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ICC-PBM 2018: PRESENTATIONS PICO QUESTIONS PREOPERATIVE ANAEMIA

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QR-code for the presentation

Pre-Operative Anemia: Adverse Outcomes & Diagnosis

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Conflict of Interest

- Founder and CEO, Patient Readiness Institute
- Patent (US, 13/576,874) Methods and devices for reducing transfusion during or after surgery and for improving quality of life and function in chronic disease
- Speaking engagements – American Regent and Medtronic Corporations
- Market Research American Regent

“Typical” introduction to Pre-Operative Anemia papers……Why studying this area is relevant.

Anemia is common in patients presenting for elective surgery and is predictive of poor post-operative outcomes after surgery as well as increased resource utilization. Previously undiagnosed anemia has been reported to occur in 5% to 75% of elective presurgical patients, depending on the patient population.[1] In addition to being an independent risk factor for perioperative morbidity and mortality,[2,3] preoperative anemia is one of the strongest predictors of perioperative blood transfusion.[4,5] Perioperative blood transfusion in turn is independently associated with an increased risk of perioperative morbidity, including lung injury, renal failure, hemolysis, and transfusion reaction, as well as mortality.[6,7] Besides its direct contribution to wors-

HOW DO I . . . ?

How do we develop and implement a preoperative anemia clinic designed to improve perioperative outcomes and reduce cost?

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TRANSFUSION 2016;56;297–303

PICO Question 1 – Adverse Events (Outcomes)

In preoperative elective surgery patients **(population)**, is anaemia **(intervention/risk factor)** a risk factor for adverse events **(outcomes)** compared to no preoperative anaemia **(comparison)**?

Population:

- ***Included:*** Preoperative elective surgery adult patients.
- ***Excluded:*** Non-elective surgeries (burns, obstetrics, trauma, transplant surgery)

Intervention/risk factor: Preoperative anaemia.

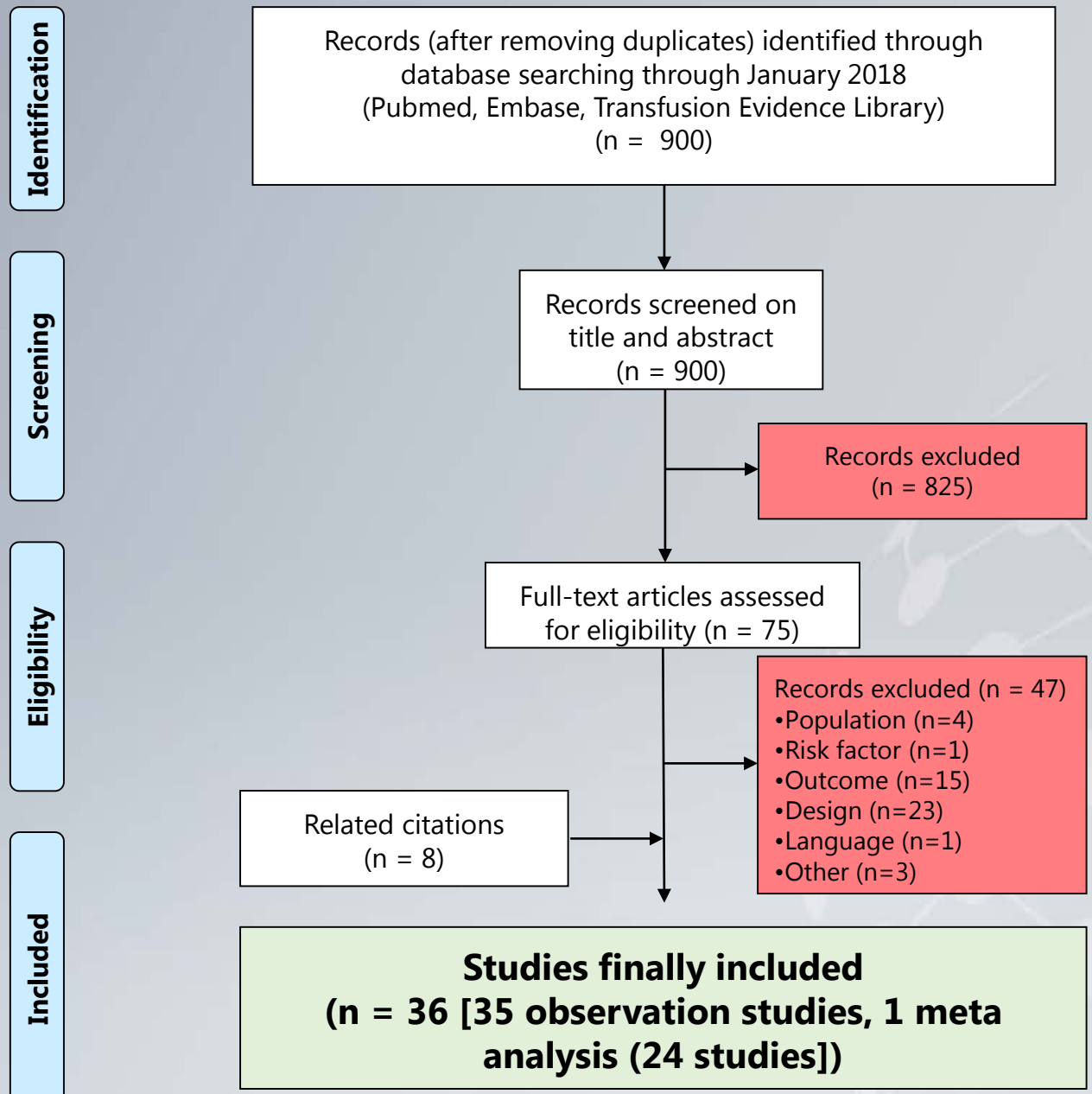
- WHO definition of anaemia (Females: Hb <12 g/dL, Males: Hb <13 g/dL) and studies that used alternative haemoglobin or haematocrit definitions.

Comparison: No preoperative anaemia

Critical outcomes:

- 30-day Mortality
- In-Hospital Mortality
- Acute Myocardial Infarction
- Acute Ischaemic Stroke
- Acute Kidney Injury

Adverse Events – Study Selection Flow Chart



Selection Criteria:

1. Preoperative
2. Anaemia
3. 1 and 2
4. Elective surgical procedures
5. 3 and 4

Inclusion:

- Preoperative elective surgery adult pts
  - Malignant
  - Non-Malignant

Exclusion:

- Burn, obstetric, trauma, transplant

Study Characteristics (Observational) – Part 1

Author, year, country	Study design	Setting	Definition preoperative anaemia
Alan, 2014, USA	National or international database retrospective review	Neurosurgery	HTC <38%
Beatie, 2009, Canada	Cohort study (retrospective)	Non-cardiac surgery	WHO definition
Blaudszun, 2018, UK	Cohort study (retrospective)	Cardiac surgery	WHO definition (females)
Bydon, 2014, USA	National or international database retrospective review	Neurosurgery	HTC <39% (males) or <36% (females)
Carrascal 2010, Spain	Cohort study	Cardiac surgery	WHO definition
Chamieh 2016, Lebanon	National or international database retrospective review	Orthopaedic surgery	WHO definition
Cladellas, 2006, Spain	Cohort study	Cardiac surgery	Hb <12 g/dL (all adults)
Dai, 2018, USA	Cohort study (retrospective)	Cardiac surgery	WHO definition
Elmistekawy, 2013, Canada	Cohort study (retrospective)	Cardiac surgery	WHO definition
Gabriel, 2017, USA	National or international database retrospective review	Non-cardiac surgery	HTC <39% (males) or <36% (females)
Greenky, 2012, USA	Cohort study (retrospective)	Orthopaedic surgery	WHO definition
Gupta, 2013, USA	National or international database retrospective review	Vascular surgery	HTC <39%
Hung, 2011, UK	Cohort study (prospective)	Cardiac surgery	WHO definition
Joshi, 2015, India	Cohort study (retrospective)	Cardiac surgery	WHO definition
Kim, 2014, USA	National or international database retrospective review	Spinal surgery	HTC <39% (males) or <36% (females)
Matsuda, 2013, Japan	Cohort study (retrospective)	Cardiac surgery	Hb <12g/dl (males) or <11g/dl (females)
Melis, 2009, USA	Cohort study (retrospective)	Gastrointestinal surgery	WHO definition
Miceli, 2014, UK	Cohort study (retrospective)	Cardiac surgery	WHO definition

Study Characteristics (Observational) – Part 2

Author, year, country	Study design	Setting	Definition preoperative anaemia
Mirhosseini, 2012, Iran	Cohort study (retrospective)	Cardiac surgery	Hb 7-10g/dl
Muñoz, 2010, Spain	Cohort study (retrospective)	Cardiac surgery	WHO definition
Musallam, 2011, Lebanon	National or international database retrospective reviews	Non-cardiac surgery	HTC <39% (males) or <36% (females)
Nuis, 2013, The Netherlands	Cohort study (prospective)	Cardiac surgery	WHO definition
Oshin, 2013, UK	Cohort study (retrospective)	Vascular surgery	Hb <14g/dl (males) or <12g/dl (females)
Padmanabhan, 2016, UK	Cohort study (retrospective)	Cardiac surgery	WHO definition
Phan, 2017, Australia	National or international database retrospective reviews	Spinal surgery	HTC <39% (males) or <36% (females)
Phan (2), 2017, Australia	National or international database retrospective reviews	Spinal surgery	HTC <39% (males) or <36% (females)
Saager, 2013, USA	National or international database retrospective reviews	Non-cardiac surgery	HTC <39% (males) or <36% (females)
Seicean, 2013, USA	National or international database retrospective reviews	Spinal surgery	HTC <38%
Shirzad, 2010, Iran	Cohort study (retrospective)	Cardiac surgery	Hb ≤12g/dl
Tee, 2015, USA	National or international database retrospective reviews	Gastrointestinal surgery	HTC 25-35%
Tohme, 2016, USA	National or international database retrospective reviews	Gastrointestinal surgery	HTC <39% (males) or <36% (females)
Van Mieghem, 2011, The Netherlands	Cohort study (prospective)	Cardiac surgery	WHO definition
Velescu, 2016, Spain	Cohort study (retrospective)	Vascular surgery	WHO definition
Wu, 2007, USA	National or international database retrospective reviews	Non-cardiac surgery	HTC <39%
Zhang, 2013, Canada	Cohort study (retrospective)	Cardiac surgery	WHO definition

