Evidence summary

to support

PICO question 3:

treatment preoperative anemia

April 2018 (version 2.0)

Centre for Evidence-Based Practice (CEBaP)

Belgian Red Cross

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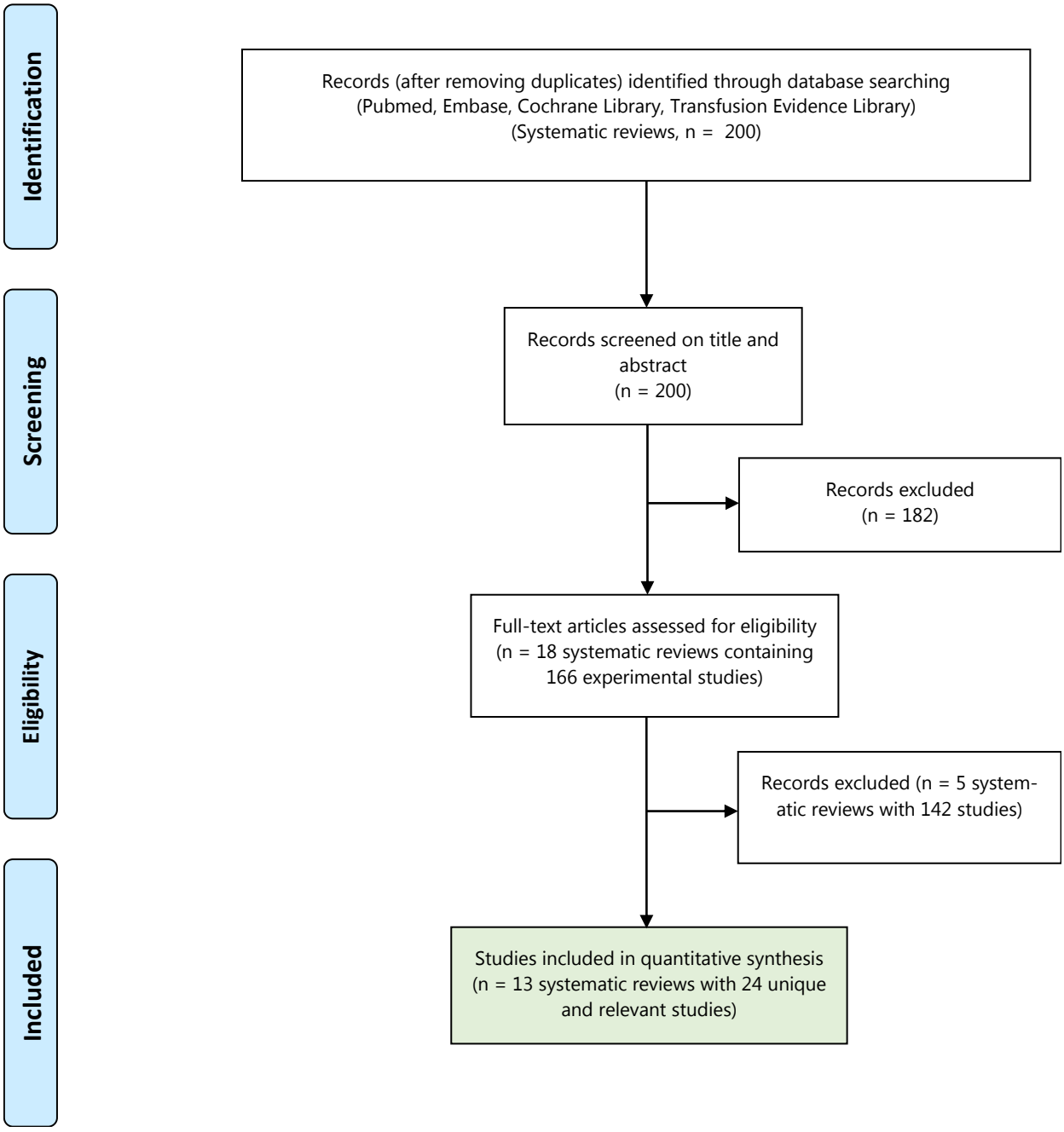
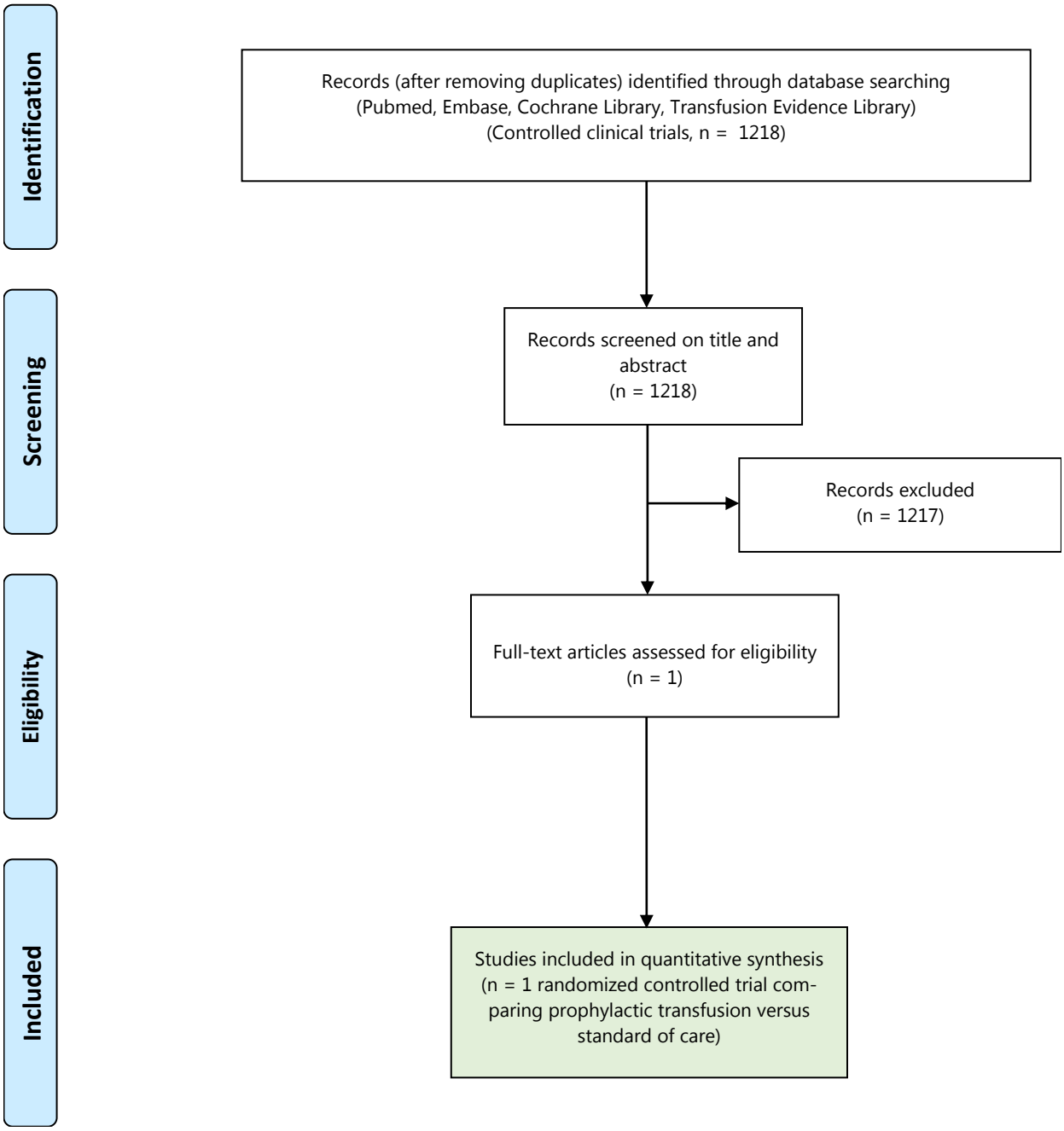
Evidence-based
by CEBaP

Content

Flow chart 1: search for systematic reviews (treatment: iron and/or ESA)



Flow chart 2: search for individual studies (treatment: transfusion)



Overview of included individual studies

Comparison	Experimental studies	Observational studies
Transfusion versus no treatment – placebo - standard of care (Comparison 1)	1 study[1]	-
Iron supplementation versus no treatment – placebo - standard of care (Comparison 2)	3 studies[2-4]	1 study[5]
ESA versus no treatment – placebo – standard of care (Comparison 3)	2 studies[6,7]	1 study[8]
Iron supplementation + ESA versus no treatment – placebo – standard of care (Comparison 4)	17 studies[9-25]	-

Reference list included studies

1. Karkouti K, Wijeysundera DN, Yau TM, et al. Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology 2012;116:613-21.

2. Edwards TJ, Noble EJ, Durran A, et al. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. Br J Surg 2009;96:1122-8.

3. Lidder PG, Sanders G, Whitehead E, et al. Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - a prospective, randomised, controlled trial. Ann R Coll Surg Engl 2007;89:418-21.

4. Okuyama M, Ikeda K, Shibata T, et al. Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. Surg Today 2005;35:36-40.

5. Munoz M, Naveira E, Seara J, et al. Role of parenteral iron in transfusion requirements after total hip replacement. A pilot study. Transfus Med 2006;16:137-42.

6. Weltert L, D'Alessandro S, Nardella S, et al. Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: a randomized blind controlled study. J Thorac Cardiovasc Surg 2010;139:621-6; discussion 6-7.

7. Weltert L, Rondinelli B, Bello R, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. Transfusion 2015;55:1644-54.

8. Bedair H, Yang J, Dwyer MK, et al. Preoperative erythropoietin alpha reduces postoperative transfusions in THA and TKA but may not be cost-effective. Clin Orthop Relat Res 2015;473:590-6.

9. Christodoulakis M, Tsiftsis DD, Hellenic Surgical Oncology Perioperative EPOSG. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. Ann Surg Oncol 2005;12:718-25.

10. Dousias V, Paraskevaidis E, Dalkalitsis N, et al. Recombinant human erythropoietin in mildly anemic women before total hysterectomy. Clin Exp Obstet Gynecol 2003;30:235-8.

11. Faris PM, Ritter MA, Abels RI. The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American Erythropoietin Study Group. J Bone Joint Surg Am 1996;78:62-72.

12. Feagan BG, Wong CJ, Kirkley A, et al. Erythropoietin with iron supplementation to prevent allogeneic blood transfusion in total hip joint arthroplasty. A randomized, controlled trial. Ann Intern Med 2000;133:845-54.

13. Heiss MM, Tarabichi A, Delanoff C, et al. Perisurgical erythropoietin application in anemic patients with colorectal cancer: A double-blind randomized study. Surgery 1996;119:523-7.

14. Kettelhack C, Hones C, Messinger D, et al. Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. Br J Surg 1998;85:63-7.

15. Kosmadakis N, Messaris E, Maris A, et al. Perioperative erythropoietin administration in patients with gastrointestinal tract cancer: prospective randomized double-blind study. Ann Surg 2003;237:417-21.

16. Larson B, Bremme K, Clyne N, et al. Preoperative treatment of anemic women with epoetin beta. Acta Obstet Gynecol Scand 2001;80:559-62.

17. Laupacis A, Feagan B, Wong C. Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. COPES Study Group. Lancet 1993;342:378.

18. Na HS, Shin SY, Hwang JY, et al. Effects of intravenous iron combined with low-dose recombinant human erythropoietin on transfusion requirements in iron-deficient patients undergoing bilateral total knee replacement arthroplasty. Transfusion 2011;51:118-24.

19. Qvist N, Boesby S, Wolff B, et al. Recombinant human erythropoietin and hemoglobin concentration at operation and during the postoperative period: reduced need for blood transfusions in patients undergoing colorectal surgery--prospective double-blind placebo-controlled study. World J Surg 1999;23:30-5.

20. Scott SN, Boeve TJ, McCulloch TM, et al. The effects of epoetin alfa on transfusion requirements in head and neck cancer patients: a prospective, randomized, placebo-controlled study. Laryngoscope 2002;112:1221-9.

21. So-Osman C, Nelissen RG, Koopman-van Gemert AW, et al. Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dl. Anesthesiology 2014;120:852-60.

22. Stowell CP, Jones SC, Enny C, et al. An open-label, randomized, parallel-group study of perioperative epoetin alfa versus standard of care for blood conservation in major elective spinal surgery: safety analysis. Spine (Phila Pa 1976) 2009;34:2479-85.

23. Weber EW, Slappendel R, Hemon Y, et al. Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: the European Epoetin Alfa Surgery Trial (EEST). Eur J Anaesthesiol 2005;22:249-57.

24. Wurnig C, Schatz K, Noske H, et al. Subcutaneous low-dose epoetin beta for the avoidance of transfusion in patients scheduled for elective surgery not eligible for autologous blood donation. Eur Surg Res 2001;33:303-10.

25. Yoo YC, Shim JK, Kim JC, et al. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. Anesthesiology 2011;115:929-37.

Overview of included systematic reviews (as a basis to select relevant individual studies)[26-38]

26. Alsaleh K, Alotaibi GS, Almodaimegh HS, et al. The Use of Preoperative Erythropoiesis-Stimulating Agents (ESAs) in Patients Who Underwent Knee or Hip Arthroplasty. A Meta-Analysis of Randomized Clinical Trials. The Journal of Arthroplasty 2013;28:1463-72.

27. Borstlap WA, Stellingwerf ME, Moolla Z, et al. Iron therapy for the treatment of preoperative anaemia in patients with colorectal carcinoma: a systematic review. Colorectal Dis 2015;17:1044-54.

28. Devon KM, McLeod RS. Pre and peri-operative erythropoeitin for reducing allogeneic blood transfusions in colorectal cancer surgery. Cochrane Database of Systematic Reviews 2009.

29. Glechner A, Gartlehner G, Nussbaumer B, et al. Perioperatives Anämiemanagement – Systematischer Review und Meta-Analyse. Wien Med Wochenschr 2014;164:330-41.

30. Gurusamy KS, Nagendran M, Broadhurst JF, et al. Iron therapy in anaemic adults without chronic kidney disease. Cochrane Database Syst Rev 2014:CD010640.

31. Hallet J, Hanif A, Callum J, et al. The Impact of Perioperative Iron on the Use of Red Blood Cell Transfusions in Gastrointestinal Surgery: A Systematic Review and Meta-Analysis. Transfusion Medicine Reviews 2014;28:205-11.

32. Hogan M, Klein AA, Richards T. The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. Eur J Cardiothorac Surg 2015;47:218-26.

33. Laupacis A, Fergusson D. Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. The International Study of Peri-operative Transfusion (ISPOT) Investigators. Transfus Med 1998;8:309-17.

34. Lin DM, Lin ES, Tran MH. Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review. Transfus Med Rev 2013;27:221-34.

35. Ng O, Keeler BD, Mishra A, et al. Iron therapy for pre-operative anaemia. Cochrane Database Syst Rev 2015:CD011588.

36. Tran DH, Wong GT, Chee YE, et al. Effectiveness and safety of erythropoiesis-stimulating agent use in the perioperative period. Expert Opin Biol Ther 2014;14:51-61.

37. Yang Y, Li H, Li B, et al. Efficacy and Safety of Iron Supplementation for the Elderly Patients Undergoing Hip or Knee Surgery: A Meta-Analysis of Randomized Controlled Trials. Journal of Surgical Research 2011;170:e201-e7.

38. Zhao Y, Jiang C, Peng H, et al. The effectiveness and safety of preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016;95:e4122.

Overview excluded studies

Study	Reason for exclusion
Braga et al (1997)[39]	Article in Italian. Selection criteria: only articles in English, French and German are included.
Cladellas et al (2012)[40]	Patients receiving iv rhEPO and iv iron were compared to a historic cohort that did not receive any treatment. --> Since this study only provides information on treatment iron+ESA, this observational study was excluded during data extraction.
Couvret et al (2004)[41]	Observational cohort study, but control group gets autologous donation
Cuenca et al (2004)[42]	Surgery for pertrochanteric hip fracture = no elective surgery
Cuenca et al (2005)[43]	Surgery for displaced subcapital hip fracture = no elective surgery
Cushner et al (2001)[44]	Patients receiving Epoetin alfa and iron replacement therapy were compared to a historic control group that had not received Epoetin alfa. --> Since this study only provides information on treatment iron+ESA, this observational study was excluded during data extraction.
D'Ambra et al (1997)[45]	Patients are not anemic --> mean Hb levels: 14 g/dl for all 3 groups (Epoetin alfa 300 IU/kg, Epoetin alfa 150 IU/kg and Placebo group)
Doodeman et al (2013)[46]	Observational cohort study
García-Erce et al (2009)[47]	Surgery for osteoporotic pertrochanteric or subcapital hip fracture = no elective surgery
Gonzalez-Porras et al (2009)[48]	Matched historic control group is not anemic (mean Hb 13.8± 1.4)
Keating et al (2007)[49]	RCT, but control group gets autologous donation
Kim et al (2009)[50]	Only reports on Hb levels, ferritin levels, serious adverse events (no definition) and tolerable adverse events (myalgia, injection pain, nausea, dyspepsia)
Kotzé et al (2012)[51]	Observational cohort study, compares outcomes (allogeneic transfusion rate and length of stay) for patients undergoing total hip or total knee arthroplasty, either before or after the implementation of a patient blood management programme (iv iron, oral iron, EPO+iron). However, both cohorts contain both anaemic (Hb <12 g/dl for women and Hb <13g/dl for men) and non-anaemic people. In the comparison between the 2 cohorts, there is no subgroup analysis for anaemic people. In the post-implementation cohort, no subgroup analysis was performed for the treatment they were given

Laffosse et al (2010)[52]	Combination of both autologous blood and allogeneic blood transfusion in the intervention and control group
Mercuriali et al (1993)[53]	Autologous blood donation as part of the intervention and control group
Mercuriali et al (1997)[54]	Autologous blood donation as part of the intervention and control group
Moonen et al (2008)[55]	RCT, compares Epoetin-alpha+oral iron with post-operative autologous retransfusion (cell salvage). We have included some studies that use cell salvage devices, but in these studies, this was used in both the control and the intervention group. This is not the case in this study
Muñoz et al (2014)[56]	Observational cohort study, patients undergoing elective surgery for total knee or total hip replacement are not anemic (mean preoperative Hb levels 13.7-13.8 g/dl)
Olijhoek et al (2001)[57]	Only reports on RBC production, Hb, Hct, reticulocytes, iron status and safety results of EPO use. The study was not powered for a comparison of allogeneic blood transfusion outcomes between groups.
Serrano-Trenas et al (2011)[58]	Hip fracture surgery = no elective surgery
Sowade et al (1997)[59]	Patients are not anemic --> mean Hb levels: Epoetin beta group 14.31±0.98 g/dl; Placebo group 13.78±1.03
Zauber et al (1992)[60]	Patients undergoing femoral head replacement, either electively or following traumatic fracture. Patients with preoperative Hb levels <13 g/dl (men) or <11.5 g/dl (women) were excluded. It is not possible to extract data only on the elective surgery patients, because they are mixed with those undergoing trauma surgery

39. Laffosse JM, Minville V, Chiron P, et al. Preoperative use of epoietin beta in total hip replacement: a prospective study. Arch Orthop Trauma Surg 2010;130:41-5.

40. Mercuriali F, Zanella A, Barosi G, et al. Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. Transfusion 1993;33:55-60.

41. Mercuriali F, Inghilleri G, Biffi E, et al. Comparison between intravenous and subcutaneous recombinant human erythropoietin (Epoetin alfa) administration in presurgical autologous blood donation in anemic rheumatoid arthritis patients undergoing major orthopedic surgery. Vox Sang 1997;72:93-100.

42. Moonen AF, Thomassen BJ, Knoors NT, et al. Pre-operative injections of epoetin-alpha versus post-operative retransfusion of autologous shed blood in total hip and knee replacement: a prospective randomised clinical trial. J Bone Joint Surg Br 2008;90:1079-83.

43. Munoz M, Gomez-Ramirez S, Cuenca J, et al. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients. Transfusion 2014;54:289-99.

44. Olijhoek G, Megens JG, Musto P, et al. Role of oral versus IV iron supplementation in the erythropoietic response to rHuEPO: a randomized, placebo-controlled trial. Transfusion 2001;41:957-63.

45. Serrano-Trenas JA, Ugalde PF, Cabello LM, et al. Role of perioperative intravenous iron therapy in elderly hip fracture patients: a single-center randomized controlled trial. Transfusion 2011;51:97-104.

46. Sowade O, Warnke H, Scigalla P, et al. Avoidance of allogeneic blood transfusions by treatment with epoetin beta (recombinant human erythropoietin) in patients undergoing open-heart surgery. Blood 1997;89:411-8.

47. Zauber NP, Zauber AG, Gordon FJ, et al. Iron supplementation after femoral head replacement for patients with normal iron stores. JAMA 1992;267:525-7.

Comparison 1: Transfusion versus no treatment – placebo – standard of care

Overview evidence table GRADE software (comparison 1)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**transfusion**	**standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Primary: mortality												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/29 (3.4%)	1/31 (3.2%)	**RR 1.07** (0.07 to 16.31)	**2 more per 1.000** (from 30 fewer to 494 more)	⨁◯◯◯ VERY LOW	CRITICAL
Primary: acute myocardial infarction												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/29 (3.4%)	1/31 (3.2%)	**RR 1.07** (0.07 to 16.31)	**2 more per 1.000** (from 30 fewer to 494 more)	⨁◯◯◯ VERY LOW	CRITICAL
Primary: acute kidney injury												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	11/29 (37.9%)	11/31 (35.5%)	**RR 1.07** (0.55 to 2.08)	**25 more per 1.000** (from 160 fewer to 383 more)	⨁◯◯◯ VERY LOW	CRITICAL
Secondary: RBC units transfused (pre-operative)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**transfusion**	**standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	median **2 RBC units higher** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Secondary: RBC units transfused (intra-operative)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	median **2 RBC units lower** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT
Secondary: RBC units transfused (total)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	median **0 RBC units** (0 to 0)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

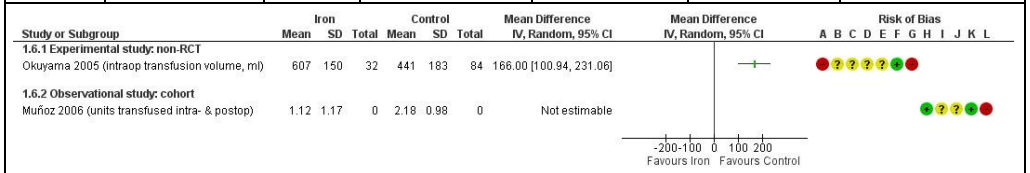
a. unblinded, pragmatic pilot study with postrandomization dropouts and important protocol deviations (i.e. delayed transfusions in the intervention arm)

b. limited sample size/low number of events and large variability in results

Comparison 2: Iron supplementation versus no treatment – placebo – standard of care

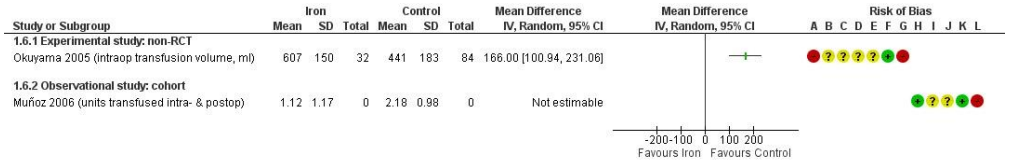
Overview evidence table GRADE software (comparison 2)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iron supplementation**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Secondary: Red blood cell utilization - Number of patients transfused												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	8/47 (17.0%)	38/107 (35.5%)	**RR 0.51** (0.27 to 0.93)	**174 fewer per 1.000** (from 25 fewer to 259 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Secondary: Red blood cell utilization - Number of units transfused (experimental studies: RCT and non-RCT)												
2	randomised trials [c]	serious [d]	not serious	not serious	serious [e]	none	See Forest plot – experimental study Okuyama et al. In addition to the 2 studies included in the forest plot, a randomised controlled trial by Lidder *et al.* in anaemic patients (Hb <13.5 g/dl in men and <11.5 g/dl in women) scheduled for colorectal surgery demonstrated that a statistically significant difference in the median number of units transfused perioperatively in patients that received oral iron supplementation compared to patients receiving standard clinical management could not be demonstrated.				⨁⨁◯◯ LOW	IMPORTANT



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias
(**H**) Inappropriate eligibility criteria
(**I**) Inappropriate methods for exposure and outcome variables
(**J**) Not controlled for confounding
(**K**) Incomplete or inadequate follow-up
(**L**) Other limitations

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iron supplementation**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Secondary: Red blood cell utilization - Number of units transfused (observational cohort study)												
1	observational studies	serious [f]	not serious	not serious	serious [g]	none	See Forest plot – observational study Muñoz et al. The observational cohort study by Muñoz, 2006 in patients undergoing total hip replacement surgery, with Hb levels < 13 g/dl, found that a statistically significant decrease in the number of units transfused intra- and postoperatively could not be demonstrated in patients that received treatment with intravenous iron, compared to no iron.				⊕◯◯◯ VERY LOW	IMPORTANT



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CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Decision to downgrade by reviewer(s) since the non-RCT of Okuyama, 2005 shows high risk of selection bias and unclear risk of selection, performance, detection and attrition bias, and this study has an important influence on the point estimate and 95% CI (assigned weight 29.3%).

