

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 2012, # EBM Reviews - ACP Journal Club 1991 to March 2012, # EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2012, # EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2012, # EBM Reviews - Cochrane Methodology Register 1st Quarter 2012, # EBM Reviews - Health Technology Assessment 1st Quarter 2012, # EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2012

1 ((critical or intensive) adj2 care*).ab,cm,ct,hw,ti,to,tw.

2 life support care*.af.

3 (critical* adj ill*).af.

4 (icu or icus).ab,cm,ct,ti,to,tw.

5 (ventilat* or Respirat* or Artificial).ab,cm,ct,hw,ti,to,tw.

Harms of off-label erythropoiesis-stimulating agents for critically ill people (Review)

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6 (thermal injur* or burn* or trauma or resuscitation*).ab,cm,ct,hw,ti,to,tw.

7 ((APACHE or intensive) adj2 score*).af.

8 ((Wounds and Injuries) or APACHE).hw.

9 (Brain Ischemia or Brain Injuries or Myocardial Infarction or Stroke or Subarachnoid Hemorrhage or Acute Coronary Syndrome or Ischemia).sh.

10 (erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hemoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*).af.

11 (r adj HuEPO).af.

12 (Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoad or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoietina or Eritropoietina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemopex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop).ab,cm,ct,ti,to,tw.

13 (erythropoietin or Epoetin Alfa or Erythroipoiesis).hw.

14 (HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697).af.

15 or/1-9

16 or/10-14

17 15 and 16

Search strategy in OvidSP International Pharmaceutical Abstracts

1 ((critical or intensive) adj2 care*).ti,ab,hw.

2 life support care*.af.

3 (critical* adj ill*).af.

4 (icu or icus).ti,ab,hw.

5 (ventilat* or Respirat* or Artificial).af.

6 acute care facilit*.af.

7 (thermal injur* or burn* or trauma or resuscitation*).af.

8 ((APACHE or intensive) adj2 score*).af.

9 (\$Cerebral Hemorrhage* or Subarachnoid Hemorrhag* or Acute Coronary Syndrome or heart infarction or aneurysm or brain infarction or brain injury or Ischemia or brain vasospasm or cerebrovascular accident or heart arrest or Myocardial Infarction or Myocardial Ischemia).af.

10 (erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hemoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*).af.

11 (r adj HuEPO).af.

12 (Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoad or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoietina or Eritropoietina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO

or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop).ti,ab,hw.

13 (HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697).af.

14 (113427-24-0 or 11096-26-7 or 209810-58-2 or 122312-54-3 or 261356-80-3 or 604802-70-2 or 130455-76-4 or 148363-16-0 or 154725-65-2 or 879555-13-2).rn.

15 or/1-9

16 or/10-14

17 15 and 16

Search strategy in OvidSP PsycINFO

1 ((critical or intensive) adj2 care*).ab,id,ol,ot,ti,hw.

2 life support care*.af.

3 (critical* adj ill*).af.

4 (icu or icus).ab,id,ol,ot,ti.

5 (ventilat* or Respirat* or Artificial).ab,id,ol,ot,ti,hw.

6 acute care facilit*.af.

7 (thermal injur* or burn* or trauma or resuscitation*).ab,id,ol,ot,ti,hw.

8 ((APACHE or intensive) adj2 score*).ab,id,ol,ot,ti.

9 exp Cerebral Hemorrhage/ or exp Subarachnoid Hemorrhage/ or exp Aneurysms/ or exp Cerebral Ischemia/ or exp Ischemia/ or exp Cerebrovascular Accidents/ or exp Myocardial Infarctions/ or exp Traumatic Brain Injury/

10 (erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*).af.

11 (Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoad or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop).ab,id,ol,ot,ti.