Study Characteristics - Summary

- **Country – 35 Observational and 1 Meta Analysis:**
  - USA/Canada: 16 studies
  - Europe: 12 studies
  - Middle East: 4 studies
  - Asia: 2 studies
  - Australia: 2 studies
- **Setting Observational Studies – 35 Studies:**
  - Cardiac surgery: 16 studies (4 CABG, 2 valve only, 2 TAVR, 7 mixed open procedures (non-TAVR)
  - Non-cardiac surgery (more than 1 surgery type): 5 studies (1 single institution, 4 NSQIP, 1 VA-SQIP)
  - Neurosurgery (cranial): 2 studies
  - Spinal surgery: 4 studies (Cervical fusion -2, LSF 1 level -1, varied procedures -1)
  - Vascular surgery: 3 studies (1 varied sites-aortic and peripheral, 2 peripheral)
  - Orthopaedic surgery (joint replacement): 2 studies
  - GI: 3 studies (1 esophagectomy, 2 hepatectomy)

Study Characteristics - Summary

- **Study design (Observational Studies, 35 studies)**
  - 21 cohort studies (prospective/retrospective)
  - 14 national or international database retrospective reviews

- **Study design (Meta Analysis – 1 total, includes 24 studies)**
  - 14 Studies included within Observational group
  - 10 studies not included in Observational group.
    - 3 didn't meet elective criteria (3 orthopedic hip fracture surgeries)
    - 3 excluded for other reasons (not elective, other) - 2 cardiac and 1 GI surgery
    - 4 studies mix of elective and non-elective/urgent surgeries with no inclusion of a subgroup analysis on elective surgery patients only

Study Characteristics - Summary

- **Definition Preoperative Anaemia (Observational Studies, n=35)**
  - WHO definition – Hb <13 g/dL (males) or <12 g/dL (females): 17 studies
  - Equivalent to WHO definition – HTC <39% (males) or <36% (females): 8 studies
  - HTC <38%: 2 studies
  - HTC <39%: 2 studies
  - Hb <12 g/dL: 2 studies
  - Hb <12 g/dL(males) or <11 g/dL(females): 1 study
  - Hb 7-10 g/dL: 1 study
  - Hb <14 g/dL (males) or <12 g/dL (females): 1 study
  - HTC 25-35%: 1 study

Outcomes Determined as CRITICAL :
-Critical as determined by PICO 3 (anemia treatment)
-Outcome by # of Studies

- Hospital Mortality: 8 studies
- 30-day Mortality: 25 studies
  - 22 anemic versus non-anemic
  - 3 subgrouped by severity of anemia
- Acute Myocardial Injury: 11 Studies
- Acute Ischemic Stroke: 14 studies
- Acute Kidney Injury: 12 studies

1. How substantial are the desirable anticipated effects?

How large are the desirable effects of the intervention taking into account the importance of the outcomes (how much they are valued) and the size of the effect (the likelihood of experiencing a benefit or how much of an improvement individuals would be likely to experience)?

- Trivial
- Small
- Moderate
- Large

- Varies
- Don't know

2. How substantial are the undesirable anticipated effects?

How large are the undesirable effects of the intervention taking into account the importance of the outcomes (how much they are valued), and the size of the effect (the likelihood of experiencing a benefit or how much of an improvement individuals would be likely to experience)?

- Large
- Moderate
- Small
- Trivial

- Varies
- Don't know

3. Does the balance between desirable and undesirable effects favor the intervention or the comparison?

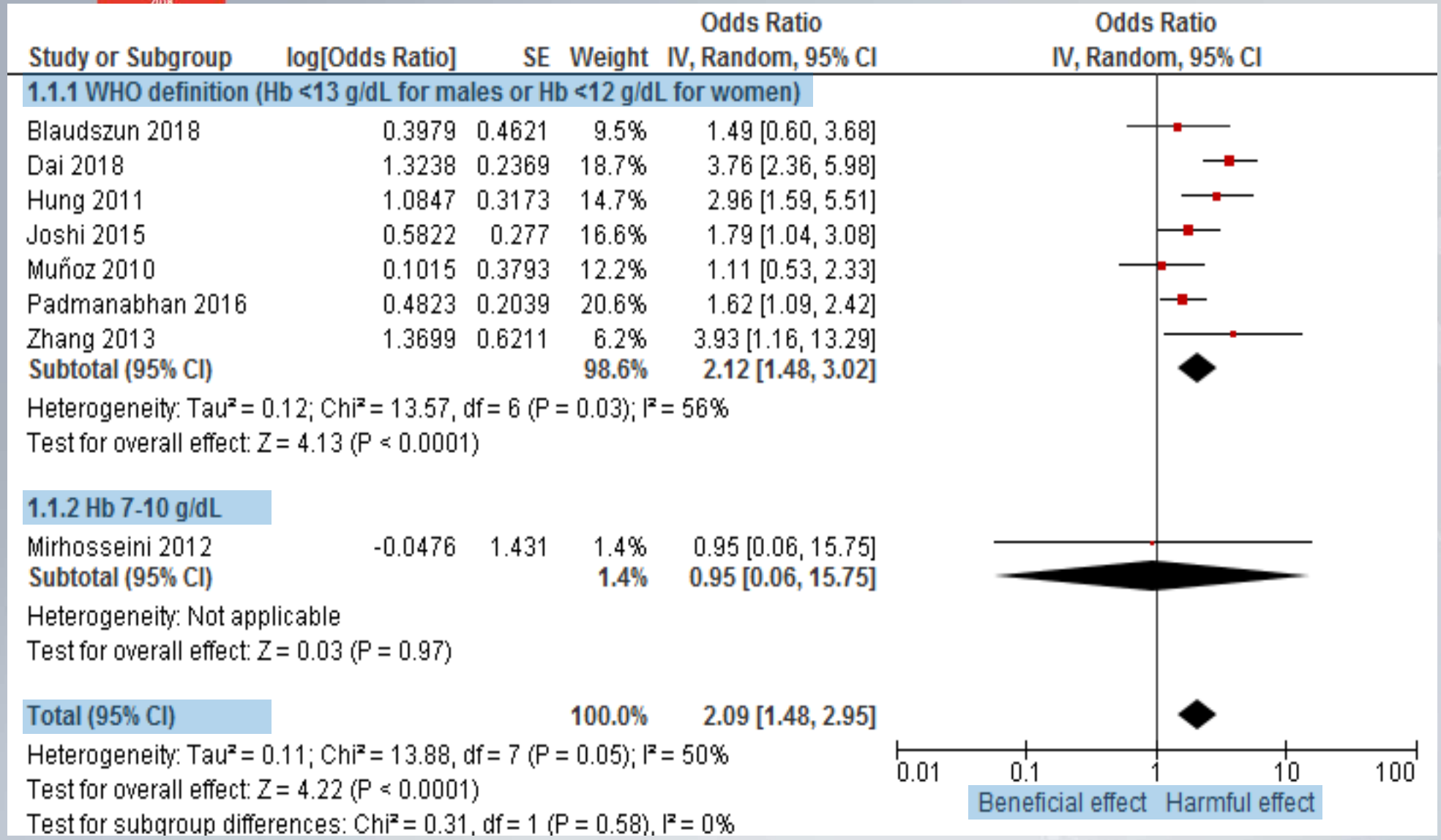
What is the balance between the desirable and undesirable effects, taking into account how much individuals value the main outcomes, how substantial the desirable and undesirable effect are, and the certainty of those estimates?

- Favors the comparison
- Probably favors the comparison
- Does not favor either the intervention or the comparison
- Probably favors the intervention
- Favors the intervention

- Varies
- Don’t know

Link Preoperative Anaemia – Adverse Events

CRITICAL OUTCOME: Hospital Mortality



Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 WHO definition (Hb <13 g/dL for males or Hb <12 g/dL for women)				
Blaudszun 2018	0.3979	0.4621	9.5%	1.49 [0.60, 3.68]
Dai 2018	1.3238	0.2369	18.7%	3.76 [2.36, 5.98]
Hung 2011	1.0847	0.3173	14.7%	2.96 [1.59, 5.51]
Joshi 2015	0.5822	0.277	16.6%	1.79 [1.04, 3.08]
Muñoz 2010	0.1015	0.3793	12.2%	1.11 [0.53, 2.33]
Padmanabhan 2016	0.4823	0.2039	20.6%	1.62 [1.09, 2.42]
Zhang 2013	1.3699	0.6211	6.2%	3.93 [1.16, 13.29]
Subtotal (95% CI)			**98.6%**	**2.12 [1.48, 3.02]**
Heterogeneity: Tau² = 0.12; Chi² = 13.57, df = 6 (P = 0.03); I² = 56%				
Test for overall effect: Z = 4.13 (P < 0.0001)				
1.1.2 Hb 7-10 g/dL				
Mirhosseini 2012	-0.0476	1.431	1.4%	0.95 [0.06, 15.75]
Subtotal (95% CI)			**1.4%**	**0.95 [0.06, 15.75]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.03 (P = 0.97)				
Total (95% CI)			**100.0%**	**2.09 [1.48, 2.95]**
Heterogeneity: Tau² = 0.11; Chi² = 13.88, df = 7 (P = 0.05); I² = 50%				
Test for overall effect: Z = 4.22 (P < 0.0001)				
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%				

Summary:

8 CV Studies

3 are not statistically significant.