b. Low number of events

c. One RCT (Lidder, 2007) and one non-RCT (Okuyama, 2005)

d. Decision to downgrade by reviewer(s). The non-RCT of Okuyama, 2005 shows high risk of selection bias and unclear risk of selection, performance, detection and attrition bias.

e. Limited sample size and lack of data

f. Decision to downgrade by reviewer(s) since Muñoz, 2006 has unclear risk of using inappropriate methods for exposure and outcome variables, and unclear risk of not controlling for confounding. In addition, the study has compared the intervention group to a historic control group.

g. Lack of data

Comparison 3: ESA versus no treatment – placebo – standard of care

Overview evidence table GRADE software (comparison 3)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**erythrocyte stimulating agents (ESAs)**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Primary: (All-cause) mortality												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	12/458 (2.6%)	13/462 (2.8%)	**RR 0.93** (0.43 to 2.01)	**2 fewer per 1.000** (from 16 fewer to 28 more)	⨁⨁◯◯ LOW	CRITICAL
Primary: Anemia-associated ischaemic events												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	See Forest plot 'Figure 7'. The RCTs by Weltert et al. 2010/2015 in patients undergoing off-pump CABG surgery, with Hb levels ≤ 14.5 g/dl, demonstrated that a statistically significant difference in perioperative myocardial infarction/acute kidney injury after receiving subcutaneous administration of EPO could not be demonstrated, compared to no treatment. For bowel ischaemia, the effect size was not estimable.				⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	erythrocyte stimulating agents (ESAs)	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		

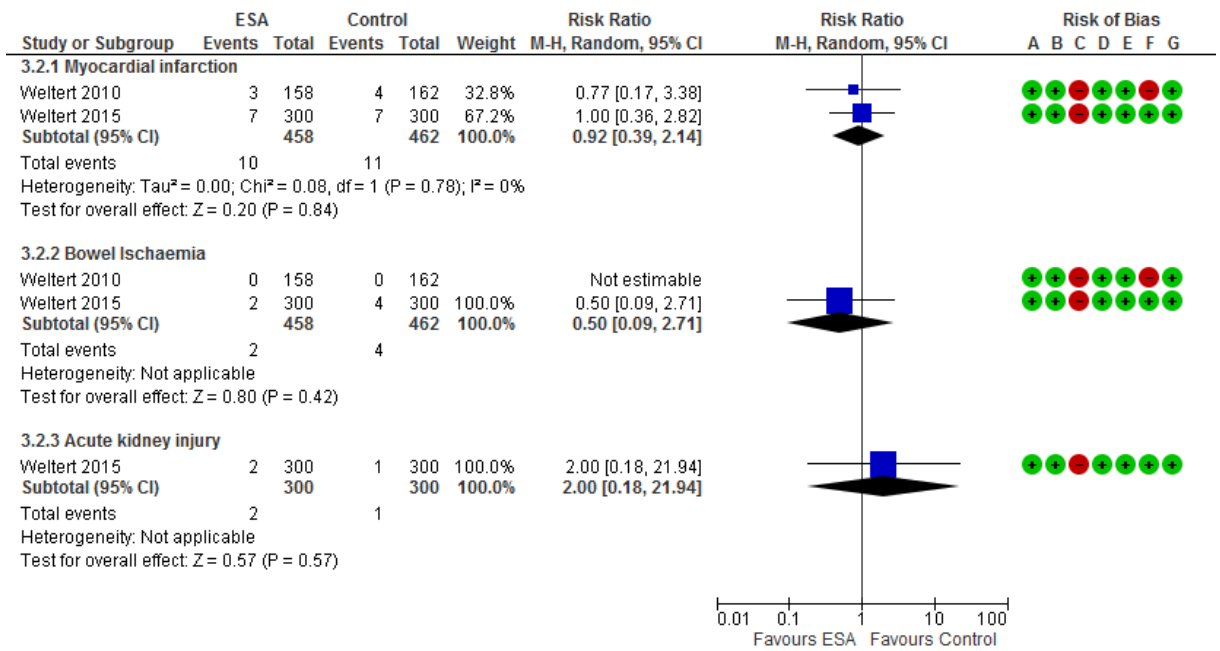

Figure 7: Forest plot of outcome: Anemia-associated ischaemic events

Secondary: Length of hospital stay (experimental study: RCT)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**erythrocyte stimulating agents (ESAs)**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	See Forest plots – experimental study (Figure 8). In the RCT by Weltert et al. 2010 a statistically significant difference in the length of stay after the operation between patients receiving EPO subcutaneously and patients receiving no treatment could not be demonstrated (p=0.065).				⊕⊕◯◯ LOW	IMPORTANT

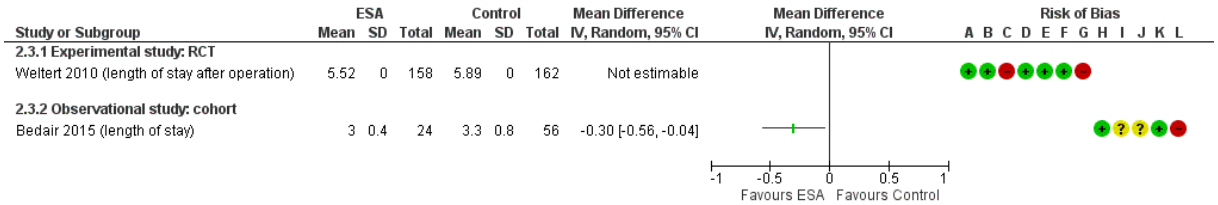

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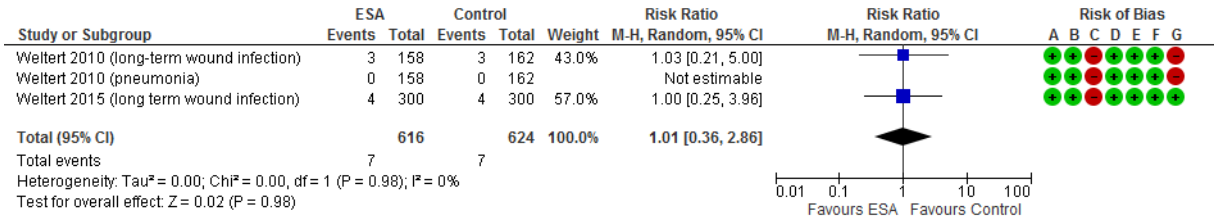
Figure 8: Forest plot of outcome: Length of hospital stay

Secondary: Length of hospital stay (observational cohort study)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**erythrocyte stimulating agents (ESAs)**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [d]	not serious	not serious	serious [e]	none	24	56	-	MD **0.3 days fewer** (0.56 fewer to 0.04 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Secondary: Infections												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	See Forest plot (Figure 9). In the RCTs by Weltert et al. 2010/2015, a statistically significant difference in long-term wound infection between patients receiving EPO subcutaneously and patients receiving no treatment could not be demonstrated. For pneumonia, the effect size was not estimable.				⨁⨁◯◯ LOW	IMPORTANT



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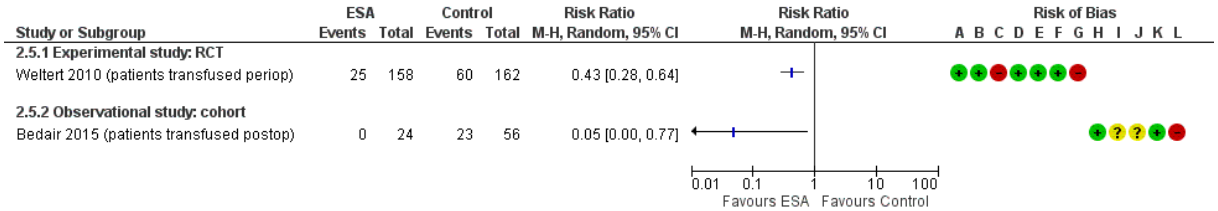
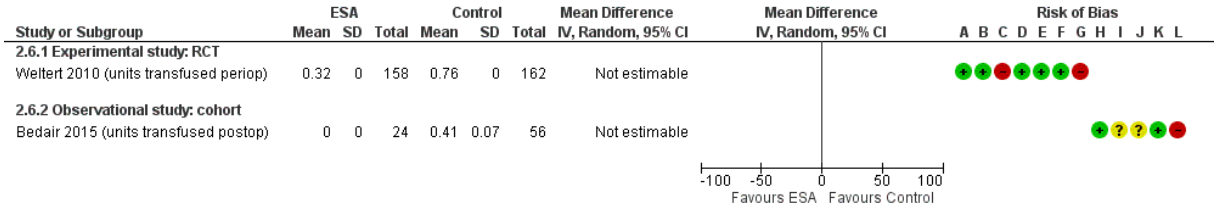
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 9: Forest plot of outcome: Infections

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**erythrocyte stimulating agents (ESAs)**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Secondary: Red blood cell utilization - Number of patients transfused (experimental study: RCT)												
1	randomised trials	serious [a]	not serious	not serious	serious [f]	none	25/158 (15.8%)	60/162 (37.0%)	**RR 0.43** (0.28 to 0.65)	**211 fewer per 1.000** (from 130 fewer to 267 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Secondary: Red blood cell utilization - Number of patients transfused (observational cohort study)												
1	observational studies	serious [d]	not serious	not serious	serious [f]	none	0/24 (0.0%)	23/56 (41.1%)	**RR 0.050** (0.003 to 0.770)	**390 fewer per 1.000** (from 94 fewer to 409 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Secondary: Red blood cell utilization - Number of units transfused (experimental study: RCT)												
1	randomised trials	serious [a]	not serious	not serious	serious [e]	none	See Forest plot – experimental study (Figure 10). In the RCT by Weltert et al 2010, no statistically significant decrease in the number of blood units transfused perioperatively could be demonstrated between patients receiving subcutaneous administration of EPO compared to no treatment (EPO vs no treatment: 0.32 vs 0.76 units, p=0.008).				⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	erythrocyte stimulating agents (ESAs)	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
 Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias (H) Inappropriate eligibility criteria (I) Inappropriate methods for exposure and outcome variables (J) Not controlled for confounding (K) Incomplete or inadequate follow-up (L) Other limitations Figure 10: Forest plot of outcome: Red blood cell utilization – Number of patients transfused											
Secondary: Red blood cell utilization - Number of units transfused (observational cohort study)												
1	observational studies	serious [d]	not serious	not serious	serious [c]	none	See Forest plot – observational study (Figure 11). For the observational cohort study by Bedair, 2005 in patients undergoing hip or knee arthroplasty, with Hb levels < 13 g/dl, the effect size was not estimable (Epoetin alpha vs control: 0 vs 0.41±0.07 units).				⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	erythrocyte stimulating agents (ESAs)	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Inappropriate eligibility criteria
(I) Inappropriate methods for exposure and outcome variables
(J) Not controlled for confounding
(K) Incomplete or inadequate follow-up
(L) Other limitations

Figure 11: Forest plot of outcome: Red blood cell utilization – Number of units transfused

Secondary: Thromboembolic events												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/458 (0.4%)	6/462 (1.3%)	**RR 0.34** (0.01 to 8.33)	**9 fewer per 1.000** (from 13 fewer to 95 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Decision to downgrade by reviewer(s). The study of Weltert, 2010 had high risk of performance bias (i.e. no blinding of participants and personnel). In addition, there was no correction for multiple testing and therefore high risk of other bias; b. Low number of events and large variability of results; c. Low sample size and lack of data

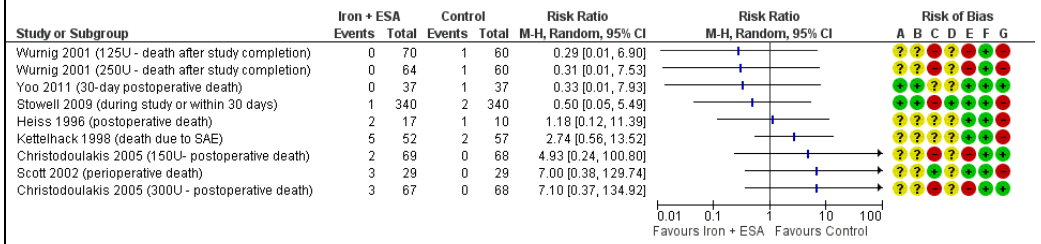
d. Decision to downgrade by reviewer(s), since Bedair, 2015 showed unclear risks of use of inappropriate methods for exposure and outcome variables, and unclear risk of not controlling for confounding. Moreover, only a small minority of the eligible patients were willing to consider taking Epoetin alpha, thereby increasing the risk of selection bias; e. Low sample size; f. Low number of events

Comparison 4: Iron + ESA versus no treatment – placebo – standard of care

Overview evidence table GRADE software (comparison 4)

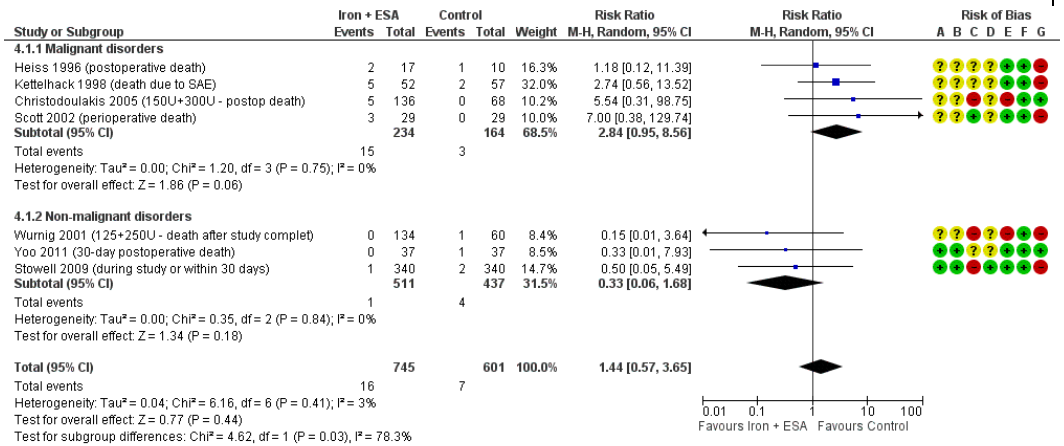
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iron supplementation + ESAs**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Primary: (All-cause) mortality												
7	randomised trials	serious [a]	not serious [b]	not serious	serious [c]	none [d]	See Forest plot A: A statistical significant effect on mortality for all events (except acute kidney injury) could not be				⨁⨁◯◯ LOW	CRITICAL

A



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

B



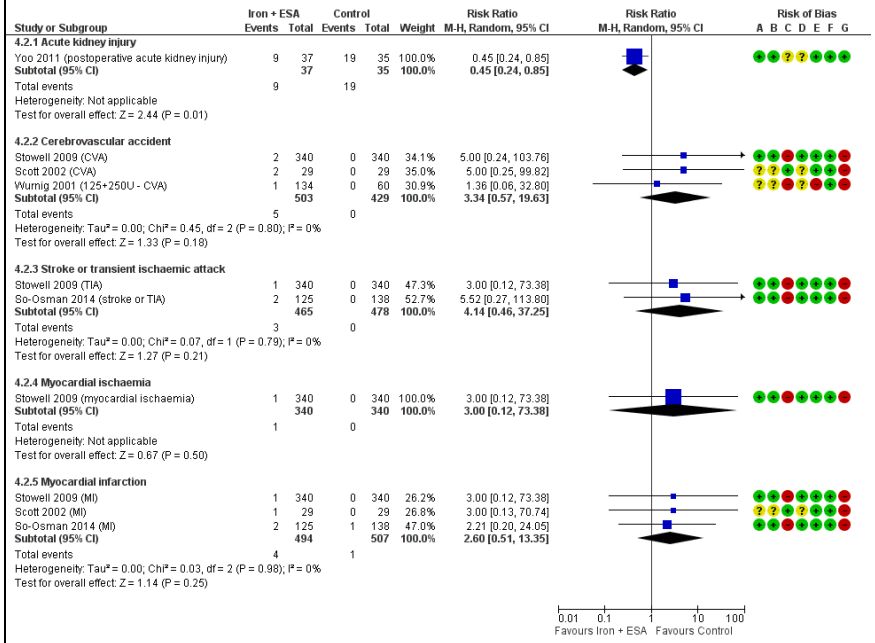
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

demonstrated and results are considered as imprecise due to low number of events and/or large variability in results.

See Forest plot B:
subgroup analysis (malignant versus non-malignant disorders): although there is a trend for an increased mortality risk in malignant disoreders and a reduced mortality risk in non-malignant disorders, the imprecise results (due to low number of events and large variability in results) indicate no evidence of effect rather than evidence of no effect.

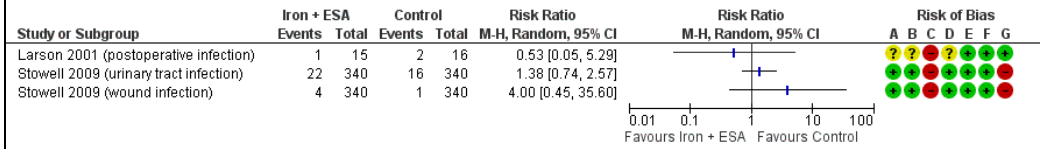
Primary: Anemia-associated ischaemic events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iron supplementation + ESAs**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
5	randomised trials	serious [e]	not serious [f]	not serious	serious [g]	none [h]	See Forest plot: Although point estimates for all events (except acute kidnety injury) are "in favour of the control group", no statistical significant reduction in anaemia-associated events could be demonstrated due to imprecise results (low number of events and/or large variability in results). Yoo 2011 found that ESA+Iron resulted in a statistical significant reduction in acute kidney injury compared to the control group.				⨁⨁◯◯ LOW	CRITICAL



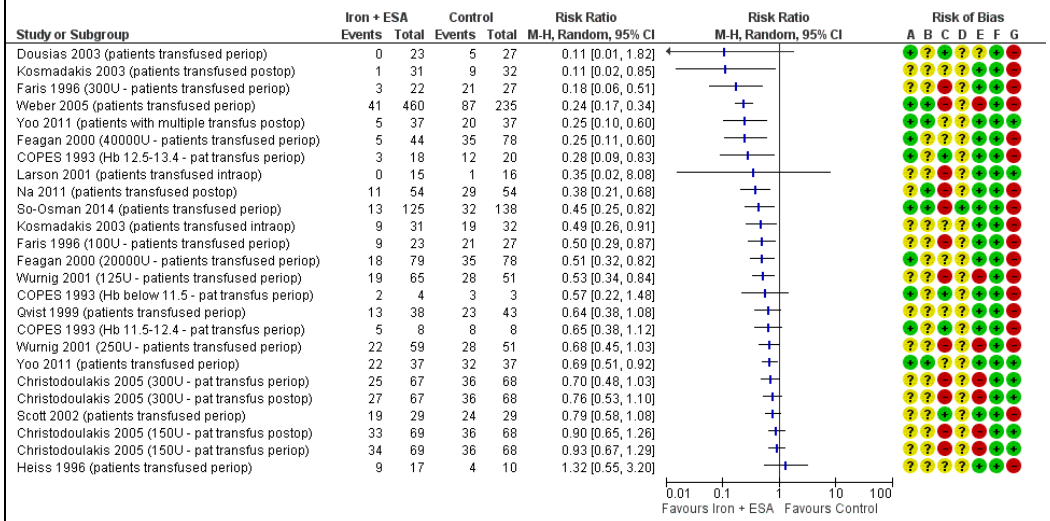
Secondary: Length of hospital stay

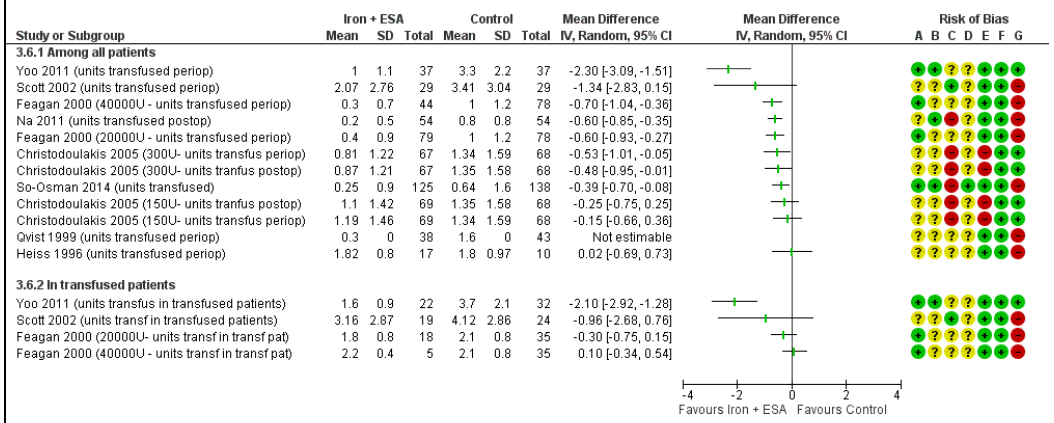
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iron supplementation + ESAs**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomised trials	serious [i]	not serious	not serious	serious [j]	none	106	112	-	MD **1.54 days fewer** (3.29 fewer to 0.21 more)	⨁⨁◯◯ LOW	IMPORTANT
Secondary: Infections												
2	randomised trials	serious [k]	not serious [b]	not serious	serious [l]	none	See forest plot. A statistically significant effect on infections could not be demonstrated due to imprecise results (low number of events and/or large variability in results)				⨁⨁◯◯ LOW	IMPORTANT

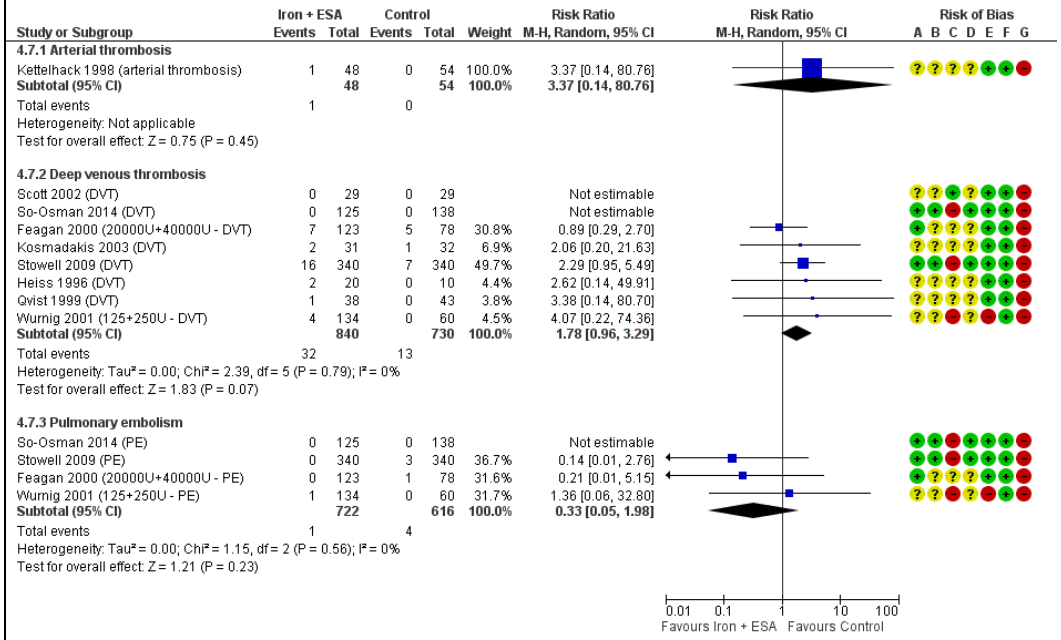


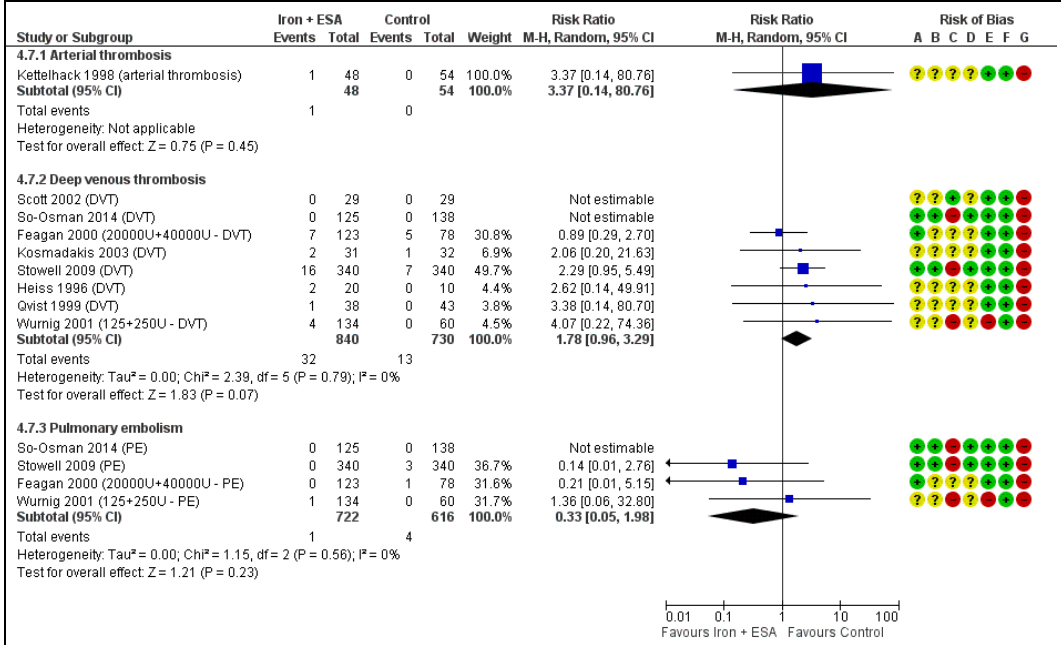
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Secondary: Red blood cell utilization - Number of patients transfused												
16	randomised trials	serious [a]	not serious [m]	not serious	not serious	none [o]					⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iron supplementation + ESAs**	**no treatment, placebo, standard of care**	**Relative (95% CI)**	**Absolute (95% CI)**		
							See Forest plot: (Statistical significant) reduction in the number of patients receiving RBC transfusion.					
Secondary: Red blood cell utilization - Number of units transfused												
8	randomised trials	serious [a]	not serious [m]	not serious	not serious	none [q]	See Forest plot: (Statistical significant) reduction in the number of patients receiving RBC transfusion.				⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementation + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
												
Secondary: Thromboembolic events (arterial and deep venous thrombosis)												
9	randomised trials	serious [a]	not serious [b]	not serious	serious [u]	none [v]	See Forest plot arterial and deep venous thrombosis.				⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementation + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
							Arterial thrombosis: although point estimate is in favor of the control group, a statistical significant reduction in arterial thrombosis when comparing iron+ESA versus the control group, could not be demonstrated (low number of events and large variability in results). Deep venous thrombosis: a trend for an increased risk for deep venous thrombosis (p=0.07) in patients receiving iron+ESA versus control group.			
Secondary: Thromboembolic events (pulmonary embolism)												
4	randomised trials	serious [a]	not serious [b]	not serious	serious [w]	none [x]	See Forest plot pulmonary embolism.				⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementation + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
							Although point estimate is in favor of iron+ESA, a statistical significant reduction in pulmonary embolism when comparing iron+ESA versus the control group, could not be demonstrated (low number of events and large variability in results).					