12 or/1-9

13 or/10-11

14 12 and 13

Search strategy in CINAHL

S1 MW critical care OR AB critical care OR TI critical care OR SC critical care OR SE critical care OR OS critical care

S2 TX life support care*

S3 TX critical* W1 ill*

S4 TI (icu or icus) OR AB (icu or icus) OR MW (icu or icus) OR OS (icu or icus) OR SC (icu or icus) OR SE (icu or icus)

S5 TI intensive care* OR AB intensive care* OR MW intensive care* OR OS intensive care* OR SC intensive care* OR SE intensive care*

S6 TX intensive score*

S7 TX ventilat* or Respirat* or Artificial

S8 TX acute care facilit*

S9 TI (thermal injur* or burn* or trauma) OR AB (thermal injur* or burn* or trauma) OR MW (thermal injur* or burn* or trauma) OR OS (thermal injur* or burn* or trauma) OR SC (thermal injur* or burn* or trauma) OR SE (thermal injur* or burn* or trauma)

S10 TX ((APACHE or intensive) W2 score*)

S11 MH Acute Coronary Syndrome OR MM Infarction OR MH Myocardial Infarction MH Aneurysm+ OR MH Cerebral Aneurysm OR MH Hemorrhage OR MH Intracranial Hemorrhage OR MH Subarachnoid Hemorrhage OR Cerebral Hemorrhage OR MH Stroke

S12 TX erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*

S13 TX r W1 HuEPO

S14 TX Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoade or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop

S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11

S16 S12 or S13 or S14

S17 S15 and S16

Search strategy in BIOSIS Previews

1 TS=((critical or intensive) NEAR/2 care*)

2 TS="life support care**"

3 TS=(critical* NEAR ill*)

4 TS=(icu or icus)

5 TS=(ventilat* or Respirat* or Artificial)

6 TS="acute care facilit**"

7 TS=(thermal injur* or burn* or trauma)

8 TS=((APACHE or intensive) NEAR/2 score*)

9 TS=("Myocardial Ischemia" OR "Myocardial Infarction" OR "subarachnoid hemorrhage" OR "heart infarction" OR "Acute Coronary Syndrome" OR "brain infarction" OR "brain ischemia" OR "Cerebral Hemorrhage" OR "brain injur*" OR "cerebrovascular accident" OR "Intracranial Aneurysm" OR "subarachnoid hemorrhage" OR "brain artery aneurysm")

10 CH=(erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*)

11 TS=(r NEAR HuEPO)

12 CH=(Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoade or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa

or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erytostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop)

13 TS=(HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697)

14 CR=(113427-24-0 or 11096-26-7 or 209810-58-2 or 122312-54-3 or 261356-80-3 or 604802-70-2 or 130455-76-4 or 148363-16-0 or 154725-65-2 or 879555-13-2)

15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

16 #10 OR #11 OR #12 OR #13 OR #14

17 #15 AND #16

Search strategy in Science Citation Index Expanded (SCI-EXPANDED)

1 TS=((critical or intensive) NEAR/2 care*)

2 TS="life support care*C

3 TS=(critical* NEAR ill*)

4 TS=(icu or icus)

5 TS=(ventilat*or Respirat* or Artificial)

6 TS="acute care facilitit**"

7 TS=("thermal injur*" or burn* or trauma)

8 TS="acute care facilitit**"

9 TS=((APACHE or intensive) NEAR/2 score*)

10 TS=("Myocardial Ischemia" OR "Myocardial Infarction" OR "subarachnoid hemorrhage" OR "heart infarction" OR "Acute Coronary Syndrome" OR "brain infarction" OR "brain ischemia" OR "Cerebral Hemorrhage" OR "brain injur*" OR "cerebrovascular accident" OR "Intracranial Aneurysm" OR "subarachnoid hemorrhage" OR "brain artery aneurysm")

11 TS=(erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*)

12 TS=(r NEAR HuEPO)

13 TS=(Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoade or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erytostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop)

14 TS=(HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697)

15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

16 #11 OR #12 OR #13 OR #14

17 #15 AND #16

Search strategy in Conference Proceedings Citation Index- Science (CPCI-S)

