

# Evidence summary to support PICO question 3: treatment preoperative anemia

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#### 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 <sup>1</sup>	-				
Iron supplementation versus no treatment – placebo - standard of care (Comparison 2)	3 studies <sup>2-4</sup>	1 study⁵				
ESA versus no treatment – placebo – standard of care (Comparison 3)	2 studies <sup>6,7</sup>	1 study <sup>8</sup>				
Iron supplementation + ESA versus no treatment – placebo – standard of care (Comparison 4)	17 studies <sup>9-25</sup>	-				

#### **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.
- 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)<sup>26-38</sup>

- 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.
- 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) <sup>39</sup>	Article in Italian. Selection criteria: only articles
	in English, French and German are included.
Cladellas et al (2012) <sup>40</sup>	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) <sup>41</sup>	Observational cohort study, but control group
	gets autologous donation
Cuenca et al (2004) <sup>42</sup>	Surgery for pertrochanteric hip fracture = no
	elective surgery
Cuenca et al (2005) <sup>43</sup>	Surgery for displaced subcapital hip fracture =
	no elective surgery
Cushner et al (2001) <sup>44</sup>	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) <sup>45</sup>	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) <sup>46</sup>	Observational cohort study
García-Erce et al (2009) <sup>47</sup>	Surgery for osteoporotic pertrochanteric or
	subcapital hip fracture = no elective surgery
Gonzalez-Porras et al (2009) <sup>46</sup>	Matched historic control group is not anemic
	(mean Hb 13.8± 1.4)
Keating et al (2007)**	RCI, but control group gets autologous
Kim at al (2000)50	Only reports on the levels for the levels serieus
Kim et al (2009) <sup>24</sup>	official adverse events (no definition) and tolerable
	adverse events (no definition) and tolerable
	dyspensia)
Kotzé et al (2012) <sup>51</sup>	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) <sup>52</sup>	Combination of both autologous blood and
	allogeneic blood transfusion in the intervention
	and control group
Mercuriali et al (1993) <sup>53</sup>	Autologous blood donation as part of the
	intervention and control group
Mercuriali et al (1997) <sup>54</sup>	Autologous blood donation as part of the
	intervention and control group
Moonen et al (2008) <sup>55</sup>	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) <sup>56</sup>	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) <sup>57</sup>	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) <sup>58</sup>	Hip fracture surgery = no elective surgery
Sowade et al (1997) <sup>59</sup>	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) <sup>60</sup>	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 as	sessment			Nº of patients Effect					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transfusion	standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Primary:	mortality											
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious	none	1/29 (3.4%)	1/31 (3.2%)	<b>RR 1.07</b> (0.07 to 16.31)	<b>2 more</b> <b>per</b> <b>1.000</b> (from 30 fewer to 494 more)	⊕○○○ VERY LOW	CRITICAL
Primary:	acute myoca	rdial infarct	ion									
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious	none	1/29 (3.4%)	1/31 (3.2%)	<b>RR 1.07</b> (0.07 to 16.31)	<b>2 more</b> <b>per</b> <b>1.000</b> (from 30 fewer to 494 more)	⊕○○○ VERY LOW	CRITICAL
Primary:	acute kidney	injury										
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious	none	11/29 (37.9%)	11/31 (35.5%)	<b>RR 1.07</b> (0.55 to 2.08)	<b>25 more</b> <b>per</b> <b>1.000</b> (from 160 fewer to 383 more)	⊕○○○ VERY LOW	CRITICAL
Seconda	ary: RBC units	transfused	(pre-operative)									

			Certainty assessment Nº of patients Effect									
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transfusion	standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious	none	29	31	-	median 2 RBC units higher (0 to 0)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Seconda	Secondary: RBC units transfused (intra-operative)											
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious	none	29	31	-	median 2 RBC units lower (0 to 0)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Seconda	Secondary: RBC units transfused (total)											
1	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious	none	29	31	-	median <b>0</b> <b>RBC</b> <b>units</b> (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 as	sessment			Nº of patients Effect					
Nº 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)	Certainty	Importance
Seconda	ry: Red blood o	ell utiliza:	ition - Number c	of patients trans	fused							
3	randomised trials	serious ª	not serious	not serious	serious <sup>b</sup>	none	8/47 (17.0%)	38/107 (35.5%)	<b>RR 0.51</b> (0.27 to 0.93)	<b>174</b> <b>fewer</b> <b>per 1.000</b> (from 25 fewer to 259 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Seconda	ry: Red blood o	ell utiliza:	ition - Number c	of units transfus	ed (experimen	tal studies: RCT ar	nd non-RCT)					
2	randomised trials <sup>c</sup>	serious <sup>d</sup>	not serious	not serious	serious <sup>e</sup>	none	See Forest plot – ex In addition to the 2	perimental st studies inclu	udy Okuya ded in the	ima et al. forest plot,	⊕⊕⊖⊖ LOW	IMPORTANT
trials c       d       In addition to the 2 studies included in the forest plot, a randomised controlled trial by Lidder <i>et al.</i> 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 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         Risk of lass leaded       (A) Random sequence generation (selection bias)       (B) Random sequ										<i>l.</i> in d <11.5 rgery difference al iron eiving		

	Certainty assessment Nº of patients Effect											
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementation	Certainty	Importance			
Seconda	ry: Red blood c	ell utiliza	tion - Number o	f units transfus	ed (observatio	nal cohort study)						
1	observational studies	serious <sup>f</sup>	not serious	not serious	serious <sup>g</sup>	none	See Forest plot – ok The observational c	z et al. 2006 in	⊕○○○ VERY LOW	IMPORTANT		
Study of Subgr 1.6.1 Experime Okuyama 2005 1.6.2 Observati Muñoz 2006 (un Risk of bias lea (A) Random se (B) Allocation cc (C) Blinding of o (B) Inlocation cc (C) Blinding of o (B) Incomplete (J) Not controlle (G) Other bias (H) Inapropriate (J) Not controlle (G) Other imitati	Image: Studies       Instruction       Instruction <thinstruction< th=""> <thinstruction< th=""></thinstruction<></thinstruction<>						patients undergoing with Hb levels < 13 significant decrease intra- and postoper in patients that rece iron, compared to r	g total hip reg g/dl, found t in the numb ratively could eived treatme no iron.	blacement : hat a statis er of units not be der nt with intr	surgery, tically transfused nonstrated ravenous		

**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				Nº of patients Effect			Nº of patients Effect			
№ 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)	Certainty	Importance
Primary:	(All-cause) mo	ortality										
2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	12/458 (2.6%)	13/462 (2.8%)	<b>RR 0.93</b> (0.43 to 2.01)	<b>2 fewer</b> <b>per</b> <b>1.000</b> (from 16 fewer to 28 more)	⊕⊕⊖⊖ LOW	CRITICAL
Primary:	Anemia-associ	iated ischae	emic events									
2	randomised trials	serious ª	not serious	not serious	serious <sup>b</sup>	none	See Forest plot 'Figure 7'. The RCTs by Weltert et al. 2010/2015 in patients undergoing off- pump CABG surgery, with Hb levels $\leq$ 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

		Cert	ainty as	sessment			Nº of p	atients	Ef	fect			
№ of studies	Study design	Risk of bias	Incons	sistency	Indirectness	Imprecision	Other considerations	erythrocyte stimulating agents (ESAs)	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
	ES	A Co	ontrol		Risk Ratio	Ris	k Ratio	Risk of Bias					
Study or S	Subgroup Events	Total Even	ts Total	Weight I	M-H, Random, 95% C	M-H, Ran	dom, 95% Cl	ABCDEFG					
3.2.1 Myo Weltert 20 Weltert 20 Subtotal ( Total even Heteroger Test for ov	2010/00/00/00/00/00/00/00/00/00/00/00/00/	158 300 <b>458</b> ni <sup>2</sup> = 0.08, df = (P = 0.84)	4 162 7 300 <b>462</b> 11 1 (P = 0.7)	32.8% 67.2% <b>100.0%</b> B); I <sup>2</sup> = 0%	0.77 (0.17, 3.38) 1.00 (0.36, 2.82) <b>0.92 (0.39, 2.14</b> )	-							
3.2.2 Bow	el Ischaemia	(1 = 0.04)											
Weltert 20 Weltert 20 <b>Subtotal (</b> Total even Heteroger Test for ov	10 0 15 2 95% CI) ts 2 leity: Not applicable erall effect: Z = 0.80	158 300 <b>458</b> (P = 0.42)	0 162 4 300 <b>462</b> 4	100.0% <b>100.0%</b>	Not estimable 0.50 (0.09, 2.71) 0.50 (0.09, 2.71)								
3.2.3 Acut Weltert 20 Subtotal ( Total even Heteroger Test for ov	e kidney injury 15 2 95% CI) ts 2 ieity: Not applicable erall effect: Z = 0.57	300 <b>300</b> (P = 0.57)	1 300 <b>300</b> 1	100.0% <b>100.0%</b>	2.00 [0.18, 21.94] 2.00 [0.18, 21.94]								
						0.01 0.1 Favours ES/	1 10 100 A Favours Control						
Risk of bia (A) Rando (B) Allocat (C) Blindin (D) Blindin (E) Incomp (F) Selecti (G) Other t	is legend m sequence genera ion concealment (se g of participants an- g of outcome asses olete outcome data ( ve reporting (reportin bias	ation (selectio election bias) d personnel (j ssment (detec (attrition bias) ng bias)	n bias) performan tion bias)	ce bias)									
Figure 7:	Forest plot of a	outcome: A	Anemia-	associate	ed ischaemic ev	ents							
Seconda	ry: Length of ho	ospital stay	(experi	mental s	study: RCT)								

			Certainty as	sessment			Nº of p	atients	nts Effect				
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)	Certainty	Importance	
1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>c</sup>	none	See Forest plo 8). In the RCT statistically sin of stay after t receiving EPC receiving no t demonstrated	ots – experim by Weltert e gnificant diffe he operation subcutaneou treatment cou d (p=0.065).	ental study t al. 2010 a prence in the between p usly and pa uld not be	r (Figure ne length patients atients	⊕⊕⊖⊖ LOW	IMPORTANT	
Study or Su	ESA Control Mean Difference Mean Difference Risk of Bias Study or Subgroup Mean SD Total Mean SD Total IV. Random, 95% CL IV. R												
2.3.1 Experi Weltert 2010	mental study: RCT I (length of stav after ope	ration) 5.52	0 158 5.89 0	162 Not estimabl	e	••••		·					
2.3.2 Observ Bedair 2015	<b>/ational study: cohort</b> (length of stay)	3	0.4 24 3.3 0.8	56 -0.30 [-0.56, -0.04	ıj — <b>i</b>		• ? ? • •						
					-1 -0.5 0 Favours ESA F	0.5 1 avours Control							
Risk of bias legend         (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Binding of participants and personnel (performance bias)         (D) Binding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias         (H) Inappropriate methods for exposure and outcome variables         (J) Not controlled for confounding         (M) Incomplete or inadequate follow-up         (J) Other limitations													
Seconda	Figure 8: Forest plot of outcome: Length of hospital stay												
Seconda	ry. Length Of H	ospital stay		conort study)									

			Certainty as	sessment			Nº of p	atients	Ef	fect		
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)	Certainty	Importance
1	observational studies	serious <sup>d</sup>	not serious	not serious	serious <sup>e</sup>	none	24	56	-	MD 0.3 days fewer (0.56 fewer to 0.04 fewer)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Seconda	ry: Infections											
2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	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
Study or S Weitert 201 Weitert 201 Weitert 201 Total (95% Total event Heterogen Test for ow <u>Risk of bia</u> (A) Randon (B) Allocati (C) Blindin (E) Blindin (E) Blindin (F) Selectiv (G) Other b	ESA       Control       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total       Events       Total       Veight       All S (2 1, 500)         Weitert 2010 (pneurmonia)       0       158       0       162       43.0%       1.03 (0.21, 500)         Weitert 2015 (ang term wound infection)       3       168       Not estimable       Image: Control wound infection)       4.300       57.0%       1.00 (0.25, 3.86)         Total       G9% C1       616       624       100.0%       1.01 (0.36, 2.86)       Image: Control wound infection)       616       624       100.0%       1.01 (0.36, 2.86)       Image: Control wound infection)       Favours ESA       Favours Control         Risk fibs legend       (A) Random sequence generation (selection bias)       Image: Control wound infection bias)       Image: Control wound infection bias)       Favours ESA       Favours Control         (B) Allocation concealment (selection bias)       (C) Blanding of outcome assessment (detection bias)       Favours ESA       Favours Control         (C) Blanding of outcome assessment (detection bias)       (C) Blanding of outcome assessment (detection bias)       Favours ESA       Favours Control         (G) Other bias       (G) Other bias       Favours Control       Favours ESA       Favours Control											
Figure 9	Forest plot of	outcome: I	ntections									

			Certainty as	sessment			Nº of patients Effe		fect			
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)	Certainty	Importance
Seconda	ry: Red blood o	cell utilizati	on - Number of	patients transfu	used (experime	ental study: RCT)						
1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	25/158 (15.8%)	60/162 (37.0%)	<b>RR 0.43</b> (0.28 to 0.65)	<b>211</b> <b>fewer</b> <b>per</b> <b>1.000</b> (from 130 fewer to 267 fewer)	⊕⊕⊖⊖ LOW	IMPORTANT
Seconda	ry: Red blood o	cell utilizati	on - Number of	patients transfu	used (observat	ional cohort study	)					
1	observational studies	serious <sup>d</sup>	not serious	not serious	serious <sup>f</sup>	none	0/24 (0.0%)	23/56 (41.1%)	<b>RR</b> <b>0.050</b> (0.003 to 0.770)	<b>390</b> <b>fewer</b> <b>per</b> <b>1.000</b> (from 94 fewer to 409 fewer)	⊕○○○ VERY LOW	IMPORTANT
Seconda	ry: Red blood o	cell utilizati	on - Number of	units transfuse	d (experimenta	al study: RCT)						
1	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>e</sup>	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).				IMPORTANT	

			Certainty as	sessment			Nº of p	atients	Ef	fect		
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)	Certainty	Importance
Study or Su	bgroup	ES Events	A Control Total Events Total I	Risk Ratio M-H, Random, 95% Cl	Risk Rat M-H, Random	tio ,95% CI ABCD	Riskof Bias EFGHIJKL					
2.5.1 Exper Weltert 201	imental study: RCT 0 (patients transfused p	periop) 25	i 158 60 162	0.43 [0.28, 0.64]	+	• • • • •	•••					
2.5.2 Obser Bedair 2019	vational study: cohort 5 (patients transfused p	iostop) O	0 24 23 56	0.05 (0.00, 0.77)	<b>← ı</b>		•??•	1				
					0.01 0.1 1 Favours ESA Fa	10 100 avours Control						
Risk of bias (A) Randon (B) Allocatic (C) Blinding (D) Blinding (E) Incompl (F) Selective (G) Other bi (H) Inapprop (J) Not coml (K) Incompl (L) Other lin Figure 1(	0.01       0.1       10       100         Favours ESA Favours Control    Favours ESA Favours Control          (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel (performance bias)         (D) Blinding of outcome assessment (idetection bias)         (E) Incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias         (H) Inappropriate eligibility criteria         (I) Inappropriate eligibility criteria         (I) Inappropriate eligibility criteria         (I) 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											
Seconda	ry: Red blood o	cell utilizatio	on - Number of	units transfuse	d (observatior	nal cohort study)						
1	observational studies	serious <sup>d</sup>	not serious	not serious	serious <sup>c</sup>	none	See Forest plo 11). For the o Bedair, 2005 i arthroplasty, size was not e control: 0 vs (	ot – observati bservational in patients ur with Hb level estimable (Ep 0.41±0.07 uni	ional study cohort stud idergoing l s < 13 g/dl oetin alpha ts).	(Figure dy by nip or knee , the effect a vs	⊕○○○ VERY LOW	IMPORTANT

			Certainty ass		Nº of pa	atients	Eff	fect				
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)	Certainty	Importance
Study or Su	bgroup	ESA Mean SD	Control Total Mean SD Tota	Mean Difference al IV, Random, 95% Cl	Mean Diffe IV, Random	rence ,95% CI ABCD	Risk of Bias EFGHIJKL					
2.6.1 Experi Weltert 201	<b>imental study: RCT</b> 0 (units transfused perio	p) 0.32 0	158 0.76 0 16	2 Not estimable		• • • •						
<b>2.6.2 Obser</b> Bedair 2015	<b>vational study: cohort</b> 5 (units transfused posto	0 0 (qı	24 0.41 0.07 5	6 Not estimable			•??•					
					-100 -50 0 Favours ESA F	50 100 avours Control						
Risk of bias (A) Random (B) Allocatio (C) Blinding (D) Blinding (E) Incompl (F) Selective (G) Other bia (H) Inapprop (J) Not cont (K) Incompl (L) Other lin	Favours ESA Favours Control         Favours ESA Favours Control         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 1.	L: Forest plot of	outcome:	Red blood cell L	itilization – iNul	mber of units	transfused						
Seconda	iry: Thromboem	bolic even	its		I		1					
2	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	2/458 (0.4%)	6/462 (1.3%)	<b>RR 0.34</b> (0.01 to 8.33)	<b>9 fewer</b> <b>per</b> <b>1.000</b> (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							Nº of patients		fect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
Primary:	(All-cause) mo	rtality										
7	randomised serious <sup>a</sup> not serious <sup>b</sup> not serious serious <sup>c</sup> none <sup>d</sup> See Forest plot A: trials See Forest plot A: A statistical significant effect on mortality for all events (except acute kidney injury) could not be						⊕⊕⊖⊖ LOW	CRITICAL				