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Decision to downgrade by the reviewer(s), as most of the studies have substantial unclear or high risk of bias.

b. Decision not to downgrade by the reviewer(s). Although there are differences in the direction of effect across the different studies, none of these effects are statistically significant, and the 95% CI show considerable overlap.
c. Decision to downgrade by the reviewer(s) for low number of events. The total number of (unique) patients included in these trials was 745 in the iron + ESA group and 601 in the control group, with only 16 and 7 (unique) events occurring in these groups, respectively. Therefore, the threshold of 400 is not reached.
d. Decision not to downgrade by the reviewer(s). 3 out of 7 studies were funded by the pharmaceutical indrustry: Heiss, 1996; Scott, 2002 and Wurnig, 2001. However, the body of evidence consists of both positive and negative trials. Moreover, the search for systematic reviews was comprehensive.
e. Decision to downgrade by the reviewer(s), as 3 out of 5 studies did not report on both selection bias (i.e. random sequence generation and allocation concealment) and detection bias (i.e. blinding of outcome assessors).
f. Decision not to downgrade by the reviewer(s): the direction and the magnitude of effect are quite similar across the studies, 95% CI show large overlap.
g. Decision to downgrade by the reviewer(s) due to low number of events (22 in iron + ESA group and 20 in control group).
h. Decision not to downgrade by the reviewer(s). Out of the 5 studies, 2 studies (Scott, 2002 and Wurnig, 2001) were funded by the pharmaceutical indrustry. However, these studies do not pull the effect in one direction or the other, as both industry-sponsored and non-industry-sponsored trials favour the control condition.
i. Decision to downgrade by the reviewer(s), as 2 out of 4 studies have unclear risk of selection bias (i.e. random sequence generation and allocation concealment) and all 4 studies show unclear risk of detection bias (i.e. blinding of outcome assessment). Moreover, there is high risk of performance bias (i.e. blinding of participants and personnel) for Larson, 2001.
j. Limited sample size: threshold of 400 is not reached.
k. Decision to downgrade by the reviewer(s). The study by Larson, 2001 shows unclear risk of selection bias (i.e. random sequence generation and allocation concealment) and detection bias (i.e. blinding of outcome assessment). Moreover, both studies show risk risk of performance bias (i.e. blinding of participants and personnel). In addition, there is high risk of other bias for Stowell, 2009 (no corrections for multiple testing, no baseline ultrasound scanning to exclude or balance pre-existing deep venous thrombosis).
l. Decision to downgrade due to low number of events (25 in the iron + ESA group and 19 in the control group).
m. Decision not to downgrade by the reviewer(s): the direction of the effect is similar across studies and the 95% CI show considerable overlap.
o. Decision not to downgrade by the reviewer(s). Out of the 16 studies included, 5 studies (Feagan, 2000; Heiss ,1996; Qvist, 1999; Scott, 2002 and Wurnig, 2001) were funded by the pharmaceutical company supplying the EPO. Although 4 of these studies are small and favour treatment with iron + ESA, these studies do not pull the effect estimate into one or the other direction. Moreover, the search for studies was comprehensive.
q. Decision not to downgrade by the reviewer(s). Out of the 8 studies included, 4 studies (Scott, 2002; Feagan, 2000; Qvist, 1999 and Heiss, 1996) were funded by the pharmaceutical company supplying the EPO. Although 2 of these studies are small and favour treatment with iron + ESA (Scott, 2002 and Feagan, 2000), the other 2 small studies (Qvist, 1999 and Heiss, 1996) do not pull the effect estimate towards the same direction. In addition, the search for studies was comprehensive.
r. Decision to downgrade by the reviewer(s). All 3 studies included show unclear risk of detection bias (i.e. blinding of outcome assessment). Moreover, 2 studies have unclear risk of selection bias (i.e. random sequence generation and/or allocation concealment).
s. Decision to downgrade by the reviewer(s). There is large variation in the magnitude of effect across the 3 different studies. Moreover, the 95% CI of the study by Yoo, 2011 and Feagan, 2000 do not overlap.
t. Decision not to downgrade by the reviewer(s). Out of the 3 studies included, 2 studies (Feagan, 2000 and Scott, 2002) were funded by the pharmaceutical company supplying the EPO. Although these studies are small, they do not favour the use of iron + ESA. Moreover, the search for studies was comprehensive.
u. Decision to downgrade by the reviewer(s) due to low number of events (33 in the iron + ESA group and 13 in the control group).
v. Decision not to downgrade by the reviewer(s). Out of the 9 studies included, 5 studies (Feagan, 2000; Heiss, 1996; Qvist, 1999; Scott, 2002 and Wurnig, 2001) are funded by the pharmaceutical company supplying the EPO. Although these studies are small, they do not pull the direction of the effect towards the other side than the non-funded studies. Instead, they also favour the control condition. Moreover, the search for studies was comprehensive.
w. Decision to downgrade by the reviewer(s) due to low number of events (1 in the iron + ESA group and 4 in the control group).

x. Decision not to downgrade by the reviewer(s). Out of the 4 studies included, 2 studies (Feagan, 2000 and Wurnig, 2001) are funded by the pharmaceutical company supplying the EPO. Although these studies are small, they are pulling the direction of the effect towards favouring the control group. The larger non-funded study by Stowell, 2009 however pulls the direction towards favouring the iron + ESA group. In addition, the search for studies was comprehensive

Resource use

<table>
<tr><th>Author, year, Country</th><th>Information on economic outcomes</th></tr>
<tr><td colspan="2">COMPARISON 1:
TRANSFUSION VS NO TREATMENT/PLACEBO/STANDARD OF CARE</td></tr>
<tr><td>Karkouti, 2012, Canada</td><td>No data on economic outcomes were reported</td></tr>
<tr><td colspan="2">COMPARISON 2:
IRON SUPPLEMENTATION VS NO TREATMENT/PLACEBO/STANDARD OF CARE</td></tr>
<tr><td>Edwards, 2009, UK</td><td>No data on economic outcomes were reported</td></tr>
<tr><td>Lidder, 2007, UK</td><td>Cost fortnight's course of ferrous sulphate 200 mg TDS = $1.82
Cost single, allogeneic unit of blood = $182 excluding extraneous costs such as giving sets and nursing care.

Control group: 47U transfused -> $6580
Intervention group (iron suppl): $2142 (FeSO4 at $42 + 15 U at $2100) representing a 66% cost reduction.</td></tr>
<tr><td>Muñoz, 2006, Spain</td><td>No data on economic outcomes were reported</td></tr>
<tr><td>Okuyama, 2005, Japan</td><td>No data on economic outcomes were reported</td></tr>
<tr><td colspan="2">COMPARISON 3:
ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE</td></tr>
<tr><td>Bedair, 2015, USA</td><td>The cost analysis demonstrated that the EPO strategy was more costly compared with no EPO ($2632 versus $2284) and its cost would need to be less than $225/dose for this to change.
Table 2. Cost data
<table><tr><th>Parameter</th><th>Cost (2012, USD)</th><th>Sensitivity analysis range</th></tr><tr><td>Hospital stay (average daily variable cost, no transfusion)</td><td>581</td><td></td></tr><tr><td>Hospital stay (average daily variable cost, transfusion)</td><td>684</td><td></td></tr><tr><td>Single unit of EPO</td><td>380</td><td>100–500</td></tr><tr><td>Transfusion single unit of allogeneic blood</td><td>300</td><td>100–500</td></tr></table>EPO = erythropoietin alpha.</td></tr>
<tr><td>Weltert, 2010, Italy</td><td>Cost protocol expense intervention group (EPO): $299 per patient
Cost of 1 unit of blood = $332
➔ Saving of approximately half a unit of blood per patient was not cost-effective.
➔ the increased length of stay of 0.57 days per patient would increase the cost of the control group by $561 per patient, thus making the protocol eventually convenient.</td></tr>
<tr><td>Weltert, 2015, Italy</td><td>Cost protocol expense intervention group (EPO): $392 per patient (expense for drug supply only due to a very simple administration of drug, requiring few minutes of care in each patient and no patient preparation or medications). However, this expense was offset by fewer aRBCt procedures in the EPO group (0.40 vs. 1.01 units per patient). Hence, a relevant cost saving per patient could be hypothesized with HRE, if we assume a mean cost for a single aRBC of $761 as reported by Shander and coworkers.</td></tr>
</table>

	we could observe a cost increase of $134 per patient in the HRE group; this additional cost, however, might be balanced by reduction in hospital length of stay of approximately 0.57 days in the HRE group (6.92 days vs. 7.49 days) and by a related cost reduction of approximately $225 (assuming the rate of approx. $395 for each additional day in hospital over the admitted length of stay, as fixed by our national health service for cardiovascular intervention).
COMPARISON 4: IRON SUPPLEMENTATION + ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE	
Canadian Orthopedic Perioperative Erythropoietin Study Group (COPES), 1993, Canada	No data on economic outcomes were reported
Christodoulakis, 2005, Greece	No data on economic outcomes were reported
Dousias, 2003, Greece	No data on economic outcomes were reported
Faris, 1996, USA	No data on economic outcomes were reported
Feagan, 2000, Canada	The retail cost of epoetin alfa is Can$267.90 per 20.000-U vial and Can$535.80 per 40.000-U vial.
Heiss, 1996, Germany	No data on economic outcomes were reported
Kettelhack, 1998, Germany	No data on economic outcomes were reported
Kosmadakis, 2003, Greece	The cost of allogenic transfusion in our hospital is estimated at $492 per unit. Conversely, the administration of erythropoietin costs $221 per day (supplemental iron administration: $25 per day), and it was found to be related to a lower postoperative complication rate and better survival outcome.
Larson, 2001, Sweden	No data on economic outcomes were reported
Na, 2011, South Korea	No data on economic outcomes were reported
Qvist, 1999, Denmark	The cost of 1 unit of leukocyte-depleted blood is approximately 1,000 Danish kronors per patient (+/- $165) compared to 7,500 kronors on average for the erythropoietin treatment in each patient in the present study per patient (+/- $1237)
Scott, 2002, USA	No data on economic outcomes were reported
So-Osman, 2014, The Netherlands	Erythropoietin increased costs by $965 per patient (95% CI, 322 to 1610), that is, $8979 per avoided transfusion (95% CI, 2337 to 29520). Compared with controls, autologous blood reinfusion did not result in erythrocyte reduction and increased costs by $660 per patient (95% CI, 55 to 1267). The total costs per unit of erythrocyte transfused was estimated at four times the product price (*i.e.*, $1019 per unit) including costs of compatibility tests and handling, according to the article by Shander *et al*.
Stowell, 2009, USA	No data on economic outcomes were reported

Weber, 2005, The Netherlands	No data on economic outcomes were reported
Wurnig, 2001, Austria	No data on economic outcomes were reported
Yoo, 2011, South Korea	No data on economic outcomes were reported

.

Detailed evidence summary

Topic	Patient Blood Management (PBM)
Subtopic	Management preoperative anaemia
Intervention	Iron supplementation, erythropoiesis-stimulating agents (ESA) or transfusion
Question (PICO)	In patients with preoperative anaemia (Population), is transfusion or the use of iron supplementation and/or erythrocyte stimulating agents (Intervention) effective to improve clinical and economic outcomes (Outcomes) compared to no intervention (Comparison)?
Search Strategy	Databases **The Cochrane Library** (controlled trials) using the following search strategy: 1. [mh "Preoperative Period"] OR [mh "Preoperative care"] OR preoperat*:ti,ab,kw OR pre-operat*:ti,ab,kw OR presurg*:ti,ab,kw OR pre-surg*:ti,ab,kw OR (before NEXT surger*):ti,ab,kw OR (before NEXT surgical*):ti,ab,kw OR (before NEXT operati*):ti,ab,kw OR ("prior to" NEXT surger*):ti,ab,kw OR ("prior to" NEXT surgical*):ti,ab,kw OR ("prior to" NEXT operati*):ti,ab,kw 2. [mh "Anemia"] OR anemi*:ti,ab,kw OR anaemi*:ti,ab,kw 3. [mh "Iron"] OR [mh "Iron Compounds"] OR iron:ti,ab,kw OR dextran:ti,ab,kw OR Venofer:ti,ab,kw OR ferrous:ti,ab,kw OR ferric:ti,ab,kw OR ferrlecit:ti,ab,kw OR [mh "Erythropoietin"] OR [mh "Hematinics"] OR epo:ti,ab,kw OR erythropoiet*:ti,ab,kw OR ("erythropoiesis-stimulating" NEXT agent*):ti,ab,kw OR hematopoiet*¨:ti,ab,kw OR haematopoiet*:ti,ab,kw OR hemopoiet*:ti,ab,kw OR haemopoiet*:ti,ab,kw OR hematinic*:ti,ab,kw OR haematinic*:ti,ab,kw OR "epoetin alfa":ti,ab,kw OR Procrit:ti,ab,kw OR Epogen:ti,ab,kw OR "epoetin beta":ti,ab,kw OR NeoRecormon:ti,ab,kw OR "darbepoetin alfa":ti,ab,kw OR Mircera:ti,ab,kw OR [mh "Blood Transfusion"] OR ((blood:ti,ab,kw OR erythrocyte*:ti,ab,kw OR (red NEXT cell*):ti,ab,kw OR ("red blood" NEXT cell*):ti,ab,kw OR RBC*:ti,ab,kw) AND (transfus*:ti,ab,kw OR infus*:ti,ab,kw OR unit*:ti,ab,kw OR therap*:ti,ab,kw)) OR hemotransfus*:ti,ab,kw OR haemotransfus*:ti,ab,kw OR hemotherap*:ti,ab,kw OR haemotherap*:ti,ab,kw OR hypertransfus*:ti,ab,kw 4. 1-3 AND **MEDLINE** (via PubMed interface) using the following search strategy: 1. "Preoperative Period"[Mesh] OR "Preoperative Care"[Mesh] OR preoperat*[TIAB] OR pre-operat*[TIAB] OR presurg*[TIAB] OR pre-surg*[TIAB] OR before surger*[TIAB] OR before surgical*[TIAB] OR before operati*[TIAB] OR prior to surger*[TIAB] OR prior to surgical*[TIAB] OR prior to operati*[TIAB] 2. "Anemia"[Mesh] OR anemi*[TIAB] OR anaemi*[TIAB] 3. "Iron"[Mesh] OR "Iron Compounds"[Mesh] OR iron[TIAB] OR dextran[TIAB] OR Venofer[TIAB] OR ferrous[TIAB] OR ferric[TIAB] OR ferrlecit[TIAB] OR "Erythropoietin"[Mesh] OR "Hematinics"[Mesh] OR epo[TIAB] OR erythropoiet*[TIAB] OR erythropoiesis-stimulating agent*[TIAB] OR hematopoiet*[TIAB] OR haematopoiet*[TIAB] OR hemopoiet*[TIAB] OR haemopoiet*[TIAB] OR hematinic*[TIAB] OR haematinic*[TIAB] OR "epoetin alfa"[TIAB] OR Procrit[TIAB] OR Epogen[TIAB] OR "epoetin beta"[TIAB] OR NeoRecormon[TIAB] OR "darbepoetin alfa"[TIAB] OR Mircera[TIAB] OR "Blood transfusion"[Mesh] OR ((blood[TIAB] OR erythrocyte*[TIAB] OR red cell*[TIAB] OR red blood cell*[TIAB] OR RBC*[TIAB]) AND (transfus*[TIAB] OR infus*[TIAB] OR unit*[TIAB] OR therap*[TIAB])) OR hemotransfus*[TIAB]

	OR haemotransfus*[TIAB] OR hemotherap*[TIAB] OR haemotherap*[TIAB] OR hypertransfus*[TIAB] 4. (("Meta-Analysis as Topic"[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR "Meta-Analysis"[PT] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR "Review Literature as Topic"[Mesh]) OR (cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR "science citation index"[TIAB] OR bids[TIAB] OR cancerlit[TIAB]) OR (reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR "relevant journals"[TIAB] OR manual search*[TIAB]) OR (("selection criteria"[TIAB] OR "data extraction"[TIAB]) AND "Review"[PT])) NOT ("Comment"[PT] OR "Letter"[PT] OR "Editorial"[PT] OR ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))) 5. "Controlled Clinical Trial"[PT] OR random*[TIAB] OR controll*[TIAB] OR "intervention study"[TIAB] OR "experimental study"[TIAB] OR "comparative study"[TIAB] 6. 1-4 AND (systematic reviews) 7. 1 AND 2 AND 3 AND 5 (controlled clinical trials) **Embase** (via Embase.com interface) using the following search strategy: 1. 'Preoperative period'/exp OR 'Preoperative care'/exp OR 'Preoperative evaluation'/exp OR preoperat*:ab,ti OR pre-operat*:ab,ti OR presurg*:ab,ti OR pre-surg*:ab,ti OR (before NEXT/1 surger*):ab,ti OR (before NEXT/1 surgical*):ab,ti OR (before NEXT/1 operati*):ab,ti OR ('prior to' NEXT/1 surger*):ab,ti OR ('prior to' NEXT/1 surgical*):ab,ti OR ('prior to' NEXT/1 operati*):ab,ti 2. 'Anemia'/exp OR anemi*:ab,ti OR anaemi*:ab,ti 3. 'Antianemic agent'/exp OR 'Iron'/exp OR 'Iron derivative'/exp OR iron:ab,ti OR dextran:ab,ti OR Venofer:ab,ti OR ferrous:ab,ti OR ferric:ab,ti OR ferrlecit:ab,ti OR epo:ab,ti OR erythropoiet*:ab,ti OR ('erythropoiesis-stimulating' NEXT/1 agent*):ab,ti OR hematopoiet*:ab,ti OR haematopoiet*:ab,ti OR hemopoiet*:ab,ti OR haemopoiet*:ab,ti OR hematinic*:ab,ti OR haematinic*:ab,ti OR 'epoetin alfa':ab,ti OR Procrit:ab,ti OR Epogen:ab,ti OR 'epoetin beta':ab,ti OR NeoRecormon:ab,ti OR 'darbepoetin alfa':ab,ti OR Mircera:ab,ti OR 'Blood transfusion'/exp OR ((blood:ab,ti OR erythrocyte*:ab,ti OR (red NEXT/1 cell*):ab,ti OR ('red blood' NEXT/1 cell*):ab,ti OR RBC*:ab,ti) AND (transfus*:ab,ti OR infus*:ab,ti OR unit*:ab,ti OR therap*:ab,ti)) OR hemotransfus*:ab,ti OR haemotransfus*:ab,ti OR hemotherap*:ab,ti OR haemotherap*:ab,ti OR hypertransfus*:ab,ti 4. (('meta analysis (topic)'/exp OR 'meta analysis'/exp OR (meta NEXT/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR (systematic NEXT/1 review*):ab,ti OR (systematic NEXT/1 overview*):ab,ti) OR (cancerlit:ab,ti OR cochrane:ab,ti OR embase:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR cinahl:ab,ti OR cinhal:ab,ti OR 'science citation index':ab,ti OR bids:ab,ti) OR ('reference list*':ab,ti OR bibliograph*:ab,ti OR hand-search*:ab,ti OR (manual NEXT/1 search*):ab,ti OR 'relevant journals':ab,ti) OR (('data extraction':ab,ti OR 'selection criteria':ab,ti) AND review/it)) NOT (letter/it OR editorial/it OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

	5. Controlled clinical trial/exp OR random*:ab,ti OR controll*:ab,ti OR "intervention study":ab,ti OR "experimental study":ab,ti OR "comparative study":ab,ti 6. 1-4 AND (systematic reviews) 7. 1 AND 2 AND 3 AND 5 (controlled clinical trials) **Transfusion Evidence Library** using the following search strategy: 1. Subject Area < Clinical Practice < Management of anaemia 2. preoperative OR pre-operative OR presurgical OR pre-surgical OR "before surgery" OR "before surgical" OR "before operating" OR "prior to surgery" OR "prior to surgical" OR "prior to operating" 3. Study design < Systematic review or Randomized Controlled Trial 4. 1-3 AND
Search date	30 January 2018
In/Exclusion criteria	**Population:** *Included:* preoperative elective surgery adult patients with anemia divided into a) elective surgery in malignant disorders (all carcinomas leading to a potential blood loss (e.g. gastrointestinal or urogenital tumors) or an infiltration of the bone marrow (e.g. metastasis in tumors) and b) elective surgery in non-malignant disorders (all other non-malignant diseases in preoperative anemic patients undergoing elective surgery), and also divided in c) high risk of bleeding operations and d) low risk of bleeding operations. Following the WHO definition, preoperative anemia is defined as haemoglobin (Hb) levels<13 g/dl (adult men) or Hb<12 g/dl (adult women). Studies were included if the Hb levels of the patients were covered by this definition. If studies also included patients whose Hb levels did not fall within the range of the WHO definition (e.g. 11-16 g/dl), only data from the most relevant subgroups were extracted if possible (e.g. <11.5, 11.5-12.4 and 12.5-13.4 g/dl). If no subgroup analyses were performed, the data from all patients were extracted. *Excluded:* non-elective surgery patients, non-anemic elective surgery patients, elective surgery patients with preoperative anemia which is not formally/explicitly defined, elective surgery patients with sickle-cell anemia or thalassemia, pediatric patients. **Intervention:** *Included:* Intervention 1: transfusion; Intervention 2: iron supplementation (intravenous or oral); Intervention 3: ESA; Intervention 4: iron supplementation + ESA. Interventions that include the use of vitamins (e.g. folic acid, vitamin B12) as a general measure to support the production of erythrocytes in the bone marrow, are included. *Excluded:* other interventions to manage anemia such as preoperative (autologous or homologous) transfusion and the use of tranexamic acid. Also excluded are interventions that combine one of the interventions of interest (iron supplementation and/or ESA) with these other treatments (e.g. combination of EPO and tranexamic acid). **Comparison:** *Included*: Comparison 1-4: no treatment, placebo, standard of care. *Excluded:* autologous blood donation, other interventions to treat anemia such as the use of tranexamic acid. **Outcome:** *Included:* Primary outcomes: • (All-cause) mortality • Anemia-associated ischaemic events, defined as: o acute myocardial infarction; o acute ischaemic stroke; o acute kidney injury;

	○ acute mesenteric ischaemia; ○ acute peripheral vascular ischaemia. <u>Secondary outcomes:</u> • Length of hospital stay • Any type of reported infection. A patient was considered to have an infection when one of the following items existed (Weber, 2005): ○ Wound infection: redness, purulent exudate or positive culture of wound fluid; ○ Wound abscess: drainage of abscess or spontaneous discharge of pus; ○ Abscess or infected haematoma in surgical area or near the implant: positive culture after collection of pus or re-exploration; ○ Urinary tract infection: abnormal urine sediment with white blood cells and/or a positive urine culture and/or clinical signs; ○ Respiratory tract infection: clinical signs according to the investigator and/or a positive sputum culture leading to treatment with antibiotics; ○ Pneumonia: clinical or radiological signs of a pulmonary infiltrate; ○ Bacteraemia: typical clinical signs (e.g. fever) and positive blood culture. • Red blood cell utilization (units transfused, number of patients receiving a transfusion). • Thromboembolic events, defined as deep venous/arterial thrombosis and/or pulmonary embolism. *Excluded:* Hb levels, drug-related adverse events. **Study design:** *Included*: Intervention 1 (transfusion): individual experimental studies; Intervention 2-3-4 (Iron and/or ESA): experimental studies that were included in the systematic reviews identified from the systematic review search, *i.e.* randomised controlled trials, quasi-randomised controlled trials, non-randomised controlled trials, controlled before and after study, or controlled interrupted time series. For comparisons 2 and 3, the experimental studies did not provide sufficient data. Therefore, for these 2 comparisons, observational cohort studies were also included. *Excluded:* studies reporting no quantitative data, studies reporting only means, but no standard deviations, effect sizes and/or p-values. **Language:** English, French and German