Overview Evidence Table GRADE Software

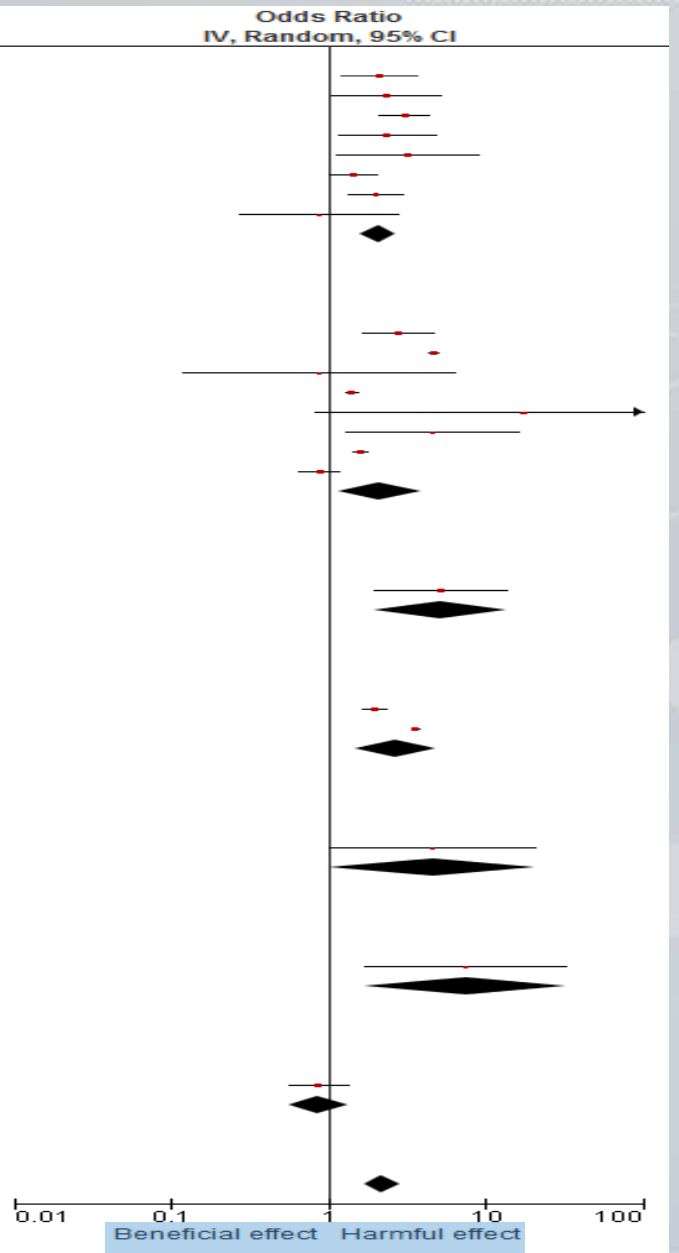
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative anaemia as a risk factor for adverse events	no preoperative anaemia	Relative (95% CI)	Absolute (95% CI)		
Hospital Mortality												
8	observational studies	not serious	not serious	not serious	not serious	none			OR 2.09 (1.48 to 2.95)	**-- per 1.000 (from -- to --) ****	⨁⨁◯◯ LOW	CRITICAL

**** Absolute effect size could not be calculated because no information on the number of events/patients was available for all studies.**

Link Preoperative Anaemia – Adverse Events

CRITICAL OUTCOME: 30-day Mortality

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 WHO definition (Hb <13 g/dL for males and Hb <12 g/dL for women)				
Beatie 2009	0.7546	0.2804	5.2%	2.13 [1.23, 3.68]
Carrascal 2010	0.8492	0.4003	4.2%	2.34 [1.07, 5.12]
Elmistekawy 2013	1.1184	0.189	5.8%	3.06 [2.11, 4.43]
Greenky 2012	0.8511	0.3624	4.5%	2.34 [1.15, 4.77]
Melis 2009	1.172	0.5307	3.3%	3.23 [1.14, 9.14]
Miceli 2014	0.3646	0.1759	5.9%	1.44 [1.02, 2.03]
Nuis 2013	0.6999	0.2031	5.8%	2.01 [1.35, 3.00]
Van Mieghem 2011	-0.1351	0.5896	3.0%	0.87 [0.28, 2.77]
Subtotal (95% CI)			**37.7%**	**2.08 [1.62, 2.69]**
Heterogeneity: Tau² = 0.05; Chi² = 11.61, df = 7 (P = 0.11); I² = 40%				
Test for overall effect: Z = 5.65 (P < 0.00001)				
1.2.2 HTC <39% (males) or <36% (females)				
Bydon 2014	1.0188	0.2643	5.3%	2.77 [1.65, 4.65]
Gabriel 2017	1.549	0.0313	6.6%	4.71 [4.43, 5.00]
Kim 2014	-0.1278	1.0166	1.4%	0.88 [0.12, 6.45]
Musallam 2011	0.3507	0.0411	6.5%	1.42 [1.31, 1.54]
Phan (2) 2017	2.867	1.5532	0.7%	17.58 [0.84, 369.15]
Phan 2017	1.5307	0.6475	2.7%	4.62 [1.30, 16.44]
Saager 2013	0.4637	0.0577	6.5%	1.59 [1.42, 1.78]
Tohme 2016	-0.1278	0.1468	6.1%	0.88 [0.66, 1.17]
Subtotal (95% CI)			**35.8%**	**2.13 [1.17, 3.91]**
Heterogeneity: Tau² = 0.57; Chi² = 705.33, df = 7 (P < 0.00001); I² = 99%				
Test for overall effect: Z = 2.46 (P = 0.01)				
1.2.3 Hb <12 g/dL (all)				
Cladellas 2006	1.6503	0.499	3.5%	5.21 [1.96, 13.85]
Subtotal (95% CI)			**3.5%**	**5.21 [1.96, 13.85]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.31 (P = 0.0009)				
1.2.4 HTC <39%				
Gupta 2013	0.6746	0.0877	6.4%	1.96 [1.65, 2.33]
Wu 2007	1.2857	0.0207	6.6%	3.62 [3.47, 3.77]
Subtotal (95% CI)			**13.0%**	**2.68 [1.47, 4.88]**
Heterogeneity: Tau² = 0.18; Chi² = 45.99, df = 1 (P < 0.00001); I² = 98%				
Test for overall effect: Z = 3.23 (P = 0.001)				
1.2.5 Hb <12 g/dL (males) or <11 g/dL (females)				
Matsuda 2013	1.5301	0.7671	2.2%	4.62 [1.03, 20.77]
Subtotal (95% CI)			**2.2%**	**4.62 [1.03, 20.77]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.99 (P = 0.05)				
1.2.6 Hb <14 g/dL (males) or <12 g/dL (females)				
Oshin 2013	2.0092	0.7578	2.2%	7.46 [1.69, 32.93]
Subtotal (95% CI)			**2.2%**	**7.46 [1.69, 32.93]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.65 (P = 0.008)				
1.2.7 HTC 25-35%				
Tee 2015	-0.1393	0.2157	5.7%	0.87 [0.57, 1.33]
Subtotal (95% CI)			**5.7%**	**0.87 [0.57, 1.33]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.65 (P = 0.52)				
Total (95% CI)			**100.0%**	**2.20 [1.68, 2.88]**
Heterogeneity: Tau² = 0.29; Chi² = 899.83, df = 21 (P < 0.00001); I² = 98%				
Test for overall effect: Z = 5.76 (P < 0.00001)				
Test for subgroup differences: Chi² = 23.70, df = 6 (P = 0.0006), I² = 74.7%				



Strong association related to a life-saving outcome:

Upgrade certainty of the evidence (**GRADE +1**)

Summary:

22 Studies include:

- CV = 7
- Non-CV = 15
  - 5 multi site
  - 10 single site

5 are not statistically significant:

- 2 spinal
- 2 hepatectomy
- 1 CV

Overview Evidence Table GRADE Software

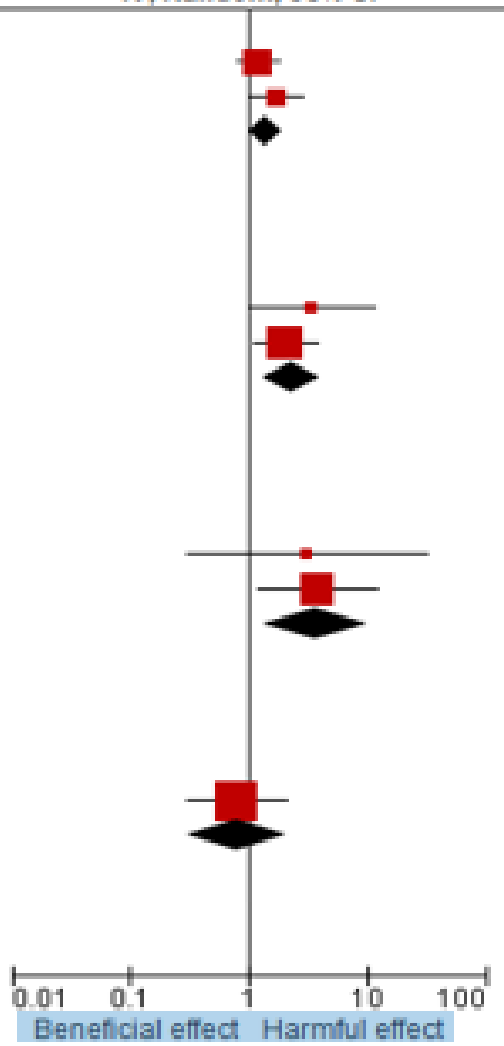
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative anaemia as a risk factor for adverse events	no preoperative anaemia	Relative (95% CI)	Absolute (95% CI)		
30-day Mortality												
22	observational studies	not serious	not serious	not serious	not serious	strong association			OR 2.20 (1.68 to 2.88)	**-- per 1.000 (from -- to --) ****	⨁⨁⨁◯ MODERATE	CRITICAL

**** Absolute effect size could not be calculated because no information on the number of events/patients was available for all studies.**

Link Preoperative Anaemia – Adverse Events

CRITICAL OUTCOME: 30-day Mortality – Severity of Anaemia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.3.1 Mild anaemia (HTC 30-37/38%)				
Alan 2014 (mild anaemia)	0.1823	0.2069	62.6%	1.20 [0.80, 1.80]
Seicean 2013 (mild anaemia)	0.5306	0.2707	37.4%	1.70 [1.00, 2.89]
Subtotal (95% CI)			**100.0%**	**1.37 [0.98, 1.90]**
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.31); I² = 4%				
Test for overall effect: Z = 1.86 (P = 0.06)				
1.3.2 Moderate anaemia (Hb 10-12 g/dL)				
Seicean 2013 (moderate anaemia)	1.2238	0.6244	20.6%	3.40 [1.00, 11.56]
Shirzad 2010 (moderate anaemia)	0.7178	0.3176	79.4%	2.05 [1.10, 3.82]
Subtotal (95% CI)			**100.0%**	**2.27 [1.31, 3.96]**
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%				
Test for overall effect: Z = 2.90 (P = 0.004)				
1.3.3 Severe anaemia (HTC ≤25% or Hb <10 g/dL)				
Seicean (2013) (severe anaemia)	1.1314	1.1915	19.5%	3.10 [0.30, 32.03]
Shirzad 2010 (severe anaemia)	1.3324	0.5868	80.5%	3.79 [1.20, 11.97]
Subtotal (95% CI)			**100.0%**	**3.64 [1.30, 10.23]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%				
Test for overall effect: Z = 2.46 (P = 0.01)				
1.3.4 Moderate-severe anaemia (HTC <30% or HTC 26-29%)				
Alan 2014 (moderate-severe anaemia)	-0.2231	0.5004	100.0%	0.80 [0.30, 2.13]
Subtotal (95% CI)			**100.0%**	**0.80 [0.30, 2.13]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.45 (P = 0.66)				