Image: Number of Subgroup         Iron + ESA         Control Events         Risk Ratio M.H, Random, 95% Cl         Risk Ratio M.H, Random, 95% Cl         Risk Ratio M.H, Random, 95% Cl         Risk of Bias           Wurnig 2001 (125U - death after study completion)         0         70         1         60         0.29 [0.01, 6.90]         1         7	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
Ite: micomplete outcome data (attrition bias)       (F) Selective reporting (reporting bias)         (G) Other bias         B         Study or Subgroup       Events       Total       Events       Total       Weight       M.H, Random, 95% CI       A B C D E F         4.1.1 Malignant disorders         Heiss 1996 (postoperative death)       2       17       1       10       16.3%       1.18 [0.12, 11.39]	than evidence of no effect.
4.1.2 Non-malignant disorders         Wurnig 2001 (125+250U - death after study complet)       0       134       1       60       8.4%       0.15 [0.01, 3.64]         Yoo 2011 (30-day postoperative death)       0       37       1       37       8.5%       0.33 [0.01, 7.93]         Stowell 2009 (during study or within 30 days)       1       340       2       340       14.7%       0.50 [0.05, 5.49]         Stabtotid (95% CL)       511       437       31.5%       0.33 [0.06, 1.68]       ••••••••••••••••••••••••••••••••••••	

			Certainty as	sessment		Nº of pa	tients	Eff	ect	Certainty	Importance	
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	serious <sup>e</sup>	not serious <sup>f</sup>	not serious	serious <sup>g</sup>	none <sup>h</sup>	See Forest plot: Although point e	stimates for all	events (	except	⊕⊕⊖⊖ LOW	CRITICAL
Study or Subgroup 4.2.1 Acute kidneyi Yoo 2011 (costoper Subtotal (9% C) Total events Heterogeneity: Not : Test for overall effec Stowell 2009 (CVA) Scott 2002 (CVA) Wurnig 2001 (125- Subtotal (9%) C) Total events Heterogeneity: Tau' Test for overall effec 4.2.3 Stroke or tran Stowell 2009 (CVA) So-Osman 2014 (d) So-Osman 2014 (d) Subtotal (9%) C) Total events Heterogeneity: Tau' Test for overall effec 4.2.4 Myocar dial ins Stowell 2009 (TVA) So-Osman 2014 (d) So-Osman 2014 (d) Subtotal (9%) C) Total events Heterogeneity: Tau' Test for overall effec 4.2.5 Myocar dial ins Stowell 2009 (TVA) So-Osman 2014 (d) So-Osman	In the second s	bm + ESA Control ents Total Events 1 9 37 19 9 37 19 9 19 2 340 0 2 29 0 1 1340 0 0.800; P = 0% 1 340 0 1 340 0 1 340 0 1 340 0 1 340 0 1 29 0 1 340 0 1 29 0 1 340 1 1 29 0 1 29 1 4 1 4 1 1 340 1	Instructure         Nisk Ratio           International         Weight         M-H, Random, 95% C           35         100.0%         0.45 [0.24, 0.85]           36         100.0%         0.45 [0.24, 0.85]           340         34.1%         5.00 [0.24, 103.76]           360         30.9% C         5.00 [0.24, 103.76]           340         47.3%         3.00 [0.12, 73.38]           340         47.3%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           340         100.0%         3.00 [0.12, 73.38]           341         100.0%         2.00 [0.51, 1.35]           342         26.2%         3.00 [0.12, 73.38]           343         100.0%         2.00 [0.51, 1.35]	Risk Ratio M-H, Random, 95% CI	Risk of Bias         A B C D E F G         • • • • • • • • • • • •         • • • • • • • • • • • • • • • • • • •		acute kidnety inju control group", n reduction in anae be demonstrated number of events results). Yoo 2012 in a statistical sig kidney injury con	ury) are "in favo o statistical sig emia-associated due to imprecess and/or large v L found that ES nificant reduction pared to the co	our of the nificant d events ise result variability A+Iron r on in act ontrol gr	e could ts (low / in esulted ute roup.		
Secondar	y: Length of h	ospital sta	y									

			Certainty as	sessment			Nº of patients Effect		ect	Certainty	Importance	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious <sup>i</sup>	not serious	not serious	serious <sup>j</sup>	none	106	112	-	MD <b>1.54</b> <b>days</b> <b>fewer</b> (3.29 fewer to 0.21 more)	⊕⊕⊖⊖ LOW	IMPORTANT
Seconda	ry: Infections											
2	randomised trials	serious <sup>k</sup>	not serious <sup>b</sup>	not serious	serious <sup>1</sup>	none	See forest plot. A on infections cou	statistically sig	gnificant onstrated	effect d due to	⊕⊕⊖⊖ LOW	IMPORTANT
Study or Subg Larson 2001 ( Stowell 2009 ( Stowell 2009 ( (A) Random s (B) Allocation ( (C) Blinding of (C) Blinding of (C) Incomplet (F) Selectiver (G) Other bias	roup postoperative infection) urinary tract infection) wound infection) agend equence generation (se concealment (selection participants and persor outcome assessment ( outcome data (attrition sporting (reporting bias)	imprecise results large variability in	(low number c	f events	and/or							
Seconda	ry: Red blood o	cell utilizati	ion - Number of	patients transfu	sed		·					
16     randomised trials     serious <sup>a</sup> not serious <sup>m</sup> not serious     not serious     none <sup>o</sup>										⊕⊕⊕⊖ MODERATE	IMPORTANT	

		Certainty assessment Nº of patients Effect				fect	Certainty	Importance				
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
Study or Subgro Dousias 2003 () Kosmadakis 20 Faris 1996 (300 Weber 2005 (pas Yoo 2011 (patie Feagan 2000 (4 COPES 1933 (+ Larson 2001 (patie So-Osma 2011 (patie So-Osma 2011 (patie So-Osma 2011 (CoPES 1933 (- Wurnig 2001 (1) COPES 1933 (- Wurnig 2001 (2) CoPES 1933 (- Murnig	Aup Datients transfused perior 30 (patients transfused perior) 10 - patients transfused perior) 11 tents transfused perior) 11 tents with multiple transfus 12 tents transfused perior) 13 transfused postop) 4 (patients transfused perior) 10 - patients transfused perior) 2005 (3000 - pat transfused 10 - patients transfused perior) 2005 (1500 - pat transfused 10 tents transfused perior) 2005 (1500 - pat transfused 2005 (1500 - pa	lron Even p) ostop) erop) postop) erop) postop) portop) periop) periop) periop) s periop) s peri	ESA         Control           ts         Total         M-1           0         23         5         27           1         31         9         32           3         22         21         27           41         460         87         235           5         37         20         37           5         44         35         78           3         12         20         0           0         15         1         16           11         54         29         54           3         125         32         138           9         31         19         32           9         31         19         32           9         31         19         32           9         31         19         32           9         32         28         51           2         4         3         37           25         67         36         68           19         29         24         29           33         69         36         68           9	Risk Ratio         0.11 [0.01, 1.82]         0.11 [0.02, 0.85]         0.11 [0.02, 0.85]         0.25 [0.10, 0.60]         0.25 [0.10, 0.60]         0.25 [0.11, 0.60]         0.25 [0.11, 0.60]         0.35 [0.02, 8.08]         0.36 [0.02, 8.08]         0.38 [0.21, 0.68]         0.48 [0.26, 0.82]         0.49 [0.26, 0.81]         0.51 [0.32, 0.82]         0.53 [0.34, 0.84]         0.57 [0.22, 1.48]         0.68 [0.38, 1.02]         0.68 [0.48, 1.03]         0.68 [0.51, 1.03]         0.68 [0.51, 1.03]         0.76 [0.53, 1.10]         0.79 [0.58, 1.08]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]         0.93 [0.67, 1.28]	Risk Ratio M-H, Random, 95% Cl +	Bisk of Bias         A       B       C       D       E       G $7$ $7$ $7$ $9$ $9$ $9$ $7$ $7$ $7$ $9$ $9$ $9$ $9$ $7$ $7$ $7$ $9$	See Forest plot: ( in the number of transfusion.	Statistical signi	ficant) re ving RBC	duction		
Secondar	y: Red blood o	cell utilizat	ion - Number of	units transfused	1							
8	randomised trials	serious <sup>a</sup>	not serious <sup>m</sup>	not serious	not serious	none <sup>q</sup>	See Forest plot: ( in the number of transfusion.	Statistical signi patients receiv	ficant) re ving RBC	duction	⊕⊕⊕⊖ MODERATE	IMPORTANT

	Certainty assessment						Nº of patients Effect		fect	Certainty	Importance	
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
		Iron	+ ESA Control	Mean Difference	Mean Difference	Risk of Bias						
Study or Subgro	up actionte	Mean	SD Total Mean SD Tota	al IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG						
3.6.1 Among an J Yoo 2011 (units 1 Scott 2002 (units Feagan 2000 (4C Christodoulakis Christodoulakis Christodoulakis Christodoulakis Gvist 1999 (units Heiss 1996 (unit 3.6.2 In transfus Yoo 2011 (units 1 Scott 2002 (units Feagan 2000 (4C Feagan 2000 (4C	namens ransfused periop) transfused periop) transfused postop) 0000U - units transfused p ansfused postop) 0000U - units transfused 2005 (300U- units transfused) 2005 (150U- units transfused) 2005 (150U- units transfused 2005 (150U- units transfused transfused periop) s transfused periop) ed patients ransfus in transfused patier 000U- units transf in transf 000U- units transf in transf 000U- units transf in transf	1 2.07 eriop) 0.3 (2 eriop) 0.4 (2 periop) 0.87 0.25 postop) 1.1 (2 periop) 1.19 0.3 1.82 erits) 1.6 trs) 3.16 tr pat) 1.2		7 -2.30 [-3.09, -1.51] 9 -1.34 [-2.83, 0.15] 9 -0.70 [-1.04, -0.36] 4 -0.60 [-0.85, -0.35] 8 -0.60 [-0.93, -0.27] 8 -0.35 [-1.01, -0.05] 8 -0.48 [-0.95, -0.01] 8 -0.39 [-0.70, -0.08] 8 -0.25 [-0.75, 0.25] 8 -0.15 [-0.66, 0.36] 3 Not estimable 0 0.02 [-0.69, 0.73] 2 -2.10 [-2.92, -1.28] 4 -0.96 [-2.66, 0.76] 5 -0.30 [-0.75, 0.15] 5 -0.10 [-0.34, 0.54] -4 Favor	++++++++++++++++++++++++++++++++++++++	•       •						
(A) Random seq (B) Allocation cor (C) Blinding of pa (D) Blinding of pa (D) Blinding of or (E) Incomplete or (F) Selective repc (G) Other bias	uence generation (selectio cealment (selection bias) irticipants and personnel (trome assessment (dete utcome data (attrition bias) rrting (reporting bias)	on bias) performance bias) ttion bias)										
Secondar	y: Thromboen	nbolic ever	nts (arterial and d	leep venous thr	ombosis)							
9	randomised trials	serious <sup>a</sup>	not serious <sup>b</sup>	not serious	serious <sup>u</sup>	none <sup>v</sup>	See Forest plot a thrombosis.	rterial and dee	o venous	5		CRITICAL

			Certainty assessment Nº of patients Effect			Certainty	Importance					
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
Study or Subgr 4.7.1 Arterial ti Kettelhack 199 Subtotal (95% ti Total events Heterogeneity: Test for overall 4.7.2 Deep ven Scott 2002 (DV So-Osman 201 Feagan 2000 (L Kosmadakis 2) Stowell 2009 (C Helss 1996 (DV Wurnig 2001 (I Subtotal (95% ti Total events Heterogeneity: Test for overall 4.7.3 Pulmonas Stowell 2009 (F Feagan 2000 (L Subtotal (95% ti Total events Heterogeneity: Test for overall Rest of bias leaf (A) Random ses Random ses Random ses Random ses	oup           irombosis           3 (arterial thrombosis)           20)           Not applicable           effect: Z = 0.75 (P = 0.45)           ous thrombosis           Th           4 (DVT)           20000U+40000U - DVT)           203 (DVT)           VT)           Th           25+250U - DVT)           21)           Tau* = 0.00; Chi* = 2.39, (effect: Z = 1.83 (P = 0.07)           yembolism           4 (PE)           25+250U - PE)           25+250U - PE)           Tau* = 0.00; Chi* = 1.15, (effect: Z = 1.21 (P = 0.23)           Tau* = 0.00; Chi* = 1.15, (effect: Z = 1.21 (P = 0.23)	Iron + ESA           Events         Total           1         48           48           1           0         29           0         125           7         123           2         20           1         340           2         20           1         34           4         134           840         32           0         125           0         340           0         123           1         722           1f = 2 (P = 0.56); P           ction blas)           as)	Control         Events         Total         Weight         M-1           0         54         100.0%         54         100.0%           0         54         100.0%         0           0         29         0         138           5         78         30.8%         1         32         6.9%           7         340         49.7%         0         10         4.4%           0         60         4.5%         730         100.0%         13           = 0%         0         138         3         340         36.7%         1         78         31.6%         0         60         31.7%         616         100.0%         4         =         0%         4         =         0%         4         =         0%         56         100.0%         56         100.0%         1         10%	Risk Ratio 4, Random, 95% Cl 3.37 (0.14, 80.76) 3.37 (0.14, 80.76) 3.37 (0.14, 80.76) Not estimable Not estimable 0.89 (0.29, 2.70) 2.06 (0.20, 2.163) 2.29 (0.95, 5.49) 2.62 (0.14, 49.91) 3.38 (0.14, 80.70) 4.07 (0.22, 74.36) 1.78 (0.96, 3.29) Not estimable 0.14 (0.01, 2.76) 0.21 (0.01, 5.16) 1.36 (0.06, 3.29) 0.33 (0.05, 1.98)	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G	Arterial thrombo in favor of the co significant reduct comparing iron+ could not be den events and large Deep venous thro increased risk for (p=0.07) in patien control group.	sis: although p ontrol group, a tion in arterial f ESA versus the nonstrated (low variability in re ombosis: a trer deep venous f nts receiving in	oint estin statistica thrombos control g v number esults). nd for an thrombos on+ESA v	nate is sis when group, · of sis versus		
(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												
Seconda	ry: Thromboen	nbolic ever	nts (pulmonary e	mbolism)								
4	randomised trials	serious <sup>a</sup>	not serious <sup>b</sup>	not serious	serious <sup>w</sup>	none <sup>x</sup>	See Forest plot pulmonary embolism.			CRITICAL		

Certainty assessment Nº of patients E				Eft	fect	Certainty	Importance							
Nº of studies	Study design	Risk of bias	Incons	sistency	Indirectnes	s Imp	recision	Other considerations	iron supplementati on + ESAs	no treatment, placebo, standard of care	Relative (95% CI)	Absolute (95% CI)		
Study or Subar	oup	Iron + ESA	Control	Woight M	Risk Ratio	Risk M H. Ban	k Ratio	Risk of Bias	Although point e	stimate is in fa	vor of irc	on+ESA,		
4.7.1 Arterial th Kettelhack 199% ( Subtotal (95% ( Total events Heterogeneity: I Test for overall	rombosis 3 (arterial thrombosis) 1) Not applicable effect: Z = 0.75 (P = 0.45)	1 48 48 1	0 54 54 0	100.0%	3.37 [0.14, 80.76] 3.37 [0.14, 80.76]				a statistical signif embolism when control group, co number of event	icant reductior comparing iron ould not be der s and large var	n in pulm +ESA ve nonstrate iability in	onary rsus the ed (low		
4.7.2 Deep vem Scott 2002 (DV So-Osman 201 Feagan 2000 (C Kosmadakis 20 Stowell 2009 (C Heiss 1996 (DV Wurig 2001 (1 Subtotal (95% C Total events Heterogeneity: Test for overall	ous thrombosis T) 4 (DVT) 20000U+40000U - DVT) 203 (DVT) 207) T) 25+250U - DVT) 21) Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.39, o effect Z = 1.83 (P = 0.07)	0 29 0 125 7 123 2 31 16 340 2 20 1 38 4 134 <b>840</b> 32 31 = 5 (P = 0.79); P	0 29 5 76 1 32 7 340 0 10 0 43 0 66 <b>730</b> 13 = 0%	3 3 3 2 6.9% 3 49.7% 4.4% 3 3.8% 0 4.5% 0 4.5%	Not estimable Not estimable 0.89 (0.29, 2.70) 2.06 (0.20, 21.63) 2.29 (0.95, 5.49) 2.62 (0.14, 49.91) 3.38 (0.14, 80.70) 4.07 (0.22, 74.36) 1.78 (0.96, 3.29)		►		results).					
4.7.3 Pulmonar So-Osman 201 Stowell 2009 (F Feagan 2000 (2 Wurnig 2001 (1 Subtotal (95% C Total events Heterogeneity: Test for overall	y embolism 4 (PE) YE) 20000U+40000U - PE) 25+250U - PE) 21) Tau <sup>a</sup> = 0.00; Chi <sup>a</sup> = 1.15, effect: Z = 1.21 (P = 0.23)	0 125 0 340 0 123 1 134 722 1 df = 2 (P = 0.56); P	0 138 3 340 1 78 0 60 616 4 = 0%	3 0 36.7% 3 31.6% 0 31.7% 5 <b>100.0</b> %	Not estimable 0.14 [0.01, 2.76] ← 0.21 [0.01, 5.15] ← 1.36 [0.06, 32.80] 0.33 [0.05, 1.98]	-								
Risk of bias leg (A) Random se (B) Allocation c (C) Bilnding of ( (D) Bilnding of ( (E) Incomplete (F) Selective rep (G) Other bias	end quence generation (sele oncealment (selection bi participants and personn outcome assessment (de outcome data (attrition bi porting (reporting bias)	ction bias) as) el (performance bi tection bias) as)	ias)		0.0* Favo	I 0.1 burs Iron + ESA	A Favours Cont	100 Irrol						