1 TS=((critical or intensive) NEAR/2 care*)

2 TS="life support care*"

3 TS=(critical* NEAR ill*)

4 TS=(icu or icus)

5 TS=(ventilat*or Respirat* or Artificial)

6 TS="acute care facilit*"

7 TS=("thermal injur*" or burn* or trauma)

8 TS="acute care facilit*"

9 TS=((APACHE or intensive) NEAR/2 score*)

10 TS=("Myocardial Ischemia" OR "Myocardial Infarction" OR "subarachnoid hemorrhage" OR "heart infarction" OR "Acute Coronary Syndrome" OR "brain infarction" OR "brain ischemia" OR "Cerebral Hemorrhage" OR "brain injur*" OR "cerebrovascular accident" OR "Intracranial Aneurysm" OR "subarachnoid hemorrhage" OR "brain artery aneurysm")

11 TS=(erythropo* or erithropo* or epo or rheupo or rhepo or rhuepo or Hempoietin* or hematopoiet* or hemopoiet* or epoetin* or darbopoiet* or darbepo*)

12 TS=(r NEAR HuEPO)

13 TS=(Abseamed or Alfaepoetina or Aranesp or Betapoietin or Binocrit or Bioetin or Biopoin or Bioyetin or Ceriton or Culat or Dynepo or EPIAO or Epiao or Epoad or Epobel or Epocim or Epoch or Epocomb or Epocrin or Epoetin Alfa Hexal or Epoetin Sedico or Epofer or Epofit or Epoform or Epogen or Epogin or Epogis S or Epoglobin or Epojet or Epokine or Epomax or Epomax or Eponis-2K or Epopen or Eporatio or Eporise or Eporon or Eposim or Eposino or Eposis or Epostim or Epotin or Epotop or Epotrex-NP or Epotrust or Epovitan or Epox or Epoxitin or Epoyet or Eprex or Eralfon or Erantin or Eritina or Eritrelan or Eritrogen or Eritrogen or Eritromax or Eritropoyetina or Eritropoyetina Alfa or Erlan or Erykine or Erypo or Erypoietin or Erypro or Erypro Safe or Erythrostim or Erythrostim or Espo or Espogen or Exetin-A or GerEPO or Globuren or Heberitro or Hemapo or Hemax or Hemax-Eritron or Hemoprex or Hepta or Hypercrit or Jimaixin or LG Espogen or Marogen or Mircera or Negortire or NeoRecormon or Nesp or Nespo or PDpoetin or Procrit or Pronivel or Recormon or Relipoietin or Renogen or Repotin or Retacrit or Sepo or Shanpoietin or Silapo or Tinax or Vero-Epoetin or Vintor or Wepox or Yepotin or YiBei or Zyrop)

14 TS=(HM10760A or 64FS3BFH5W or 15UQ94PT4P or BM06019 or DRG-0062 or KRN 321 or KRN321 or KRN 5702 or KRN5702 or BI71052 or TYB 5220 or TYB5220 or SNB 5001 or SNB5001 or HSDB 7584 or HSDB7584 or LS 64697 or LS64697)

15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

16 #11 OR #12 OR #13 OR #14

17 #15 AND #16

Search strategy in TOXLINE

1 *critical care [not] PubMed [org] [not] pubdart [org]

2 "life support care*" [not] PubMed [org] [not] pubdart [org]

3 "critical* ill*" [not] PubMed [org] [not] pubdart [org]

4 *critical illness [not] PubMed [org] [not] pubdart [org]

5 icu* [not] PubMed [org] [not] pubdart [org]

6 "intensive care*" [not] PubMed [org] [not] pubdart [org]

7 ventilat* [not] PubMed [org] [not] pubdart [org]

8 respirat* [not] PubMed [org] [not] pubdart [org]

9 artificial [not] PubMed [org] [not] pubdart [org]

10 resuscitation* [not] PubMed [org] [not] pubdart [org]

11 subarachnoid hemorrhage [not] PubMed [org] [not] pubdart [org]

12 cardiac arrest [not] PubMed [org] [not] pubdart [org]

13 myocardial infarction [not] PubMed [org] [not] pubdart [org]