Summary:

3 Studies include:

- CV = 1
- Neurosurgery = 1
- Spinal = 1

2 are not statistically significant:

- 1 neurosurgery
- 1 spinal

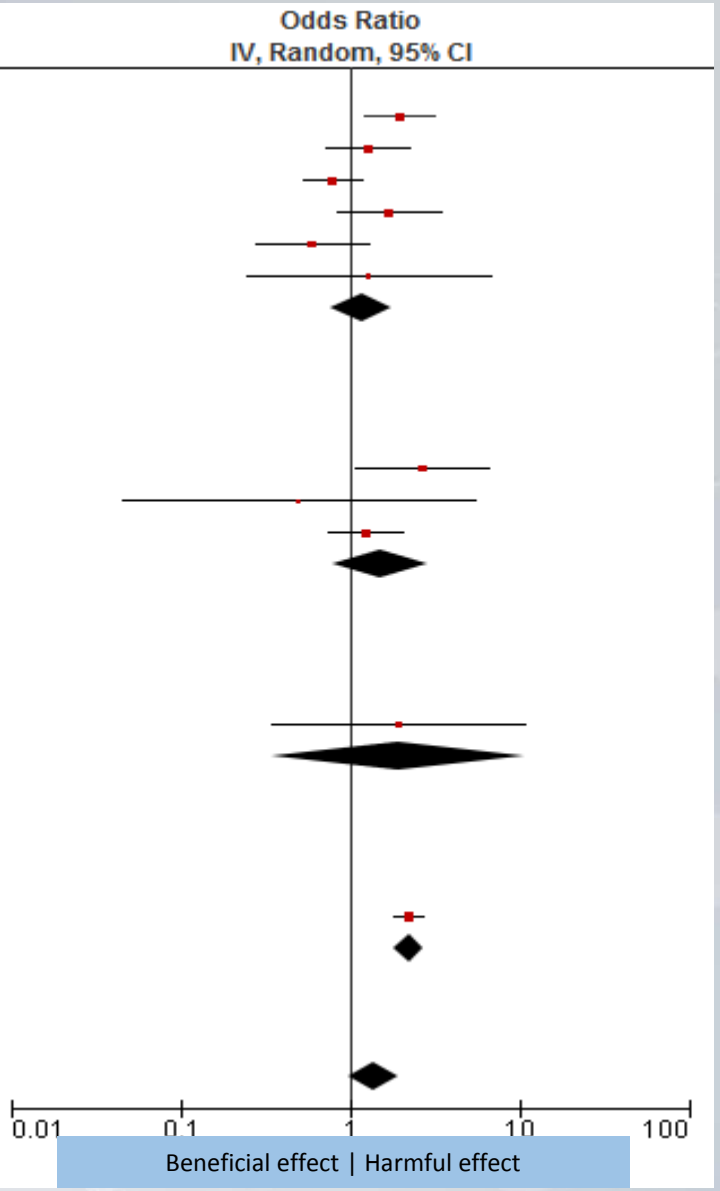
Overview Evidence Table GRADE Software

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative anaemia as a risk factor for adverse events	no preoperative anaemia	Relative (95% CI)	Absolute (95% CI)		
30-day Mortality – Severity of Anaemia												
3	observational studies	not serious	not serious	not serious	not serious	none					⨁⨁◯◯ LOW	CRITICAL

Link Preoperative Anaemia – Adverse Events

CRITICAL OUTCOME: Acute Myocardial Infarction

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.4.1 WHO definition (Hb <13 g/dL for males and Hb <12 g/dL for women)				
Chamieh 2016	0.6729	0.2461	12.5%	1.96 [1.21, 3.17]
Elmistekawy 2013	0.2502	0.2864	11.5%	1.28 [0.73, 2.25]
Miceli 2014	-0.2357	0.2037	13.5%	0.79 [0.53, 1.18]
Muñoz 2010	0.5266	0.3596	9.7%	1.69 [0.84, 3.43]
Nuis 2013	-0.5189	0.3904	9.1%	0.60 [0.28, 1.28]
Zhang 2013	0.2577	0.8408	3.4%	1.29 [0.25, 6.72]
Subtotal (95% CI)			**59.7%**	**1.17 [0.78, 1.75]**
Heterogeneity: Tau² = 0.14; Chi² = 12.26, df = 5 (P = 0.03); I² = 59%				
Test for overall effect: Z = 0.76 (P = 0.45)				
1.4.2 HTC <39% (males) or <36% (females)				
Bydon 2014	0.9887	0.4655	7.6%	2.69 [1.08, 6.69]
Kim 2014	-0.6952	1.2264	1.8%	0.50 [0.05, 5.52]
Tohme 2016	0.2161	0.2648	12.0%	1.24 [0.74, 2.09]
Subtotal (95% CI)			**21.4%**	**1.51 [0.79, 2.86]**
Heterogeneity: Tau² = 0.11; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%				
Test for overall effect: Z = 1.26 (P = 0.21)				
1.4.3 Hb <12 g/dL (all)				
Cladellas 2006	0.6614	0.884	3.2%	1.94 [0.34, 10.96]
Subtotal (95% CI)			**3.2%**	**1.94 [0.34, 10.96]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.75 (P = 0.45)				
1.4.4 HTC <39%				
Gupta 2013	0.8066	0.1006	15.7%	2.24 [1.84, 2.73]
Subtotal (95% CI)			**15.7%**	**2.24 [1.84, 2.73]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 8.02 (P < 0.00001)				
Total (95% CI)			**100.0%**	**1.39 [0.99, 1.96]**
Heterogeneity: Tau² = 0.18; Chi² = 33.67, df = 10 (P = 0.0002); I² = 70%				
Test for overall effect: Z = 1.89 (P = 0.06)				
Test for subgroup differences: Chi² = 8.63, df = 3 (P = 0.03), I² = 65.2%				



Inconsistency:

Downgrade certainty of the evidence (**GRADE -1**)

I^2>50%

Chi^2 test statistical significant

Difference in point estimates

No optimal overlap in 95% CIs

Summary:

11 Studies include:

- CV = 6
- Non-CV = 5
  - All single site

8 are not statistically significant:

- 6 CV
- 1 Spinal
- 1 GI

Overview Evidence Table GRADE Software

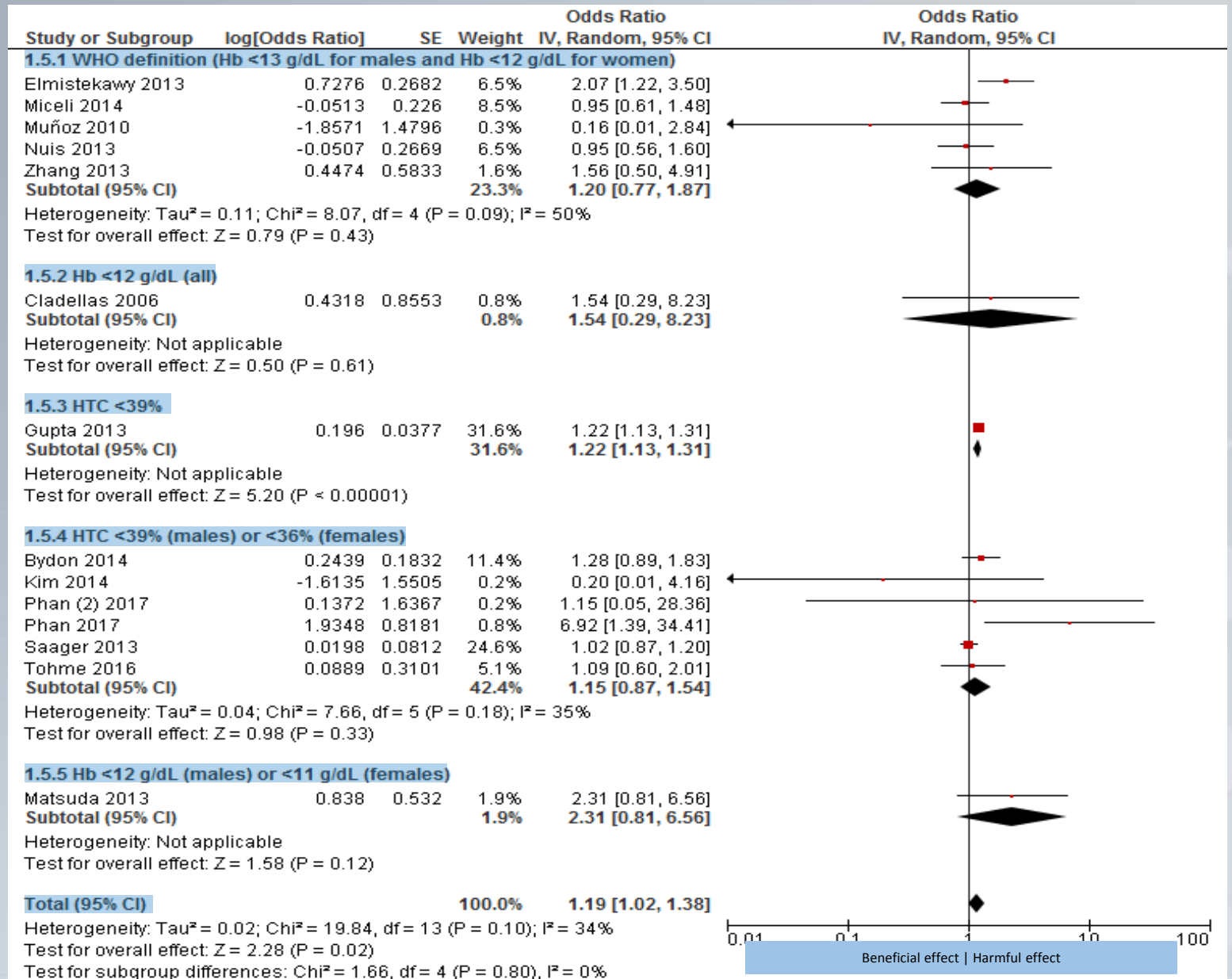
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative anaemia as a risk factor for adverse events	no preoperative anaemia	Relative (95% CI)	Absolute (95% CI)		
Acute Myocardial Infarction												
11	observational studies	not serious	**serious ****	not serious	not serious	none			OR 1.39 (0.99-1.96)	**-- per 1.000 (from -- to --) ****	⨁◯◯◯ VERY LOW	CRITICAL