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison/Risk factor	Remarks
COMPARISON 1: TRANSFUSION VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Karkouti, 2012, Canada	Experimental: Randomized controlled trial	60 anaemic patients (haemoglobin 10-1 g/dL) undergoing cardiac surgery with cardiopulmonary bypass were randomized (1:1) to one of the 2 groups: 1) prophylactic transfusion (n=29, 73 years (IQR: 65-75), 72% males) 2) standard of care (n=31, 71 years (IQR: 62-79), 29% males) Analysis was carried out on an intention-to-treat basis.	<u>Prophylactic transfusion:</u> 2 units of erythrocytes transfused 1 to 2 days before surgery (same-day admit patients were transfused as outpatients in the medical day unit) <u>Standard of care:</u> Erythrocyte transfusions during or after surgery at the discretion of the clinical team, according to standard guidelines. All other aspects of care were according to routine clinical management.	The trial was registered at ClinicalTrials.gov (identifier: NCT00861822). The sample size estimate was based on the expected efficacy of the intervention in reducing the need for erythrocyte transfusion during surgery from 80% to 36% (estimates based on the prestudy rates in anemic and nonanemic patients). A sample size of 50 patients was deemed to be adequate to detect this effect size (power=0.8; α=0.05). To allow for dropouts after randomization, the sample size was increased to 60 patients.
COMPARISON 2: IRON SUPPLEMENTATION VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Edwards, 2009, UK	Experimental: Randomized controlled trial	62 patients (11 anaemic at recruitment, 22 with normal Hb levels and 29 without recent records of anaemia status) scheduled to undergo bowel	<u>Iron sucrose:</u> Iron sucrose 300 mg intravenously, two infusions (minimally 24 hours apart from each other, the second one completed within a	Identified from the systematic review of Borstlap, 2015. The trial was registered with the UK

		resection for suspected colorectal cancer were randomly assigned to one of 2 groups: 1) Iron sucrose (n=34, ratio men:women 22:12, median age 67 years) 2) Placebo (n=26, ratio men:women 17:9, median age 70 years) Analysis was carried out on an intention-to-treat basis.	minimum of 14 days before surgery) <u>Placebo:</u> Placebo 250 ml intravenously, 2 infusions (minimally 24 hours apart from each other, the second one completed within a minimum of 14 days before surgery) *Transfusion policy for all patients:* - Hb >10 g/dl: no transfusion - Hb 8-10 g/dl: transfuse if * abnormal ECG * ischaemic heart disease * obstructive lung disease * consultant's discretion * unable to absorb oral iron - Hb <8 g/dl: transfuse to target 10 g/dl [As our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on anaemic patients (baseline Hb levels <13.5 g/dl for men and <12.5 g/dl for women) were extracted.]	Medicines and Healthcare products Regulatory Agency (registration number: 2005-003 608-13). The study was powered at 80% to detect a difference in the mean change in serum Hb concentration between recruitment and treatment of 0,5 g/dl in anaemic patients. This power analysis indicated that 10 people were needed in each group.
Lidder, 2007, UK	Experimental: Randomized controlled trial	49 patients with colorectal malignancies scheduled for surgery were randomly assigned to one of 2 groups: 1) Ferrous sulphate (n=24, 14 men and 8 women, aged 47-89 years; 3 men and 3 women anaemic) 2) Standard clinical management (n=25,	<u>Ferrous sulphate:</u> Oral ferrous sulphate 200 mg 3 times per day <u>Standard clinical management:</u> not defined *Transfusion policy for all patients:* - Hb >10 g/dl: no transfusion - Hb 8-10 g/dl: transfuse if * abnormal ECG	Identified from the systematic review of Borstlap, 2015. In order to detect a change in haemoglobin of 0,5 g/dl with a SD of 0,5 g/dl, power of 80% and 2-tailed significance of 0,05, n = 10. In

		14 men and 9 women, aged 57-80 years; 8 men and 6 women anaemic) Analysis was performed on an intention-to-treat basis.	* ischaemic heart disease * obstructive lung disease * consultant's discretion * unable to absorb oral iron - Hb <8 g/dl: transfuse to target 10 g/dl [As our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on anaemic patients (Hb levels <13.5 g/dl in men and <11.5 g/dl in women) were extracted.]	recruiting 20 anaemic patients, we anticipated seeing 52 (20x100/38) in total.
Muñoz, 2006, Spain	Observational: cohort study	24 consecutive patients (7 men and 17 women, aged on average 74±11 years) undergoing surgery for total hip replacement received the iron sucrose intervention. A retrospective series of 22 patients (3 men and 19 women, aged on average 77±10 years) served as the control group.	<u>Iron sucrose:</u> Iron sucrose 100 mg intravenously once per day for 3 days, starting after surgery <u>Control:</u> no iron *Transfusion policy for all patients:* Transfusion was performed when Hb levels <8 g/dl (target Hb: 9 g/dl) and/or in the presence of symptoms of acute anaemia. Only leucoreduced red cell concentrates were used. [As our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on patients with Hb levels <13 g/dl were extracted.]	Identified from the systematic review of Lin, 2013.
Okuyama, 2005, Japan	Experimental: Non-randomized controlled trial	116 patients undergoing colorectal cancer surgery via the abdominal approach only, with Hb levels ≤10 g/dl, were	<u>Iron:</u> Oral sodium ferrous citrate 200 mg daily, after meals in the morning and evening,	Identified from the systematic review of Hallet, 2014.

		assigned to one of 2 groups: 1) Iron (n=32, 15 men and 17 women, aged on average 68.7±9.6 years, Hb levels at first presentation 8.1±1.4 g/dl) 2) Control (n=84, 42 men and 42 women, aged on average 66.7±11.2 years, Hb levels at first presentation 8.0±1.6 g/dl)	during at least 2 preoperative weeks <u>Control:</u> no iron *Transfusion policy for all patients:* intraoperative Hb levels of about 7 g/dl with unstable haemodynamics	
COMPARISON 3: ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Bedair, 2015, USA	Observational: cohort study	80 patients scheduled to undergo unilateral primary total hip or total knee arthroplasty, with Hb levels <13 g/dl, were all recommended to be treated preoperatively with Epoetin alpha. 56 of these 80 patients refused the Epoetin alpha treatment or were unable to pay for the treatment in cases in which the patient's health insurer refused to cover the cost. This rendered 2 groups: 1) Epoetin alpha (n=24, 4 men and 20 women, aged on average 60.8±2.5 years, mean preoperative Hb levels 12.3±0.1 g/dl) 2) Control (n=56, 12 men and 44 women, aged on average 66.2±1.6 years, mean preoperative Hb levels 12.1±0.7 g/dl)	<u>Epoetin alpha:</u> Received at least 1 dose (median 2 doses; range 2-4) of Epoetin alpha preoperatively <u>Control:</u> no Epoetin alpha *Transfusion policy for all patients:* No specific transfusion triggers were used in any of these patients. Only patients with postoperative Hb <10 g/dL who were also symptomatic (hypotension, tachycardia, dizziness, and/or an inability to participate in therapy) and whose symptoms were resistant to fluid boluses were transfused.	Identified from the systematic review of Alexander, 2017. Demographic and clinical data for these patients were retrospectively reviewed. For the Epoetin alpha treatment, the timing, route of administration and number of units is not reported by the authors.

Weltert, 2010, Italy	Experimental: Randomized controlled trial	320 patients with isolated coronary vessel disease undergoing off-pump coronary artery bypass grafting surgery, with Hb levels ≤14.5 g/dl were randomly assigned to one of 2 groups: 1) EPO (n=158, 84% male, aged on average 67±9 years) 2) Control (n=162, 83% male, aged on average 66±11 years) Analysis was performed on an intention-to-treat basis.	<u>EPO:</u> - 14 000 IU EPO subcutaneously on preoperative day 2 and 1 - 8000 IU EPO subcutaneously on operative day and postoperative days 1 and 2. <u>Control:</u> no treatment Both groups used the cell-saver system during the operation. *Transfusion policy for all patients:* Hb <8 g/dl and/or in the case of blood exsanguination, as estimated by saturation of venous blood <50%	Identified from the systematic review of Lin, 2013. Preliminary power analysis suggested that 160 patients per sample were needed to obtain a 90% power goal, considering an alpha error level of 5% and expecting the incidence of transfusion to decrease from the previously observed 30% to 15%.
Weltert, 2015, Italy	Experimental: Randomized controlled trial	600 patients undergoing heart surgery with Hb levels ≤14.5 g/dl were randomly assigned to one of 2 groups: 1) EPO (n=300, 75% male, aged on average 75 (47-96) years) 2) Control (n=300, 73% male, aged on average 74 (40-90) years) Analysis was performed on an intention-to-treat basis.	<u>EPO:</u> - 80 000 IU EPO subcutaneously on preoperative day 2 <u>Control:</u> no treatment All patients received iron supplement per os (routine practice). *Transfusion policy for all patients:* Hb <8 g/dl. All patients requiring RBC transfusion received prestorage leukoreduced aRBC units. Using a thromboelastometric-guided approach, solvent/detergent (S/D)-treated plasma and single-donor apheresis PLT units were administered when indicated.	Not included in a systematic review, added via experts. The primary endpoint was the incidence of perioperative transfusion from the start of surgery through Postoperative Day. A power analysis was conducted to determine the sample size to maintain adequate statistical power. Considering an alpha error of 5%, a two-tailed Pearson chi-square test, and expecting to

				obtain a reduction in fraction of transfused patients from 50% to 35%, a sample of 300 patients per arm was required to achieve a power of 96%.
COMPARISON 4: IRON SUPPLEMENTATION + ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Canadian Orthopedic Perioperative Erythropoietin Study Group (COPES), 1993, Canada	Experimental: Randomized controlled trial	208 patients (50% men, average age 63±13 years) scheduled for elective unilateral hip-joint replacement, with preoperative Hb levels >11 and <16 g/dl were randomly assigned to one of 3 groups: 1) 14 days EPO (n=77) 2) 9 days EPO (n=53) 3) 14 days placebo (n=78) Analysis was performed on an intention-to-treat basis.	<u>14 days EPO:</u> - EPO 300 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 3 - Oral iron sulphate 300 mg, 3 times daily starting on preoperative day 21 until discharge <u>9 days EPO:</u> - Placebo subcutaneously from preoperative day 10 to 6 - EPO 300 IU/kg/day subcutaneously from preoperative day 5 until postoperative day 3 - Oral iron sulphate 300 mg, 3 times daily starting on preoperative day 21 until discharge <u>14 days placebo:</u> - Placebo subcutaneously from preoperative day 10 until postoperative day 3 - Oral iron sulphate 300 mg, 3 times daily starting on preoperative day 21 until discharge *Transfusion policy for all patients:* according to the usual practice of the clinicians, provided the following	Identified from the systematic review of Alsaleh, 2013. Calculations showed that the final sample size of 79 patients in the 14 days EPO and the 9 days EPO group and 54 patients would provide 80% power to detect a difference between the two EPO groups and 53% power to detect a difference between the two EPO groups and the placebo group.

			guidelines were followed: - Intraoperative: blood loss of more than 15% of the intravascular volume - Postoperative: Hb < 9 g/dl [Only data from the 14 days EPO and 14 days placebo groups were extracted. In addition, as our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on patients with Hb levels <11.5, 11.5-12.4 and 12.5-13.4 g/dl were extracted.]	
Christodoulakis, 2005, Greece	Experimental: Randomized controlled trial	223 patients undergoing elective colorectal surgery for resectable colorectal cancer, with Hb levels >9 and <12 g/dl, were randomly assigned to one of 3 groups: 1) Epoetin alfa 150 IU (n=69, 31 men and 38 women, median age 72 years (range 43-91)) 2) Epoetin alfa 300 IU (n=67, 30 men and 37 women, median age 71 years (range 36-92)) 3) Control (n=68, 28 men and 40 women, median age 70 years (range 44-89) Of 223 patients in the intention-to-treat population, 204 (91.5%) were assessable for response (per-protocol	<u>Epoetin alfa 150 IU:</u> - Epoetin alfa 150 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 1 - Oral iron supplements 200 mg/day from preoperative day 10 until postoperative day 1 - In patients with iron deficiency: iron sulphate 40 mg intravenously daily until the day of discharge - Folic acid 15 mg/day for the first 10 days after randomization <u>Epoetin alfa 300 IU:</u> - Epoetin alfa 300 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 1 - Oral iron supplements 200 mg/day from preoperative day 10	Identified from the systematic review of Lin, 2013. Bonferroni correction was applied when multiple comparisons of independent or related variables were made.

		population). Analyses were performed on the per-protocol population.	until postoperative day 1 - In patients with iron deficiency: iron sulphate 40 mg intravenously daily until the day of discharge - Folic acid 15 mg/day for the first 10 days after randomization <u>Control:</u> - Oral iron supplements 200 mg/day from preoperative day 10 until postoperative day 1 - In patients with iron deficiency: iron sulphate 40 mg intravenously daily until the day of discharge - Folic acid 15 mg/day for the first 10 days after randomization *Transfusion policy for all patients:* <u>Preoperatively:</u> - Hb <11 g/dl and severe heart disease, chronic obstructive lung disease or arterial disease - Received beta-blockers - Lost a significant amount of blood -Younger patients or patients in good health: Hb <9 g/dl <u>Intraoperatively:</u> - Blood loss > 300 ml and heart or lung or arterial disease - Received beta-blockers - Elderly - Younger patients or patients in good health: blood loss > 400 ml <u>Postoperatively:</u> - Hb <10 g/dl and poor prognostic features	

			- Younger patients or patients in good health: Hb <8 g/dl	
Dousias, 2003, Greece	Experimental: Randomized controlled trial	50 women with benign uterine leiomyomas scheduled for abdominal total hysterectomy, with Hb levels ≥9 and <12 g/dl, were randomly allocated to one of 2 groups: 1) EPO + iron (n=23, average age 48±4 years) 2) Iron (n=27, average age 49±5 years)	<u>EPO + iron:</u> - EPO 600 U/ml subcutaneously on preoperative days 14 and 7 and the morning before the operation - Iron supplementation 200 mg/day <u>Iron:</u> - Normal saline subcutaneously on preoperative days 14 and 7 and the morning before the operation - Iron supplementation 200 mg/day *Transfusion policy for all patients:* No information provided	Identified from the systematic review of Lin, 2013.
Faris, 1996, USA	Experimental: Randomized controlled trial	200 patients (67 men and 133 women, average age 66±13 years) scheduled for major elective orthopaedic operation, in which transfusion of ≥ 2 units of whole blood or red blood cells is usually required, were randomly assigned to one of 3 groups: 1) EPO 300 IU (n=60) 2) EPO 100 IU (n=71) 3) Placebo (n=69)	<u>EPO 300 IU:</u> - EPO 300 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 4 - Oral iron sulphate 325 mg, 3 times per day <u>EPO 100 IU:</u> - EPO 100 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 4 - Oral iron sulphate 325 mg, 3 times per day <u>Placebo:</u> - Placebo subcutaneously from preoperative day 10 until postoperative day 4 - Oral iron sulphate 325 mg, 3 times per day	Identified from the systematic review of Alsaleh, 2013.

			Transfusion policy for all patients: Intraoperative and postoperative: at the discretion of the surgeon. However, every effort was made to avoid transfusion if Hct > 27%, unless the clinical situation warranted it. The use of intraoperative and postoperative reinfusion systems was allowed in all three groups. [As our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on patients with baseline Hb levels >10 and ≤13 g/dl were extracted.]	
Feagan, 2000, Canada	Experimental: Randomized controlled trial	216 adult patients undergoing total hip joint arthroplasty in 13 teaching and 4 community hospitals, with Hb levels 9.8 – 13.7 g/dl, were randomly assigned to one of 3 groups: 1) High-dose Epoetin alfa (n=46, 13% men, aged 68±12 years) 2) Low-dose Epoetin alfa (n=86, 8% men, aged 69±11 years) 3) Placebo (n=82, 11% men, aged 67±11 years) 10 patients did not undergo surgery within the specified time window, and 3 patients withdrew consent. Therefore, 201 patients were	<u>High-dose Epoetin alfa:</u> - Oral iron 3 times per day from preoperative day 42 until hospital discharge - 40 000 IU subcutaneously weekly for 4 weeks before the operation <u>Low-dose Epoetin alfa:</u> - Oral iron 3 times per day from preoperative day 42 until hospital discharge - 20 000 IU subcutaneously weekly for 4 weeks before the operation <u>Placebo:</u> - Oral iron 3 times per day from preoperative day 42 until hospital discharge	Identified from the systematic review of Alsaleh, 2013. 80% power analysis indicated that 83 patients per group were required in the low-dose and placebo groups and 50 patients were needed in the high-dose group. Accordingly, the total sample size requirement was 216 patients.

		included in the intention-to-treat analysis.	- Placebo subcutaneously weekly for 4 weeks before the operation *Transfusion policy for all patients:* according to usual practice of attending surgeons and anesthesiologists. Usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific Hb threshold.	Study medication was withheld if Hb levels ≥ 15 g/dl, if systolic blood pressure ≥ 200 mm Hg, or if diastolic blood pressure ≥ 105 mm Hg. Bonferroni correction was used as a conservative method of adjusting for multiple comparisons.
Heiss, 1996, Germany	Experimental: Randomized controlled trial	30 patients with primary diagnosis of resectable colorectal cancer, with moderate anaemia (defined as Hb 9-13 g/dl), were randomly assigned to one of 2 groups: 1) EPO (n=20, 7 men and 10 women, aged 66 (range: 42-80) years) 2) Control (n=10, 2 men and 8 women, aged 61 (range 42-74) years) 3 patients from the EPO group dropped out of the study. The analysis concerning transfusion characteristics was performed on: 1) EPO (n=17, Hb levels at hospital admission 12.2±0.39 g/dl) 2) Control (n=10, Hb levels at hospital admission 12.6±0.74 g/dl))	<u>EPO:</u> - 150 IU/kg body weight EPO subcutaneously every 2 days, starting on preoperative day 10 until postoperative day 2 - Oral iron 200 mg ferrous sulfate daily each day until the operation - Oral folate 5 mg daily each day until the operation <u>Control:</u> - Placebo subcutaneously every 2 days, starting on preoperative day 10 until postoperative day 2 - Oral iron 200 mg ferrous sulfate daily each day until the operation - Oral folate 5 mg daily each day until the operation *Transfusion policy for all patients:* According to the patient's attending	Identified from the systematic review of Tran, 2014.

			anesthesiologist or surgeon and recommended at Hb ≤9 g/dl, depending on the recorded blood loss.	
Kettelhack, 1998, Germany	Experimental: Randomized controlled trial	109 patients with colon cancer scheduled for right hemicolectomy, with Hb levels > 8.5 and ≤13.5 g/dl, were randomly assigned to one of 2 groups: 1) Epoetin beta (n=48, men:women 21:27, median age 71 years (range 53-57)) 2) Placebo (n=54, men:women 22:32, median age 67 years (range 37-91)) 7 patients (Epoetin beta: n=4; Placebo: n=3) were excluded from the efficacy analysis, but included in the safety analysis.	<u>Epoetin beta:</u> - 20 000 IU Epoetin beta subcutaneously for a minimum of 5 (maximum 10) preoperative days until postoperative day 4 - Oral iron in case of iron deficiency, and on postoperative day 1 (40 mg iron sulphate intravenously) <u>Placebo:</u> - Placebo subcutaneously for a minimum of 5 (maximum 10) preoperative days until postoperative day 4 - Oral iron in case of iron deficiency, and on postoperative day 1 (40 mg iron sulphate intravenously) *Transfusion policy for all patients:* Hb ≤7.5 g/dl	Identified from the systematic review of Lin, 2013. Two groups of 90 patients (180 in total) were to be evaluable to detect a reduction in transfusion need from 50 % in the control group to 25% in the epoetin beta treatment group with a power of 90%. Transfusion need was adjusted to age, blood loss and baseline haemoglobin levels.
Kosmadakis, 2003, Greece	Experimental: Randomized controlled trial	75 patients with non-metastatic gastrointestinal tract cancer, with Hb levels between 8.5 and 13 g/dl, were randomly assigned to one of 2 groups: 1) Epoetin alfa 2) Control 12 randomized patients were excluded because they did not fulfil the inclusion criteria. Therefore, only 63 patients were evaluated:	<u>Epoetin alfa:</u> - 300 IU/kg body weight Epoetin alfa subcutaneously daily starting from preoperative day 7 until postoperative day 7 - Intravenous iron 100 mg daily <u>Control:</u> - Placebo subcutaneously daily starting from preoperative day 7 until postoperative day 7 - Intravenous iron 100 mg daily	Identified from the systematic review of Tran, 2014.

		1) Epoetin alfa (n=31, 15 men and 16 women, aged on average 67.1±2.1 years, mean Hb 10.6±0.18 g/dl) 2) Control (n=32, 19 men and 13 women, aged on average 66.4±2 years, mean Hb 11.1±0.19 g/dl)	*Transfusion policy for all patients:* Hb ≤8.5 g/dl	
Larson, 2001, Sweden	Experimental: Randomized controlled trial	32 anaemic women with uterine myoma scheduled for hysterectomy, with Hb levels <12 g/dl, were randomly assigned to one of 2 groups: 1) Epoetin beta + oral iron (n=15, aged on average 46±1 years) 2) Oral iron (n=16, aged on average 44±1 years)	<u>Epoetin beta + oral iron:</u> - 5000 IU Epoetin beta subcutaneously twice per week during 4 preoperative weeks - Oral iron succinate 100 mg twice per day during 4 preoperative weeks <u>Oral iron:</u> Oral iron succinate 100 mg twice per day during 4 preoperative weeks	Identified from the systematic review of Lin, 2013. The study has been dimensioned in order to detect a difference in increase of Hb between the groups of 1g/dL, with a significance level of 5% and a power of 80%. With 15 patients in each group these conditions would be met.
Na, 2011, South Korea	Experimental: Randomized controlled trial	113 women with physical status I or II by the American Society of Anesthesiologist classification, scheduled for bilateral total knee replacement arthroplasty, with Hb levels >10 g/dl, were assigned to one of 2 groups: 1) Epoetin beta + iron (n=54, aged 69±4 years) 2) Control (n=54, aged 68±5 years)	<u>Epoetin beta + iron:</u> - 3000 IU Epoetin beta subcutaneously during surgery and up to 2 times after surgery if Hb levels 7-8 g/dl (on day 1, 2, 3 and/or 5) - Iron sucrose 200 mg intravenously, simultaneously with the Epoetin beta injection <u>Control:</u> no iron, no Epoetin beta *Transfusion policy for all patients:* - Hb 6-6.9 g/dl: 1 unit of RBC	Identified from the systematic review of Alsaleh, 2013. Power analysis indicated that 54 patients per group would be sufficient to detect a reduction from 45% to 20% in RBC transfusion incidence, for Type I error of 0,05 and a power of 80%.