#### **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). I. 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**

Author, year,	Information on economic outo	omes		
COMPARISON 1	•			
TRANSFUSION	 VS NO TREATMENT/PLACEBO/S	TANDARD OF	CARE	
Karkouti, 2012,	No data on economic outcomes	were reported		
Canada		•		
COMPARISON 2	:			
IRON SUPPLEM	ENTATION VS NO TREATMENT/	PLACEBO/STAN	NDARD OF CAP	RE
Edwards, 2009, UK	No data on economic outcomes	were reported		
Lidder, 2007,	Cost fortnight's course of ferrou	s sulphate 200 m	ng TDS = \$1.82	
UK	Cost single, allogeneic unit of blessets and nursing care.	ood = \$182 excl	uding extraneo	us costs such as giving
	Control group: 47U transfused -	> \$6580		
	Intervention group (iron suppl):	\$2142 (FeSO4 at	: \$42 + 15 U at	\$2100) representing a
	66% cost reduction.			
Muñoz, 2006, Spain	No data on economic outcomes	were reported		
Okuyama, 2005, Japan	No data on economic outcomes	were reported		
COMPARISON 3	:			
ESA VS NO TREA	ATMENT/PLACEBO/STANDARD	OF CARE		
Bedair, 2015,	The cost analysis demonstrated	that the EPO stra	ategy was more	costly compared with
USA	no EPO (\$2632 versus \$2284) an	d its cost would	need to be less	s than \$225/dose for
	Table 2 Cost date			
	Parameter	Cost (2012, USD)	Sensitivity analysis range	
	Hospital stay (average daily variable cost, no transfusion)	581		
	Hospital stay (average daily variable cost, transfusion)	684		
	Single unit of EPO	380	100-500	
	Transfusion single unit of allogeneic blood	300	100-500	
	EPO = erythropoietin alpha.			
Weltert, 2010,	Cost protocol expense intervent	ion group (EPO):	\$299 per patie	nt
Italy	$rac{1}{2}$ Cost of 1 unit of blood = \$332	half a unit of bl	ood per patient	was not cost-effective
	→ the increased length of s	stav of 0.57 davs	s per patient wo	uld increase the cost
	of the control group by	\$561 per patient	t, thus making t	the protocol eventually
	convenient.			. ,
Weltert, 2015,	Cost protocol expense intervent	ion group (EPO):	\$392 per patie	nt (expense for drug
Italy	supply only due to a very simple	administration	of drug, requirir	ng few minutes of care
	in each patient and no patient p	reparation or me	edications). Hov	vever, this expense was
	offset by fewer aRBCt procedure	s in the EPO gro	oup (0.40 vs. 1.0)	L units per patient).
	assume a mean cost for a single	aRBC of \$761 as	s reported by Sh	nander and coworkers.

	we could observe a cost increase of \$134 per patient in the HRE group; this additional	
	cost, nowever, 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	
	nearth service for cardiovascular intervention).	
COMPARISON 4:		
Canadian	No data on economic outcomes were reported	
Orthonedic		
Perioperative		
Enythropoietin		
Study Group		
(COPES) 1993		
Canada		
Christodoulakis	No data on economic outcomes were reported	
2005 Greece	No data on economic outcomes were reported	
Dousias 2003	No data on economic outcomes were reported	
Greece		
Faris 1996	No data on economic outcomes were reported	
USA		
Feagan, 2000,	The retail cost of epoetin alfa is Can\$267.90 per 20.000-U vial and Can\$535.80 per	
Canada	40.000-U vial.	
Heiss, 1996,	No data on economic outcomes were reported	
Germany		
Kettelhack,	No data on economic outcomes were reported	
1998, Germany		
Kosmadakis,	The cost of allogenic transfusion in our hospital is estimated at \$492 per unit.	
2003, Greece	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,	No data on economic outcomes were reported	
Sweden		
Na, 2011, South	No data on economic outcomes were reported	
Korea		
Qvist, 1999,	The cost of 1 unit of leukocyte-depleted blood is approximately 1,000 Danish kronors	
Denmark	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,	No data on economic outcomes were reported	
USA		
So-Osman,	Erythropoietin increased costs by \$965 per patient (95% CI, 322 to 1610), that is, \$8979	
2014, The	per avoided transfusion (95% CI, 2337 to 29520).	
Netherlands		
	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>i.e.</i> , \$1019 per unit) including costs of compatibility tests and handling,	
Channell 2000	according to the article by Shander <i>et al.</i>	
Stowell, 2009,	No data on economic outcomes were reported	
USA		

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

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# Detailed evidence summary

Торіс	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
Search Strategy	<ul> <li><b>Databases</b></li> <li><b>The Cochrane Library</b> (controlled trials) using the following search strategy: <ol> <li>[mh "Preoperative Period"] OR [mh "Preoperative care"] OR preoperat*:ti,ab,kw OR pre-operat*:ti,ab,kw OR presurg*:ti,ab,kw OR presurg*:ti,ab,kw OR (before NEXT surger*):ti,ab,kw OR (before NEXT surger*):ti,ab,kw OR ("prior to" NEXT operati*):ti,ab,kw OR ("prior to" NEXT operati*):ti,ab,kw OR ("prior to" NEXT surger*):ti,ab,kw OR ("prior to" NEXT operati*):ti,ab,kw</li> <li>[mh "Anemia"] OR anemi*:ti,ab,kw OR anaemi*:ti,ab,kw OR ("prior to" NEXT operati*):ti,ab,kw OR Venofer:ti,ab,kw OR ferrous:ti,ab,kw OR ferric:ti,ab,kw OR ("erythropoiets-stimulating" NEXT agent*):ti,ab,kw OR heematopoiet*:ti,ab,kw OR heematopoiet*:ti,ab,kw OR heematinic*:ti,ab,kw OR heematinic*:ti,ab,kw OR feroetin alfa":ti,ab,kw OR heematinic*:ti,ab,kw OR heematinic*:ti,ab,kw OR feroetin alfa":ti,ab,kw OR heematinic*:ti,ab,kw OR "epoetin alfa":ti,ab,kw OR NeoRecormon:ti,ab,kw OR "darbepoetin alfa":ti,ab,kw OR miccera:ti,ab,kw OR fielood Transfusion"] OR ((blood:ti,ab,kw OR erythrocyte*:ti,ab,kw OR (red NEXT cell*):ti,ab,kw OR (red NEXT cell*):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</li> </ol> </li> </ul>
	<ul> <li>MEDLINE (via PubMed interface) using the following search strategy:</li> <li>1. "Preoperative Period"[Mesh] OR "Preoperative Care"[Mesh] OR preoperat*[TIAB] OR pre-operat*[TIAB] OR presurg*[TIAB] OR presurg*[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] OR prior to surger*[TIAB] OR prior to surgical*[TIAB] OR prior to operati*[TIAB] OR anaemi*[TIAB]</li> <li>2. "Anemia"[Mesh] OR anemi*[TIAB] OR anaemi*[TIAB]</li> <li>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 erythropoieti*[TIAB] OR hematopoiet*[TIAB] OR hematopoiet*[TIAB] OR hematinic*[TIAB] OR hematopoiet*[TIAB] OR hematinic*[TIAB] OR hematinic*[TIAB] OR hematopoiet*[TIAB] OR hematinic*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR ferrous[TIAB] OR hematinic*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR hematinic*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR hematinic*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR menopoiet*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR hematinic*[TIAB] OR menopoiet*[TIAB] OR ned cell*[TIAB] OR "darbepoetin alfa"[TIAB] OR miccera[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]</li> </ul>
OR haemotransfus*[TIAB] OR hemotherap*[TIAB] OR haemotherap*[TIAB]	
--	
OR hypertransfus*[TIAB]	
4. (("Meta-Analysis as Topic"[Mesh] OR meta analy*[TIAB] OR	
metaanaly*[IIAB] OR "Meta-Analysis"[PI] OR systematic review*[IIAB] OR	
systematic overview*[TIAB] OR "Review Literature as Topic"[Mesh]) OR	
(cochrane[IIAB] OR embase[IIAB] OR psychit[IIAB] OR psychit[IIAB] OR	
psychinto[TIAB] OR psycinto[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. I AND 2 AND 3 AND 5 (controlled clinical trials)	
<b>Embase</b> (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	
stimulating' NEVT/1 agent*) ab ti OP hematopoiet ab, II OR (ery(iiropoiesis-	
sumulating NEAT/I agent ).ab,ti OK hematopolet .ab,ti OK	
haematinic*:ab ti OR haematinic*:ab ti OR 'anactin alfa':ab ti OR Bracrit:ab ti	
OP Enogen ab ti $OP$ (an extin beta' ab ti $OP$ NeoPerermon ab ti $OP$	
(darbapoetin alfa':ab ti OR Mircera:ab ti OR 'Blood transfusion'/evn OR	
(blood ab ti $OR$ enthrocyte* 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 UK :selection criteria :ab,ti) AND review/it)) NOT (letter/it OR	
euitoriai/it OK ( animai /exp NOT ( animai /exp AND numan /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)					
	<b>Transfusion Evidence Library</b> 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	<b>Population:</b> <i>Included</i> : preoperative elective surgery adult patients with anemia					
criteria	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/di), 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/di). If no subgroup					
	analyses were performed, the data from all patients were extracted.					
	elective surgery patients with preoperative anemia which is not formally/explicitly					
	defined elective surgery patients with sickle-cell anemia or thalassemia pediatric					
	natients					
	<b>Intervention:</b> <i>Included</i> : 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).					
	<b>Comparison:</b> <i>Included</i> : <u>Comparison 1-4</u> : no treatment, placebo, standard of care.					
	<i>Excluded</i> : autologous blood donation, other interventions to treat anemia such as					
	the use of tranexamic acid.					
	Outcome:					
	Included. Drimany outcomposi					
	<u>Frinary outcomes.</u> (All-cause) mortality					
	<ul> <li>(All-Cause) mortality</li> <li>Anemia-associated ischaemic events defined as:</li> </ul>					
	- acute myocardial infarction:					
	$\circ$ acute injuction indiction,					
	$\circ$ acute kidney injury:					

<ul> <li>acute mesenteric ischaemia;</li> </ul>
<ul> <li>acute peripheral vascular ischaemia.</li> </ul>
Secondary outcomes:
Length of hospital stay
<ul> <li>Any type of reported infection. A patient was considered to have an</li> </ul>
infection when one of the following items existed (Weber, 2005):
<ul> <li>Wound infection: redness, purulent exudate or positive culture of</li> </ul>
wound fluid;
<ul> <li>Wound abscess: drainage of abscess or spontaneous discharge of</li> </ul>
pus;
<ul> <li>Abscess or infected haematoma in surgical area or near the</li> </ul>
implant: positive culture after collection of pus or re-exploration;
<ul> <li>Urinary tract infection: abnormal urine sediment with white blood</li> </ul>
cells and/or a positive urine culture and/or clinical signs;
<ul> <li>Respiratory tract infection: clinical signs according to the</li> </ul>
investigator and/or a positive sputum culture leading to treatment
with antibiotics;
<ul> <li>Pneumonia: clinical or radiological signs of a pulmonary infiltrate;</li> </ul>
<ul> <li>Bacteraemia: typical clinical signs (e.g. fever) and positive blood</li> </ul>
culture.
<ul> <li>Red blood cell utilization (units transfused, number of patients receiving a</li> </ul>
transfusion).
<ul> <li>Thromboembolic events, defined as deep venous/arterial thrombosis</li> </ul>
and/or pulmonary embolism.
Excluded: Hb levels, drug-related adverse events.
<b>Study design:</b> <i>Included</i> : 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>i.e.</i> 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.
<i>Excluded</i> : 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	S NO TREATME	NT/PLACEBO/STANDAR	RD 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.	Prophylactic transfusion: 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; $\alpha$ =0.05). To allow for dropouts after randomization, the sample size was increased
				to 60 patients.
COMPARISON 2 IRON SUPPLEM	:: ENTATION VS NO	D TREATMENT/PLACEBO	D/STANDARD OF CARE	
Edwards, 2009,	Experimental:	62 patients (11	Iron sucrose:	Identified from
UK	Randomized	anaemic at	Iron sucrose 300 mg	the systematic
	controlled trial	recruitment, 22 with	intravenously, two	review of
		normal Hb levels and	infusions (minimally 24	Borstlap, 2015.
		29 without recent	nours apart from each	The trial was
		status) schodulod to	completed within a	registered with
		undergo bowel		the UK

		resection for	minimum of 14 days	Medicines and
		suspected colorectal	before surgery)	Healthcare
		cancer were randomly		products
		assigned to one of 2	Placebo:	Regulatory
		groups:	Placebo 250 ml	Agency
		1) Iron sucrose (n=34,	intravenously, 2	(registration
		ratio men:women	infusions (minimally 24	number: 2005-
		22:12, median age 67	hours apart from each	003 608-13).
		vears)	other, the second one	····
		2) Placebo (n=26.	completed within a	The study was
		ratio men:women	minimum of 14 days	powered at 80%
		17:9. median age 70	before surgery)	to detect a
		years)	5 ,,	difference
		<b>,</b>	Transfusion policy for all	in the mean
		Analysis was carried	patients:	change in serum
		out on an intention-	- Hb >10 g/dl: no	Hb
		to-treat basis.	transfusion	concentration
			- Hb 8-10 g/dl: transfuse	between
			if * abnormal ECG	recruitment and
			* ischaemic heart	treatment of 0,5
			disease	g/dl in anaemic
			* obstructive lung	patients. This
			disease	power analysis
			* consultant's discretion	indicated that
			* unable to absorb oral	10 people were
			iron	needed in each
			- Hb <8 g/dl: transfuse	group.
			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.]	
Lidder, 2007,	Experimental:	49 patients with	Ferrous sulphate:	Identified from
UK	Randomized	colorectal	Oral ferrous sulphate	the systematic
	controlled trial	malignancies	200 mg 3 times per day	review of
		scheduled for surgery		Borstlap, 2015.
		were randomly	Standard clinical	
		assigned to one of 2	<u>management:</u>	In order to
		groups:	not defined	detect a change
		1) Ferrous sulphate		in haemoglobin
		(n=24, 14 men and 8	Transfusion policy for all	of 0,5 g/dl with
		women, aged 47-89	patients:	a SD of 0,5 g/dl,
		years; 3 men and 3	- Hb >10 g/dl: no	power of 80%
		women anaemic)	transfusion	and 2-tailed
		2) Standard clinical	- Hb 8-10 g/dl: transfuse	significance of
		management (n=25,	if * abnormal ECG	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.	<ul> <li>* ischaemic heart disease</li> <li>* obstructive lung disease</li> <li>* consultant's discretion</li> <li>* unable to absorb oral iron</li> <li>- Hb &lt;8 g/dl: transfuse to target 10 g/dl</li> <li>[As our PICO specifically concerns patients with preoperative anaemia, only outcomes analysed in the subgroup analysis on anaemic patients (Hb levels &lt;13.5 g/dl in men and &lt;11.5 g/dl in</li> </ul>	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.	Iron sucrose:Iron sucrose 100 mgintravenously once perday for 3 days, startingafter surgeryControl:no ironTransfusion policy for allpatients:Transfusion wasperformed when Hblevels <8 g/dl (target	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	during at least 2	
		arouns.	preoperative weeks	
		1) Iron (n=32, 15 men		
		and 17 women, aged	Control:	
		on average 68.7±9.6	no iron	
		years, Hb levels at first		
		presentation 8.1±1.4	Transfusion policy for all	
		g/dl)	patients:	
		2) Control (n=84, 42	, intraoperative Hb levels	
		men and 42 women,	of about 7 g/dl with	
		aged on average	unstable	
		66.7±11.2 years, Hb	haemodynamics	
		levels at first		
		presentation 8.0±1.6		
		g/dl)		
COMPARISON 3	:			
ESA VS NO TREA	ATMENT/PLACEB	O/STANDARD OF CARE		
Bedair, 2015,	Observational:	80 patients scheduled	<u>Epoetin alpha:</u>	Identified from
USA	cohort study	to undergo unilateral	Received at least 1 dose	the systematic
		primary total hip or	(median 2 doses; range	review of
		total knee	2-4) of Epoetin alpha	Alexander, 2017.
		arthroplasty, with Hb	preoperatively	
		levels <13 g/dl, were		Demographic
		all recommended to	<u>Control:</u>	and clinical data
		be treated	no Epoetin alpha	for these
		preoperatively with		patients were
		Epoetin alpha.	Transfusion policy for all	retrospectively
		56 of these 80	No specific transfusion	reviewed.
		patients refused the	triggers were used in	For the Epoetin
		Epoetin alpha	any of these patients.	alpha treatment.
		treatment or were	Only patients with	the timing,
		unable to pay for the	postoperative Hb <10	route of
		treatment in cases in	g/dL who were also	administration
		which the patient's	symptomatic	and number of
		health insurer refused	(hypotension,	units is not
		to cover the cost.	tachycardia, dizziness,	reported by the
		This rendered 2	and/or an inability to	authors.
		groups:	participate in	
		1) Epoetin alpha	therapy) and whose	
		(n=24, 4 men and 20	symptoms were resistant	
		women, aged on	to fluid boluses were	
		average 60.8±2.5	transfused.	
		years, mean		
		preoperative Hb levels		
		$12.3 \pm 0.1 \text{ g/dl}$		
		2) Control (n=56, 12		
		men and 44 women,		
		aged on average		
		00.2±1.0 years, mean		
		12.1±0.7 g/ai)		