**** Absolute effect size could not be calculated because no information on the number of events/patients was available for all studies.**

**** I^2>50%, Chi^2 test statistical significant, difference in point estimates, no optimal overlap in 95% CIs.**

Link Preoperative Anaemia – Adverse Events

CRITICAL OUTCOME: Acute Ischaemic Stroke



Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.5.1 WHO definition (Hb <13 g/dL for males and Hb <12 g/dL for women)				
Elmistekawy 2013	0.7276	0.2682	6.5%	2.07 [1.22, 3.50]
Miceli 2014	-0.0513	0.226	8.5%	0.95 [0.61, 1.48]
Muñoz 2010	-1.8571	1.4796	0.3%	0.16 [0.01, 2.84]
Nuis 2013	-0.0507	0.2669	6.5%	0.95 [0.56, 1.60]
Zhang 2013	0.4474	0.5833	1.6%	1.56 [0.50, 4.91]
Subtotal (95% CI)			**23.3%**	**1.20 [0.77, 1.87]**
Heterogeneity: Tau² = 0.11; Chi² = 8.07, df = 4 (P = 0.09); I² = 50%				
Test for overall effect: Z = 0.79 (P = 0.43)				
1.5.2 Hb <12 g/dL (all)				
Cladellas 2006	0.4318	0.8553	0.8%	1.54 [0.29, 8.23]
Subtotal (95% CI)			**0.8%**	**1.54 [0.29, 8.23]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.50 (P = 0.61)				
1.5.3 HTC <39%				
Gupta 2013	0.196	0.0377	31.6%	1.22 [1.13, 1.31]
Subtotal (95% CI)			**31.6%**	**1.22 [1.13, 1.31]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.20 (P < 0.00001)				
1.5.4 HTC <39% (males) or <36% (females)				
Bydon 2014	0.2439	0.1832	11.4%	1.28 [0.89, 1.83]
Kim 2014	-1.6135	1.5505	0.2%	0.20 [0.01, 4.16]
Phan (2) 2017	0.1372	1.6367	0.2%	1.15 [0.05, 28.36]
Phan 2017	1.9348	0.8181	0.8%	6.92 [1.39, 34.41]
Saager 2013	0.0198	0.0812	24.6%	1.02 [0.87, 1.20]
Tohme 2016	0.0889	0.3101	5.1%	1.09 [0.60, 2.01]
Subtotal (95% CI)			**42.4%**	**1.15 [0.87, 1.54]**
Heterogeneity: Tau² = 0.04; Chi² = 7.66, df = 5 (P = 0.18); I² = 35%				
Test for overall effect: Z = 0.98 (P = 0.33)				
1.5.5 Hb <12 g/dL (males) or <11 g/dL (females)				
Matsuda 2013	0.838	0.532	1.9%	2.31 [0.81, 6.56]
Subtotal (95% CI)			**1.9%**	**2.31 [0.81, 6.56]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.58 (P = 0.12)				
Total (95% CI)			**100.0%**	**1.19 [1.02, 1.38]**
Heterogeneity: Tau² = 0.02; Chi² = 19.84, df = 13 (P = 0.10); I² = 34%				
Test for overall effect: Z = 2.28 (P = 0.02)				
Test for subgroup differences: Chi² = 1.66, df = 4 (P = 0.80), I² = 0%				

Summary:

14 Studies include:

- CV = 7
- Non-CV = 7
  - 1 Multi site
  - 6 Single site

11 are not statistically significant:

- 6 CV
- 1 Non-CV – Multi site
- 1 Neurosurgery
- 2 Spinal
- 1 GI

Overview Evidence Table GRADE Software

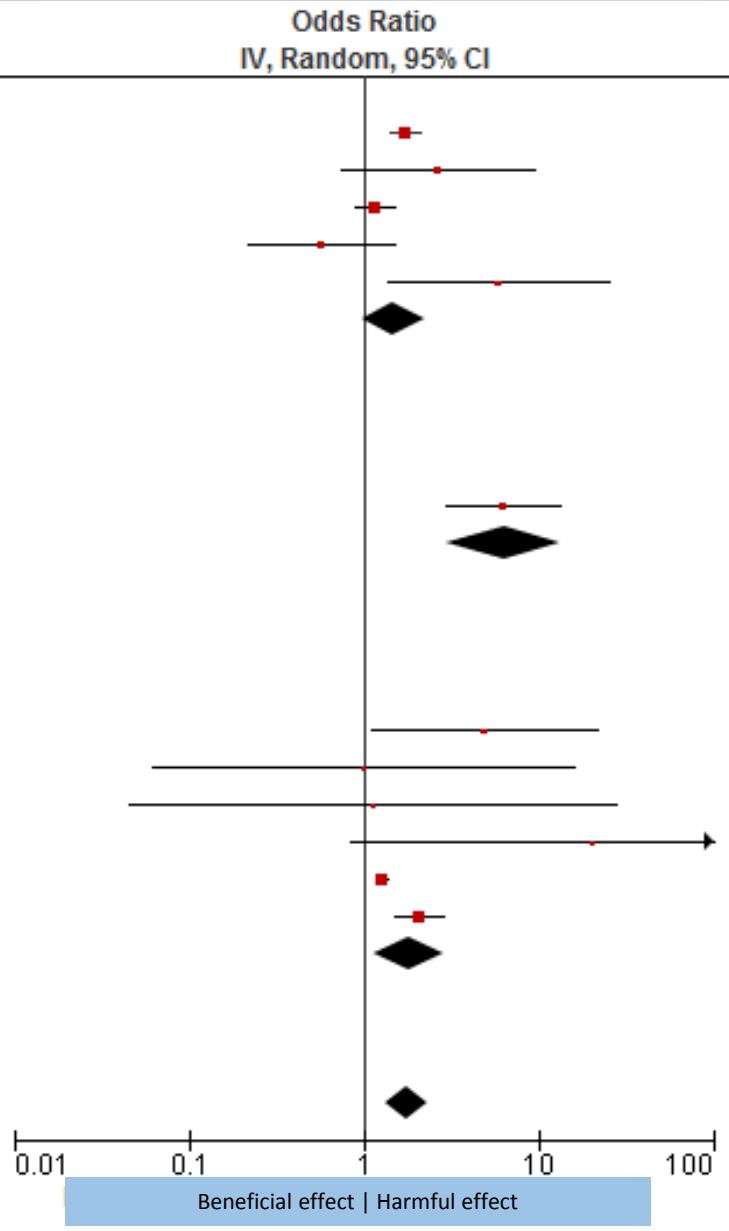
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative anaemia as a risk factor for adverse events	no preoperative anaemia	Relative (95% CI)	Absolute (95% CI)		
Acute Ischaemic Stroke												
14	observational studies	not serious	not serious	not serious	not serious	none			OR 1.19 (1.02 to 1.38)	**per 1.000 (from -- to --)****	⨁⨁◯◯ LOW	CRITICAL

** Absolute effect size could not be calculated because no information on the number of events/patients was available for all studies.

Link Preoperative Anaemia – Adverse Events

CRITICAL OUTCOME: Acute Kidney Injury

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.6.1 WHO definition (Hb <13 g/dL for males and Hb <12 g/dL for women)				
Miceli 2014	0.5481	0.0972	19.1%	1.73 [1.43, 2.09]
Muñoz 2010	0.979	0.6514	3.8%	2.66 [0.74, 9.54]
Nuis 2013	0.1469	0.1292	17.9%	1.16 [0.90, 1.49]
Van Mieghem 2011	-0.5474	0.4932	5.8%	0.58 [0.22, 1.52]
Zhang 2013	1.7799	0.7432	3.0%	5.93 [1.38, 25.45]
Subtotal (95% CI)			**49.6%**	**1.48 [0.97, 2.24]**
Heterogeneity: Tau² = 0.11; Chi² = 14.09, df = 4 (P = 0.007); I² = 72%				
Test for overall effect: Z = 1.82 (P = 0.07)				
1.6.2 Hb <12 g/dL (all)				
Cladellas 2006	1.8434	0.3907	8.0%	6.32 [2.94, 13.59]
Subtotal (95% CI)			**8.0%**	**6.32 [2.94, 13.59]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.72 (P < 0.00001)				
1.6.3 HTC <39% (males) or <36% (females)				
Bydon 2014	1.5938	0.7643	2.9%	4.92 [1.10, 22.02]
Kim 2014	0	1.4157	0.9%	1.00 [0.06, 16.03]
Phan (2) 2017	0.1372	1.6367	0.7%	1.15 [0.05, 28.36]
Phan 2017	3.0289	1.6338	0.7%	20.67 [0.84, 508.31]
Saager 2013	0.2469	0.0329	20.8%	1.28 [1.20, 1.37]
Tohme 2016	0.7265	0.1623	16.4%	2.07 [1.50, 2.84]
Subtotal (95% CI)			**42.5%**	**1.80 [1.13, 2.86]**
Heterogeneity: Tau² = 0.12; Chi² = 14.30, df = 5 (P = 0.01); I² = 65%				
Test for overall effect: Z = 2.48 (P = 0.01)				
Total (95% CI)			**100.0%**	**1.78 [1.35, 2.34]**
Heterogeneity: Tau² = 0.09; Chi² = 46.75, df = 11 (P < 0.00001); I² = 76%				
Test for overall effect: Z = 4.12 (P < 0.0001)				
Test for subgroup differences: Chi² = 10.88, df = 2 (P = 0.004), I² = 81.6%				



Inconsistency:

Downgrade certainty of the evidence (**GRADE -1**)

$I^2 > 50\%$

Chi^2 test statistical significant

Difference in point estimates

No optimal overlap in 95% CIs

Summary:

12 Studies include:

- CV = 6
- Non-CV = 6
  - 1 Multi site
  - 5 Single site

6 are not statistically significant:

- 3 CV – 2 TAVR
- 3 Spinal

Overview Evidence Table GRADE Software

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative anaemia as a risk factor for adverse events	no preoperative anaemia	Relative (95% CI)	Absolute (95% CI)		
Acute Kidney Injury												
12	observational studies	not serious	**serious** **	not serious	not serious	none			OR 1.78 (1.35 to 2.34)	**-- per 1.000 (from -- to --)****	⨁◯◯◯ VERY LOW	CRITICAL

** **Absolute effect size could not be calculated because no information on the number of events/patients was available for all studies.**

** **I^2>50%, chi-square test statistical significant, difference in point estimates and no optimal overlap in 95% CIs**

4. What is the Overall Certainty of the Evidence of Effects?

How good an indication does the research provide of the likely effects across all critcal outcomes (i.e. the likelihood that the effects will be different enough from what the research found that it might affect a decision about the intervention)?