			- Hb 5-5.9 g/dl: 2 units of RBC - Hb < 5 g/dl or clinical symptoms of anemia and hypovolemia: immediate transfusion and exclusion from study	
Qvist, 1999, Denmark	Experimental: Randomized controlled trial	100 patients scheduled for colorectal surgery because of cancer with Hb levels ≤8.5 mmol/L were randomly assigned to one of 2 groups: 1) EPO (n=38, 12 men and 26 women, aged on average 69 years (age range 48-86)) 2) Placebo (n=43, 20 men and 23 women, aged on average 69 years (age range 40-85))	<u>EPO:</u> - EPO 300 IU/kg subcutaneously on preoperative day 4 - EPO 150 IU/kg subcutaneously daily from preoperative day 3 to postoperative day 3 - Oral iron 200 mg daily from preoperative day 4 to preoperative day 1 <u>Placebo</u>: - Placebo subcutaneously daily from preoperative day 4 to postoperative day 3 - Oral iron 200 mg daily from preoperative day 4 to preoperative day 1 *Transfusion policy for all patients:* Need for transfusion was determined by the attending anesthesiologist and surgeon in cooperation and depended on the clinical condition of each patient. No fixed Hb level was the indication alone.	Identified from the systematic review of Borstlap, 2015.
Scott, 2002, USA	Experimental: Randomized controlled trial	60 patients scheduled for major head and neck oncologic surgery, with Hb levels ≥10 and ≤13.5 g/dl, were randomly assigned into one of 2 groups: 1) Epoetin alfa (n=29, 16 men and 13 women, aged on average 68±11 years)	<u>Epoetin alfa:</u> - 600 IU/kg Epoetin alfa, 3 times: between preoperative days 19 and 10, between preoperative days 12 and 6, on the day of the surgery. - Oral iron sulphate 150 mg twice per day, from the time of administration of the	Identified from the systematic review of Lin, 2013. Allogeneic blood transfusions administered during surgery or within 21 days

		2) Control (n=29, 18 men and 11 women, aged on average 62±11 years)	first dose of Epoetin alfa until the day of surgery. <u>Control:</u> - Placebo, 3 times: between preoperative days 19 and 10, between preoperative days 12 and 6, on the day of the surgery. - Oral iron sulphate 150 mg twice per day, from the time of administration of the first dose of placebo until the day of surgery. *Transfusion policy for all patients:* At the discretion of the attending surgeon; however an effort was made not to transfuse patients with Hb levels ≥9 g/dl unless clinically indicated.	from the surgical date were recorded.
So-Osman, 2014, The Netherlands	Experimental: Randomized controlled trial	730 patients scheduled for primary or revision total hip- or knee-replacement surgery, with preoperative Hb levels 10-13 g/dl, were randomly assigned to either of 4 groups. Of these, 683 were evaluated: 1) EPO + AUTO (n=214, 30 men and 184 women, aged on average 70±13 years, 69 anaemic *i.e.* Hb <12 g/dl (women) and <13 g/dl (men)) 2) EPO + no AUTO (n=125, 12 men and 113 women, aged on average 71±12 years, 36 anaemic) 3) No EPO + AUTO (n=206, 29 men and 177 women, aged on	<u>EPO + AUTO:</u> - 40 000 U EPO (Neorecormon or Eprex) subcutaneously on preoperative days 21, 14, 7 and on the day of surgery. If Hb level, determined before the fourth dose, exceeded 15 g/dl, the final erythropoietin dose was withheld. - Oral iron (ferrofumarate) 200 mg 3 times per day during 3 preoperative weeks. - AUTO: use of cell saver system (both intra- and postoperatively) or of a postoperative reinfusion drainage system <u>EPO + no AUTO:</u> - 40 000 U EPO (Neorecormon or Eprex) subcutaneously on	Identified from the systematic review of Zhao, 2016. This trial was registered in the public registry: controlled-trials.com, (No. ISRCTN 96327523) and the Dutch Trial Register (No. NTR303). Power analysis indicated that to demonstrate a reduction of 75% in the mean erythrocyte use (from 1.0 to 0.25 U erythrocyte), twice

		average 71±12 years, 64 anaemic) 4) No EPO + no AUTO (n=138, 17 men and 121 women, aged on average 70±11 years, 26 anaemic) Statistical analyses were performed according to intention-to-treat.	preoperative days 21, 14, 7 and on the day of surgery. If Hb level, determined before the fourth dose, exceeded 15 g/dl, the final erythropoietin dose was withheld. - Oral iron (ferrofumarate) 200 mg 3 times per day during 3 preoperative weeks. <u>No EPO + AUTO:</u> Use of cell saver system (both intra- and postoperatively) or of a postoperative reinfusion drainage system <u>No EPO + no AUTO:</u> No intervention. *Transfusion policy for all patients:* The Dutch national transfusion protocol was applied for the use of allogeneic erythrocyte transfusions. This guideline considers age and comorbidity as triggers for transfusion. High risk included incapability to enlarge cardiac output to compensate for anemia, serious pulmonary disease, or symptomatic cerebrovascular disease. The following pretransfusion thresholds were used: - Hb 6.4 g/dl (4.0 mmol/l) for younger than 60 yr of age and normal risk - Hb 8.1 g/dl (5.0 mmol/l) for age 60 yr or older and normal risk - Hb 9.7 g/dl (6.0	the number of 125 erythropoietin-eligible patients (250 patients) were required. Haybittle-Peto correction and Bonferroni correction for multiple outcome measures for the primary endpoint (both mean erythrocyte use and proportion of transfused patients) were applied. This indicated that a p value < 0.017 should be considered statistically significant. For the other endpoints, a p value <0.05 was considered statistically significant.

			mmol/l) in case of high risk irrespective of age [As our PICO specifically concerns patients who only receive allogeneic blood, and not autologous blood, only data of patients in the EPO + no AUTO and no EPO + no AUTO groups were extracted.]	
Stowell, 2009, USA	Experimental: Randomized controlled trial	681 patients (78 men and 601 women, aged on average 60±14 years,) scheduled for elective spinal surgery for which anticipated blood loss was 2 to 4 units, with Hb levels >10 and ≤13 g/dl, were randomly assigned to one of 2 groups: 1) Epoetin alfa (n=341, 36 men and 303 women, aged on average 61±14 years) 2) Standard of care (n=340, 42 men and 298 women, aged on average 59±14 years) 1 subject in the Epoetin alfa group was enrolled twice in error and was only included in the intention-to-treat analyses for the first enrolment.	<u>Epoetin alfa:</u> - 600 IU/kg Epoetin alfa subcutaneously on preoperative days 21, 14 and 7 and on the day of the operation - Standard of care treatment - Oral iron therapy from preoperative day 21 until the day of the operation <u>Standard of care:</u> - No ESA, treated according to the institution's policy for blood conservation - Oral iron therapy from preoperative day 21 until the day of the operation	Identified from the systematic review of Lin, 2013. A revised enrollment target of 674 subjects was projected to provide 572 evaluable subjects, which was calculated to have 80% power to demonstrate noninferiority for the primary study end point (incidence of deep vein thrombosis).
Weber, 2005, The Netherlands	Experimental: Randomized controlled trial	Patients scheduled for elective major orthopaedic surgery (hip, knee or spine; primary or revision), with preoperative Hb levels 10-13 g/dl were randomly assigned to one of 2 groups: 1) Epoetin alfa (n=467, 89.9% women, aged on	<u>Epoetin alfa:</u> - 40 000 IU Epoetin alfa (Eprex®/Erypro®) subcutaneously once weekly for 3 weeks before surgery and on the day of the surgery - Oral iron daily for 3 weeks <u>No Epoetin alfa:</u> - Could take oral or iv	Identified from the systematic review of Alsaleh, 2013. A 1:2 ratio was chosen in order to improve trial acceptability and participation by the patients.

		average 67±11 years) 2) No Epoetin alfa (n=237, 89.5% women, aged on average 66.7±10.8 years) Patients for whom the operation was postponed for more than 10 days were excluded, bringing the actual surgery population to 695 (Epoetin alfa n=460, No Epoetin alfa n=235). The analysis on transfusion requirements was performed on this on-treatment population.	iron, if this was part of the usual standard of care in that hospital *Transfusion policy for all patients:* According to an Hb-based transfusion trigger, as laid down in the hospital transfusion protocol. If no transparent local protocol was available, transfusion with packed cells could only be given during and after surgery if Hb<8 g/dl. In most cases, these transfusions were allogeneic. However, some patients received autologous or mixed transfusions. [As our PICO specifically concerns patients who only receive allogeneic transfusion, and not autologous transfusion, only outcomes analysed in patients receiving allogeneic transfusions only were extracted.]	Patients in the control group could take oral or iv iron, because "many centres include treatment with iron, but it has not been demonstrated that its administration has any effect on transfusion requirements".
Wurnig, 2001, Austria	Experimental: Randomized controlled trial	194 patients from Austria, France, Portugal and Sweden, scheduled for elective surgery (mainly orthopaedic and cardiac) where blood loss was expected to be >1 liter and transfusion of 2-3 RBC units would be required, with Hct levels between 30 and 42%, were randomly assigned to one of 3 groups: 1) Epoetin beta 125 IU (n=70, 14 men and 56 women, median age	<u>Epoetin beta 125 IU:</u> - 125 IU/kg Epoetin beta (NeoRecormon) subcutaneously once weekly during the 3 or 4 preoperative weeks - Oral iron supplementation (200-300 mg/day) <u>Epoetin beta 250 IU:</u> - 250 IU/kg Epoetin beta (NeoRecormon) subcutaneously once weekly during the 3 or 4 preoperative weeks - Oral iron supplementation (200-300 mg/day)	Identified from the systematic review of Tran, 2014. The between-group analysis of allogeneic RBC transfusion rates was performed using the exact trend test of Cochran-Armitage with a closed testing procedure (to prevent multiple testing) and by calculating

		62.5 years (range 52-70 years)) 2) Epoetin beta 250 IU (n=64, 20 men and 44 women, median age 66 years (range 56-73 years)) 3) Control (n=60, 23 men and 37 women, median age 62 years (range 51.5-71 years)) 175 out of the 194 underwent elective surgery: 1) Epoetin beta 125 IU (n=65, median Hb 13.5 (IQR 12.8-14.1) g/dl) 2) Epoetin beta 250 IU (n=59, median Hb 13.2 (IQR 12.4-14) g/dl) 3) Control (n=61, median Hb 12.7 (IQR 12.2-14) g/dl) Safety analysis was based on the intention-to-treat population (n=194). Efficacy analysis was based on the population that underwent surgery (n=175).	Control: Oral iron supplementation (200-300 mg/day) *Transfusion policy for all patients:* Hb ≤8.5 g/dl	confidence intervals for differences of transfusion rates.
Yoo, 2011, South Korea	Experimental: Randomized controlled trial	74 patients scheduled for valvular heart surgery, with Hb levels <13 g/dl (men) or <12 g/dl (women) were randomly assigned to one of 2 groups: 1) EPO (n=37, 13 men and 24 women, aged on average 56±12 years) 2) Control (n=37, 14 men and 23 women, aged on average 59±12 years)	EPO: 500 IU/kg EPO intravenously + iron sucrose 200 mg intravenously 16-24 hours before surgery Control: Normal saline intravenously 16-24 hours before surgery In all patients, blood salvaged by the cell salvage device was reinfused into the	Identified from the systematic review of Glechner, 2014. Power analysis suggested that 32 patients per group would be required to obtain a power of 80%, considering a type I error of 0.05, and expecting

			patient before the end of surgery. *Transfusion policy for all patients:* - Intraoperatively: Hb levels <7 mg/dl - Postoperatively: Hb levels <8 mg/dl	a reduction from 44% to 13% in the incidence of allogeneic erythrocyte transfusion.

Synthesis of findings

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
COMPARISON 1: TRANSFUSION VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Primary outcomes				
1. (All-cause) mortality				
Mortality	Transfusion vs standard of care	Not statistically significant: 1/29 vs 1/31 § RR: 1.07, 95%CI [0.07;16.31] ¥ (p=0.96)*	1, 29 vs 31	Karkouti, 2012
2. Anemia-associated ischaemic events				
Acute myocardial infarction	Transfusion vs standard of care	Not statistically significant: 1/29 vs 1/31 § RR: 1.07, 95%CI [0.07;16.31] ¥ (p=0.96)*	1, 29 vs 31	Karkouti, 2012
Acute kidney injury	Transfusion vs standard of care	Not statistically significant: 11/29 vs 11/31 § RR: 1.07, 95%CI [0.55;2.08] ¥ (p=0.96)*	1, 29 vs 31	Karkouti, 2012
Secondary outcomes				
1. Length of hospital stay				
2. Infections				
3. Red blood cell utilization – RBC transfusions				
RBC transfusions (units) – pre-operative	Transfusion vs standard of care	Statistically significant: 2 (2,2) (median, (IQR)) vs 0 (0,0) Median difference: +2 (p<0.0001)	1, 29 vs 31	Karkouti, 2012
RBC transfusions (units) - perioperative	Transfusion vs standard of care	Statistically significant: 0 (0,2) (median, (IQR)) vs 2 (1,4) Median difference: -2 (p=0.0002)	1, 29 vs 31	Karkouti, 2012
RBC transfusions (units) - total	Transfusion vs standard of care	Not statistically significant: 4 (3,6) (median, (IQR)) vs 4 (2,5) Median difference: 0 (p=0.3)	1, 29 vs 31	Karkouti, 2012
4. Thromboembolic events				
COMPARISON 2: IRON SUPPLEMENTATION VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Primary outcomes				
1. (All-cause) mortality				
2. Anemia-associated ischaemic events				
Secondary outcomes				
1. Length of hospital stay				
2. Infections				
3. a) Red blood cell utilization – Number of patients transfused				
Number of patients receiving perioperative transfusion	300 mg iron iv vs Placebo iv	*Hb <13.5 (men) or <12.5 g/dl (women)* Not statistically significant: 2/9 vs 5/9 § RR: 0.40, 95%CI [0.10;1.55] ¥ (p=0.185)*	1, 9 vs 9	Edwards, 2009

Number of patients receiving perioperative transfusion	Oral iron vs standard clinical management	*Hb <13.5 (men) or <11.5 g/dl (women)* Not statistically significant: 3/6 vs 10/14 § RR: 0.70, 95%CI [0.29;1.66] ¥ (p=0.42)*	1, 6 vs 14	Lidder, 2007
Number of patients receiving intraoperative transfusion	Oral iron vs no iron	*Hb ≤10 g/dl* Not statistically significant: 3/32 vs 23/84 § RR: 0.34, 95%CI [0.11;1.06] ¥ (p=0.0635)*	1, 32 vs 84	Okuyama, 2005
3. b) Red blood cell utilization – Number of units transfused				
Units of leucoreduced red cell concentrates transfused intra- and postoperatively (mean±SD)	100 mg iron iv vs no iron	*Hb <13 g/dl* Statistically significant: 1.12±1.17 vs 2.18±0.98 MD: -1.06 ££† (p=0.019) *in favour of iv iron*	1, number of participants unknown	Muñoz, 2006
Units of blood transfused perioperatively (median (IQR))	Oral iron vs standard clinical management	*Hb <13.5 (men) or <11.5 g/dl (women)* Not statistically significant: Median (IQR): 1 (0-2) vs 2.5 (0-11) £££† (p>0.05)	1, 6 vs 14 §	Lidder, 2007
Intraoperative transfusion volume (ml, mean±SD)	Oral iron vs no iron	*Hb ≤10 g/dl* Statistically significant: 607±150 vs 441±183 MD: 166, 95%CI [100.94;231.06] ¥ (p<0.00001)* *in favour of no iron*	1, 32 vs 84 §	Okuyama, 2005
4. Thromboembolic events				
COMPARISON 3: ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE				
Primary outcomes				
1. (All-cause) mortality				
45-day mortality	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Not statistically significant: 12/458 vs 13/462 § RR: 0.93, 95%CI [0.43;2.01] ¥ (p=0.85)*	2, 458 vs 462	Weltert, 2010; Weltert, 2015
2. Anemia-associated ischaemic events				
Perioperative myocardial infarction	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Not statistically significant: 10/458 vs 11/462 § RR: 0.92, 95%CI [0.39;2.14] ¥ (p=0.78)*	2, 458 vs 462	Weltert, 2010; Weltert, 2015
Renal failure (new onset)		*Hb ≤14.5 g/dl* Not statistically significant: 2/300 vs 1/300 § RR: 2.00, 95%CI [0.18;21.94] ¥	1, 300 vs 300	Weltert, 2015

		(p=0.57)*		
Bowel ischemia	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Not statistically significant: 2/458 vs 4/462 § RR: 0.50, 95%CI [0.09;2.71] ¥ (p=0.42)*	2, 458 vs 462	Weltert, 2010; Weltert, 2015
Secondary outcomes				
1. Length of hospital stay				
Length of stay after operation (days)	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Not statistically significant: 5.52 vs 5.89 £† (p=0.065)	1, 158 vs 162 §	Weltert, 2010
		Hb ≤14.5 g/dl Statistically significant: 6 (4-28) vs 6 (4-28)£† (p=0.01)	1, 300 vs 300	Weltert, 2015
Length of stay (days, mean±SD)		*Hb <13 g/dl* Not statistically significant: 3.0±0.4 vs 3.3±0.8 MD: -0.30, 95%CI [-0.56;-0.04] (p=0.09)*	1, 24 vs 56 §	Bedair, 2015
2. Infections				
Long-term wound infection	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Not statistically significant: 3/158 vs 3/162 § RR: 1.02, 95%CI [0.21;5.00] ¥ (p=0.98)*	1, 158 vs 162	Weltert, 2010
		Hb ≤14.5 g/dl Not statistically significant: 4/300 vs 4/300 § RR: 1.00, 95%CI [0.25;3.96] ¥ (p=1.00)*	1, 300 vs 300	Weltert, 2015
Pneumonia		*Hb ≤14.5 g/dl* 0/158 vs 0/162 § Effect size not estimable £	1, 158 vs 162	Weltert, 2010
3. a) Red blood cell utilization – Number of patients transfused				
Number of patients receiving any perioperative transfusion	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Statistically significant: 25/158 vs 60/162 § RR: 0.43, 95%CI [0.28;0.65] (p=0.0001)* *in favour of EPO sc*	1, 158 vs 162	Weltert, 2010
Number of patients receiving postoperative transfusion	Epoetin alpha vs no Epoetin alpha	*Hb <13 g/dl* Statistically significant: 0/24 vs 23/56 § RR: 0.05, 95%CI [0.003;0.77] (p=0.0317)* *in favour of Epoetin alpha*	1, 24 vs 56	Bedair, 2015
3. b) Red blood cell utilization – Number of units transfused				
Units of blood transfused	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Statistically significant: 0.32 vs 0.76	1, 158 vs 162 §	Weltert, 2010

perioperatively (mean)		MD: -0.44 £ (p=0.008) *in favour of EPO sc*		
Units of RBC transfused perioperatively (median)		*Hb ≤14.5 g/dl* Statistically significant: 0 (0-11) vs 0 (0 to 16) MD: 0 £ (p<0.0005) *in favour of EPO sc*	1, 300 vs 300	Weltert, 2015
Units of blood transfused postoperatively (mean±SD)	Epoetin alpha vs no Epoetin alpha	*Hb <13 g/dl* 0 vs 0.41±0.07 MD: -0.41 £† *Effect size not estimable*	1, 24 vs 56 §	Bedair, 2015
4. Thromboembolic events				
Deep vein thrombosis	EPO sc vs no treatment	*Hb ≤14.5 g/dl* Not statistically significant: 2/458 vs 6/462 § RR: 0.39, 95%CI [0.09;1.66] ¥ (p=0.20)*	2, 458 vs 462	Weltert, 2010; Weltert, 2015
COMPARISON 4: **IRON SUPPLEMENTATION + ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE**				
Primary outcomes				
1. (All-cause) mortality				
Death during the study or within 30 days after study completion (due to pneumonia (Epoetin alfa), sudden cardiac death and acute myeloid leukemia (standard of care))	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl*:: Not statistically significant: 1/340 vs 2/340 RR: 0.50, 95%CI [0.05;5.49] ¥ (p=0.57)*	1, 340 vs 340	Stowell, 2009
Death (after withdrawal from the study or during the post-treatment period, due to serious adverse events)	20 000 IU Epoetin beta sc + iron (oral and/or iv) vs Placebo sc + iron (oral and/or iv)	*Hb >8.5 and ≤13.5 g/dl* Not statistically significant: 5/52 vs 2/57 § RR: 2.74, 95%CI [0.56;13.52] ¥ (p=0.22)*	1, 52 vs 57	Kettelhack, 1998
Perioperative death (due to cerebral vascular accident (n=2) or acute respiratory distress syndrome (n=1)	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* Not statistically significant: 3/29 vs 0/29 § RR: 7.00, 95%CI [0.38;129.74] ¥ (p=0.19)*	1, 29 vs 29	Scott, 2002
Postoperative death (30-day)	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* Not statistically significant: 0/37 vs 1/37 RR: 0.33, 95%CI [0.01;7.93] ¥ (p=0.50)*	1, 37 vs 37	Yoo, 2011

Postoperative death	150 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 2/69 vs 0/68 § RR: 4.93, 95%CI [0.24;100.80] ¥ (p=0.30)*	1, 69 vs 68	Christodoulakis, 2005
	300 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 3/67 vs 0/68 § RR: 7.10, 95%CI [0.37;134.92] ¥ (p=0.19)*	1, 67 vs 68	
Postoperative death (EPO: septic shock or multiorgan failure; Placebo: mesenteric venous thrombosis with subtotal small bowel infarction)	150 IU/kg EPO sc + oral iron + oral folate vs Placebo sc + oral iron + oral folate	*Hb 9-13 g/dl* Not statistically significant: 2/17 vs 1/10 § RR: 1.18, 95%CI [0.12;11.39] ¥ (p=0.89)*	1, 17 vs 10	Heiss, 1996
Death after study completion (due to multiple organ failure, 10 days after completion)	125 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Not statistically significant: 0/70 vs 1/60 § RR: 0.29, 95%CI [0.01;6.90] ¥ (p=0.44)*	1, 70 vs 60	Wurnig, 2001
	250 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Not statistically significant: 0/64 vs 1/60 § RR: 0.31, 95%CI [0.01;7.53] ¥ (p=0.47)*	1, 64 vs 60	
2. Anemia-associated ischaemic events				
Postoperative acute kidney injury	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* <u>Statistically significant:</u> 9/37 vs 19/35 RR: 0.45, 95%CI [0.24;0.85] (p=0.015)* *in favour of EPO iv + iv iron*	1, 37 vs 35	Yoo, 2011
Cerebrovascular accident	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 2/340 vs 0/340 RR: 5.00, 95%CI [0.24;103.76] ¥ (p=0.30)*	1, 340 vs 340	Stowell, 2009
Cerebrovascular accident	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* Not statistically significant: 2/29 vs 0/29 § RR: 5.00, 95%CI [0.25;99.82] ¥ (p=0.29)*	1, 29 vs 29	Scott, 2002

Cerebrovascular accident	125 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Not statistically significant: 1/70 vs 0/60 § RR: 2.58, 95%CI [0.11;62.12] ¥ (p=0.56)*	1, 70 vs 60	Wurnig, 2001
	250 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* 0/64 vs 0/60 § Effect size not estimable £	1, 64 vs 60	
Transient ischaemic attack	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 1/340 vs 0/340 RR: 3.00, 95%CI [0.12;73.38] ¥ (p=0.50)*	1, 340 vs 340	Stowell, 2009
Stroke or transient ischaemic attack	40 000 U EPO sc + oral iron vs no intervention	*Hb 10-13 g/dl* Not statistically significant: 2/125 vs 0/138 RR: 5.52, 95%CI [0.27;113.80] ¥ (p=0.27)*	1, 125 vs 138	So-Osman, 2014
Myocardial ischemia	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 1/340 vs 0/340 RR: 3.00, 95%CI [0.12;73.38] ¥ (p=0.50)*	1, 340 vs 340	Stowell, 2009
Myocardial infarction	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 1/340 vs 0/340 RR: 3.00, 95%CI [0.12;73.38] ¥ (p=0.50)*	1, 340 vs 340	Stowell, 2009
Intraoperative myocardial infarction	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* Not statistically significant: 1/29 vs 0/29 § RR: 3.00, 95%CI [0.13;70.74] ¥ (p=0.50)*	1, 29 vs 29	Scott, 2002
Myocardial infarction	40 000 U EPO sc + oral iron vs no intervention	*Hb 10-13 g/dl* Not statistically significant: 2/125 vs 1/138 RR: 2.21, 95%CI [0.20;24.05] ¥ (p=0.52)*	1, 125 vs 138	So-Osman, 2014
Secondary outcomes				
1. Length of hospital stay				
Length of hospital stay (days, mean±SD)	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* Not statistically significant: 11.3±4.1 vs 13.5±8.0 MD: -2.20, 95%CI [-5.10;0.70] (p=0.14)*	1, 37 vs 37	Yoo, 2011

Length of hospital stay (days, mean±SD)	5000 IU Epoetin beta sc + oral iron vs Oral iron	*Hb <12 g/dl (women)* Not statistically significant: 6.4±2.4 vs 8.1±7.1 MD: -1.70, 95%CI [-5.38;1.98] ¥ (p=0.39)*	1, 15 vs 16	Larson, 2001
Length of hospital stay (days, mean±SD)	300 IU/kg Epoetin alfa sc + iv iron vs Placebo sc + iv iron	*Hb 8.5-13 g/dl* Statistically significant: 10±2.78 vs 13±5.09** MD: -3, 95%CI [-5.02;-0.98] (p=0.0053)* *in favour of Epoetin alfa sc + iv iron*	1, 31 vs 32 §	Kosmadakis, 2003
Length of postoperative stay (days, mean±SD)	EPO 600 U/ml sc + iron vs Normal saline + iron	*Hb ≥9 and <12 g/dl (women)* Not statistically significant: 7.6±0.5 vs 7.8±0.9 MD: -0.20, 95%CI [-0.60;0.20] (p=0.35)*	1, 23 vs 27 §	Dousias, 2003
2. Infections				
Postoperative infection (superficial wound infection, severe streptococcal septicaemia, urinary tract infection)	5000 IU Epoetin beta sc + oral iron vs Oral iron	*Hb <12 g/dl (women)* Not statistically significant: 1/15 vs 2/16 RR: 0.53, 95%CI [0.05;5.29] ¥ (p=0.59)*	1, 15 vs 16	Larson, 2001
Wound infection	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 4/340 vs 1/340 RR: 4.00, 95%CI [0.45;35.60] ¥ (p=0.21)*	1, 340 vs 340	Stowell, 2009
Urinary tract infection	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl*: Not statistically significant: 22/340 vs 16/340 RR: 1.38, 95%CI [0.74;2.57] ¥ (p=0.32)*	1, 340 vs 340	Stowell, 2009
3. a) Red blood cell utilization – Number of patients transfused				
Number of patients receiving perioperative transfusion	EPO 300 IU sc + oral iron vs Placebo sc + oral iron	*Hb < 11.5 g/dl* Not statistically significant: 2/4 vs 3/3 § RR: 0.57, 95%CI [0.22;1.48] ¥ (p=0.25)*	1, 4 vs 3	COPES, 1993
		Hb 11.5-12.4 g/dl Not statistically significant: 5/8 vs 8/8 § RR: 0.65, 95%CI [0.38;1.12] ¥ (p=0.12)*	1, 8 vs 8	
		Hb 12.5-13.4 g/dl Statistically significant: 3/18 vs 12/20 § RR: 0.28, 95%CI [0.09;0.83]	1, 18 vs 20	