Weltert, 2010,	Experimental:	320 patients with	EPO:	Identified from
Italy	Randomized	isolated coronary	- 14 000 IU EPO	the systematic
,	controlled trial	vessel disease	subcutaneously on	review of Lin,
		undergoing off-pump	preoperative day 2 and	2013.
		coronary artery	1	
		bypass grafting	- 8000 IU EPO	Preliminary
		surgery, with Hb levels	subcutaneously on	power analysis
		≤14.5 g/dl were	operative day and	suggested that
		randomly assigned to	postoperative days 1	160 patients per
		one of 2 groups:	and 2.	sample
		1) EPO (n=158, 84%		were needed to
		male, aged on	<u>Control:</u>	obtain a 90%
		average 67±9 years)	no treatment	power goal,
		2) Control (n=162,		considering an
		83% male, aged on	Both groups used the	alpha error
		average 66±11 years)	cell-saver system during	level of 5% and
			the operation.	expecting the
		Analysis was		incidence of
		performed on an	Transfusion policy for all	transfusion to
		Intention-to-treat	patients:	decrease from
		Dasis.	HD <8 g/di and/or in the	the previously
			case of blood	observed 30%
			exsanguination, as	to 15%.
			of vonous blood < 50%	
Waltart 2015	Evporimontal	600 patients		Not included in
Italy	Randomized	undergoing heart		a systematic
Italy		surgery with Hb levels	subcutaneously on	a systematic
	controlled that	<14.5 a/dl were	preoperative day 2	via experts
		randomly assigned to		via experts.
		one of 2 groups:	Control:	The primary
		1) EPO (n=300, 75%	no treatment	endpoint was
		male, aged on		the incidence of
		average 75 (47-96)	All patients received iron	perioperative
		years)	supplement per os	transfusion from
		2) Control (n=300,	(routine practice).	the start of
		73% male, aged on		surgery through
		average 74 (40-90)	Transfusion policy for all	Postoperative
		years)	patients:	Day. A power
			Hb <8 g/dl. All patients	analysis was
		Analysis was	requiring RBC	conducted to
		performed on an	transfusion received	determine the
		intention-to-treat	prestorage	sample size to
		basis.	leukoreduced aRBC	maintain
			units. Using a	adequate
			thromboelastometric-	statistical
			guided approach,	power.
			solvent/detergent	Considering an
			(5/U)-treated plasma	alpha error of
			and single-donor	5%, a two-talled
			aprieresis PLT units were	redison Chi-
			auministered when	square test, and
			mulcated.	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%.
IRON SUPPLEMI	ENTATION + ESA	VS NO TREATMENT/PL	ACEBO/STANDARD OF CA	ARE
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.	14 days EPO:         - EPO 300 IU/kg/day         subcutaneously from         preoperative day 10         until postoperative day 10         until postoperative day 10         until postoperative day 3         - Oral iron sulphate 300         mg, 3 times daily         starting on preoperative         day 21 until discharge         9 days EPO:         - Placebo         subcutaneously from         preoperative day 10 to 6         - EPO 300 IU/kg/day         subcutaneously from         preoperative day 5 until         postoperative day 5 until         postoperative day 3         - Oral iron sulphate 300         mg, 3 times daily         starting on preoperative         day 21 until discharge         14 days placebo:         - Placebo         subcutaneously from         preoperative day 10         until postoperative day 21         until discharge         Transf	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.

Christodoulakis, 2005, Greece	Experimental: Randomized controlled trial	223 patients undergoing elective colorectal surgery for resectable colorectal cancer, with Hb levels	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.] <u>Epoetin alfa 150 IU:</u> - Epoetin alfa 150 IU/kg/day subcutaneously from preoperative day 10 until postoperative day	Identified from the systematic review of Lin, 2013.
		>9 and <12 g/dl, were randomly assigned to	1	correction was
		one of 3 groups: 1) Epoetin alfa 150 IU	- Oral iron supplements 200 mg/day from	applied when multiple
		(n=69, 31 men and 38 women median age	preoperative day 10	comparisons of
		72 years (range 43-	1	related variables
		91)) 2) Fractin alfa 200 II.I	- In patients with iron	were made.
		(n=67, 30  men and  37)	40 mg intravenously	
		women, median age	daily until the day of	
		71 years (range 36-	discharge	
		92)) 3) Control (n=68, 28	- Folic acid 15 mg/day for the first 10 days after	
		men and 40 women,	randomization	
		median age 70 years		
		(range 44-89)	Epoetin alfa 300 IU:	
		$\cap f$ 223 natients in the	- Epoetin alfa 300 Il l/kg/day	
		intention-to-treat	subcutaneously from	
		population,	preoperative day 10	
		204 (91.5%) were	until postoperative day	
		assessable for	1 Oral iron gunnlamanta	
		protocol	- Oral iron supplements 200 mg/day from	
		p.0.0001	preoperative day 10	

	population). Analyses	until postoperative day	
	were performed on	1	
	the per-protocol	- In patients with iron	
	population.	deficiency: iron sulphate	
		40 mg intravenously	
		daily until the day of	
		discharge	
		- Folic acid 15 mg/day	
		for the first 10 days after	
		randomization	
		Control:	
		- 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:	
		Preoperatively:	
		- 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	
		Intraoperatively:	
		- 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	
		Postoperatively:	
		- HD <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)	EPO + iron: - 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 <i>Transfusion policy for all</i> <i>patients:</i> 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 $66\pm13$ years) scheduled for major elective orthopaedic operation, in which transfusion of $\geq 2$ 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)	EPO 300 IU:- EPO 300 IU/kg/daysubcutaneously frompreoperative day 10until postoperative day4- Oral iron sulphate 325mg, 3 times per dayEPO 100 IU:- EPO 100 IU/kg/daysubcutaneously frompreoperative day 10until postoperative day 10until postoperative day 24- Oral iron sulphate 325mg, 3 times per dayPlacebo:- Placebosubcutaneously frompreoperative day 10until postoperative day4- Oral iron sulphate 325mg, 3 times per dayPlacebo:- Placebosubcutaneously frompreoperative day 10until postoperative day 20until postoperative day 30until postoperative day 4- Oral iron sulphate 325mg, 3 times per day	Identified from the systematic review of Alsaleh, 2013.

			Transfusion policy for all	
			nationts:	
			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	
			nostoperative 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 woro	
			and SIS g/di were	
Easgan 2000	Evporimontal	216 adult patients	High doce Epoctin alfa:	Identified from
Feagan, 2000, Canada	Experimental.	210 autit patients	Angli-dose Epoetin ana.	
Canada	Randomized	undergoing total nip	- Oral from 3 times per	the systematic
	controlled trial	Joint arthroplasty in	day from preoperative	review of
		13 teaching and 4	day 42 until nospital	Alsalen, 2013.
		community nospitals,	discharge	0.001
		with Hb levels 9.8 –	- 40 000 IU	80% power
		13.7 g/dl, were	subcutaneously weekly	analysis
		randomly assigned to	for 4 weeks before the	indicated that
		one of 3 groups:	operation	83 patients per
		1) High-dose Epoetin		group were
		alfa (n=46, 13% men,	Low-dose Epoetin alfa:	required in the
		aged 68±12 years)	- Oral iron 3 times per	low-dose and
		2) Low-dose Epoetin	day from preoperative	placebo
		alfa (n=86, 8% men,	day 42 until hospital	groups and 50
		aged 69±11 years)	discharge	patients were
		3) Placebo (n=82, 11%	- 20 000 IU	needed in the
		men, aged 67±11	subcutaneously weekly	high-dose
		years)	for 4 weeks before the	group.
			operation	Accordingly, the
		10 patients did not		total sample
		undergo surgery	<u>Placebo:</u>	size
		within the specified	- Oral iron 3 times per	requirement
		time window, and 3	day from preoperative	was 216
		patients withdrew	day 42 until hospital	patients.
		consent. Therefore,	discharge	
		201 patients were		

		included in the intention-to-treat analysis.	<ul> <li>Placebo</li> <li>subcutaneously weekly</li> <li>for 4 weeks before the operation</li> <li><i>Transfusion policy for all patients:</i></li> <li>according to usual practice of attending</li> <li>surgeons and</li> <li>anesthesiologists. Usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific Hb threshold.</li> </ul>	Study medication was withheld if Hb levels $\geq$ 15 g/dl, if systolic blood pressure $\geq$ 200 mm Hg, or if diastolic blood pressure $\geq$ 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))	EPO: - 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 Control: - 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	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	Epoetin beta: - 20 000 IU Epoetin beta subcutaneously for a minimum of 5 (maximum 10)	Identified from the systematic review of Lin, 2013.
		<ul> <li>≤13.5 g/dl, were</li> <li>randomly assigned to</li> <li>one of 2 groups:</li> <li>1) Epoetin beta (n=48,</li> <li>men:women 21:27,</li> <li>median age 71 years</li> <li>(range 53-57))</li> <li>2) Placebo (n=54,</li> </ul>	preoperative days until postoperative day 4 - Oral iron in case of iron deficiency, and on postoperative day 1 (40 mg iron sulphate intravenously)	Two groups of 90 patients (180 in total) were to be evaluable to detect a reduction in transfusion
		men:women 22:32, median age 67 years (range 37-91))	<u>Placebo:</u> - Placebo subcutaneously for a minimum of 5	need from 50 % in the control group to 25% in the
		7 patients (Epoetin beta: n=4; Placebo: n=3) were excluded from the efficacy analysis, but included	(maximum 10) preoperative days until postoperative day 4 - Oral iron in case of iron deficiency, and on	epoetin beta treatment group with a power of 90%.
		in the safety analysis.	postoperative day 1 (40 mg iron sulphate intravenously)	Transfusion need was adjusted to age, blood loss and
			Transfusion policy for all patients: Hb ≤7.5 g/dl	baseline haemoglobin levels.
Kosmadakis, 2003, Greece	Experimental: Randomized controlled trial	<ul> <li>75 patients with nonmetastatic</li> <li>gastrointestinal tract</li> <li>cancer, with Hb levels</li> <li>between 8.5 and 13</li> <li>g/dl, were randomly</li> <li>assigned to one of 2</li> <li>groups:</li> <li>1) Epoetin alfa</li> <li>2) Control</li> <li>12 randomized</li> <li>patients were</li> <li>excluded because</li> <li>they did not fulfil the</li> <li>inclusion criteria.</li> <li>Therefore, only 63</li> </ul>	Epoetin alfa: - 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	Identified from the systematic review of Tran, 2014.
		patients were evaluated:	mg daily	

		1) Epoetin alfa (n=31, 15 men and 16 women, aged on average $67.1\pm2.1$ years, mean Hb $10.6\pm0.18$ g/dl) 2) Control (n=32, 19 men and 13 women, aged on average $66.4\pm2$ years, mean Hb $11.1\pm0.19$ 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)	Epoetin beta + oral iron: - 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)	Epoetin beta + iron: - 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 <i>Transfusion policy for all</i> <i>patients:</i> - 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%.

			<ul> <li>Hb 5-5.9 g/dl: 2 units of RBC</li> <li>Hb &lt; 5 g/dl or clinical symptoms of anemia and hypovolemia: immediate transfusion and exclusion from study</li> </ul>	
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))	EPO: - 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 Placebo: - Placebo subcutaneously daily from preoperative day 4 to postoperative day 3 - Oral iron 200 mg daily from preoperative day 3 - Oral iron 200 mg daily from preoperative day 4 to preoperative day 1 <i>Transfusion policy for all</i> <i>patients:</i> 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)	Epoetin alfa: - 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.	from the surgical date were recorded.
			Transfusion policy for all patients: At the discretion of the attending surgeon; however an effort was made not to transfuse patients with Hb levels $\geq 9$ g/dl unless clinically indicated.	
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>i.e.</i> 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	EPO + AUTO: - 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 EPO + no AUTO: - 40 000 U EPO (Neorecormon or Eprex)	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),

	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. <i>Transfusion policy for all patients:</i> 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	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.
		guideline considers age and comorbidity as triggers for transfusion. High risk included incapability to enlarge cardiac output to compensate for anemia, serious	value <0.05 was considered statistically significant.
		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 ago 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	

			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 1	
Stowell 2009	Exporimontal	681 patients (78 mon	Epoptin alfa:	Identified from
11SA	Randomized	and 601 women aged	- 600 III/kg Epoetin alfa	the systematic
USA	controlled trial	and our women, aged on average $60 \pm 14$	subcutaneously on	roviow of Lip
	controlled that	voars) schodulod for	propagative days 21, 14	
		olactive chinal curgany	and 7 and on the day of	2015.
		for which anticipated	the operation	A rovicod
		blood loss was 2 to 4	Standard of care	anrollmont
		UDUU IUSS Was 2 tu 4		target of
		10 and (12 g/dl	Oral iron therapy from	674 subjects
		>10 and $\leq$ 13 g/di,	- Oral from therapy from	674 Subjects
		were randomly	preoperative day 21	was projected
		assigned to one of 2	until the day of the	to provide 572
		groups:	operation	evaluable
		1) Epoetin alfa		subjects,
		(n=341, 30 men and	Standard of care.	which was
		303 women, aged on	- NO ESA, treated	calculated to
		average $61 \pm 14$ years)	according to the	nave 80% power
		2) Standard of care	Institution's policy for	to demonstrate
		(n=340, 42 men and	blood conservation	noninteriority
		298 women, aged on	- Oral iron therapy from	for the primary
		average 59±14 years)	preoperative day 21	study end point
		a 1	until the day of the	(incidence of
		I subject in the	operation	deep vein
		Epoetin alfa		thrombosis).
		group was enrolled		
		twice in error and was		
		only included		
		in the intention-to-		
		treat analyses for the		
N/ 1 2005	<b>F</b> 1 1 1	first enrolment.	<b>F</b> (1) (6)	
weber, 2005,	Experimental:	Patients scheduled for	Epoetin alta:	Identified from
Ine	Randomized	elective major	- 40 000 IU Epoetin alfa	the systematic
ivetheriands	controlled trial	(him lunce and surgery	(Eprex®/Erypro®)	review of
		(nip, knee or spine;	subcutaneously once	Alsalen, 2013.
		primary or revision),	weekly for 3 weeks	A 1.2 matin
		with preoperative Hb	before surgery and on	A 1.2 ratio was
		reveis 10-13 g/dl were	Oral iron deily for 2	to impress total
		randomly assigned to	- Oral from daily for 3	to improve trial
		1) Fragetic alfa	weeks	acceptability
		L) Epoetin alta	No Expertine offer	and northeir stime by
		(11=467, 89.9%	<u>INO Epoetin alfa:</u>	participation by
	1	women, aged on	- Could take oral or IV	the patients.