14 aneurysm [not] PubMed [org] [not] pubdart [org]

15 brain infarction [not] PubMed [org] [not] pubdart [org]

16 stroke [not] PubMed [org] [not] pubdart [org]

17 "acute care facilit*" [not] PubMed [org] [not] pubdart [org]

18 "thermal injur*" [not] PubMed [org] [not] pubdart [org]

19 burn* [not] PubMed [org] [not] pubdart [org]

20 (trauma OR " wounds injuries ") AND (trauma injuries) [not] PubMed [org] [not] pubdart [org]

21 (apache) [not] PubMed [org] [not] pubdart [org]

22 intensive score [not] PubMed [org] [not] pubdart [org]

23 (erythropo* OR erithropo* OR epo OR *heupo OR *hepo OR *huepo OR epoetin* OR darbopoiet* OR darbepo* OR epogen OR eprex OR erypo OR procrit OR *recormon OR dynepo OR aranesp OR nespo OR mircera OR retacrit OR silapo OR culat) NOT PubMed [org] NOT pubdart [org]

24 (hm10760a OR 64fs3bfh5w OR 15uq94pt4p OR bm06019 OR " drg 0062 " OR " krn 321" OR krn321 OR " krn 5702 " OR krn5702 OR bi71052 OR " tyb 5220 " OR tyb5220 OR " snb 5001 " OR snb5001 OR " hsdb 7584 " OR hsdb7584 OR " ls 64697 " OR ls64697) NOT PubMed [org] NOT pubdart [org]

25 (113427-24-0 [rn] OR 11096-26-7 [rn] OR 209810-58-2 [rn] OR 122312-54-3 [rn] OR 261356-80-3 [rn] OR 604802-70-2 [rn] OR 130455-76-4 [rn] OR 148363-16-0 [rn] OR 154725-65-2 [rn] OR 879555-13-2 [rn]) NOT PubMed [org] NOT pubdart [org]

26 1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

27 #23 OR #24 OR #25

28 #26 AND #27

Appendix 2. Definition of serious adverse events in included studies

Study	serious adverse event defined as
Corwin 2002	Respiratory system disorders (respiratory insufficiency, dyspnoea, pneumonia); resistance mechanism disorders (sepsis, abscess); heart rate and rhythm disorders (cardiac arrest); vascular (extracardiac) disorders (thrombophlebitis (deep)); urinary system disorders (renal failure (acute)); general disorders (multiple organ failure); gastrointestinal system disorders; platelet, bleeding, and clotting disorders; central and peripheral nervous system disorders; general cardiovascular disorders*
Corwin 2007a	Respiratory-system disorders (respiratory insufficiency, dyspnoea); resistance-mechanism disorders (sepsis, abscess); multiple-organ failure; clinically relevant thrombotic vascular event (pulmonary embolism, deep venous thrombosis, cerebrovascular event, myocardial infarction, cardiac arrest or ventricular fibrillation **
Endre 2010	Deep venous thrombosis; superficial vein thrombosis; pulmonary embolism; thromboembolism; ischaemic; hypertension stroke; seizure; cardiac failure; myocardial infarction; allergic response; ventricular fibrillation arrest and atrial fibrillation

(Continued)