		(p=0.02)* *In favour of EPO sc + oral iron*		
Number of patients receiving perioperative transfusion	EPO 600 U/ml sc + iron vs Normal saline + iron	*Hb ≥9 and <12 g/dl (women)* Not statistically significant: 0/23 vs 5/27 § RR: 0.11, 95%CI [0.01;1.82] ¥ (p=0.12)*	1, 23 vs 27	Dousias, 2003
Number of patients receiving perioperative transfusion	EPO 300 IU sc + oral iron vs Placebo sc + oral iron	*Hb >10 and ≤13 g/dl* Statistically significant: 3/22 vs 21/27 § RR: 0.18, 95%CI [0.06;0.51] (p=0.001)* *in favour of EPO sc + oral iron*	1, 22 vs 27	Faris, 1996
	EPO 100 IU sc + oral iron vs Placebo sc + oral iron	*Hb >10 and ≤13 g/dl* Statistically significant: 9/23 vs 21/27 § RR: 0.50, 95%CI [0.29;0.87] (p=0.014)* *in favour of EPO sc + oral iron*	1, 23 vs 27	
Number of patients receiving perioperative transfusion	EPO sc + oral iron vs Placebo sc + oral iron	*Hb ≤8.5 mmol/L* Not statistically significant: 13/38 vs 23/43 § RR: 0.64, 95%CI [0.38;1.08] ¥ (p=0.09)*	1, 38 vs 43	Qvist, 1999
Number of patients receiving perioperative transfusion	40 000 U EPO sc + oral iron vs no intervention	*Hb 10-13 g/dl* Statistically significant: 13/125 vs 32/138 RR: 0.45, 95%CI [0.25;0.82] (p=0.009)* *in favour of EPO sc + oral iron*	1, 125 vs 138	So-Osman, 2014
Number of patients receiving perioperative transfusion	150 IU/kg EPO sc + oral iron + oral folate vs Placebo sc + oral iron + oral folate	*Hb 9-13 g/dl* Not statistically significant: 9/17 vs 4/10 § RR: 1.32, 95%CI [0.55;3.20] ¥ (p=0.53)*	1, 17 vs 10	Heiss, 1996
Number of patients receiving perioperative transfusion	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* Statistically significant: 22/37 vs 32/37 RR: 0.69, 95%CI [0.51;0.92] (p=0.01)* *in favour of EPO iv + iv iron*	1, 37 vs 37	Yoo, 2011
Number of patients receiving perioperative transfusion	40 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Statistically significant: 5/44 vs 35/78 § RR: 0.25, 95%CI [0.11;0.60] (p=0.0018)* *in favour of Epoetin alfa sc + oral iron*	1, 44 vs 78	Feagan, 2000
	20 000 IU Epoetin alfa sc	*Hb 9.8-13.7 g/dl* Statistically significant:	1, 79 vs 78	

	+ oral iron vs Placebo sc + oral iron	18/79 vs 35/78 § RR: 0.51, 95%CI [0.32;0.82] (p=0.0051)* *in favour of Epoetin alfa sc + oral iron*		
Number of patients receiving perioperative transfusion	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* Not statistically significant: 19/29 vs 24/29 § RR: 0.79, 95%CI [0.58;1.08] ¥ (p=0.14)*	1, 29 vs 29	Scott, 2002
Number of patients receiving perioperative transfusion	40 000 IU Epoetin alfa sc + oral iron vs Oral or iv iron	*Hb 10-13 g/dl* Statistically significant: 41/460 vs 87/235 § RR: 0.24, 95%CI [0.17;0.34] (p<0.0000)* *in favour of Epoetin alfa sc + oral iron*	1, 460 vs 235	Weber, 2005
Number of patients receiving perioperative transfusion	150 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 34/69 vs 36/68 § RR: 0.93, 95%CI [0.67;1.29] ¥ (p=0.67)*	1, 69 vs 68	Christodoulakis, 2005
	300 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 25/67 vs 36/68 § RR: 0.70, 95%CI [0.48;1.03] ¥ (p=0.07)*	1, 67 vs 68	
Number of patients receiving perioperative transfusion	20 000 IU Epoetin beta sc + iron (oral and/or iv) vs Placebo sc + iron (oral and/or iv)	*Hb >8.5 and ≤13.5 g/dl* Not statistically significant: 16/48 vs 15/54 § aOR: 0.67, 95%CI [0.22;2.02] ¥ (p=0.478)	1, 48 vs 54	Kettelhack, 1998
Number of patients receiving perioperative transfusion	125 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Statistically significant: 19/65 vs 28/51 §££££ (p=0.0045) *in favour of Epoetin beta sc + oral iron*	1, 65 vs 51	Wurnig, 2001
	250 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Statistically significant: 22/59 vs 28/51 §££££ (p=0.048) *in favour of Epoetin beta sc + oral iron*	1, 59 vs 51	
Number of patients receiving intraoperative transfusion	5000 IU Epoetin beta sc + oral iron	*Hb <12 g/dl (women)* Not statistically significant: 0/15 vs 1/16	1, 15 vs 16	Larson, 2001

	vs Oral iron	RR: 0.35, 95%CI [0.02;8.08] ¥ (p=0.51)*		
Number of patients receiving intraoperative transfusion	300 IU/kg Epoetin alfa sc + iv iron vs Placebo sc + iv iron	*Hb 8.5-13 g/dl* Statistically significant: 9/31 vs 19/32 § RR: 0.49, 95%CI [0.26;0.91] (p=0.0238)* *in favour of Epoetin alfa sc + iv iron*	1, 31 vs 32	Kosmadakis, 2003
Number of patients receiving postoperative transfusion	300 IU/kg Epoetin alfa sc + iv iron vs Placebo sc + iv iron	*Hb 8.5-13 g/dl* Statistically significant: 1/31 vs 9/32 § RR: 0.11, 95%CI [0.02;0.85] (p=0.0344)* *in favour of Epoetin alfa sc + iv iron*	1, 31 vs 32	Kosmadakis, 2003
Number of patients receiving postoperative transfusion	150 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 33/69 vs 36/68 § RR: 0.90, 95%CI [0.65;1.26] ¥ (p=0.55)*	1, 69 vs 68	Christodoulakis, 2005
	300 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 27/67 vs 36/68 § RR: 0.76, 95%CI [0.53;1.10] ¥ (p=0.14)*	1, 67 vs 68	
Number of patients receiving postoperative transfusion	3000 IU Epoetin beta sc + iron iv vs no treatment	*Hb >10 g/dl (women)* Statistically significant: 11/54 vs 29/54 RR: 0.38, 95%CI [0.21;0.68] (p=0.0011)* *in favour of Epoetin beta sc + iv iron*	1, 54 vs 54	Na, 2011
Number of patients receiving multiple postoperative transfusion	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* Statistically significant: 5/37 vs 20/37 RR: 0.25, 95%CI [0.11;0.60] (p=0.0017)* *in favour of EPO iv + iv iron*	1, 37 vs 37	Yoo, 2011
3. b) Red blood cell utilization – Number of units transfused				
Units of blood transfused perioperatively (mean)	EPO sc + oral iron vs Placebo sc + oral iron	*Hb ≤8.5 mmol/L* Statistically significant: 0.3 vs 1.6 MD: -1.3 £ (p<0.05) *in favour of EPO*	1, 38 vs 43 §	Qvist, 1999
Units of erythrocytes	40 000 U EPO sc + oral iron	*Hb 10-13 g/dl* Statistically significant:	1, 125 vs 138	So-Osman, 2014

transfused among all patients (mean±SD)	vs no intervention	0.25±0.9 vs 0.64±1.6 MD: -0.39, 95%CI [-0.70;-0.08] (p=0.017)* *in favour of EPO sc + oral iron*		
Units of packed erythrocytes transfused perioperatively among all patients (mean±SD)	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* Statistically significant: 1.0±1.1 vs 3.3±2.2 MD: -2.30, 95%CI [-3.09;-1.51] (p<0.0001)* *in favour of EPO iv + iv iron*	1, 37 vs 37	Yoo, 2011
Units of packed erythrocytes transfused perioperatively among transfused patients (mean±SD)	500 IU/kg EPO iv + iv iron vs Saline iv	*Hb <13 g/dl (men) or <12 g/dl (women)* Statistically significant: 1.6±0.9 vs 3.7±2.1 MD: -2.10, 95%CI [-2.92;-1.28] (p=0.001)* *in favour of EPO iv + iv iron*	1, 22 vs 32	Yoo, 2011
Units of blood transfused perioperatively per patient (mean±SD)	150 IU/kg EPO sc + oral iron + oral folate vs Placebo sc + oral iron + oral folate	*Hb 9-13 g/dl* Not statistically significant: 1.82±0.80 vs 1.80±0.97 MD: 0.02, 95%CI [-0.69;0.73] (p=0.95)*	1, 17 vs 10 §	Heiss, 1996
Units of blood transfused perioperatively (mean±SD)	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* Not statistically significant: 2.07±2.76 vs 3.41±3.04 MD: -1.34, 95%CI [-2.83;0.15] ¥ (p=0.08)*	1, 29 vs 29 §	Scott, 2002
Units of blood transfused perioperatively in transfused patients (mean±SD)	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* Not statistically significant: 3.16±2.87 vs 4.12±2.86 MD: -0.96, 95%CI [-2.68;0.76] ¥ (p=0.28)*	1, 19 vs 24 §	Scott, 2002
Units of blood transfused at any time among all patients (mean±SD)	40 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Statistically significant: 0.3±0.7 vs 1.0±1.2 MD: -0.70, 95%CI [-1.04;-0.36] (p=0.0006)* *in favour of Epoetin alfa sc + oral iron*	1, 44 vs 78 §	Feagan, 2000
	20 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Statistically significant: 0.4±0.9 vs 1.0±1.2 MD: -0.60, 95%CI [-0.93;-0.27] (p=0.0005)* *in favour of Epoetin alfa sc + oral iron*	1, 79 vs 78 §	
Units of blood transfused at any time among	40 000 IU Epoetin alfa sc + oral iron	*Hb 9.8-13.7 g/dl* Not statistically significant: 2.2±0.4 vs 2.1±0.8	1, 5 vs 35 §	Feagan, 2000

transfused patients (mean±SD)	vs Placebo sc + oral iron	MD: 0.10, 95%CI [-0.34;0.54] (p=0.79)*		
	20 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Not statistically significant: 1.8±0.8 vs 2.1±0.8 MD: -0.30, 95%CI [-0.75;0.15] (p=0.20)*	1, 18 vs 35 §	
Units of blood transfused perioperatively (mean±SD)	150 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 1.19±1.46 vs 1.34±1.59 MD: -0.15, 95%CI [-0.66;0.36] (p=0.57)*	1, 69 vs 68 §	Christodoulakis, 2005
	300 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Statistically significant: 0.81±1.22 vs 1.34±1.59 MD: -0.53, 95%CI [-1.01;-0.05] (p=0.03)* *in favour of Epoetin alfa sc + oral/iv iron + folic acid*	1, 67 vs 68 §	
Units of blood transfused postoperatively (mean±SD)	3000 IU Epoetin beta sc + iron iv vs no treatment	*Hb >10 g/dl (women)* Statistically significant: 0.2±0.5 vs 0.8±0.8 MD: -0.60, 95%CI [-0.85;-0.35] (p=0.0000)* *in favour of Epoetin beta sc + iv iron*	1, 54 vs 54	Na, 2011
Units of blood transfused postoperatively (mean±SD)	150 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Not statistically significant: 1.10±1.42 vs 1.35±1.58 MD: -0.25, 95%CI [-0.75;0.25] ¥ (p=0.33)*	1, 69 vs 68 §	Christodoulakis, 2005
	300 IU Epoetin alfa sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	*Hb >9 and <12 g/dl* Statistically significant: 0.87±1.21 vs 1.35±1.58 MD: -0.48, 95%CI [-0.95;-0.01] (p=0.0498)* *in favour of Epoetin alfa sc + oral/iv iron + folic acid*	1, 67 vs 68 §	
4. Thromboembolic events				
Arterial thrombosis	20 000 IU Epoetin beta sc + iron (oral and/or iv) vs Placebo sc + iron (oral and/or iv)	*Hb >8.5 and ≤13.5 g/dl* Not statistically significant: 1/48 vs 0/54 § RR: 3.37, 95%CI [0.14;80.76] ¥ (p=0.45)*	1, 48 vs 54	Kettelhack, 1998
Deep venous thrombosis	EPO sc + oral iron	*Hb ≤8.5 mmol/L* Not statistically significant:	1, 38 vs 43	Qvist, 1999

	vs Placebo sc + oral iron	1/38 vs 0/43 § RR: 3.38, 95%CI [0.14;80.70] ¥ (p=0.45)*		
Deep venous thrombosis	40 000 U EPO sc + oral iron vs no intervention	*Hb 10-13 g/dl* 0/125 vs 0/138 Effect size not estimable £	1, 125 vs 138	So-Osman, 2014
Deep venous thrombosis	150 IU/kg EPO sc + oral iron + oral folate vs Placebo sc + oral iron + oral folate	*Hb 9-13 g/dl* Not statistically significant: 2/20 vs 0/10 § RR: 2.62, 95%CI [0.14;49.91] ¥ (p=0.52)*	1, 20 vs 10	Heiss, 1996
Deep venous thrombosis	40 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Not statistically significant: 2/44 vs 5/78 § RR: 0.71, 95%CI [0.14;3.50] ¥ (p=0.67)*	1, 44 vs 78	Feagan, 2000
	20 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Not statistically significant: 5/79 vs 5/78 § RR: 0.99, 95%CI [0.30;3.28] ¥ (p=0.98)*	1, 79 vs 78	
Deep venous thrombosis	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 16/340 vs 7/340 RR: 2.29, 95%CI [0.95;5.49] ¥ (p=0.06)*	1, 340 vs 340	Stowell, 2009
Deep venous thrombosis	600 IU Epoetin alfa + oral iron vs Placebo + oral iron	*Hb ≥10 and ≤13.5 g/dl* 0/29 vs 0/29 § Effect size not estimable £	1, 29 vs 29	Scott, 2002
Deep venous thrombosis	300 IU/kg Epoetin alfa sc + iv iron vs Placebo sc + iv iron	*Hb 8.5-13 g/dl* Not statistically significant: 2/31 vs 1/32 § RR: 2.06, 95%CI [0.20;21.63] ¥ (p=0.54)*	1, 31 vs 32	Kosmadakis, 2003
Deep venous thrombosis	125 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Not statistically significant: 2/70 vs 0/60 § RR: 4.30, 95%CI [0.21;87.76] ¥ (p=0.34)*	1, 70 vs 60	Wurnig, 2001
	250 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Not statistically significant: 2/64 vs 0/60 §	1, 64 vs 60	

		RR: 4.69, 95%CI [0.23;95.79] ¥ (p=0.32)*		
Pulmonary embolism	40 000 U EPO sc + oral iron vs no intervention	*Hb 10-13 g/dl* 0/125 vs 0/138 Effect size not estimable £	1, 125 vs 138	So-Osman, 2014
Pulmonary embolism	40 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Not statistically significant: 0/44 vs 1/78 § RR: 0.59, 95%CI [0.02;14.07] ¥ (p=0.74)*	1, 44 vs 78	Feagan, 2000
	20 000 IU Epoetin alfa sc + oral iron vs Placebo sc + oral iron	*Hb 9.8-13.7 g/dl* Not statistically significant: 0/79 vs 1/78 § RR: 0.33, 95%CI [0.01;7.96] ¥ (p=0.49)*	1, 79 vs 78	
Pulmonary embolism	600 IU/kg Epoetin alfa sc + oral iron vs Standard of care + oral iron	*Hb >10 and ≤13 g/dl* Not statistically significant: 0/340 vs 3/340 RR: 0.14, 95%CI [0.01;2.76] ¥ (p=0.20)*	1, 340 vs 340	Stowell, 2009
Pulmonary embolism	125 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* 0/70 vs 0/60 § Effect size not estimable £	1, 70 vs 60	Wurnig, 2001
	250 IU/kg Epoetin beta sc + oral iron vs Oral iron	*Hct 30-42%* Not statistically significant: 1/64 vs 0/60 § RR: 2.82, 95%CI [0.12;67.80] ¥ (p=0.52)*	1, 64 vs 60	

Mean ± SD (unless otherwise indicated), MD: mean difference, RR: risk ratio, OR: odds ratio, aOR: adjusted odds ratio, SD: standard deviation, IQR: interquartile range

* Calculations done by the reviewer using Review Manager software

** Calculations (SD, based on the standard error and number of participants) done by the reviewer using Excel

£ No SD's available (continuous outcomes) or no events (dichotomous outcomes), effect size and CI cannot be calculated

ff Number of participants not available, CI cannot be calculated

fff Median, but no effect size and CI reported

ffff Use of Cochran-Armitage test, no effect size and CI reported

¥ Imprecision (large variability of results)

† Imprecision (lack of data)

§ Imprecision (limited sample size or low number of events)

Forest plots

COMPARISON 1: TRANSFUSION VS NO TREATMENT/PLACEBO/STANDARD OF CARE

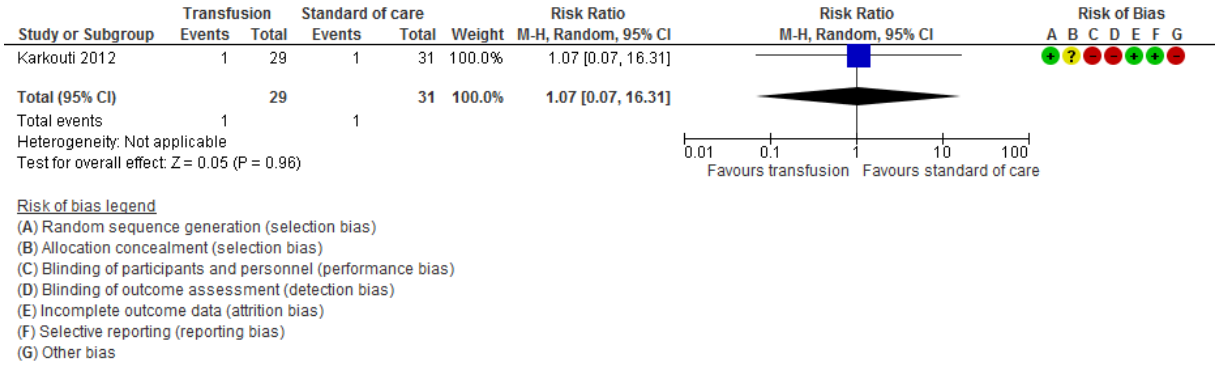


Figure 1: Forest plot of outcome: Mortality.

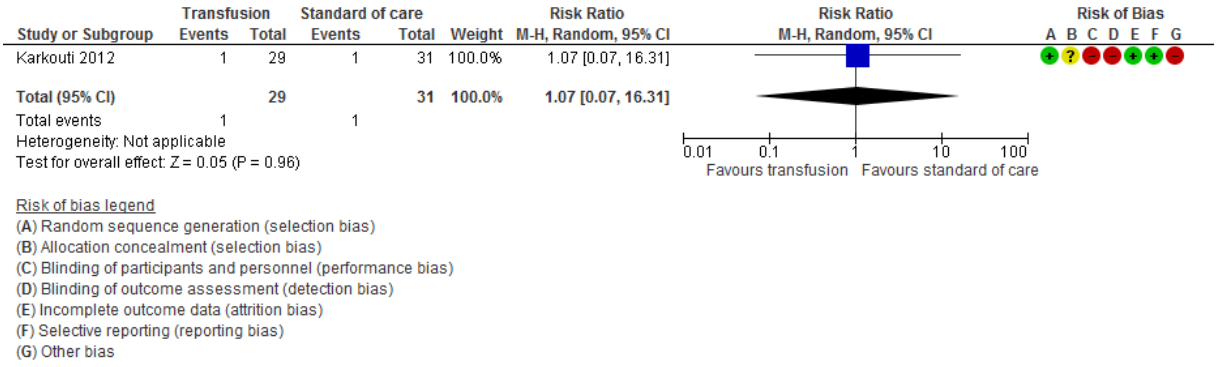


Figure 2: Forest plot of outcome: Acute myocardial infarction.

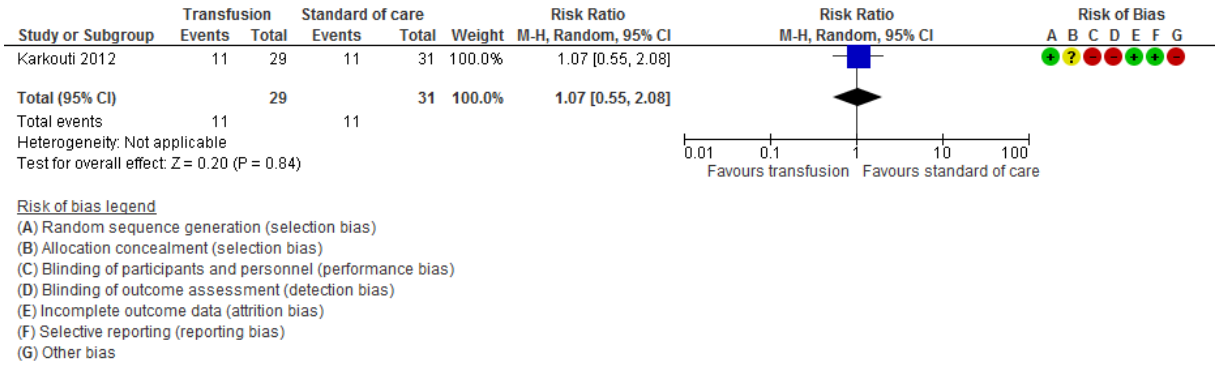


Figure 3: Forest plot of outcome: Acute kidney injury.

COMPARISON 2: IRON SUPPLEMENTATION VS NO TREATMENT/PLACEBO/STANDARD OF CARE

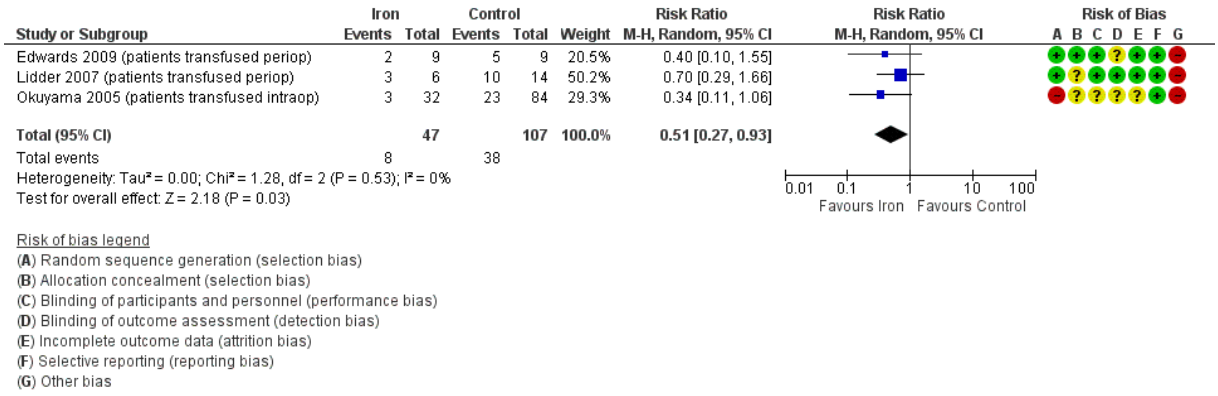


Figure 4: Forest plot of outcome: Red blood cell utilization – Number of patients transfused

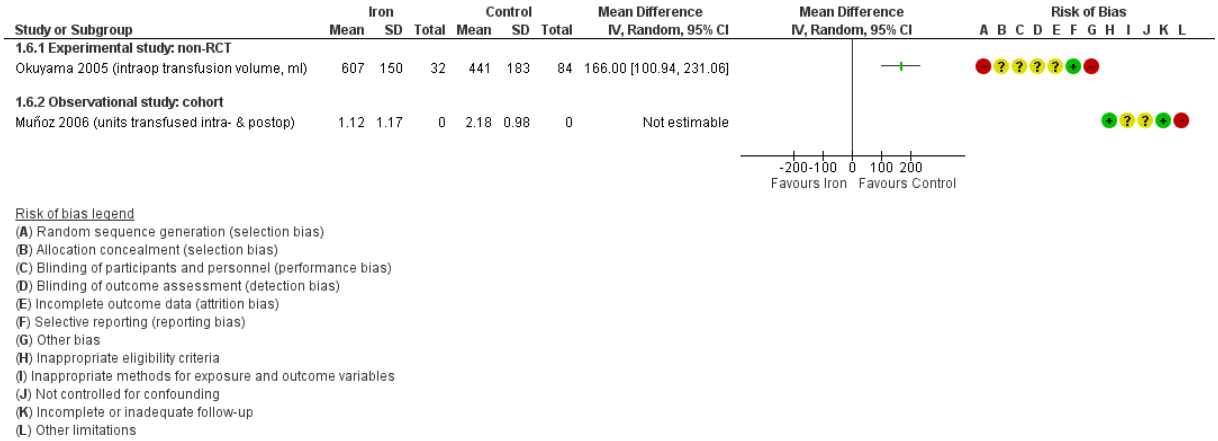


Figure 5: Forest plot of outcome: Red blood cell utilization – Number of units transfused

In addition to the 2 studies mentioned in the forest plot depicted above, a randomised controlled trial by Lidder *et al.* in anaemic patients (Hb <13.5 g/dl in men and <11.5 g/dl in women) scheduled for colorectal surgery demonstrated that oral iron supplementation did not result in a statistically significant difference in the median number of units transfused perioperatively compared to patients receiving standard clinical management (Lidder, 2007).