	1			
		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 <i>Transfusion policy for all</i> <i>patients:</i> 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	Epoetin beta 125 IU: - 125 IU/kg Epoetin beta (NeoRecormon) subcutaneously once weekly during the 3 or 4 preoperative weeks - Oral iron supplementation (200- 300 mg/day) Epoetin beta 250 IU: - 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 E voars (rango E2	Control:	confidence
		70 years)	<u>Control.</u> Oral iron	intervals
		2) Francis hata 250 III		
		2) Epoelin bela 250 IO	Supplementation (200-	for differences
		(n=64, 20 men and 44	300 mg/day)	of transfusion
		women, median age		rates.
		66 years (range 56-73	Transfusion policy for all	
		years))	patients:	
		3) Control (n=60, 23	Hb ≤8.5 g/dl	
		men and 37 women,		
		median age 62 years		
		(range 51.5-71 years))		
		175 out of the 19/		
		underwent elective		
		surgery:		
		1) Epoctin both 12E III		
		1) Epoelin bela 125 10		
		(n=65, median HD		
		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		
		nonulation $(n=194)$		
		Efficacy analysis was		
		based on the		
		pased of the		
		population that		
		(n=175)		
Yoo, 2011,	Experimental:	74 patients scheduled	EPO:	Identified from
South Korea	Randomized	for valvular heart	500 IU/kg EPO	the systematic
	controlled trial	surgery, with Hb levels	intravenously + iron	review of
		<13 g/dl (men) or <12	sucrose 200 ma	Glechner, 2014.
		g/dl (women) were	intravenously	- ,
		randomly assigned to	16-24 hours before	Power analysis
		one of 2 groups:	surgery	suggested
		1) EPO ( $n=37$ 13 men	9-7	that 32 patients
		and 24 women aged	Control:	ner aroun
		on average $56+12$	Normal saling	would be
		vears)	intravenously 16-21	required to
		2) Control (n-27.1)	hours before surgery	obtain a
		men and 23 women.	nous before surgery	power of 80%,
		aged on average	In all patients, blood	considering a
		$59\pm12$ years)	salvaged by the cell	type I error of
			salvage device was	0.05, and
			reinfused into the	expecting

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

Outcome	Comparison/Risk factor	Effect Size	#studies, # participants	Reference
COMPARISON 1:		•		
TRANSFUSION V	S NO TREATMENT/	PLACEBO/STANDARD OF CARE		
Primary outcome	S			
1. (All-cause) mort	ality		T	I
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-associa	ted 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 outco	mes			
1. Length of hospit	al stay			
2. Infections				
3. Red blood cell u	tilization – RBC trans	fusions		
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. Thromboemboli	c events			
COMPARISON 2: IRON SUPPLEME	NTATION VS NO TR	REATMENT/PLACEBO/STANDAR	RD OF CARE	
Primary outcome	es la			
1. (All-cause) mort	ality			
2. Anemia-associa	ted ischaemic events			
Secondary outco	mes			
1. Length of hospit	al stay			
2. Infections				
3. a) Red blood cel	l utilization – Numbe	r of patients transfused	1	T
Number of patients receiving perioperative	300 mg iron iv vs Placebo iv	Hb <13.5 (men) or <12.5 g/dl (women) Not statistically significant:	1, 9 vs 9	Edwards, 2009
transfusion		2/9 vs 5/9 § RR: 0.40, 95%CI [0.10;1.55] ¥ (p=0.185)*		

Number of	Oral iron	Hb <13.5 (men) or <11.5 g/dl	1, 6 vs 14	Lidder, 2007
patients receiving	VS	(women)		
perioperative	standard clinical	Not statistically significant:		
transfusion	management	3/6 vs 10/14 §		
		RR: 0.70, 95%CI [0.29;1.66] ¥		
		(p=0.42)*		
Number of	Oral iron	Hb ≤10 g/dl	1, 32 vs 84	Okuyama,
patients receiving	vs	Not statistically significant:		2005
intraoperative	no iron	3/32 vs 23/84 §		
transfusion		RR: 0.34, 95%CI [0.11;1.06] ¥		
		(p=0.0635)*		
3. b) Red blood cell	utilization – Number	r of units transfused		1
Units of	100 mg iron iv	Hb <13 g/dl	1, number of	Muñoz,
leucoreduced red	VS	Statistically significant:	participants unknown	2006
cell concentrates	no iron	1.12±1.17 vs 2.18±0.98		
transfused intra-		MD: -1.06 ££† (p=0.019)		
and		in favour of iv iron		
postoperatively				
(mean±SD)				
Units of blood	Oral iron	Hb <13.5 (men) or <11.5 g/dl	1, 6 vs 14 §	Lidder, 2007
transfused	VS	(women)		
perioperatively	standard clinical	Not statistically significant:		
(median (IQR))	management	Median (IQR): 1 (0-2) vs 2.5		
		(0-11) £££†		
		(p>0.05)		
Intraoperative	Oral iron	Hb ≤10 g/dl	1, 32 vs 84 §	Okuyama,
transfusion	VS	Statistically significant:		2005
volume (ml,	no iron	607±150 vs 441±183		
mean±SD)		MD: 166,		
		95%CI [100.94;231.06] ¥		
		(p<0.00001)*		
		ın favour of no ıron		
4. Thromboembolic	c events			
COMPARISON 3:				
ESA VS NU TREA	I MEN I/PLACEBO/S	TANDARD OF CARE		
1 (All-cause) mort	s ality			
45-day mortality	EPO sc	Hb < 14.5 a/dl	2 158 vs 162	Woltert
-J-day montainty		Not statistically significant:	2, 400 v3 402	2010
	no treatment	12/458  yr 13/462  s		Woltert
		RP: 0.93, 95% CI [0.43·2.01] ¥		2015
		(n - 0.85)*		2015
2 Anemia-associat	L red ischaemic events	()=0.03)		
Perioperative	FPO sc	Hb <14.5 a/dl	2 458 vs 462	Weltert
myocardial		Not statistically significant:	2, 430 V3 402	2010
infarction	no treatment	10/458 vs 11/462 §		Weltert
		RR: 0.92, 95%CI [0.39·2.14] ¥		2015
		$(n=0.78)^*$		_010
Renal failure (new)	1	Hb < 14.5 a/dl	1 300 vs 300	Weltert
onset)		Not statistically significant	<u>-, 500 v5 500</u>	2015
		2/300 vs 1/300 §		<b></b>
		RR: 2.00, 95%CI [0 18·21 94] ¥		
		····· =······· [0·······················	1	1

		(- 0 57)*		
	500	(p=0.57)^	2 450 462	
Bowel ischemia	EPO sc	$HD \leq 14.5 \text{ g/al}$	2, 458 vs 462	Weltert,
	VS	Not statistically significant:		2010;
	no treatment	2/458 VS 4/462 §		weitert,
		RR: 0.50, 95%CI [0.09;2./1] ¥		2015
		(p=0.42)*		
Secondary outco	mes			
1. Length of hospit	al stay	I		
Length of stay	EPO sc	Hb ≤14.5 g/dl	1, 158 vs 162 §	Weltert,
after operation	VS	Not statistically significant:		2010
(days)	no treatment	5.52 vs 5.89 £†		
		(p=0.065)		
		Hb ≤14.5 g/dl	1, 300 vs 300	Weltert,
		Statistically significant:		2015
		6 (4-28) vs 6 (4-28)£†		
		(p=0.01)		
Length of stay		Hb <13 g/dl	1, 24 vs 56 §	Bedair, 2015
(days, mean±SD)		Not statistically significant:		
		3.0±0.4 vs 3.3±0.8		
		MD: -0.30, 95%CI [-0.56;-0.04]		
		(p=0.09)*		
2. Infections				
Long-term wound	EPO sc	Hb ≤14.5 g/dl	1, 158 vs 162	Weltert,
infection	vs	Not statistically significant:		2010
	no treatment	3/158 vs 3/162 §		
		RR: 1.02, 95%CI [0.21;5.00] ¥		
		(p=0.98)*		
		Hb ≤14.5 g/dl	1, 300 vs 300	Weltert,
		Not statistically significant:		2015
		4/300 vs 4/300 §		
		RR: 1.00, 95%CI [0.25;3.96] ¥		
		(p=1.00)*		
Pneumonia		Hb ≤14.5 g/dl	1, 158 vs 162	Weltert,
		0/158 vs 0/162 §		2010
		Effect size not estimable £		
3. a) Red blood cell	l utilization – Number	r of patients transfused		
Number of	EPO sc	Hb ≤14.5 g/dl	1, 158 vs 162	Weltert,
patients receiving	vs	Statistically significant:		2010
any perioperative	no treatment	25/158 vs 60/162 §		
transfusion		RR: 0.43, 95%CI [0.28;0.65]		
		(p=0.0001)*		
		in favour of EPO sc		
Number of	Epoetin alpha	Hb <13 g/dl	1, 24 vs 56	Bedair, 2015
patients receiving	VS	Statistically significant:		
postoperative	no Epoetin alpha	0/24 vs 23/56 §		
transfusion		RR: 0.05, 95%CI [0.003;0.77]		
		(p=0.0317)*		
		in favour of Epoetin alpha		
3. b) Red blood cel	l utilization – Number	r of units transfused	- -	•
Units of blood	EPO sc	Hb ≤14.5 g/dl	1, 158 vs 162 §	Weltert,
transfused	vs	Statistically significant:		2010
	no treatment	0.32 vs 0.76		
L	1	J		1

			1	
perioperatively		MD: -0.44 £ (p=0.008)		
(mean)		in favour of EPO sc		
Units of RBC		Hb ≤14.5 g/dl	1, 300 vs 300	Weltert,
transfused		Statistically significant:		2015
perioperatively		0 (0-11) vs 0 (0 to 16)		
(median)		MD: 0 £ (p<0.0005)		
		in favour of EPO sc		
Units of blood	Epoetin alpha	Hb <13 g/dl	1, 24 vs 56 §	Bedair, 2015
transfused	vs	0 vs 0.41±0.07	,	
postoperatively	no Epoetin alpha	MD: -0.41 £†		
(mean±SD)		Effect size not estimable		
4. Thromboembolic	c events		•	•
Deep vein	EPO sc	Hb ≤14.5 g/dl	2, 458 vs 462	Weltert,
thrombosis	vs	Not statistically significant:	,	2010;
	no treatment	2/458 vs 6/462 §		Weltert.
		RR: 0.39. 95%CI [0.09:1.66] ¥		2015
		$(p=0.20)^*$		
COMPARISON 4:				
IRON SUPPLEMEN	NTATION + ESA VS	NO TREATMENT/PLACEBO/ST	ANDARD OF CARE	
Primary outcome	s			
1 (All-cause) mort	ality			
Death during the	600 IU/ka Epoetin	Hb >10 and <13 a/dl	1 340 vs 340	Stowell
study or within 30	alfa sc	Not statistically significant	2, 0 10 10 0 10	2009
davs after study	+ oral iron	1/340  vs  2/340		2005
completion	vs	RR: 0.50, 95%CI [0.05.5.49] ¥		
(due to	Standard of care	$(n=0.57)^*$		
pneumonia	+ oral iron	(p 0.07)		
(Epoetin alfa)				
sudden cardiac				
death and acute				
myeloid leukemia				
(standard of care))				
Death	20.000 ILL Epoetin	Hb > 85 and < 135 a/dl	1 52 vs 57	Kettelback
(after withdrawal	beta sc $\pm$ iron	Not statistically significant:	1, 52 v3 57	1998
from the study or	(oral and/or iv)	5/52  yr 2/57  s		1990
during the post-		RP: 2.74 95%CI [0.56:13.52] ¥		
treatment period	V3 Placebo sc +	(n-0.22)*		
due to serious	iron (oral and/or iv)	(p=0.22)		
adverse events)				
Perionerative	600 ILL Epoetin alfa	Hb > 10 and < 13 5 a/dl	1 29 vs 29	Scott 2002
death	+ oral iron	Not statistically significant:	1, 25 15 25	50011, 2002
(due to cerebral	vs	3/29  vs 0/29  s		
vascular accident	Placeho	RR: 7 00 95%CI [0 38:129 74] ¥		
(n=2) or acute	+ oral iron	$(n=0.19)^*$		
respiratory distress		(p=0.13)		
syndrome $(n=1)$				
		Hb < 13 a/dl (men) or < 12 a/dl	1 37 vs 37	Voo 2011
death (30-day)	+ iv iron	(women)	±, J/ V3 J/	100, 2011
		Not statistically significant:		
	Saline iv	0/37  vs  1/37		
		RR: 0.33 95%CI IO 01.7 931 ¥		
		$(p=0.50)^*$		
	1			

Postoperative	150 IU Epoetin alfa	Hb >9 and <12 g/dl	1, 69 vs 68	Christodoula
death	sc	Not statistically significant:	,	kis, 2005
	+ oral/iv iron	2/69 vs 0/68 §		
	+ folic acid	RR: 4.93, 95%CI [0.24;100.80] ¥		
	vs	(p=0.30)*		
	Oral/iv iron			
	+ folic acid			
	300 IU Epoetin alfa	Hb >9 and <12 a/dl	1. 67 vs 68	
	sc	Not statistically significant:	_,	
	+ oral/iv iron	3/67 vs 0/68 §		
	+ folic acid	RR: 7.10. 95%CI [0.37:134.92] ¥		
	vs	(p=0.19)*		
	Oral/iv iron	ų		
	+ folic acid			
Postoperative	150 IU/kg EPO sc	Hb 9-13 a/dl	1, 17 vs 10	Heiss, 1996
death	+ oral iron	Not statistically significant	1, 1, 1, 1, 1, 20	110100/ 2000
(FPO: sentic shock	+ oral folate	2/17 vs 1/10 §		
or multiorgan	VS	RR 1 18 95%CI [0 12:11 39] ¥		
failure: Placebo:	Placebo sc	$(n=0.89)^{*}$		
mesenteric venous	+ oral iron	(p 0.03)		
thrombosis with	+ oral folate			
subtotal small				
bowel infarction)				
Death after study	125 ILL/ka Epoetin	Hct 30-12%	1 70 vs 60	Murnia
completion (due	heta sc	Not statistically significant:	1, 70 V3 00	2001
to multiple organ	+ oral iron	0/70  yrs 1/60  s		2001
failure 10 days		RR: 0.29, 95%CI [0.01:6.90] ¥		
after completion)	vs Oral iron	(n - 0.44)*		
	250 ILL/kg Epostin	(p = 0.44)	1 64 vc 60	-
	bota sc	Not statistically significant:	1, 04 VS 00	
	+ oral iron	0/64  yrs 1/60  s		
		$PP \cdot 0.21  0.5\% CI (0.01.7.52) \times$		
	vs Oral iron	(n - 0.47)*		
2 Anomia-associat	oral lischaemic events	()-0.47)		
2. Allelliu-ussociul		Hh < 12 a/dl (man) ar < 12 a/dl	1 27 1 25	Voo 2011
	SUU IU/KY EPO IV	HD < 13  g/u (HeII)  of  < 12  g/u (HeII)	1, 57 VS 55	100, 2011
acute kiuney injury		(WOMEN) Statistically significant:		
	vs Salina iv	$\frac{5 (a fistically significant.}{10/25}$		
	Saline IV	9/3/ VS 19/35		
		RR. 0.45, 95% $CI [0.24, 0.65]$		
		(p=0.013)		
Carabravacaular	600 ILL/kg Engetin	(1) $(1)$	1 240 vo 240	Ctowall
Cerebrovascular	olo io/kg Epoelin	$HD > 10 \text{ and } \leq 13 \text{ g/al}$	1, 340 VS 340	Stowell,
accident				2009
	VS	RR: 5.00, 95%CI [0.24;103.76] ¥		
	Standard of care	(p=0.30)^		
Canalan I			1 20 20	C
	buu IU Epoetin alfa	$HD \ge 10 \text{ and } \le 13.5 \text{ g/dl}$	1, 29 vs 29	Scott, 2002
accident	+ oral iron	Not statistically significant:		
	VS	2/29 VS U/29 9		
	Ріасеро	кк: 5.00, 95%СI [0.25;99.82] ¥		
	+ oral iron	(p=0.29)*		

Cerebrovascular	125 IU/ka Epoetin	Hct 30-42%	1 70 vs 60	Wurnia
accident	beta sc	Not statistically significant:	1, 70 13 00	2001
	+ oral iron	1/70 vs 0/60 §		
	VS	RR: 2.58. 95%CI [0.11:62.12] ¥		
	Oral iron	(p=0.56)*		
	250 IU/ka Epoetin	Hct 30-42%	1. 64 vs 60	
	beta sc	0/64 vs 0/60 §	,	
	+ oral iron	Effect size not estimable £		
	vs			
	Oral iron			
Transient	600 IU/kg Epoetin	Hb >10 and ≤13 g/dl	1, 340 vs 340	Stowell,
ischaemic attack	alfa sc	Not statistically significant:		2009
	+ oral iron	1/340 vs 0/340		
	vs	RR: 3.00, 95%CI [0.12;73.38] ¥		
	Standard of care	(p=0.50)*		
	+ oral iron			
Stroke or transient	40 000 U EPO sc	Hb 10-13 g/dl	1, 125 vs 138	So-Osman,
ischaemic attack	+ oral iron	Not statistically significant:		2014
	VS	2/125 vs 0/138		
	no intervention	RR: 5.52, 95%CI [0.27;113.80] ¥		
		(p=0.27)*		
Myocardial	600 IU/kg Epoetin	$Hb > 10 and \leq 13 g/dl$	1, 340 vs 340	Stowell,
ischemia	alta sc	Not statistically significant:		2009
	+ oral iron	1/340 vs 0/340		
	VS Chanadand of some	RR: 3.00, 95%CI [0.12;73.38] ¥		
	Standard of care	(p=0.50)*		
Muccardial	+ Oral Iron	11b > 10 and (12 a)(d)	1 240 vo 240	Ctowall
inforction	olfa cc	$HD > 10 \text{ and } \leq 13 \text{ g/al}$	1, 340 VS 340	Stowell,
Infarction	+ oral iron	1/340  yr 0/340		2009
	vs	RR: 3 00 95%CI [0 12:73 38] ¥		
	Standard of care	$(n=0.50)^*$		
	+ oral iron	(p 0.00)		
Intraoperative	600 IU Epoetin alfa	Hb >10 and <13.5 a/dl	1, 29 vs 29	Scott, 2002
mvocardial	+ oral iron	Not statistically significant:	1, 23 13 23	50010, 2002
infarction	VS	1/29 vs 0/29 §		
	Placebo	RR: 3.00, 95%CI [0.13;70.74] ¥		
	+ oral iron	(p=0.50)*		
Myocardial	40 000 U EPO sc	Hb 10-13 g/dl	1, 125 vs 138	So-Osman,
infarction	+ oral iron	Not statistically significant:		2014
	vs	2/125 vs 1/138		
	no intervention	RR: 2.21, 95%CI [0.20;24.05] ¥		
		(p=0.52)*		
Secondary outcor	nes			
1. Length of hospite	al stay		-	
Length of hospital	500 IU/kg EPO iv	Hb <13 g/dl (men) or <12 g/dl	1, 37 vs 37	Yoo, 2011
stay (days,	+ iv iron	(women)		
mean±SD)	VS	Not statistically significant:		
	Saline iv	11.3±4.1 vs 13.5±8.0		
		MD: -2.20, 95%CI [-5.10;0.70]		
		(p=0.14)*		