- Very low
- Low
- Moderate
- High

- No included studies

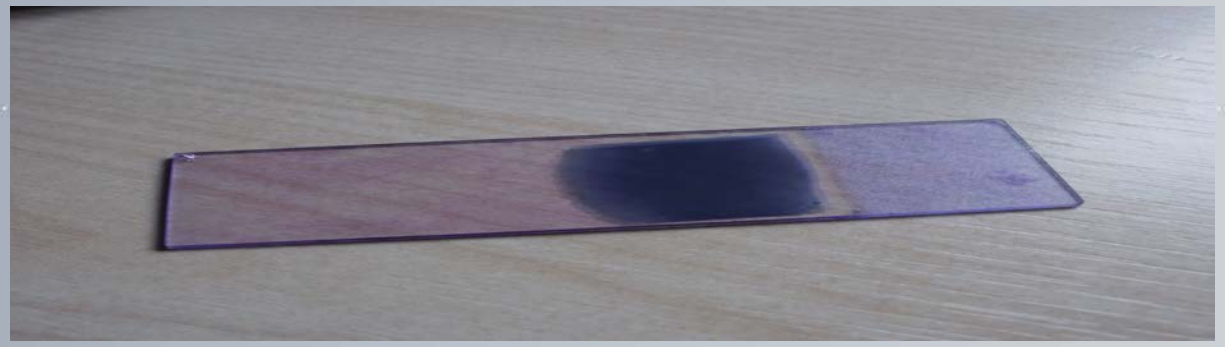
Observational studies start with low quality of evidence. They can be downgraded for uncertainty or upgraded if the evidence is related to a life-saving outcome.

Link Preoperative Anaemia – Adverse Events

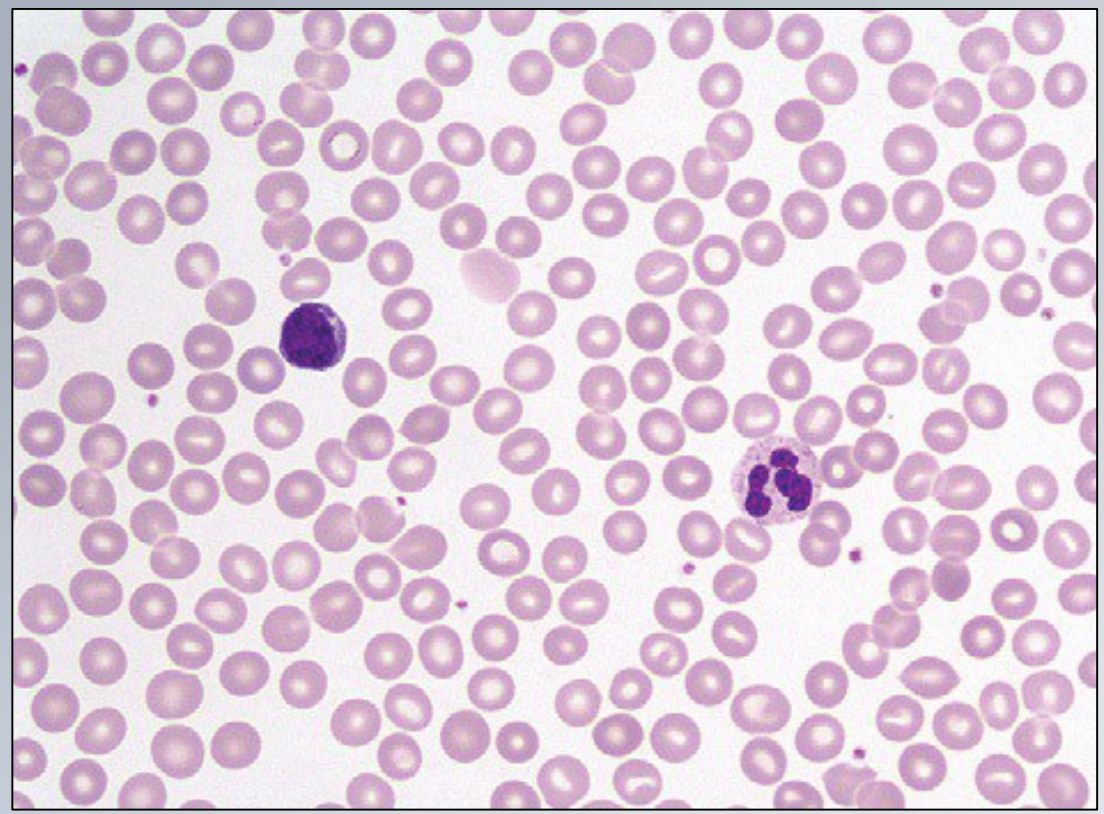
Certainty of the Body of Evidence – Critical Outcomes

Outcomes	Certainty of the Evidence (GRADE)
Hospital Mortality	⊕⊕◯◯ LOW
30-day Mortality	⊕⊕⊕◯ MODERATE[a]
Acute Myocardial Infarction	⊕◯◯◯ VERY LOW[b]
Acute Ischaemic Stroke	⊕⊕◯◯ LOW
Acute Kidney Injury	⊕◯◯◯ VERY LOW[b]

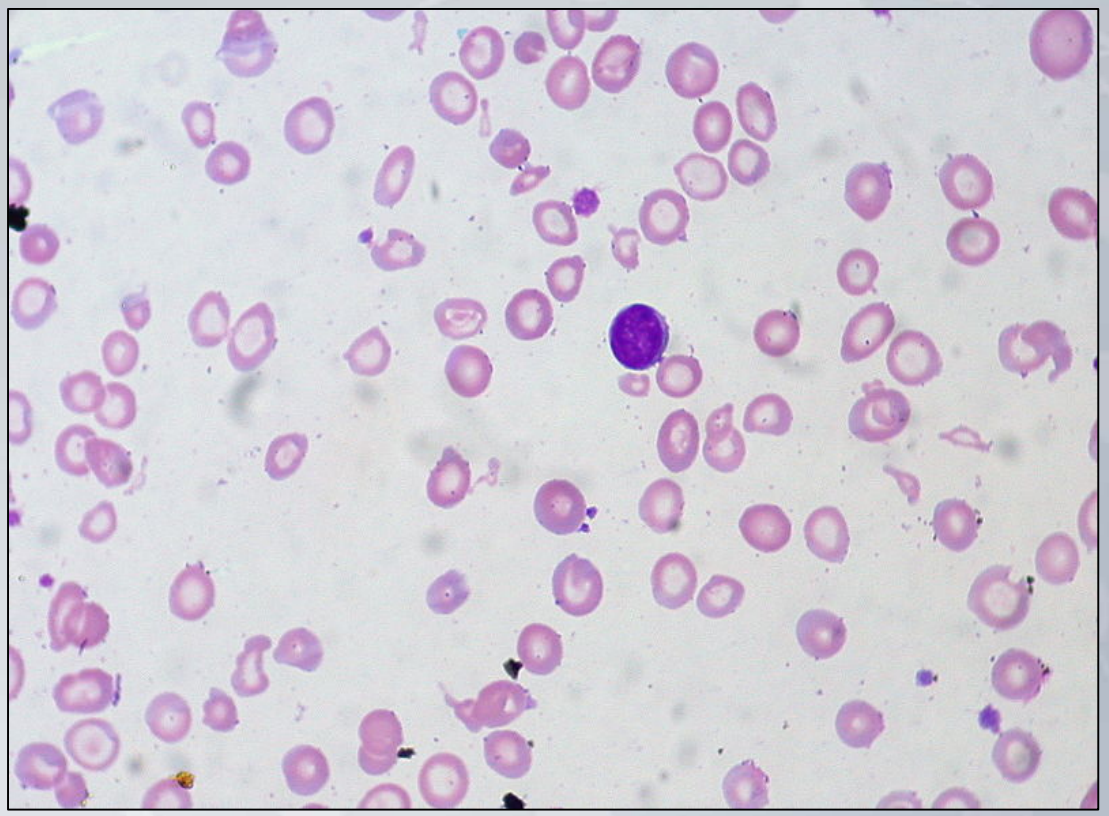
a. Strong association (upgrade +1)
b. Inconsistency (downgrade -1): I^2>50%, Chi^2 test statistical significant, difference in point estimates, no optimal overlap in 95% CIs



Healthy



Anaemic



PICO Question 2 – Anaemia Diagnosis

In preoperative elective surgery patients **(population)**, should Hb levels according to the WHO definition or other Hb levels **(intervention)** be used to diagnose anaemia **(outcome)**?

Population:

- ***Included:*** Preoperative elective surgery adult patients.
- ***Excluded:*** Non-elective surgery (burns, obstetrics, trauma, transplant surgery).

Index test:

- Hb levels according to WHO definition anaemia (i.e. Hb <12 g/dL (adult females) and Hb <13 g/dL (adult males)) or other Hb levels.

Comparator test: Alternative Hb levels.

Outcome:

- Diagnosis of preoperative anaemia – true positives, false positives, true negatives, false negatives, sensitivity, specificity.
- Level of agreement between two methods.