COMPARISON 3: ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE

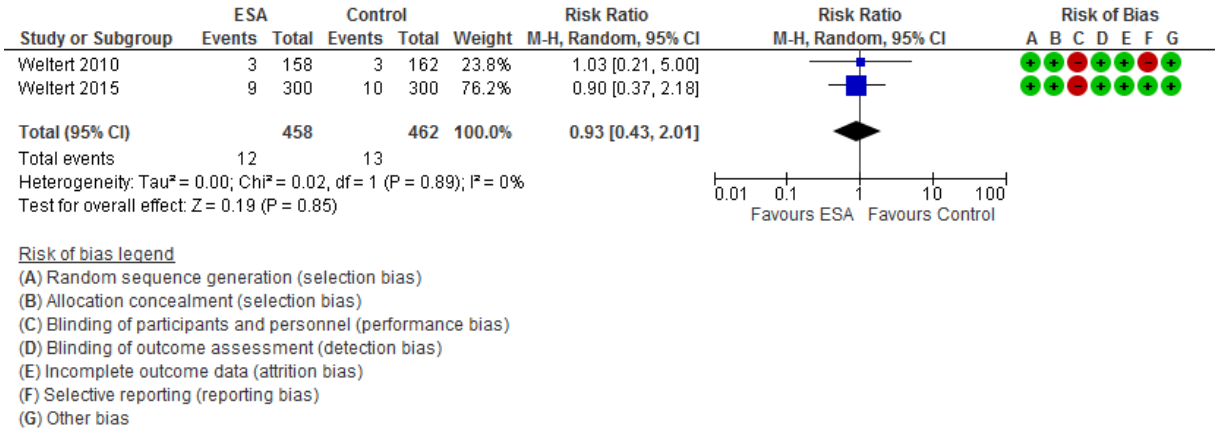


Figure 6: Forest plot of outcome: 45-day mortality

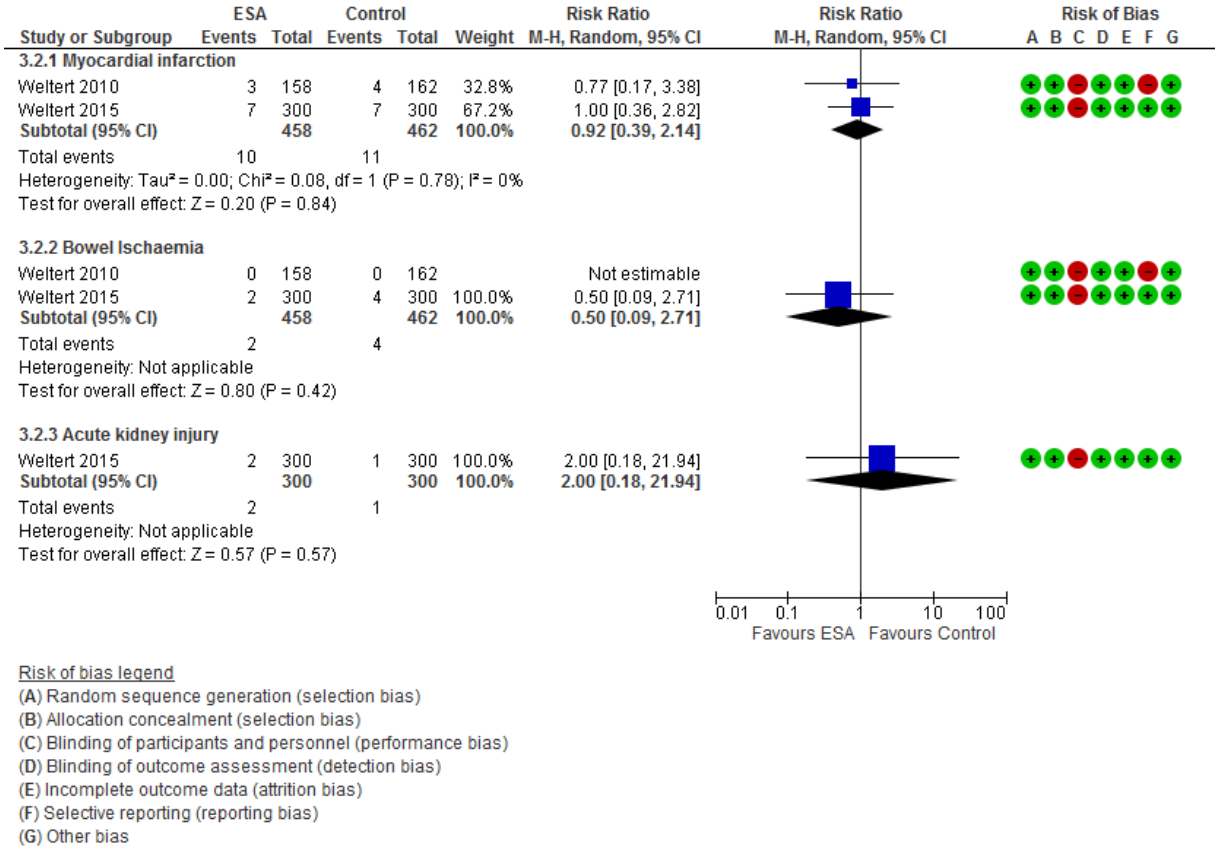
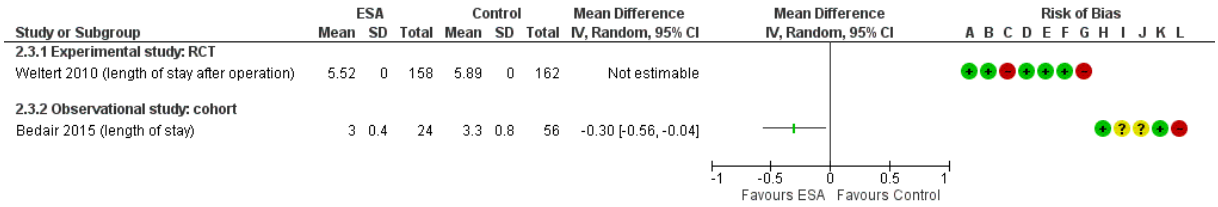
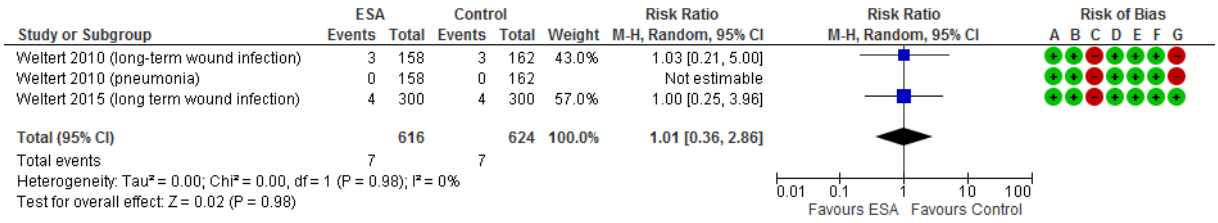


Figure 7: Forest plot of outcome: Anemia-associated ischaemic events



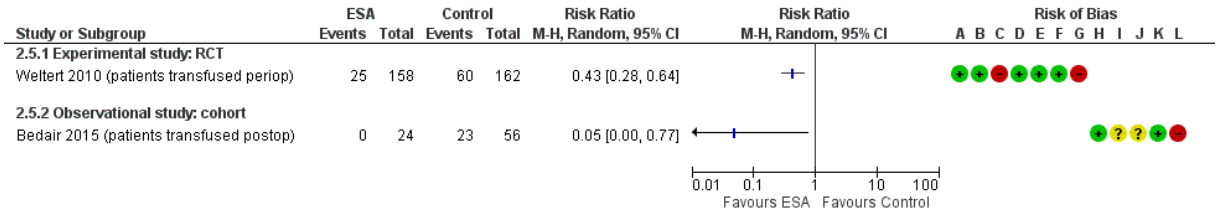
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Inappropriate eligibility criteria
(I) Inappropriate methods for exposure and outcome variables
(J) Not controlled for confounding
(K) Incomplete or inadequate follow-up
(L) Other limitations

Figure 8: Forest plot of outcome: Length of hospital stay



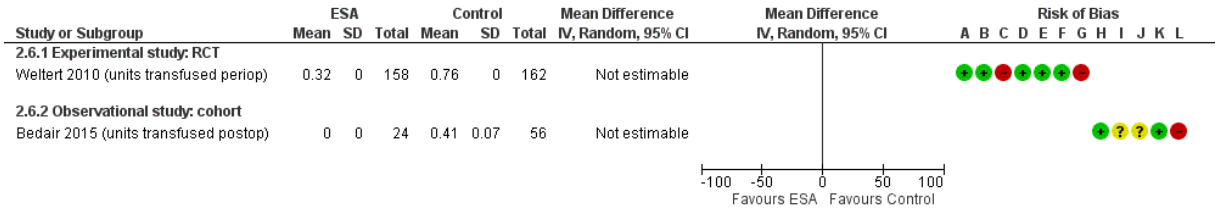
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 9: Forest plot of outcome: Infections



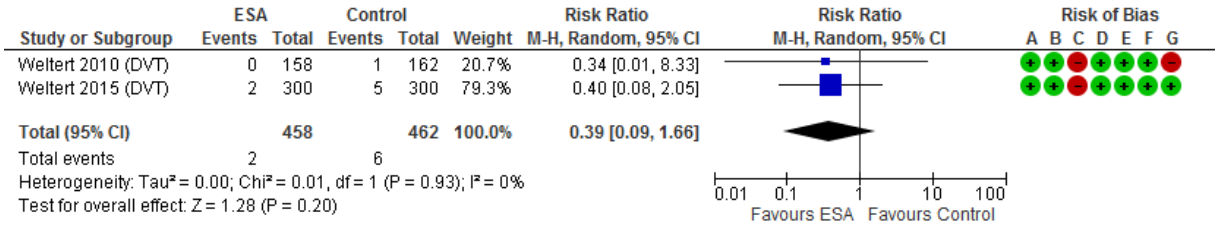
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Inappropriate eligibility criteria
(I) Inappropriate methods for exposure and outcome variables
(J) Not controlled for confounding
(K) Incomplete or inadequate follow-up
(L) Other limitations

Figure 10: Forest plot of outcome: Red blood cell utilization – Number of patients transfused



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Inappropriate eligibility criteria
(I) Inappropriate methods for exposure and outcome variables
(J) Not controlled for confounding
(K) Incomplete or inadequate follow-up
(L) Other limitations

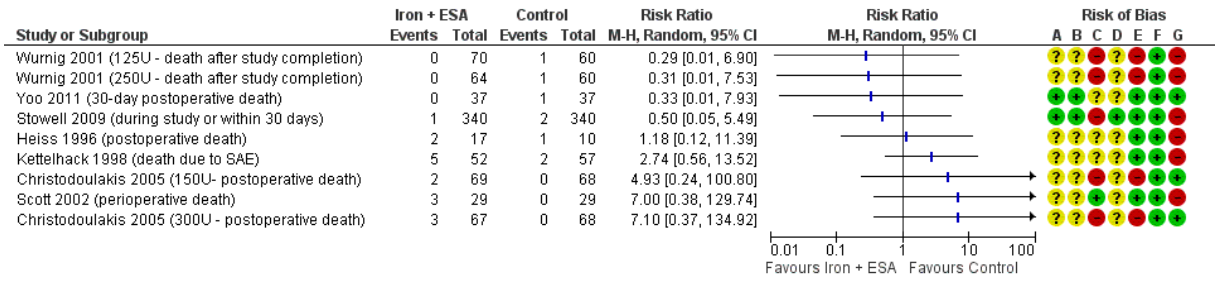
Figure 11: Forest plot of outcome: Red blood cell utilization – Number of units transfused



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 12: Forest plot of outcome: Thromboembolic events *(DVT: deep venous thrombosis)*

COMPARISON 4: IRON SUPPLEMENTATION + ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 13 A: Forest plot of outcome: (All-cause) mortality *(Sorted according to effect size; SAE: serious adverse events)*

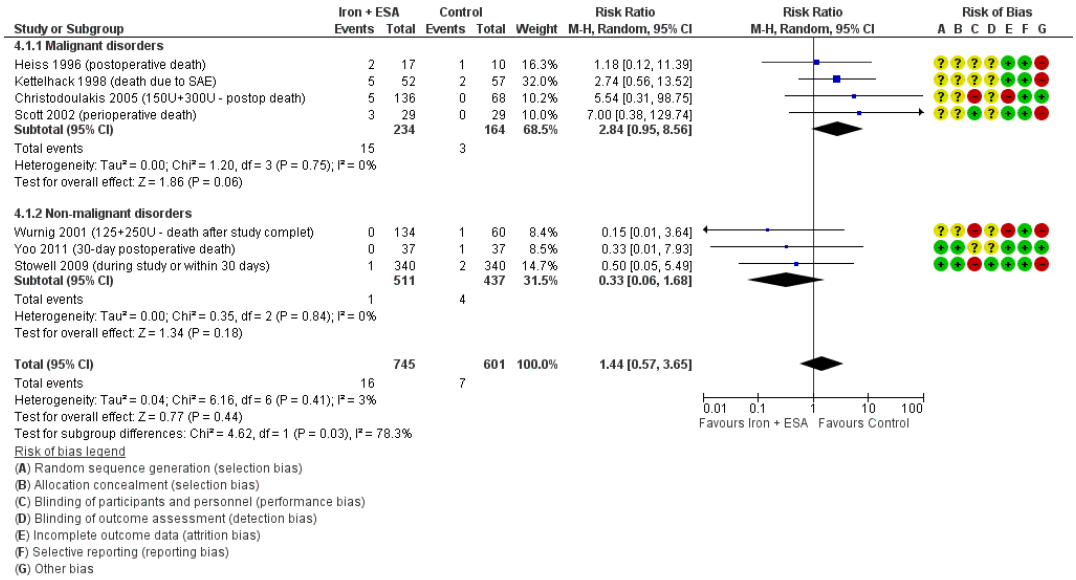


Figure 13 B: Figure 10 B: Forest plot of outcome: (All-cause) mortality *(Subgroup analysis: malignant versus non-malignat disorders)*

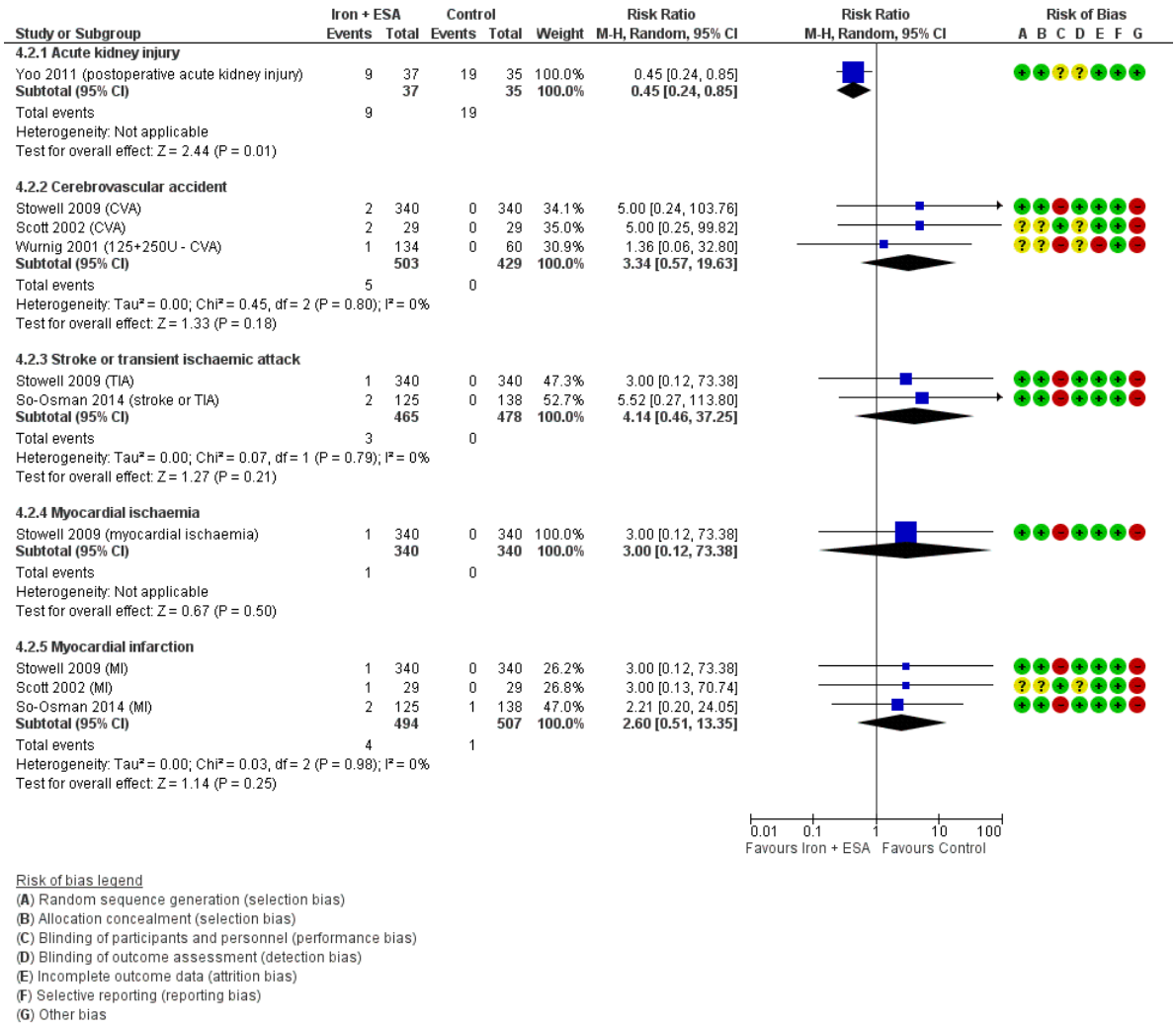
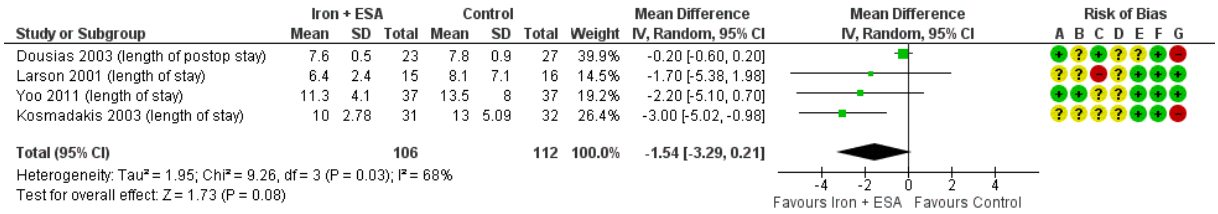
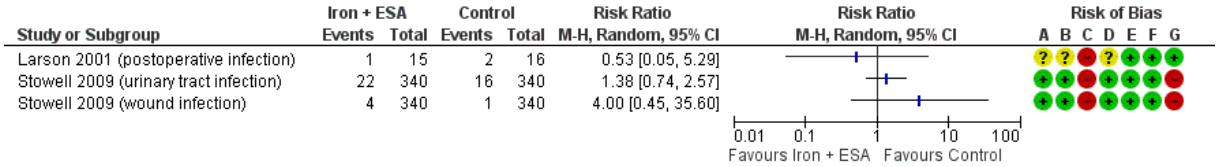


Figure 14: Forest plot of outcome: Anemia-associated ischaemic events *(Sorted according to the type of event; CVA: cerebrovascular accident, TIA: transient ischaemic attack, MI: myocardial infarction)*



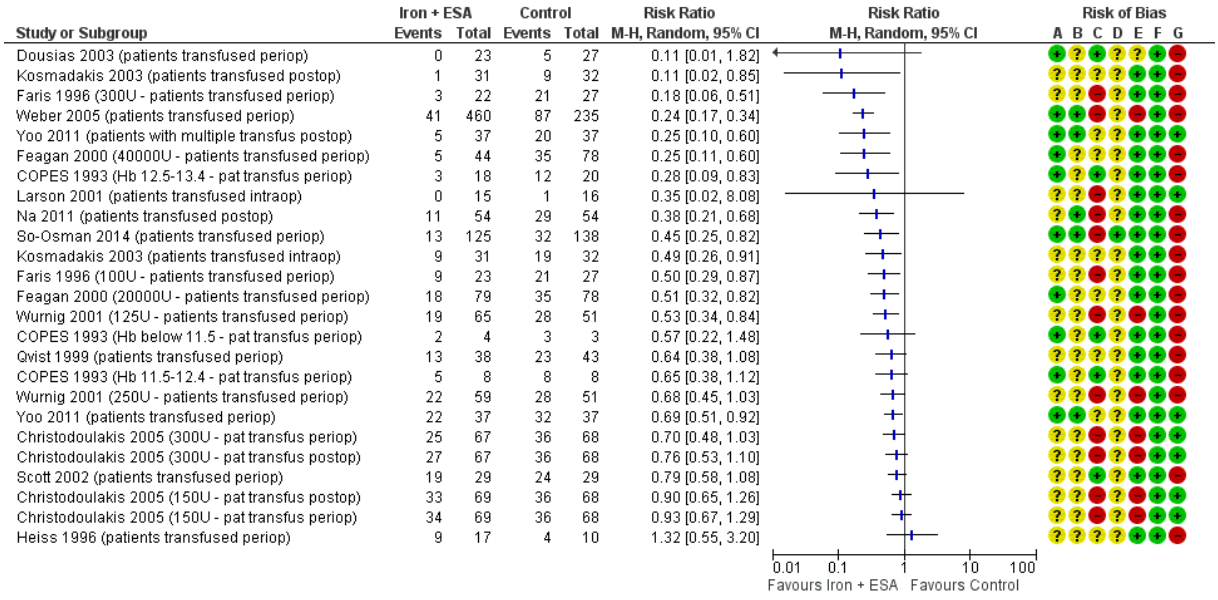
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 15: Forest plot of outcome: Length of hospital stay *(Sorted according to effect size)*



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

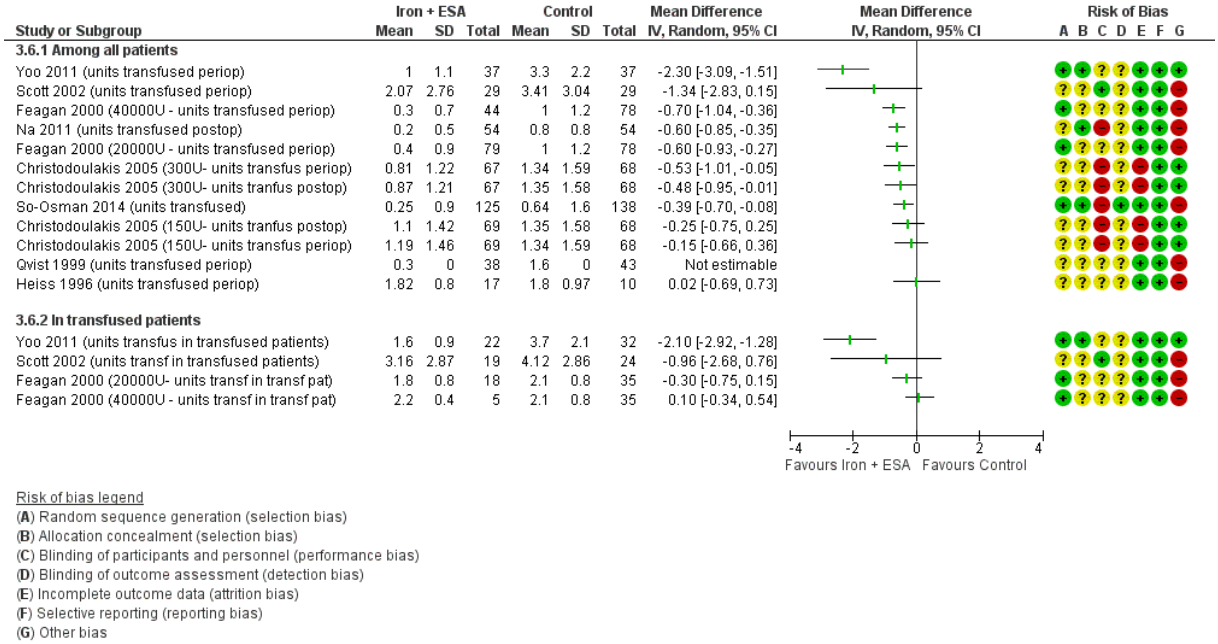
Figure 16: Forest plot of outcome: Infections *(Sorted according to effect size; Larson 2001: Postoperative infection = superficial wound infection, severe streptococcal septicaemia or urinary tract infection)*



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 17: Forest plot of outcome: Red blood cell utilization – Number of patients transfused. *(Sorted according to effect size)*

In addition to the studies depicted in the above forest plot, a study by Kettelhack *et al.* in patients with colon cancer scheduled for right hemicolectomy with Hb levels >8.5 and ≤13.5 g/dl, demonstrated that there was no significant difference in the number of patients transfused perioperatively between the patients treated with both subcutaneous Epoetin beta and iron (oral and/or intravenous) and those treated with oral iron only (odds ratio adjusted for age, Hb level at baseline and blood loss: 0.67, p=0.478) (Kettelhack, 1998).