Length of hospital	5000 IU Epoetin	Hb <12 g/dl (women)	1, 15 vs 16	Larson, 2001
stay (days,	beta sc	Not statistically significant:		
mean±SD)	+ oral iron	6.4±2.4 vs 8.1±7.1		
	VS	MD: -1.70, 95%CI [-5.38;1.98] ¥		
	Oral iron	(p=0.39)*		
Length of hospital	300 IU/kg Epoetin	Hb 8.5-13 g/dl	1, 31 vs 32 §	Kosmadakis,
stay (days,	alfa sc	Statistically significant:		2003
mean±SD)	+ iv iron	10±2.78 vs 13±5.09**		
	VS	MD: -3, 95%CI [-5.02;-0.98]		
	Placebo sc	(p=0.0053)*		
	+ iv iron	in favour of Epoetin alfa sc + iv iron		
Lenath of	EPO 600 U/ml sc	$Hb \ge 9$ and $< 12$ a/dl (women)	1, 23 vs 27 §	Dousias,
postoperative stav	+ iron	Not statistically significant:	,	2003
(days, mean±SD)	VS	7.6±0.5 vs 7.8±0.9		
()-, ,	Normal saline	MD: -0.20, 95%CI [-0.60;0.20]		
	+ iron	(p=0.35)*		
2. Infections			I	
Postoperative	5000 IU Epoetin	Hb <12 g/dl (women)	1, 15 vs 16	Larson, 2001
infection	beta sc	Not statistically significant:		
(superficial wound	+ oral iron	1/15 vs 2/16		
infection, severe	vs	RR: 0.53, 95%CI [0.05;5.29] ¥		
streptococcal	Oral iron	(p=0.59)*		
septicaemia,				
urinary tract				
infection)				
Wound infection	600 IU/kg Epoetin	Hb >10 and ≤13 g/dl	1, 340 vs 340	Stowell,
	alfa sc	Not statistically significant:		2009
	+ oral iron	4/340 vs 1/340		
	VS	RR: 4.00, 95%CI [0.45;35.60] ¥		
	Standard of care	(p=0.21)*		
	+ oral iron			
Urinary tract	600 IU/kg Epoetin	$Hb > 10 and \leq 13 g/dl$ :	1, 340 vs 340	Stowell,
Infection	alta sc	Not statistically significant:		2009
	+ oral iron	22/340 vs 16/340		
	VS Chanaland a faana	RR: 1.38, 95%CI [0.74;2.57] ¥		
	Standard of care	(p=0.32)*		
2 a) Dad bload call	+ oral Iron	w of patients transfused		
3. a) Rea blood cell		H of patients transfused	1 1 1 1 2	
nationts receiving	+ oral iron	Not statistically significant:	1,4 15 5	COFL3, 1993
patients receiving				
transfusion	Placebo sc	RR 0 57 95%CI [0 22.1 48] ¥		
	+ oral iron	(n=0.25)*		
		Hb 11 5-12 4 a/dl	1 8 vs 8	
		Not statistically significant:	1,0,00	
		5/8 vs 8/8 §		
		RR: 0.65. 95%CI [0.38:1.12] ¥		
		(p=0.12)*		
			1, 18 vs 20	
		Statistically significant:		
		3/18 vs 12/20 §		
		RR: 0.28, 95%CI [0.09;0.83]		

		(p=0.02)*		
		In favour of EPO sc + oral iron		
Number of	EPO 600 U/ml sc	$Hb \ge 9$ and $< 12$ a/dl (women)	1, 23 vs 27	Dousias,
patients receiving	+ iron	Not statistically significant:	,	2003
perioperative	vs	0/23 vs 5/27 §		
transfusion	Normal saline	RR: 0.11, 95%CI [0.01;1.82] ¥		
	+ iron	(p=0.12)*		
Number of	EPO 300 IU sc	Hb >10 and ≤13 g/dl	1, 22 vs 27	Faris, 1996
patients receiving	+ oral iron	Statistically significant:		
perioperative	vs	3/22 vs 21/27 §		
transfusion	Placebo sc	RR: 0.18, 95%CI [0.06;0.51]		
	+ oral iron	(p=0.001)*		
		in favour of EPO sc + oral iron		
	EPO 100 IU sc	Hb >10 and ≤13 g/dl	1, 23 vs 27	
	+ oral iron	Statistically significant:		
	vs	9/23 vs 21/27 §		
	Placebo sc	RR: 0.50, 95%CI [0.29;0.87]		
	+ oral iron	(p=0.014)*		
		in favour of EPO sc + oral iron		
Number of	EPO sc	Hb ≤8.5 mmol/L	1, 38 vs 43	Qvist, 1999
patients receiving	+ oral iron	Not statistically significant:		
perioperative	vs	13/38 vs 23/43 §		
transfusion	Placebo sc	RR: 0.64, 95%CI [0.38;1.08] ¥		
	+ oral iron	(p=0.09)*		
Number of	40 000 U EPO sc	Hb 10-13 g/dl	1, 125 vs 138	So-Osman,
patients receiving	+ oral iron	Statistically significant:		2014
perioperative	VS	13/125 vs 32/138		
transfusion	no intervention	RR: 0.45, 95%CI [0.25;0.82]		
		$(p=0.009)^{\circ}$		
Number of		in favour of EPO sc + oral iron	1 17 10	
number of	150 IU/Ky EPO SC	Not statistically significant:	1, 17 VS 10	Heiss, 1990
		0/17  yr 4/10  s		
transfusion		RR 1 32 95% CI IO 55.3 201 ¥		
	Placebo sc	$(n=0.53)^*$		
	+ oral iron	(p 0.00)		
	+ oral folate			
Number of	500 IU/ka EPO iv	Hb <13 a/dl (men) or <12 a/dl	1, 37 vs 37	Yoo, 2011
patients receiving	+ iv iron	(women)	,	
perioperative	vs	Statistically significant:		
transfusion	Saline iv	22/37 vs 32/37		
		RR: 0.69, 95%CI [0.51;0.92]		
		(p=0.01)*		
		in favour of EPO iv + iv iron		
Number of	40 000 IU Epoetin	Hb 9.8-13.7 g/dl	1, 44 vs 78	Feagan,
patients receiving	alfa sc	Statistically significant:		2000
perioperative	+ oral iron	5/44 vs 35/78 §		
transfusion	vs	RR: 0.25, 95%CI [0.11;0.60]		
	Placebo sc	(p=0.0018)*		
	+ oral iron	in favour of Epoetin alfa sc +		
		oral iron		
	20 000 IU Epoetin	Hb 9.8-13.7 g/dl	1, 79 vs 78	
	alfa sc	Statistically significant:		

Number of patients receiving perioperative transfusion Number of	+ oral iron vs Placebo sc + oral iron 600 IU Epoetin alfa + oral iron vs Placebo + oral iron 40 000 IU Epoetin	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 Hb $\geq 10$ and $\leq 13.5$ g/dl Not statistically significant: 19/29 vs 24/29 § RR: 0.79, 95%CI [0.58;1.08] ¥ (p=0.14)* Hb 10-13 g/dl	1, 29 vs 29 1, 460 vs 235	Scott, 2002 Weber, 2005
patients receiving perioperative transfusion	alfa sc + oral iron vs Oral or iv iron	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		
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	Christodoula kis, 2005
	sc + oral/iv iron + folic acid vs Oral/iv iron + folic acid	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 250 IU/kg Epoetin beta sc	Hct 30-42% <u>Statistically significant:</u> 19/65 vs 28/51 §££££ (p=0.0045) in favour of Epoetin beta sc + oral iron Hct 30-42% <u>Statistically</u> significant:	1, 65 vs 51 1, 59 vs 51	Wurnig, 2001
Number of patients receiving	+ oral iron vs Oral iron 5000 IU Epoetin beta sc	22/59 vs 28/51 §££££ (p=0.048) in favour of Epoetin beta sc + oral iron Hb <12 g/dl (women) Not statistically significant:	1, 15 vs 16	Larson, 2001
transfusion		0112 A2 T10		

	vs	RR: 0.35, 95%CI [0.02;8.08] ¥		
	Oral iron	(p=0.51)*		
Number of	300 IU/kg Epoetin	Hb 8.5-13 g/dl	1, 31 vs 32	Kosmadakis,
patients receiving	alfa sc	Statistically significant:		2003
intraoperative	+ iv iron	9/31 vs 19/32 §		
transfusion	vs	RR: 0.49, 95%CI [0.26;0.91]		
	Placebo sc	(p=0.0238)*		
	+ iv iron	in favour of Epoetin alfa sc + iv		
		iron		
Number of	300 IU/kg Epoetin	Hb 8.5-13 g/dl	1, 31 vs 32	Kosmadakis,
patients receiving	alfa sc	Statistically significant:		2003
postoperative	+ iv iron	1/31 vs 9/32 §		
transfusion	vs	RR: 0.11, 95%CI [0.02;0.85]		
	Placebo sc	(p=0.0344)*		
	+ iv iron	in favour of Epoetin alfa sc + iv		
		iron		
Number of	150 IU Epoetin alfa	Hb >9 and <12 g/dl	1, 69 vs 68	Christodoula
patients receiving	sc	Not statistically significant:		kis, 2005
postoperative	+ oral/iv iron	33/69 vs 36/68 §		
transfusion	+ folic acid	RR: 0.90, 95%CI [0.65;1.26] ¥		
	vs	(p=0.55)*		
	Oral/iv iron			
	+ folic acid			
	300 IU Epoetin alfa	Hb >9 and <12 g/dl	1, 67 vs 68	
	sc	Not statistically significant:		
	+ oral/iv iron	27/67 vs 36/68 §		
	+ folic acid	RR: 0.76, 95%CI [0.53;1.10] ¥		
	vs	(p=0.14)*		
	Oral/iv iron			
	+ folic acid			
Number of	3000 IU Epoetin	Hb >10 g/dl (women)	1, 54 vs 54	Na, 2011
patients receiving	beta sc	Statistically significant:		
postoperative	+ iron iv	11/54 vs 29/54		
transfusion	vs	RR: 0.38, 95%CI [0.21;0.68]		
	no treatment	(p=0.0011)*		
		in favour of Epoetin beta sc + iv		
		iron		
Number of	500 IU/kg EPO iv	Hb <13 g/dl (men) or <12 g/dl	1, 37 vs 37	Yoo, 2011
patients receiving	+ iv iron	(women)		
multiple	vs	Statistically significant:		
postoperative	Saline iv	5/37 vs 20/37		
transfusion		RR: 0.25, 95%CI [0.11;0.60]		
		(p=0.0017)*		
		in favour of EPO iv + iv iron		
3. b) Red blood cell	l utilization – Number	r of units transfused		
Units of blood	EPO sc	$Hb \leq 8.5 mmol/L$	1, 38 vs 43 §	Ovist, 1999
transfused	+ oral iron	Statistically significant:	_,	2
perioperatively	vs	0.3 vs 1.6		
(mean)	Placebo sc	MD: -1.3 f		
	+ oral iron	(p < 0.05)		
		in favour of FPO		
Units of	40 000 U FPO sc	Hb 10-13 a/dl	1, 125 vs 138	So-Osman
ervthrocytes	+ oral iron	Statistically significant	_, 10 10 100	2014

transfused among	vs	0.25 + 0.9 vs $0.64 + 1.6$		
all patients	no intervention	MD: -0.39, 95%CI		
(mean+SD)		[-0.70; -0.08] (p=0.017)*		
(mean_00)		in favour of FPO sc + oral iron		
Units of packed	500 IU/ka EPO iv	Hb <13 a/dl (men) or <12 a/dl	1. 37 vs 37	Yoo, 2011
ervthrocytes	+ iv iron	(women)	_, ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;	,
transfused	vs	Statistically significant:		
perioperatively	Saline iv	1.0+1.1 vs $3.3+2.2$		
among all patients		$MD^{-2} = 230 = 95\%$ CI		
(mean+SD)		[-3.09:-1.51] (p<0.0001)*		
(11001200)		in favour of FPO iv $+$ iv iron		
Units of packed	500 IU/ka EPO iv	Hb < 13 a/dl (men) or < 12 a/dl	1 22 vs 32	Yoo 2011
ervthrocytes	+ iv iron	(women)	_,	,
transfused	vs	Statistically significant		
perioperatively	Saline iv	1.6+0.9  ys 3.7+2.1		
among transfused		MD = -2.10, 95%		
natients		[-2.92:-1.28] (p=0.001)*		
(mean+SD)		in favour of FPO iv $+$ iv iron		
Units of blood	150 IU/ka EPO sc	Hb 9-13 a/dl	1 17 vs 10 §	Heiss 1996
transfused	+ oral iron	Not statistically significant:	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	110135, 1990
nerioneratively per	+ oral folate	1 82+0 80 vs 1 80+0 97		
natient		MD: 0.02 95%CI		
(mean+SD)	Placebo sc	[-0.69:0.73] (n=0.95)*		
(mean±5b)	+ oral iron	[ 0.05,0.75] (p=0.55)		
	+ oral folate			
Linits of blood	600 II I Epoetin alfa	Hh > 10 and < 13 5 a/dl	1 29 vc 29 8	Scott 2002
transfused		Not statistically significant:	1, 25 V3 25 3	50011, 2002
nerioneratively		207+276 vs 341+304		
(mean+SD)	Placebo	$MD_{-1} = 1.34 = 95\%$ (1 [-2 83:0 15] ¥		
(mean±3D)		(n - 0.08)*		
Linits of blood	600 II I Epoetin alfa	(p=0.00) Hb >10 and <135 a/dl	1 19 vc 2/ 8	Scott 2002
transfused	+ oral iron	Not statistically significant:	1, 15 V3 24 3	50011, 2002
nerioneratively in		316+287  yrs / 12+286		
transfused	Placebo	MD: -0.96, 95%CI [-2.68:0.76] ¥		
nationts		(n=0.28)*		
(mean+SD)		(p=0.28)		
Units of blood	40.000 ILL Epoetin	Hb 9 8-13 7 a/dl	1 AA vs 78 8	Feagan
transfused at any	alfa sc	Statistically significant:	1, 11 V3 70 3	2000
time among all	+ oral iron	0.3+0.7  ys 1.0+1.2		2000
natients		MD = 0.70, 95%CI		
(mean+SD)	Placebo sc	[-1, 04:-0, 36] (p=0,0006)*		
(mean±5D)	+ oral iron	[1:0+, 0:00] (p=0:0000)		
		oral iron		
	20.000 ILL Epoetin	Hb 98-137 a/dl	1 79 vs 78 8	-
	alfa sc	Statistically significant:	1, 75 45 70 5	
	+ oral iron	0.4+0.9  ys 1.0+1.2		
		MD: -0.60.95%CI		
	Placebo sc	[-0.93:-0.27] (p=0.0005)*		
	+ oral iron	in favour of Enoptin alfa sc $\pm$		
		oral iron		
Linits of blood	40.000 ILL Epoction	$Hb 9 8-137 \alpha/dl$	1 5 vs 35 8	Feagan
transfused at any	alfa sc	Not statistically significant	±, J v J J 3	2000
time among	+ oral iron	22+04 vs 21+08		
and among		$r_{1}r_{2} = 0.1 + 0.2 r_{1}r_{2} = 0.0$		

transfused	vs	MD: 0.10, 95%CI		
patients	Placebo sc	[-0.34;0.54] (p=0.79)*		
(mean±SD)	+ oral iron			
	20 000 IU Epoetin	Hb 9.8-13.7 g/dl	1, 18 vs 35 §	
	alfa sc	Not statistically significant:		
	+ oral iron	1.8±0.8 vs 2.1±0.8		
	vs	MD: -0.30, 95%CI		
	Placebo sc	[-0.75;0.15] (p=0.20)*		
	+ oral iron			
Units of blood	150 IU Epoetin alfa	Hb >9 and <12 g/dl	1, 69 vs 68 §	Christodoula
transfused	sc	Not statistically significant:		kis, 2005
perioperatively	+ oral/iv iron	1.19±1.46 vs 1.34±1.59		
(mean±SD)	+ folic acid	MD: -0.15, 95%CI [-0.66;0.36]		
	vs	(p=0.57)*		
	Oral/iv iron			
	+ folic acid			
	300 IU Epoetin alfa	Hb >9 and <12 g/dl	1, 67 vs 68 §	
	sc	Statistically significant:	,	
	+ oral/iv iron	$0.81\pm1.22$ vs $1.34\pm1.59$		
	+ folic acid	MD: -0.53, 95%CI [-1.01:-0.05]		
	VS	$(n=0.03)^*$		
	Oral/iv iron	in favour of Encetin alfa sc +		
	+ folic acid	oral/iv iron + folic acid		
Linits of blood	3000 ILL Epoctin	$H_{h} > 10 a/dl (women)$	1 51 vc 51	No. 2011
transfused	bota co	Statistically significant:	I, J4 VS J4	INd, 2011
(mean±SD)	vs	MD: -0.60, 95%CI		
	no treatment	[-0.85, -0.35] (p=0.0000) <sup>2</sup>		
		in favour of Epoetin beta sc + iv		
			1 60 60 6	
Units of blood	150 IU Epoetin alfa	HD >9 ana <12 g/al	1, 69 VS 68 9	Christodoula
transfused	SC	Not statistically significant:		kis, 2005
postoperatively	+ oral/iv iron	1.10±1.42 vs 1.35±1.58		
(mean±SD)	+ folic acid	MD: -0.25, 95%CI [-0.75;0.25] ¥		
	VS	(p=0.33)*		
	Oral/iv iron			
	+ folic acid			
	300 IU Epoetin alfa	Hb >9 and <12 g/dl	1, 67 vs 68 §	
	SC	Statistically significant:		
	+ oral/iv iron	0.87±1.21 vs 1.35±1.58		
	+ folic acid	MD: -0.48, 95%CI [-0.95;-0.01]		
	vs	(p=0.0498)*		
	Oral/iv iron	in favour of Epoetin alfa sc +		
	+ folic acid	oral/iv iron + folic acid		
4. Thromboembol	ic events		r	
Arterial	20 000 IU Epoetin	Hb >8.5 and ≤13.5 g/dl	1, 48 vs 54	Kettelhack,
thrombosis	beta sc + iron	Not statistically significant:		1998
	(oral and/or iv)	1/48 vs 0/54 §		
	vs	RR: 3.37, 95%CI [0.14;80.76] ¥		
	Placebo sc +	(p=0.45)*		
	iron (oral and/or iv)			
Deep venous	EPO sc	Hb ≤8.5 mmol/L	1, 38 vs 43	Qvist, 1999
thrombosis	+ oral iron	Not statistically significant:		