Georgopoulos 2005	CNS disorders (new ischaemic or haemorrhagic stroke); deep venous thrombosis; heart rate and rhythm disorders; nosocomial infection; thrombocytosis and death
Luchette 2012	SAEs occurring in more than one participant in any treatment group: gastrointestinal disorders; infections and infestations; Injury, poisoning, and procedural complications (post-procedural haemorrhage); musculoskeletal disorder; nervous system disorders; respiratory, thoracic, and mediastinal disorders (respiratory failure, pulmonary embolism); vascular disorders (deep venous thrombosis)
Ott 2010	Major adverse cardiac and cerebrovascular events: composite of death, recurrent MI, revascularization of the infarct-related artery, and stroke
Robertson 2014	Central Nervous System (CNS) Complications: intracranial hypertension requiring second- or third-tier therapy, brain tissue hypoxia, delayed/recurrent intracranial haematoma, seizure, hydrocephalus, stroke, CSF leak, subgaleal fluid collection, pneumocephalus, chronic subdural haematoma, carotid cavernous fistula; Cardiovascular Complications: hypotension, thrombophlebitis – deep venous (Jugular venous, lower extremity venous, upper extremity venous), pulmonary embolus, cardiac arrest with CPR, acute myocardial infarction, other cardiovascular complications***; Gastrointestinal Complications: elevated transaminases, other GI complications; Haematological Complications: anaemia, other; Infection Complications: pneumonia, urinary tract infection, meningitis/ventriculitis, bacteraemia, other infections, sepsis/SIRS/MODS/septic shock; Metabolic Complications: diabetes insipidus, severe hyperglycaemia, other metabolic complications; Renal/electrolyte Complications: electrolyte disturbances, acid-base abnormalities, renal insufficiency/failure; Respiratory Complications: atelectasis, ARDS, pneumothorax, pleural effusion, airway obstruction requiring re-intubation, haemothorax
Taniguchi 2010	Major adverse cardiac events (MACE): death, new myocardial infarction, revascularization, admission to hospital due to aggravation of ischaemic or heart failure

*Authors did not explicitly indicate these AEs as SAEs.

**Those that occurred in more than 2% of participants in either study group are listed as SAEs.

***Other cardiovascular complications included superficial thrombophlebitis, gangrene of extremities due to pressors, severe hypertension, and atrial arrhythmia.

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: BM, HH

Co-ordinating the review: HH

Undertaking manual searches: BM

Screening search results: BM

Organizing retrieval of papers: BM

Screening retrieved papers against inclusion criteria: BM, BHH, DR, HH

Appraising quality of papers: BM, BHH, DR, HH

Abstracting data from papers: BM, BHH, DR, HH

Writing to authors of papers for additional information: BM

Providing additional data about papers: BM

Obtaining and screening data on unpublished studies: BM, BHH

Managing data for the review: BM

Entering data into Review Manager 5 ([RevMan 5.3](#)): BM, DR

Handling RevMan statistical data: BM, HH

Performing other statistical analyses not using RevMan: SS, CDW

Interpreting data: BM, SS, CDW, HH

Making statistical inferences: SS, CDW, HH

Securing funding for the review: HH

Performing previous work that was the foundation of the present study: BM, BHH, SS, CDW, HH

Serving as guarantor for the review (one author): HH

Taking responsibility for reading and checking the review before submission: BM

DECLARATIONS OF INTEREST

Bitá Mesgarpour: none known.

Benedikt H Heidinger: none known.

Dominik Roth: none known.

Susanne Schmitz: none known.

Cathal D Walsh: none known.

Harald Herkner: none known.

SOURCES OF SUPPORT

Internal sources

- Medical University of Vienna, Austria.
- Trinity College Dublin, Ireland.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol ([Mesgarpour 2014](#)):

In electronic searches, we did not search Ovid SP PASCAL because of access limitations. We searched CENTRAL as a part of 'All EBM Reviews' database via Ovid SP. We extended the subgroup analysis to a post hoc test on subgroup effects of trauma and sensitivity analysis to assess the robustness of our estimates by excluding studies on biosimilar ESAs. We further assessed the sensitivity of our estimates by excluding studies on biosimilar ESAs.

We changed the title from 'Safety of off-label erythropoiesis-stimulating agents for critically ill patients' to 'Harms of off-label erythropoiesis-stimulating agents for critically ill people' to reflect current methodological discussions. Also, throughout the text we now use 'harms' instead of 'safety', to comply with contemporary standards.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; *Off-Label Use; Anemia [blood] [*drug therapy] [mortality]; Biosimilar Pharmaceuticals [adverse effects]; Erythropoiesis [*drug effects]; Hematinics [*adverse effects]; Observational Studies as Topic; Randomized Controlled Trials as Topic; Venous Thromboembolism [chemically induced]

MeSH check words

Humans