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 18: Forest plot of outcome: Red blood cell utilization – Number of units transfused *(Sorted according to effect size)*

Subgroups were made by the reviewer to distinguish between the mean number of units transfused peri- and/or post-operatively in (1) all patients and (2) transfused patients only.

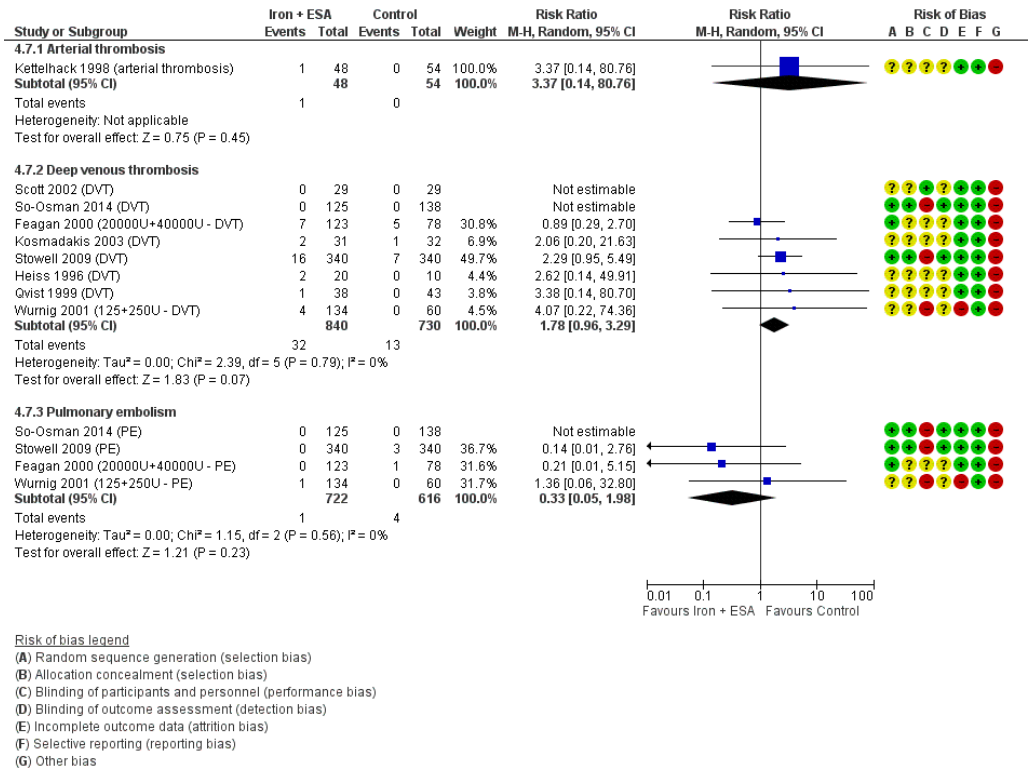


Figure 19: Forest plot of outcome: Thromboembolic events *(Sorted according to effect size within each subgroup; DVT: deep venous thrombosis, PE: pulmonary embolism)*
Subgroups were made by the reviewer for (1) arterial and (2) deep venous thrombosis and (3) pulmonary embolism.

Quality of evidence

Experimental studies

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations
COMPARISON 1: TRANSFUSION VS NO TREATMENT/PLACEBO/STANDARD OF CARE					
Karkouti, 2012	Randomization: No, a restricted stratified randomization scheme was used for patient allocation. Stratification was by baseline kidney function (eGFR less than or equal to, or greater than, 60 ml/min). In each stratum, patients were randomized in randomly permuted blocks of four or six patients. The assignments were computer generated and maintained in sequentially numbered, opaque, sealed envelopes. Allocation concealment: unclear, no information provided.	Participants: Yes Personnel: Yes Outcome assessors: Yes	No	No	Yes, multiple comparisons were conducted without adjusting the significance threshold, which increases the potential for a type I error.
COMPARISON 2: IRON SUPPLEMENTATION VS NO TREATMENT/PLACEBO/STANDARD OF CARE					
Edwards, 2009	Randomization: no, randomization sequence was computer-generated. To ensure equal numbers of	Participants: no, participants were blinded by using an opaque sheath to cover the druggiving	No. After randomization, 2 patients (one from each group) were found to be unsuitable for surgery and were	No	Only 9 anaemic patients were included in the subgroup analysis, instead of the 10 required by the power calculation

	anaemic patients in each treatment group, randomization was stratified according to prerecruitment Hb status using block randomization. Allocation concealment: no, allocation codes were sealed in sequentially numbered opaque envelopes which were secured within a locked store room in a dedicated research unit. Only after recruitment was an envelope opened by the investigator administering the infusion, following the inscribed strict numerical order and for the relevant subset appropriate to the Hb status of the participant.	set Personnel: no, the chief investigator and clinicians involved in perioperative care were blinded to the treatment group. However, the investigator administering the infusion was not blinded. Outcome assessors: unclear, no information provided	not included in the analysis. Two other patients (one from each group) did not attend for the second infusion.		Conflict of interest: Syner-Med Pharmaceutical Products Limited, the provider of the iron supplement, funded the blood tests.
Lidder, 2007	Randomization: no, patients were randomised by telephone to a distant centre Allocation concealment: unclear, no information provided	Participants: yes, but blinding was impeded because oral iron alters stool colour Personnel: no, the clinical team (surgeons, nurses,	No, but 4 patients (1 in the iron group, 3 in the standard clinical management group) were deemed unsuitable for resective surgery at admission.	No	No information on protocol registration for this trial Although this trial was externally randomised, the proportion of anaemic patients on recruitment into the trial was higher in the no-iron group (n=14) than in the iron

		anaesthetists) were blinded to treatment allocation Outcome assessors: no, the collection of data was performed by a research fellow not involved in the direct care of the patient, and gathered from the clinical notes			group (n=6). The difference in transfusion requirements for the 2 groups may, therefore, represent a type I statistical error.
Okuyama, 2005	Randomization: yes, from 2001 (study ran from 1998 to 2003), all anaemic patients who were able to be treated for at least 2 weeks preoperatively received iron supplementation. Allocation concealment: unclear, no information provided	Participants: unclear, no information provided Personnel: unclear, no information provided Outcome assessors: unclear, no information provided	Unclear	No	No information on protocol registration for this trial No correction for multiple testing
COMPARISON 3: ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE					
Weltert, 2010	Randomization: no, a custom simple application running in Windows XP was used to obtain randomization tables. Allocation concealment:	Participants: yes, the patients knew whether EPO was being administered or not. Personnel: yes, the nurses and ward physician knew	No. Two patients in the EPO group and 1 patient in the control group were converted to on-pump revascularization. These patients were considered as intention-to-	No	No information on protocol registration for this trial Power analysis indicated that 160 patients per group should have been included; the investigators however included

	no, the next value of the table was kept secret until a suitable patient was enrolled.	whether EPO was being administered or not. Outcome assessors: no, the investigators did not know whether EPO was being administered or not, nor did they have any chance to influence the clinical decision as to whether or not to give allogenic blood.	treat and were therefore included in the analysis.		groups of 158 and 162 patients Cell-saver systems were used during the operation in all patients; this might confound data on red blood cell utilization No correction for multiple testing

COMPARISON 4: **IRON SUPPLEMENTATION + ESA VS NO TREATMENT/PLACBO/STANDARD OF CARE**					
COPES, 1993	Randomization: no, randomization was computer generated at the coordinating centre and was stratified by centre and type of surgery (revision or primary) Allocation concealment: unclear, no information provided	Participants: unclear, the study is called a double-blind study, but no information is provided on the blinding process Personnel: no, physicians were blinded to the treatment allocation. Surgeons, study nurses, anaesthetists and other medical personnel did not know the Hb levels at baseline or 3 days before surgery. The Hb level the day before surgery and all postoperative Hb values were made available to the surgeon and attending medical staff. An unblinded physician who had no contact with the patients or physicians treating the patient reviewed the preoperative Hb levels to ensure that they had not risen too quickly. Outcome assessors:	No	No	No information on protocol registration for this trial After 30 patients had been randomized into each group, an interim analysis on Hb levels and transfusion frequency was conducted. On the basis of the results, the randomization scheme was altered to an unequal scheme: 40% for both EPO groups and 20% for the placebo group. In addition, the sample size was adjusted to detect a decrease in transfusion rate from 40% to 20%. No correction for multiple testing

		unclear, the study is called a double-blind study, but no information is provided on the blinding process			
Christodoulakis, 2005	Randomization: unclear, "patients were randomized (by a third party)" Allocation concealment: unclear, no information provided	Participants: yes, although patients in the two EPO groups were blind to the dosage received Personnel: yes, no blinding (open-label trial) Outcome assessors: unclear, no information provided	Yes, because all analyses were performed on the per-protocol population. Of the intention-to-treat population, 19 patients were excluded for protocol violations: refused operation (n=3), refused to complete the study (n=7), underwent operation before the scheduled time (n=4), allocated to the wrong group (n=2), received preoperative transfusion outside study eligibility (n=3).	No	No information on protocol registration for this trial
Dousias, 2003	Randomization: no, a random number generator was used Allocation concealment: unclear, no information provided	Participants: no, patients were unaware of their grouping. Controls were given similarly looking subcutaneous injections with normal saline on the same days. Personnel: no, operators were unaware of their grouping. Controls were	Unclear, insufficient information provided	No	No information on protocol registration for this trial No correction for multiple testing

		given similarly looking subcutaneous injections with normal saline on the same days. Outcome assessors: unclear, no information provided			
Faris, 1996	Randomization: unclear, no information on randomization process Allocation concealment: unclear, no information provided	Participants: unclear, the study is called a double-blind study, but no information is provided on the blinding process Personnel: yes, although the investigators were blinded with regard to the identity of the medication, they were not blinded with regard to the patient's preoperative reticulocyte count. If elevation of the reticulocyte count was a consideration in the decision to perform a transfusion, then bias favoring non-transfusion might have occurred in the two groups of patients receiving EPO. Outcome assessors: unclear, the	No, 15 patients were not evaluated, because they did not have the scheduled operation (n=12) or because they did not receive the full medication (n=3).	No	No information on protocol registration for this trial Use of intraoperative and postoperative reinfusion systems was allowed in all patients; this might confound data on red blood cell utilization No adjustments for multiple comparisons were made, and multiple comparisons may yield spurious significant differences

		study is called a double-blind study, but no information is provided on the blinding process			
Feagan, 2000	Randomization: no, randomization was performed according to a computer-generated schedule using a block size of 13 and an allocation ratio of 3:5:5 to the high-dose epoetin group, lowdose epoetin group, or placebo group, respectively Allocation concealment: unclear, no information provided	Participants: unclear, the study is called a double-blind study, but no information is provided on the blinding process Personnel: unclear, the study is called a double-blind study, but no information is provided on the blinding process Outcome assessors: unclear, the study is called a double-blind study, but no information is provided on the blinding process	No, of the intention-to-treat group, 197 (98%) received all 4 scheduled doses of study medication. The remaining 4 patients received 3 doses: 1 dose was withheld in 3 patients in the high-dose epoetin group because the Hb levels exceeded the maximum value of 15 g/dl and in 1 patient in the low-dose epoetin group because of elevated blood pressure.	No	No information on protocol registration for this trial The number of patients included in this study was lower than the required number as indicated by the power analysis Conflict of interest: the study was funded by Janssen-Ortho Inc., the supplier of the Epoetin alfa, which had input into its design, conduct, and reporting
Heiss, 1996	Randomization: unclear, no information on randomization process, although the authors mention "the sequence of erythropoietin or placebo medication was determined in advance". Allocation concealment: unclear, no	Participants: no, patients were blinded for the performed application by use of preparations of EPO or placebo with identical feature and differentiated by successive numbers. Personnel: Unclear. Although the authors state	No, although 3 patients in the EPO group dropped out of the study due to deep venous thrombosis at the second day in the study (n=1), refusal to continue (n=1) and suspending of the surgery (n=1).	No	No information on protocol registration for this trial Conflict of Interest: Cilag GmbH, the supplier of the EPO, was in some way involved in this trial (see author information).

	information provided, although the authors mention "the sequence of erythropoietin or placebo medication was determined in advance".	that the "investigators were blinded for the performed application by use of preparations of EPO or placebo with identical feature and differentiated by successive numbers", it is unclear if this refers to the personnel administering the trial medication or to the outcome assessors. Outcome assessors: Unclear. Although the authors state that the "investigators were blinded for the performed application by use of preparations of EPO or placebo with identical feature and differentiated by successive numbers", it is unclear if this refers to the personnel administering the trial medication or to the outcome assessors.			
Kettelhack, 1998	Randomization: unclear, no information on randomization process	Participants: unclear, the study is called a double-blind study, but no	No, although 7 patients (4 in Epoetin beta group and 3 in placebo group)	No	No information on protocol registration for this trial

	Allocation concealment: unclear, no information provided	information is provided on the blinding process Personnel: unclear, the study is called a double-blind study, but no information is provided on the blinding process Outcome assessors: unclear, the study is called a double-blind study, but no information is provided on the blinding process	were excluded from analysis, due to adverse events before surgery (Epoetin beta n=2), preoperative transfusion (Placebo n=2), no hemicolectomy because colonic carcinoma was not confirmed at operation (Epoetin beta n=2), performance of palliative ileotransverse colostomy (Placebo n=1).		Only 102 patients were included in the efficacy analysis, instead of the 180 required by the power calculation No correction for multiple testing
Kosmadakis, 2003	Randomization: unclear, no information on randomization process Allocation concealment: unclear, no information provided	Participants: unclear, patients are said to be blinded to the performed application, but no information is provided on the blinding process Personnel: unclear, "investigators" are said to be blinded to the performed application, but it is not clear whether this refers to the personnel or the outcome assessors, and in addition, no information is provided on the blinding process	No, although 12 randomized patients were excluded from the study because of blood transfusions within 1 month before the study (n=2), personal reasons (n=4), protocol violation (n=2) and distant metastases proven at operation (n=4)	No	No information on protocol registration for this trial No correction for multiple testing

		Outcome assessors: unclear, "investigators" are said to be blinded to the performed application, but it is not clear whether this refers to the personnel or the outcome assessors, and in addition, no information is provided on the blinding process			
Larson, 2001	Randomization: unclear, no information on randomization process Allocation concealment: unclear, no information provided	Participants: yes, no blinding (open-labelled trial) Personnel: yes, no blinding (open-labelled trial) Outcome assessors: unclear, no information provided	No, but one patients from the oral iron group was lost to follow-up due to severe streptococcal septicemia	No	No information on protocol registration for this trial
Na, 2011	Randomization: unclear, no information on randomization process Allocation concealment: no, sealed envelopes were used	Participants: yes, but blinding was impeded by the dark brown colour of the iron Personnel: yes, but blinding was impeded by the dark brown colour of the iron Outcome assessors: unclear, no information provided	No, but 5 patients were lost during follow-up due to change to unilateral total knee replacement arthroplasty (control: n=3) or withdrawal of consent (EPO+iron: n=2)	No	No information on protocol registration for this trial No correction for multiple testing

Qvist, 1999	Randomization: Unclear, no information on randomization process Allocation concealment: unclear, no information provided	Participants: unclear, the study is called a double-blind study, but no information is provided on the blinding process Personnel: unclear, the study is called a double-blind study, but no information is provided on the blinding process Outcome assessors: unclear, the study is called a double-blind study, but no information is provided on the blinding process	No, but 19 patients (11 in the EPO, 8 in the placebo group) were excluded from analysis, because of death within 2 weeks after surgery due to widespread neoplastic disease (n=2), personal reasons (n=6) and protocol violation (n=11).	No	No information on protocol registration for this trial No correction for multiple testing Conflict of interest: the study was funded by Janssen-Cilag, the company supplying the EPO
Scott, 2002	Randomization: unclear, no information on randomization process Allocation concealment: unclear, no information provided	Participants: no, patients were blinded to the drug administered by use of identical Epoetin alfa and placebo preparations that were successively numbered Personnel: no, investigators were blinded to the drug administered by use of identical Epoetin alfa and placebo preparations that were successively numbered	No, but one patient from each group was disqualified from the study as a result of surgery cancellation after enrolment and receiving the study medication.	No	No information on protocol registration for this trial The study was funded by Ortho Biotech Products, L.P.. Although it is not explicitly mentioned in the text, this company is probably the provider of the Epoetin alfa

		Outcome assessors: unclear, no information provided			
So-Osman, 2014	Randomization: No, computer-generated randomization was used Allocation concealment: no, for each subject to be randomized, a sheet of paper with all relevant stratification and group-allocation information was produced and placed in a sealed opaque envelope. The exact moment of opening the envelope and its associated sequence number was verified against a centrally stored randomization list to check for selection bias.	Participants: yes, but due to the nature of the interventions, to avoid protocol violations, clinical-site staff members, clinicians, research nurses, and patients were aware of study group assignments. Personnel: yes, but due to the nature of the interventions, to avoid protocol violations, clinical-site staff members, clinicians, research nurses, and patients were aware of study group assignments. The chart data were written on the Case Report Form by the research nurses. All written information was transferred from the paper Case Report Form to the secure online Webbased data management	No, of the 47 not-evaluated patients, for the majority (83%) surgery had been cancelled or performed elsewhere, six of these patients had received at least one erythropoietin dose.	No	There was 34% non-adherence to the EPO randomization, mainly due to the surgery date being brought forward when surgery time became suddenly available, resulting in lack of time to prescribe 3 weeks of EPO therapy. Because the results are based on intention-to-treat analyses, this non-adherence to EPO may provide an underestimation of its effect. As a consequence of major protocol deviations, the intention-to-treat analysis differed from the as-treated analysis, analyzed in addition as complementary analysis.

		system (ProMISe) of the department of Medical Statistics and BioInformatics in Leiden. A built-in quality management system checked for irregularities, inconsistencies, and coding errors, and clarification was asked for whenever necessary. Outcome assessors: no, study investigators were blinded.			
Stowell, 2009	Randomization: no, a computer-generated randomization schedule was used Allocation concealment: no, an interactive voice-response system was used	Participants: yes, no blinding (open-label trial) Personnel: yes, no blinding (open-label trial) Outcome assessors: no, after local review, Doppler images were reanalyzed by an independent reviewer at a core laboratory who was blinded to the local findings and the study arm assignment. If the local and core laboratory interpretations differed, a third party adjudicator	No, but 60 and 33 patients were discontinued in the Epoetin alfa group and Standard of care group respectively, due to loss to follow-up (Standard n=1), subject or MD request (Epoetin n=16; Standard n=8), surgical delay (Epoetin n=17, Standard n=8), death (Standard n=1), adverse events (Epoetin n=9, Standard n=4), other reasons including surgery cancellations or insurance issues, failure to meet study	No	No information on protocol registration for this trial No baseline ultrasound scanning was performed to exclude or balance pre-existing deep venous thrombosis No correction for multiple testing

		blinded to the prior interpretations and the study arm assignment reviewed the image and rendered the definitive interpretation.	inclusion/exclusion criteria, ineligible, randomization error, and miscellaneous (subject request, subject identification missing at time of dosing, physician wanted standard of care subject on Epoetin alfa, and subject discharged) (Epoetin n=18, Standard n=11). Calculations were done on the intention-to-treat population.		
Weber, 2005	Randomization: no, patients were randomized in blocks of nine patients per hospital by telephone operated interactive voice randomization system Allocation concealment: no, telephone operated interactive voice randomization system allocated the patients to receive either no Epoetin alfa or Epoetin alfa.	Participants: yes, no blinding (open trial) Personnel: yes, no blinding (open trial) Outcome assessors: unclear, no information provided	Yes, because all analyses were performed on the on-treatment population. Of the intention-to-treat population, 9 patients were excluded, because their operation was postponed for more than 10 days.	No	No information on protocol registration for this trial Conflict of interest: This trial was sponsored by Ortho Biotech Europe and at the time of the study, one of the authors was an employee of the sponsoring company.

Wurnig, 2001	Randomization: unclear, no information on randomization process Allocation concealment: unclear, no information provided	Participants: unclear, no information provided Personnel: yes. It is stated that transfusions were administered at the discretion of the anaesthesiologist or surgeon, and that the anaesthetists were not informed on the study group allocation. However, the aim of keeping the anaesthetist unaware of a patient's allocation to a treatment group was achieved only in approximately 30% of the cases. Nothing is mentioned on the blinding of the surgeons. Outcome assessors: unclear, no information provided	Yes, a total of 20 patients were prematurely withdrawn from the study. The authors mention that the most common reason was non-compliance with the selection criteria (n = 7). However, no information is provided on the other 13 participants. Moreover, the efficacy analysis was not performed on the intention-to-treat population.	No	No information on protocol registration for this trial Conflict of interest: This study was supported by F. Hoffmann-La Roche, the supplier of the Epoetin beta.
Yoo, 2011	Randomization: no, computer-generated randomization was used and was performed by a ward physician not involved in the current trial	Participants: unclear, no information provided Personnel: no, medications were prepared and administered by a ward physician	No, no missing data	No	No information on protocol registration for this trial Blood cell salvage devices were used during the operation; this might confound data on red blood cell utilization

	Allocation concealment: no, a ward physician not involved in the current trial performed assignment	recognizing the patient's group but not involved in the current study, whereas the surgeon and anesthesiologist involved in the study and patient management were blinded to the patients' groups until the end of the study Outcome assessors: unclear, no information provided			No correction for multiple testing

Observational studies

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
COMPARISON 2: IRON SUPPLEMENTATION VS NO TREATMENT/PLACEBO/STANDARD OF CARE					
Muñoz, 2006	No, there were no significant differences between the historic control group and the intervention group with respect to age, gender, comorbidities, type of anaesthesia or perioperative Hb levels	Unclear, no information provided on how surveillance of the outcome measures was done, both in the historic control and intervention group	Unclear, no information provided	No	A historic control group was used
COMPARISON 3: ESA VS NO TREATMENT/PLACEBO/STANDARD OF CARE					
Bedair, 2015	No, there were no significant differences between the two groups in terms of age, preoperative Hb levels or medical comorbidities	Unclear, the authors state that all data were retrospectively reviewed, but it unclear how these outcomes were measured	Unclear, no information provided	No	Only a small minority of the eligible patients were willing to consider taking Epoetin alpha. This may introduce a selection bias, particularly because it concerns social and/or religious beliefs, type of insurance, and socioeconomic status.

Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
Reference(s)	See overview of included studies **Systematic reviews** Alexander DP, Frew N. *Preoperative optimisation of anaemia for primary total hip arthroplasty: a systematic review.* Hip Int 2017, 27(6):515-522 Alsaleh K, Alotaibi GS, Almodaimegh HS, Aleem AA, Kouroukis CT. *The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials.* J Arthroplasty 2013, 28(9):1463-1472 Borstlap WAA, Stellingwerf ME, Moolla Z, Musters GD, Buskens CJ, Tanis PJ, Bemelman WA. *Iron therapy for the treatment of preoperative anaemia in patients with colorectal carcinoma: a systematic review.* Colorectal Dis 2015, 17(12):1044-1054 Glechner A, Gartlehner G, Nuβbaumer B, Kozek-Langenecker S. *Perioperatives anämiemanagement – systematischer review und meta-analyse.* Wien Med Wochenschr 2014, 164(15-16):330-341 Hallet J, Hanif A, Callum J, Pronina I, Wallace D, Yohanathan L, McLeod R, Coburn N. *The impact of perioperative iron on the use of red blood cell transfusions in gastrointestinal surgery: a systematic review and meta-analysis.* Transfus Med Rev 2014, 28(4):205-211 Lin DM, Lin ES, Tran MH. *Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review.* Transfus Med Rev 2013, 27(4):221-234 Tran DHD, Wong GTC, Chee YE, Irwin MG. *Effectiveness and safety of erythropoietis-stimulating agent use in the perioperative period.* Expert Opin Biol Ther 2014, 14(1):51-61 Zhao Y, Jiang C, Peng H, Feng B, Li Y, Weng X. *The effectiveness and safety of preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty: a systematic review and meta-analysis of randomized controlled trials.* Medicine 2016, 95(27):e4122
Evidence used for	Guideline
Project	PBM consensus meeting
Reviewer(s)	Jorien Laermans and Hans Van Remoortel