	VS	1/38 vs 0/43 §		
	Placebo sc	RR: 3.38, 95%CI [0.14;80.70] ¥		
	+ oral iron	(p=0.45)*		
Deep venous	40 000 U EPO sc	Hb 10-13 g/dl	1, 125 vs 138	So-Osman,
thrombosis	+ oral iron	0/125 vs 0/138		2014
	vs	Effect size not estimable £		
	no intervention			
Deep venous	150 IU/ka EPO sc	Hb 9-13 a/dl	1, 20 vs 10	Heiss, 1996
thrombosis	+ oral iron	Not statistically significant:	,	,
	+ oral folate	2/20 vs 0/10 §		
	VS	RR: 2.62, 95%CI [0.14:49.91] ¥		
	Placebo sc	$(p=0.52)^*$		
	+ oral iron	(p)		
	+ oral folate			
Deen venous	40.000 ILL Epoetin	Hb 9 8-13 7 a/dl	1 44 vs 78	Feagan
thrombosis	alfa sc	Not statistically significant:	1, 11 03 70	2000
	+ oral iron	2/44  ys 5/78  s		2000
		RR: 0.71 95%CI [0.14:3.50] ¥		
	Placebo sc	$(n=0.67)^*$		
	+ oral iron	(p=0.07)		
		Hb 9 8-137 a/dl	1 79 vs 78	
	alfa sc	Not statistically significant:	1, 7 5 7 5 7 6	
		5/79  yrs 5/78  s		
		RP: 0.99, 95% CI [0.30:3.28] ¥		
	vs Diacobo co	(n = 0.98)*		
		(p=0.38)		
Doopyopour		Hb > 10 and < 12 a/dl	1 240 vc 240	Stowell
thrombosis	alfa sc	Not statistically significant:	1, 540 vs 540	
	alla sc	16/340  yrs 7/340		2009
	vs Standard of caro	(n-0.06)*		
		(p=0.00)		
	600 ILL Epoctin alfa	Hb > 10 and < 13.5 a/dl	1 20 1 20	Scott 2002
thrombosis		0/29  yr 0/29  s	1, 25 V3 25	5001, 2002
		Effect size not estimable f		
	VS Diacobo			
		$\mu_{b} = 85 - 13 a/dl$	1 21 vc 22	Kosmadakis
thrombosic	alfa sc	Not statistically significant:	1, 51 VS 52	2002
		2/31  yrs 1/32  s		2005
		RP: 2.06.95% CI IO 20:21.631 ¥		
	V3 Placebo sc	(n-0.54)*		
		(p=0.54)		
	125 ILL/kg Epoetin	Hct 30-42%	1 70 vs 60	Wurnia
thrombosis	heta sc	Not statistically significant:	1,70 13 00	2001
	+ oral iron	2/70  ys  0/60  s		2001
	vs	RR 4 30 95%CI [0 21.87 76] ¥		
	Oral iron	(n-0.34)*		
	250 ILL/kg Epoptin	Hct 30-42%	1 64 vs 60	—
	hota sc	Not statistically significant	<u>+</u> , 0+ v3 00	
	+ oral iron	2/64  vs 0/60  s		
	Oral iron			
		RR: 4.69, 95%CI [0.23;95.79] ¥ (p=0.32)*		
-----------------------	--	---	---------------	-------------------
Pulmonary embolism	40 000 U EPO sc + oral iron vs no intervention	<i>Hb 10-13 g/dl</i> 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

££ Number of participants not available, CI cannot be calculated

£££ Median, but no effect size and CI reported

££££ 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.



(G) Other bias

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

	Transfu	sion	Standard o	f care		Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG		
Karkouti 2012	11	29	11	31	100.0%	1.07 [0.55, 2.08]		•?•••		
Total (95% CI)		29		31	100.0%	1.07 [0.55, 2.08]	+			
Total events	11		11							
Heterogeneity: Not ap	plicable									
Test for overall effect: Z = 0.20 (P = 0.84) U.01 U.01 I U 100 Eavours transfusion Eavours standard of care										
Risk of bias legend										
(A) Random sequence	e generat	ion (sel	ection bias)							
(B) Allocation conceal	ment (sel	ection b	ias)							
(C) Blinding of particip	ants and	person	nel (perform	ance bia	s)					
(D) Blinding of outcom	ne assess	ment (o	letection bia	s)						
(E) Incomplete outcom	ne data (a	ttrition b	ias)							
(F) Selective reporting (reporting bias)										
(G) Other bias										

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

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

	Iron		Control			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Edwards 2009 (patients transfused periop)	2	9	5	9	20.5%	0.40 [0.10, 1.55]		••••
Lidder 2007 (patients transfused periop)	3	6	10	14	50.2%	0.70 [0.29, 1.66]	— <b>—</b> —	• ? • • • • •
Okuyama 2005 (patients transfused intraop)	3	32	23	84	29.3%	0.34 [0.11, 1.06]		•????
Total (95% CI)		47		107	100.0%	0.51 [0.27, 0.93]	•	
Total events	8		38					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.28, df = 2 (	(P = 0.53);	$ ^{2} = 0.9$	%					l
Test for overall effect: Z = 2.18 (P = 0.03)							Favours Iron Favours Control	
<u>Risk of bias legend</u>								
(A) Random sequence generation (selection b)	ias)							
(B) Allocation concealment (selection bias)								
(C) Blinding of participants and personnel (per	formance	bias)						
(D) Blinding of outcome assessment (detection	n bias)							

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

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

				6			Maan Difference	Many Difference	Diels of Dieg
Study or Subgroup	Moan	SD	Total	Mean	SD	Total	Mean Difference	Mean Difference	RISKOI BIAS
1.6.1 Experimental study: non-RCT	Wear	30	Total	Mean	30	Total	14, Random, 55% Ci	10, Randolli, 33% Ci	ABCDETGHTORE
Okuyama 2005 (intraop transfusion volume, ml)	607	150	32	441	183	84	166.00 [100.94, 231.06]	-+	•????
1.6.2 Observational study: cohort									
Muñoz 2006 (units transfused intra- & postop)	1.12	1.17	0	2.18	0.98	0	Not estimable		• ? ? • •
Risk of bias legend         (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel (perforn 0) Blinding of outcome assessment (detection bias)         (F) Selective reporting (reporting bias)         (G) Other bias         (H) Inappropriate eligibility criteria         (J) Not controlled for confounding	nance b as) ne varia	ias) bles						-200-100 0 100 200 Favours Iron Favours Control	
(K) Incomplete or inadequate follow-up (L) Other limitations									

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



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 6: Forest plot of outcome: 45-day mortality



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

	E	SA		Control			Mean Difference	Mean Difference	Risk of Bias		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFGHIJKL		
2.3.1 Experimental study: RCT											
Weltert 2010 (length of stay after operation)	5.52	0	158	5.89	0	162	Not estimable				
2.3.2 Observational study: cohort											
Bedair 2015 (length of stay)	3	0.4	24	3.3	0.8	56	-0.30 [-0.56, -0.04]		• ? ? • •		
								-1 -0.5 0 0.5 <sup>2</sup> Favours ESA Favours Control	H 1		
Risk of bias legend (A) Random sequence generation (selection (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (pe (D) Blinding of outcome assessment (detecti (E) Incomplete outcome data (attrition bias) (G) Other bias (H) Inappropriate eligibility criteria (I) Inappropriate methods for exposure and o (J) Not controlled for confounding (K) Incomplete or inadequate follow-up (L) Other limitations	bias) erforman on bias) utcome v	ce bi variat	as) Des								

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

	ESA		Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG		
Weltert 2010 (long-term wound infection)	3	158	3	162	43.0%	1.03 [0.21, 5.00]				
Weltert 2010 (pneumonia)	0	158	0	162		Not estimable				
Weltert 2015 (long term wound infection)	4	300	4	300	57.0%	1.00 [0.25, 3.96]				
Total (95% CI)		616		624	100.0%	1.01 [0.36, 2.86]	•			
Total events	7		7							
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.00, df = 1 (P = 0.98); i <sup>2</sup> = 0%										
Test for overall effect: Z = 0.02 (P = 0.98)							Favours ESA Favours Control			
Risk of bias legend										
(A) Random sequence generation (selection	on bias)									
(B) Allocation concealment (selection bias)	)									
(C) Blinding of participants and personnel	(performa	nce bia	as)							
(D) Blinding of outcome assessment (dete	ction bias	)								
(E) Incomplete outcome data (attrition bias	)									
(F) Selective reporting (reporting bias)										
(G) Other bias										

## Figure 9: Forest plot of outcome: Infections

	ESA		Contr	ol	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% Cl	M-H, Random, 95%	CI ABCDEFGHIJKL
2.5.1 Experimental study: RCT							
Weltert 2010 (patients transfused periop)	25	158	60	162	0.43 [0.28, 0.64]	+	
2.5.2 Observational study: cohort							
Bedair 2015 (patients transfused postop)	0	24	23	56	0.05 [0.00, 0.77]	← +	• ? ? • 🖷
						0.01 0.1 1 Favours ESA Favour	10 100 s Control
Risk of bias legend         (A) Random sequence generation (selection (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel ((D) Blinding of outcome assessment (deteret) incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias         (H) Inappropriate eligibility criteria         (J) Not controlled for confounding         (K) Incomplete or inadequate follow-up         (J.) Other limitations	n bias) performar tion bias; outcome	nce bia ) variabl	s) es				

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

	ESA		Control			Mean Difference	Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFGHIJKL
2.6.1 Experimental study: RCT									
Weltert 2010 (units transfused periop)	0.32	0	158	0.76	0	162	Not estimable		
2.6.2 Observational study: cohort									
Bedair 2015 (units transfused postop)	0	0	24	0.41	0.07	56	Not estimable		. ?? ? .
								-100 -50 0 50 10 Favours ESA Favours Control	
Risk of bias legend									
(A) Random sequence generation (sele	ction bia	is)							
(B) Allocation concealment (selection bia	as)								
(C) Blinding of participants and personne	el (perfo	rmar	nce bia:	s)					
(D) Blinding of outcome assessment (de	etection	bias)							
(E) Incomplete outcome data (attrition bia	as)								
(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

	ESA		Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG
Weltert 2010 (DVT)	0	158	1	162	20.7%	0.34 [0.01, 8.33]		
Weltert 2015 (DVT)	2	300	5	300	79.3%	0.40 [0.08, 2.05]		
Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: (A) Random sequence (B) Allocation conceal (C) Blinding of particip (D) Blinding of outcom (E) Incomplete outcom (F) Selective reporting	2 0.00; Chi Z = 1.28 ( iment (sei pants and he assess ne data (a (reportin	458 <sup>2</sup> = 0.0' (P = 0.2) tion (se lection persor sment ( attrition g bias)	6 1, df = 1 ( 20) election b bias) nnel (perf (detection bias)	462 P = 0.9 ias) forman n bias)	79.3% <b>100.0%</b> 3); I <sup>2</sup> = 09 ce bias)	0.39 [0.09, 1.66]	0.01 0.1 10 100 Favours ESA Favours Control	
(u) Other bids								

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

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

	lron + E	Iron + ESA		ol	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Events Total I		Total	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Wurnig 2001 (125U - death after study completion)	0	70	1	60	0.29 [0.01, 6.90]		2 2 🔴 2 🖨 🖶 🖨
Wurnig 2001 (250U - death after study completion)	0	64	1	60	0.31 [0.01, 7.53]		?? 🔴 ? 🖨 🖶 🖨
Yoo 2011 (30-day postoperative death)	0	37	1	37	0.33 [0.01, 7.93]		•••??•••
Stowell 2009 (during study or within 30 days)	1	340	2	340	0.50 [0.05, 5.49]		
Heiss 1996 (postoperative death)	2	17	1	10	1.18 [0.12, 11.39]		????? 🗣 🗣 🛑
Kettelhack 1998 (death due to SAE)	5	52	2	57	2.74 [0.56, 13.52]	- <b></b>	??????
Christodoulakis 2005 (150U- postoperative death)	2	69	0	68	4.93 [0.24, 100.80]		+ ?? 🖨 ? 🖨 🗣 🗣
Scott 2002 (perioperative death)	3	29	0	29	7.00 [0.38, 129.74]		+ ?? 🗣 ? 🗣 🗣 🛑
Christodoulakis 2005 (300U - postoperative death)	3	67	0	68	7.10 [0.37, 134.92]		+ ?? \varTheta ? 🖨 🗣 🗣
							H D
						Favours Iron + ESA Favours Control	

<u>Risk of bias legend</u>

(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)

	Iron + E	SA	Contr	o		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
4.1.1 Malignant disorders								
Heiss 1996 (postoperative death)	2	17	1	10	16.3%	1.18 [0.12, 11.39]	<b>_</b>	????? 🗣 🗣 🛑
Kettelhack 1998 (death due to SAE)	5	52	2	57	32.0%	2.74 [0.56, 13.52]		????? 🗣 🗣 🛑
Christodoulakis 2005 (150U+300U - postop death)	5	136	0	68	10.2%	5.54 [0.31, 98.75]		- ?? \varTheta ? 🕒 🗣
Scott 2002 (perioperative death)	3	29	0	29	10.0%	7.00 [0.38, 129.74]		+ ?? 🗣 ? 🗣 🗣 🛑
Subtotal (95% CI)		234		164	68.5%	2.84 [0.95, 8.56]	-	
Total events	15		3					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.20, df = 3 (P = 0.75)	; I² = 0%							
Test for overall effect: Z = 1.86 (P = 0.06)								
4.1.2 Non-malignant disorders								
Wurnig 2001 (125+250U - death after study complet)	0	134	1	60	8.4%	0.15 [0.01. 3.64]	· · · · · · · · · · · · · · · · · · ·	??
Yoo 2011 (30-day postoperative death)	0	37	1	37	8.5%	0.33 [0.01, 7.93]		
Stowell 2009 (during study or within 30 days)	1	340	2	340	14.7%	0.50 [0.05, 5.49]		
Subtotal (95% CI)		511		437	31.5%	0.33 [0.06, 1.68]		
Total events	1		4					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.35, df = 2 (P = 0.84)	<sup>2</sup> = 0%							
Test for overall effect: Z = 1.34 (P = 0.18)								
Total (95% CI)		745		601	100.0%	1.44 [0.57, 3.65]	•	
Total events	16		7					
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 6.16, df = 6 (P = 0.41)	I <sup>2</sup> = 3%							d d
Test for overall effect: Z = 0.77 (P = 0.44)							U.U1 U.1 1 10 10 Eavoure Irop + ESA Eavoure Control	U
Test for subgroup differences: Chi <sup>2</sup> = 4.62, df = 1 (P = 0.1	03), I² = 7	8.3%					Favours Ion + ESA Favours Control	
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 B: Figure 10 B: Forest plot of outcome: (All-cause) mortality (Subgroup analysis: malignant versus nonmalignat disorders)

	Iron +	ESA	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
4.2.1 Acute kidney injury							_	
Yoo 2011 (postoperative acute kidney injury) Subtotal (95% CI)	9	37 37	19	35 35	100.0% <b>100.0</b> %	0.45 [0.24, 0.85] 0.45 [0.24, 0.85]		••??•••
Total events	9		19					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.44 (P = 0.01)								
4.2.2 Cerebrovascular accident								
Stowell 2009 (CVA)	2	340	0	340	34.1%	5.00 [0.24, 103.76]		$\rightarrow \odot \odot \odot \odot \odot \odot \odot \odot$
Scott 2002 (CVA)	2	29	0	29	35.0%	5.00 [0.25, 99.82]		— ??.?
Wurnig 2001 (125+250U - CVA)	1	134	0	60	30.9%	1.36 [0.06, 32.80]		?? 🗣 ? 🗣 ? 🗣
Subtotal (95% CI)		503		429	100.0%	3.34 [0.57, 19.63]		
Total events	5		0					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.45, df = 3 Test for overall effect: Z = 1.33 (P = 0.18)	2 (P = 0.80)	); I² = 0%	6					
4.2.3 Stroke or transient ischaemic attack								
Stowell 2009 (TIA)	1	340	0	340	47.3%	3.00 [0.12, 73.38]		- •••••••
So-Osman 2014 (stroke or TIA)	2	125	0	138	52.7%	5.52 [0.27, 113.80]		$\rightarrow$
Subtotal (95% CI)		465		478	100.0%	4.14 [0.46, 37.25]		
Total events	3		0					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.07, df = 1	1 (P = 0.79)	); I² = 0%	6					
Test for overall effect: Z = 1.27 (P = 0.21)								
4.2.4 Myocardial ischaemia								
Stowell 2009 (myocardial ischaemia)	1	340	0	340	100.0%	3.00 [0.12, 73.38]		- •••••••
Subtotal (95% CI)		340		340	100.0%	3.00 [0.12, 73.38]		
Total events	1		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
4.2.5 Myocardial infarction								
Stowell 2009 (MI)	1	340	0	340	26.2%	3.00 [0.12, 73.38]		
Scott 2002 (MI)	1	29	0	29	26.8%	3.00 [0.13, 70.74]		- ?? 😔 ? 😔 🖶
So-Osman 2014 (MI)	2	125	1	138	47.0%	2.21 [0.20, 24.05]		
Subtotal (95% CI)		494		507	100.0%	2.60 [0.51, 13.35]		
Total events	4		1					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 2 Test for overall effect: Z = 1.14 (P = 0.25)	2 (P = 0.98)	); I <sup>2</sup> = 0%	6					
							0.01 0.1 1 10 1	100
							Favours Iron + ESA Favours Control	1

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) (E) Selective reporting (reporting hise)

(F) Selective reporting (reporting bias) (G) Other bias

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)

	Iroi	1 + ES.	A	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG
Dousias 2003 (length of postop stay)	7.6	0.5	23	7.8	0.9	27	39.9%	-0.20 [-0.60, 0.20]	-	\varTheta ? 🖶 ? ? 🗣 🛑
Larson 2001 (length of stay)	6.4	2.4	15	8.1	7.1	16	14.5%	-1.70 [-5.38, 1.98]		?? \varTheta ? 🖶 🗣 🗣
Yoo 2011 (length of stay)	11.3	4.1	37	13.5	8	37	19.2%	-2.20 [-5.10, 0.70]		•••??
Kosmadakis 2003 (length of stay)	10	2.78	31	13	5.09	32	26.4%	-3.00 [-5.02, -0.98]		?????
Total (95% CI)			106			112	100.0%	-1.54 [-3.29, 0.21]		
Heterogeneity: Tau <sup>2</sup> = 1.95; Chi <sup>2</sup> = 9.26, df = 3 (P = 0.03); l <sup>2</sup> = 68% Test for overall effect: Z = 1.73 (P = 0.08)									-4 -2 0 2 4 Favours Iron + ESA Favours Control	
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)

	Iron + E	SA	Contr	ol	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Larson 2001 (postoperative infection)	1	15	2	16	0.53 [0.05, 5.29]		?? 🗣 ? 🗣 🗣
Stowell 2009 (urinary tract infection)	22	340	16	340	1.38 [0.74, 2.57]	-++	
Stowell 2009 (wound infection)	4	340	1	340	4.00 [0.45, 35.60]		
						0.01 0.1 1 10 100 Favours Iron + ESA Favours Control	4
Dick of bigg lagend							

<u>Risk of bias legend</u> (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)

	Iron + E	SA	Contr	ol	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Dousias 2003 (patients transfused periop)	0	23	5	27	0.11 [0.01, 1.82]	< <u>+</u> + −	•?•?•
Kosmadakis 2003 (patients transfused postop)	1	31	9	32	0.11 [0.02, 0.85]		?????
Faris 1996 (300U - patients transfused periop)	3	22	21	27	0.18 [0.06, 0.51]		?? \varTheta ? 🛨 🖶 🕒
Weber 2005 (patients transfused periop)	41	460	87	235	0.24 [0.17, 0.34]	+	•••?••
Yoo 2011 (patients with multiple transfus postop)	5	37	20	37	0.25 [0.10, 0.60]	- <b>-</b>	•••??
Feagan 2000 (40000U - patients transfused periop)	5	44	35	78	0.25 [0.11, 0.60]	- <b>-</b>	🛨 ? ? ? 🛨 🖶 🛑
COPES 1993 (Hb 12.5-13.4 - pat transfus periop)	3	18	12	20	0.28 [0.09, 0.83]		•••••
Larson 2001 (patients transfused intraop)	0	15	1	16	0.35 [0.02, 8.08]		?? \varTheta ? 🛨 🛨 🛨
Na 2011 (patients transfused postop)	11	54	29	54	0.38 [0.21, 0.68]	-+	? 🛨 🖨 ? 🛨 🖶 🖨
So-Osman 2014 (patients transfused periop)	13	125	32	138	0.45 [0.25, 0.82]	-+	
Kosmadakis 2003 (patients transfused intraop)	9	31	19	32	0.49 [0.26, 0.91]	-+-	?????
Faris 1996 (100U - patients transfused periop)	9	23	21	27	0.50 [0.29, 0.87]	-+-	?? 🗣 ? 🗣 🗣 🗣
Feagan 2000 (20000U - patients transfused periop)	18	79	35	78	0.51 [0.32, 0.82]	-+-	••••
Wurnig 2001 (125U - patients transfused periop)	19	65	28	51	0.53 [0.34, 0.84]	+	??
COPES 1993 (Hb below 11.5 - pat transfus periop)	2	4	3	3	0.57 [0.22, 1.48]	-++	•••••
Qvist 1999 (patients transfused periop)	13	38	23	43	0.64 [0.38, 1.08]	-+-	?????
COPES 1993 (Hb 11.5-12.4 - pat transfus periop)	5	8	8	8	0.65 [0.38, 1.12]	-+-	•••••
Wurnig 2001 (250U - patients transfused periop)	22	59	28	51	0.68 [0.45, 1.03]	-+-	?? 🗣 ? 🗣 🗣 🗣
Yoo 2011 (patients transfused periop)	22	37	32	37	0.69 [0.51, 0.92]	+	•••??
Christodoulakis 2005 (300U - pat transfus periop)	25	67	36	68	0.70 [0.48, 1.03]	-+-	?? 🗣 ? 🗣 🕈
Christodoulakis 2005 (300U - pat transfus postop)	27	67	36	68	0.76 [0.53, 1.10]	-++	?? 🗣 ? 🗣 🕈
Scott 2002 (patients transfused periop)	19	29	24	29	0.79 [0.58, 1.08]	-+-	?? 🗣 ? 🗣 🗣 🛑
Christodoulakis 2005 (150U - pat transfus postop)	33	69	36	68	0.90 [0.65, 1.26]	+	?? 🗣 ? 🗣 🛨
Christodoulakis 2005 (150U - pat transfus periop)	34	69	36	68	0.93 [0.67, 1.29]	+	?? 🗣 ? 🗣 🛨
Heiss 1996 (patients transfused periop)	9	17	4	10	1.32 [0.55, 3.20]	- <del> </del>	?????
							4 1
						Favours Iron + ESA Favours Control	,

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  $\leq$ 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).

	Iron + ESA		Control			Mean Difference	Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% Cl	ABCDEFG
3.6.1 Among all patients									
Yoo 2011 (units transfused periop)	1	1.1	37	3.3	2.2	37	-2.30 [-3.09, -1.51]		•••??•••
Scott 2002 (units transfused periop)	2.07	2.76	29	3.41	3.04	29	-1.34 [-2.83, 0.15]		??????
Feagan 2000 (40000U - units transfused periop)	0.3	0.7	44	1	1.2	78	-0.70 [-1.04, -0.36]	+	•••••
Na 2011 (units transfused postop)	0.2	0.5	54	0.8	0.8	54	-0.60 [-0.85, -0.35]	+	? • • ? • • •
Feagan 2000 (20000U - units transfused periop)	0.4	0.9	79	1	1.2	78	-0.60 [-0.93, -0.27]	+	•••••
Christodoulakis 2005 (300U- units transfus periop)	0.81	1.22	67	1.34	1.59	68	-0.53 [-1.01, -0.05]	-+	? ? <b>9</b> ? <b>9</b> • •
Christodoulakis 2005 (300U- units tranfus postop)	0.87	1.21	67	1.35	1.58	68	-0.48 [-0.95, -0.01]	-+-	?? 🗣 ? 🗣 🗣
So-Osman 2014 (units transfused)	0.25	0.9	125	0.64	1.6	138	-0.39 [-0.70, -0.08]	+	
Christodoulakis 2005 (150U- units tranfus postop)	1.1	1.42	69	1.35	1.58	68	-0.25 [-0.75, 0.25]	-++	<b>3 3 0 3 0 0 0 0</b>
Christodoulakis 2005 (150U- units transfus periop)	1.19	1.46	69	1.34	1.59	68	-0.15 [-0.66, 0.36]	-+-	?? <b>??????</b>
Qvist 1999 (units transfused periop)	0.3	0	38	1.6	0	43	Not estimable		????? <b>?</b> •••
Heiss 1996 (units transfused periop)	1.82	0.8	17	1.8	0.97	10	0.02 [-0.69, 0.73]		?????
3.6.2 In transfused patients									
Yoo 2011 (units transfus in transfused patients)	1.6	0.9	22	3.7	2.1	32	-2.10 [-2.92, -1.28]	<del></del>	••??•••
Scott 2002 (units transf in transfused patients)	3.16	2.87	19	4.12	2.86	24	-0.96 [-2.68, 0.76]		??
Feagan 2000 (20000U- units transf in transf pat)	1.8	0.8	18	2.1	0.8	35	-0.30 [-0.75, 0.15]	-++	• ? ? ? • • •
Feagan 2000 (40000∪ - units transf in transf pat)	2.2	0.4	5	2.1	0.8	35	0.10 [-0.34, 0.54]	+	•???••
								-4 -2 0 2 4 Favours Iron + ESA Favours Control	H t

<u>Risk of bias legend</u>

(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.

	lron + I	SA	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
4.7.1 Arterial thrombosis								
Kettelhack 1998 (arterial thrombosis) Subtotal (95% CI)	1	48 48	0	54 54	100.0% <b>100.0</b> %	3.37 [0.14, 80.76] 3.37 [0.14, 80.76]		?????
Total events	1		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.75 (P = 0.45)								
4.7.2 Deep venous thrombosis								
Scott 2002 (DVT)	0	29	0	29		Not estimable		22020
So-Osman 2014 (DVT)	0	125	0	138		Not estimable		
Feagan 2000 (20000U+40000U - DVT)	7	123	5	78	30.8%	0.89 [0.29, 2.70]		📵 ? ? ? 🗣 🖶 🛑
Kosmadakis 2003 (DVT)	2	31	1	32	6.9%	2.06 [0.20, 21.63]		<b>? ? ? ? • • •</b>
Stowell 2009 (DVT)	16	340	7	340	49.7%	2.29 [0.95, 5.49]	<b>⊢</b> ∎−-	
Heiss 1996 (DVT)	2	20	0	10	4.4%	2.62 [0.14, 49.91]		??????
Qvist 1999 (DVT)	1	38	0	43	3.8%	3.38 [0.14, 80.70]		· ? ? ? ? • • •
Wurnig 2001 (125+250U - DVT)	4	134	0	60	4.5%	4.07 [0.22, 74.36]		?? 🗣 ? 🗣 🗣
Subtotal (95% CI)		840		730	100.0%	1.78 [0.96, 3.29]	◆	
Total events	32		13					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.39, d	f= 5 (P =	0.79); P	²=0%					
Test for overall effect: Z = 1.83 (P = 0.07)								
4.7.3 Pulmonary embolism								
So-Ocman 2014 (PE)	0	125	0	120		Not actimable		
Stowell 2009 (PE)	0	340	3	340	36.7%	0.14/0.01/2.761	<	
Fearan 2000 (2000011+4000011- PE)	ň	123	1	78	31.6%	0.21 [0.01, 5.15]	<	
Wurnig 2001 (125+250U - PE)	1	134	'n	60	31.7%	1 36 0 06 32 80	<b>_</b>	220200
Subtotal (95% CI)		722	Ŭ	616	100.0%	0.33 [0.05, 1.98]		
Total events	1		4					
Heterogeneity: Tau <sup>2</sup> = 0.00: Chi <sup>2</sup> = 1.15. d	f=2(P=	0.56): P	= 0%					
Test for overall effect: Z = 1.21 (P = 0.23)								
,								
								-
							Eavours Iron + ESA Eavours Control	J
							ravours ion - EoA - ravours control	
Risk of bias legend								

 Hisk of bias leagend

 (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 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,	Lack of	Lack of	Incomplete	Selective	Other limitations
Year	allocation	blinding	accounting of	outcome	
	concealment		outcome events	reporting	
COMPARIS	50N 1:				
TRANSFUS	ION VS NO TREAT	MENT/PLACEBO	STANDARD OF CA	RE	
Karkouti,	Randomization:	Participants:	No	No	Yes, multiple
2012	No, a restricted	Yes			comparisons were
	stratified	Personnel: Yes			conducted without
	randomization	Outcome			adjusting the
	scheme was	assessors: Yes			significance
	used for patient				threshold, which
	allocation.				increases
	Stratification				the potential for a
	was by baseline				type I error.
	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				
	woro computor				
	deperated and				
	maintained in				
	sequentially				
	numbered				
	opaque, sealed				
	envelopes.				
	Allocation				
	concealment:				
	unclear, no				
	information				
	provided.				
COMPARIS	50N 2:				
IRON SUP	PLEMENTATION VS	S NO TREATMEN	T/PLACEBO/STAND	ARD OF CAF	RE
Edwards,	Randomization:	Participants:	No. After	No	Only 9 anaemic
2009	no,	no,	randomization, 2		patients were
	randomization	participants	patients (one		included in the
	sequence was	were blinded	from each group)		subgroup analysis,
	computer-	by using an	were found to be		instead of the 10
	generated. To	opaque sheath	unsuitable for		required by the
	ensure equal	to cover the	surgery and were		power calculation
	numbers of	druggiving			

	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
	SON 3: TREATMENT/DLA				
Weltert,	Randomization:	Participants:	No. Two patients	No	No information on
2010	no, a custom simple application running in Windows XP was used to obtain randomization tables.	yes, the patients knew whether EPO was being administered or not. Personnel: yes, the nurses	in the EPO group and 1 patient in the control group were converted to on- pump revascularization. These patients were considered		protocol registration for this trial Power analysis indicated that 160 patients per group should have been included; the investigators
	Allocation concealment:	and ward physician knew	as intention-to-		however included

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

COMPARISON 4: IRON SUPPLEMENTATION + ESA VS NO TREATMENT/PLACBO/STANDARD OF CARE									
COPES, 1993	Randomization: no, randomization was computer	Participants: unclear, the study is called a double-blind	No	No	No information on protocol registration for this trial				
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	Νο	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				
		treating the patient reviewed the preoperative Hb levels to ensure that they had not risen too quickly. Outcome							
		assessors:		<u> </u>					

		unclear, the study is called a double-blind study, but no information is provided on the blinding process			
Christodoula kis, 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.	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).	Νο	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			
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	blinding process 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 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			
		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 is called a double-blind study, but no information is provided on the	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	blinding process 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 woro blindod			
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 adiudication	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	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/exclusi on 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 anaesthesiologis t 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.	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.
		assessors: unclear, no information provided			
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'		No correction for multiple testing
	the patients' groups until the end of the study		
	Outcome assessors: unclear, no information provided		

observation		-	••	_	
Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations
COMPARIS	ON 2:	•			
IRON SUPP	LEMENTATION VS	NO TREATMENT	/PLACEBO/STAN	DARD 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	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
COMPARIS ESA VS NO	ON 3: TREATMENT/PLAC	EBO/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.

# **Observational studies**

## Certainty of the body of evidence: see GRADE evidence tables

Conclusion	See Evidence-to-Decision template
	See overview of included studies
Reference(s)	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.
Faidenes wood fam	Medicine 2016, 95(27):e4122
Evidence used for	
Project	PBM consensus meeting
Reviewer(s)	Jorien Laermans and Hans Van Remoortel