Who Definition of Anaemia – Hb <12 F, <13 M

- Anaemia definition based arbitrarily on selected cut-offs determined in 1958 (WHO Study Group) and revised in 1968. Revision references are as follows:

- **Reference 1:**

- Sturgeon P. Studies of Iron Requirements in Infants. III . Influence of Supplemental Iron during Normal Pregnancy on Mother and Infant. The Mother. Br J Haematol 1959; 5:31-44.
- 600 men – 35-64 yo, 200 women 55-64 yo in Wales. Venous blood samples. Included individuals who responded to iron therapy. No specific recommendations for anaemia were given.

- **Reference 2:**

- Natvig K. Studies on Hemoglobin Values in Norway. V. Hemoglobin Concentration and Hematocrit in Men Aged 15-21 years. Acta Med Scand. 1966; 180:613-20
- 312 healthy Norwegian men – 15-21 yo. Capillary samples. Hb < 130 g/L observed in 3.5%.

Most Recent WHO Anaemia References

Food and Agriculture Organization of the United Nations, World Health Organization. International Conference on Nutrition. World Declaration and Plan of Action for Nutrition.; 1992.

World Health Organization, Centers for Disease Control and Prevention. Assessing the iron status of populations. Second edition. Including Literature Reviews.; 2004.

- Refers to 1958 definition, noting thresholds chosen arbitrarily.
- Cite 3 additional papers:
  - 2 from 1960's – pregnant women only
  - 1 from 1985
- DeMaeyer E, Adiels-Tegman M. The Prevalence of Anaemia in the World. World Health Stat Q. 1985: 38:302-16.
- Additional anaemia definition added in 2004 – pregnant women anaemia at < 11 g/dL.

Evidence-base WHO Definition?

World Health Organization

Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity

WHO/NMH/NHD/MNM/11.1

Recommendations

Table 1

Haemoglobin levels to diagnose anaemia at sea level (g/l)

±

Population	Non -Anaemia*	Anaemia*		
		Mild[a]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

± Adapted from references 5 and 6

* Haemoglobin in grams per litre

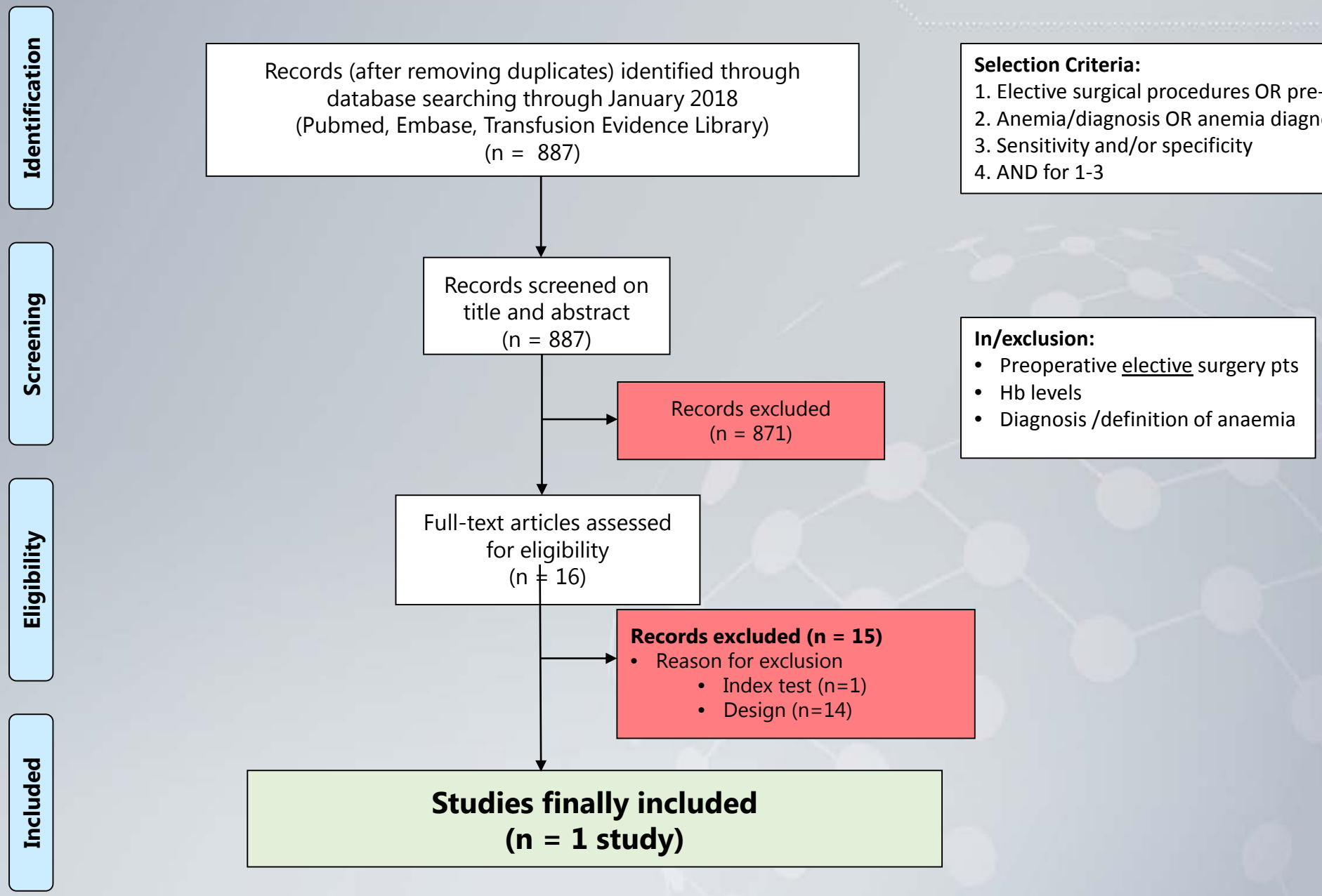
a "Mild" is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent.

Evidence-base WHO Definition?

- The WHO definition (Hb <13 g/dL (males) or <12 g/dL (females)) to diagnose anaemia is based on **arbitrarily selected cut-offs** (expert opinion) from **1958** and revised in 1968.
- **Supporting evidence:**
  - 5 "scientific" papers/reports:
    - Natvig 1966
    - Kilpatrick 1961
    - De Leeuw 1966
    - Sturgeon 1959
    - DeMaeyer 1985

- Very low quality evidence:
  - Observational / Cross-sectional studies
  - Indirectness:
    - Outdated
    - 3 studies in pregnant women
    - 2 studies in general (healthy) population

Anaemia Definition – Study Selection Flow Chart



What Should Define Preoperative Anemia in Primary THA?

Mitchell R. Klement MD, Ashwin Peres-Da-Silva BS, Brian T. Nickel MD, Cynthia L. Green PhD, Samuel S. Wellman MD, David E. Attarian MD, Michael P. Bolognesi MD, Thorsten M. Seyler MD, PhD

Clin. Orthop. Relat. Res 2017, 475:2683-2691

Variable	No transfusion	Transfusion	Sn	Sp	PPV	p value	p value*
Male (number)	265	12					
Hgb category							
< 11.0	2 (1%)	4 (33%)	33	99	67		< 0.001
11.0–13.0†	32 (12%)	4 (33%)	50	96	35		0.002
> 13.0	231 (87%)	4 (33%)	67	87	48	< 0.001	Reference
Female (number)	233	48					
Hgb category						< 0.001	
< 10.0	2 (1%)	4 (8%)	8	99	67		< 0.001
10.0–12.0†	30 (13%)	25 (52%)	29	97	64		< 0.001
> 12.0	201 (86%)	19 (40%)	60	86	19		Reference

- **TXA – 96% (536)**
  - IV 80% (429)
  - Topical 20% (107)
- **Overall TX = 11%**
  - Female – 17%
  - Male – 4.3%
- **Best Hb cut-offs to predict transfusion:**
  - Hb 12.5 g/dL (females): sensitivity 85%, specificity 77%
  - Hb 13.5 g/dL (males): sensitivity 92%, specificity 77%
  - Hb 12.6 g/dL (combined): sensitivity 83%, specificity 84%

Level of evidence (test accuracy)
⊕⊕◯◯ LOW
Dowgrading (-1) due to imprecision (limited sample size) and indirectness (lack of external validity)

INTERNATIONAL CONSENSUS CONFERENCE
ICC·PBM
FRANKFURT
2018

ICC-PBM 2018: PRESENTATIONS PICO QUESTIONS PREOPERATIVE ANAEMIA

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ASSOCIATE PROFESSOR, DEPARTMENTS OF LABORATORY MEDICINE AND MEDICINE,
UNIVERSITY OF TORONTO, TORONTO, CANADA

Conflict of Interest

- Advisory board participation: Alexion, Shire, Ablynx
- Honoraria for speaking: Alexion, Novartis, Shire
- Clinical trials: Ablynx, CSL Behring, Octapharma

Background

- Preoperative anemia is common and is associated with adverse outcomes
- Peri-operative transfusion can treat anemia but is also associated with adverse outcomes
- Patient blood management (PBM) may improve anemia and reduce risks of both anemia and transfusion

What is Patient Blood Management (PBM)?

- Timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome

SOCIETY FOR THE ADVANCEMENT OF BLOOD MANAGEMENT®

Elements of PBM

1. Diagnosis and treatment of anemia
    1. Iron, erythropoiesis stimulating agents (ESA)
2. Appropriate use of blood components (ex. Restrictive RBC transfusion triggers)
3. Reduction in unnecessary diagnostic phlebotomy
4. Minimally invasive surgery and good surgical technique
5. Autotransfusion, cell salvage
6. Management of coagulopathy
    - Timely discontinuation and/or reversal of anticoagulant or antiplatelet drugs, etc.
    - Use of hemostatic agents (ex. Anti-fibrinolytic agents)
7. Many, many others…

Iron Replacement

Oral

- Cons
  - For stable, well patients
  - Poorly absorbed (other medications, infection, inflammation) and poorly tolerated (adherence is an issue!)
  - Need time to see effect; not suitable for severe anemia, active bleeding, impending surgery
- Pros
  - Cheap and widely available

Intravenous

- Cons
  - Contraindication: acute infection
  - Challenges: expense, administration logistics
  - Risk of severe allergic reaction (very low)
- Pros
  - May be given to ill patients
  - No concerns about absorption
  - Fast response
    - In a patient with IDA, expected increment in Hb is 1g/dL per week (equivalent to 1 unit of RBC)

Drugs and treatment regimens vary

Erythropoiesis Stimulating Agents (ESA)

- Mechanism of action:
  - Promote survival, proliferation, and differentiation of erythroid progenitors
  - Accelerate release of reticulocytes from the bone marrow
- Expected increment in Hb is 1g/dL per week (equivalent to 1 unit of RBC)
  - Requires adequate supplies of hematinics
- Efficacy in anemia of renal failure, anemia of inflammation, cancer/chemotherapy, HIV, etc.
- PBM indication was approved by FDA in 1996
  - Patients undergoing major elective surgery and Hb 10 to <13 g/dL

Tran et al 2014

Erythropoiesis Stimulating Agents (ESA)

- Typical PBM prescription:
  - Epoietin alpha 100-600IU/kg or 40 000 IU subcutaneously or IV
  - Timing, frequency, number of doses and Hb target vary
- Contraindications
  - Recent arterial or venous thrombosis, unstable angina, severe carotid stenosis, uncontrolled hypertension
- Significant side effects
  - Hypertension, seizure, hyperuricemia
  - Arterial thrombosis – patients with CKD (Palmer et al 2010)
  - Venous thrombosis – patients with cancer (Glaspy et al 2010)
  - Cancer progression, reduced survival in cancer patients (Bohlius et al 2009; Glaspy et al 2010)

PICO question 1

In preoperative elective surgery patients **(population)**, is transfusion or the use of iron supplementation and/or erythrocyte stimulating agents (ESA) **(intervention)** effective to improve clinical and economic outcomes **(outcomes)**?

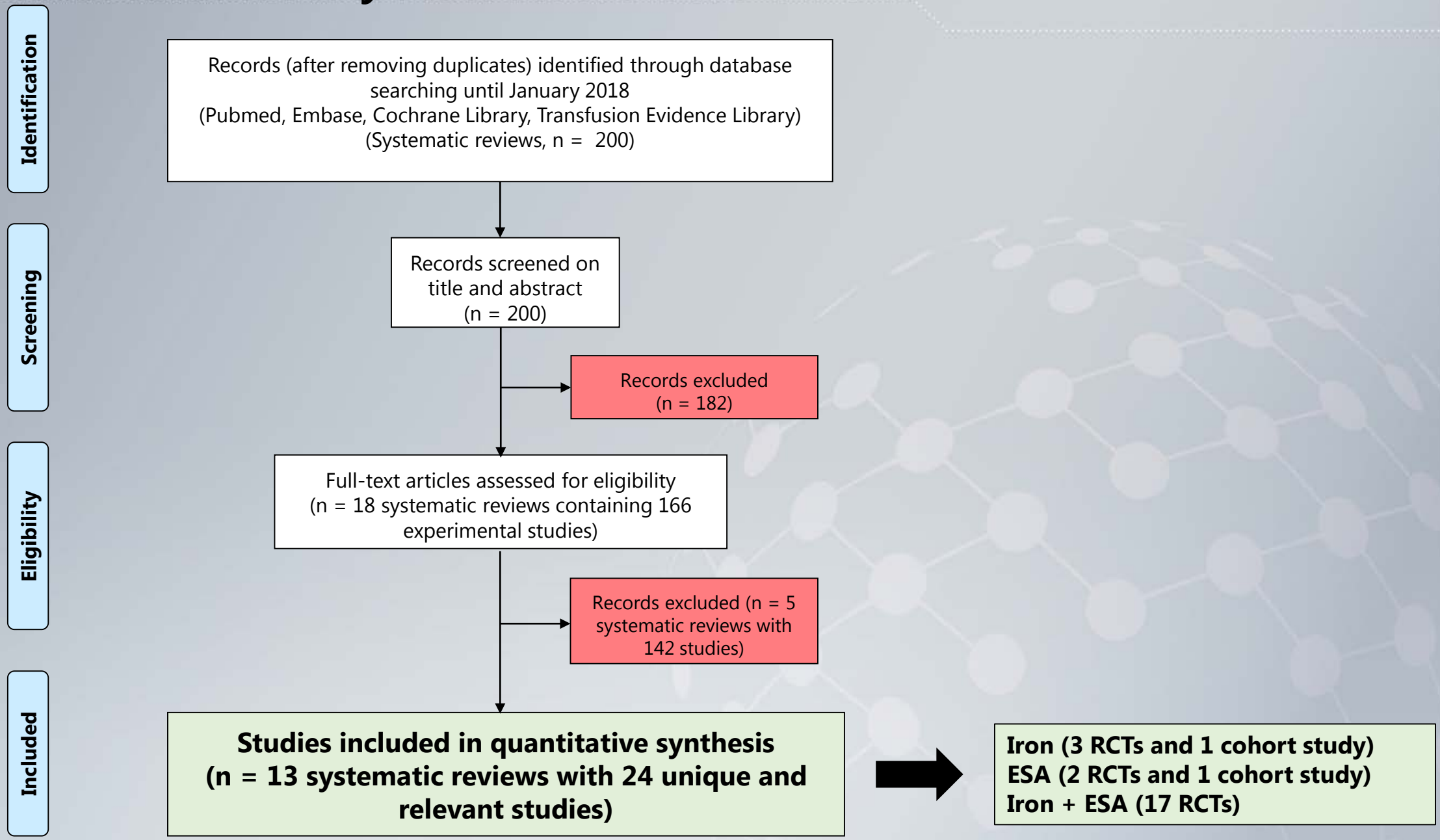
Population: preoperative elective surgery adult patients with anaemia.

Intervention 1: transfusion
Intervention 2: iron supplementation (intravenous or oral)
Intervention 3: ESA
Intervention 4: iron + ESA

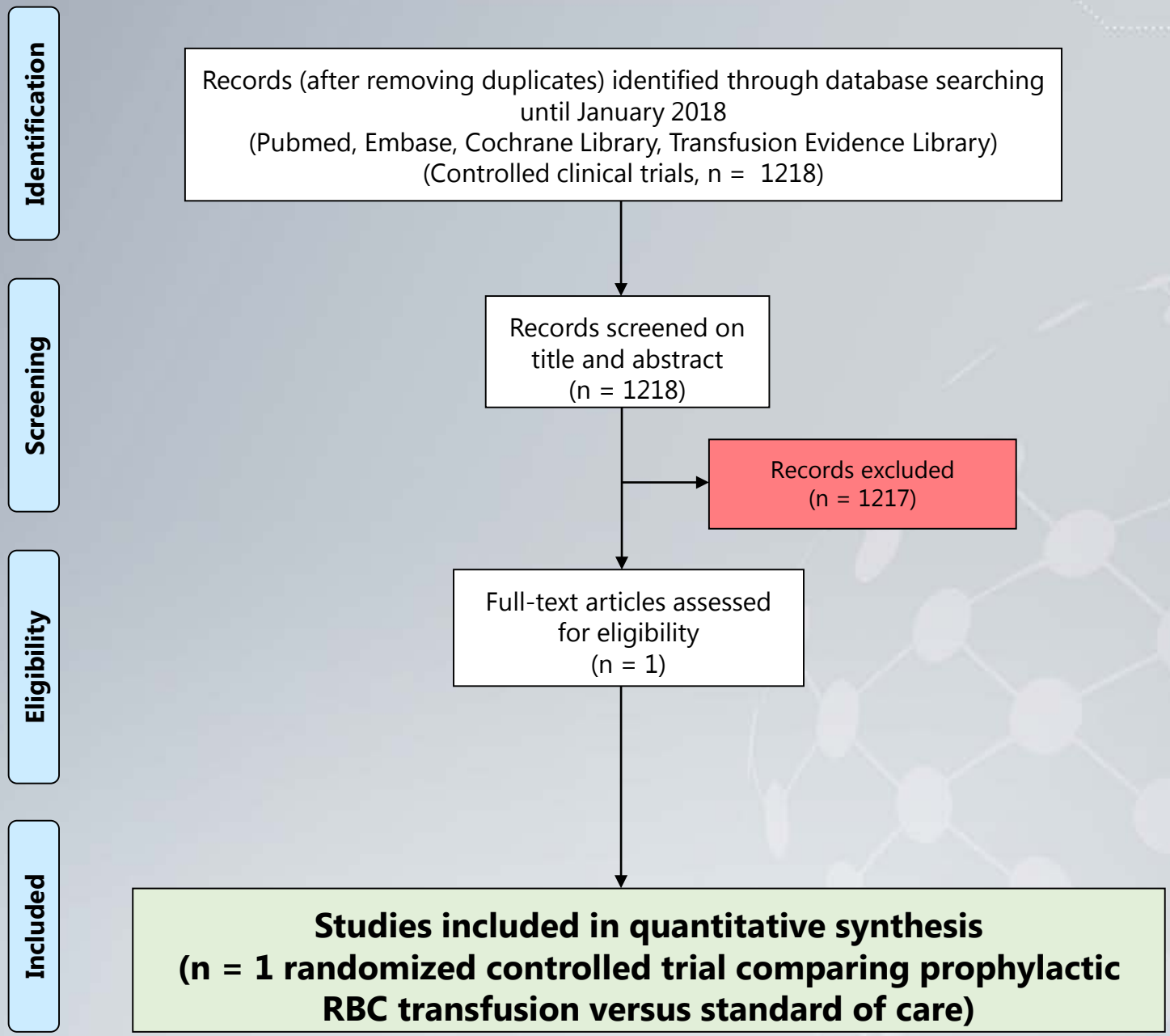
Comparison: no treatment – placebo – standard of care.

Critical outcomes:
All-cause mortality, anaemia-associated ischaemic events and thromboembolic events
Important outcomes:
RBC utilization, infections and length of hospital stay

Flow chart (systematic reviews)



Flow chart (individual studies (RBC transfusion))



1. How substantial are the desirable anticipated effects? (= how large are the desirable effects of the intervention taking into account the importance of the outcomes (how much they are valued), and the size of the effect (the likelihood of experiencing a benefit or how much of an improvement individuals would be likely to experience)?)

- Trivial
- Small
- Moderate
- Large

- Varies
- Don’t know

2. How substantial are the undesirable anticipated effects? (= how large are the undesirable effects of the intervention taking into account the importance of the outcomes (how much they are valued), and the size of the effect (the likelihood of experiencing a benefit or how much of an improvement individuals would be likely to experience)?)

- Large
- Moderate
- Small
- Trivial

- Varies
- Don’t know

5. Does the balance between desirable and undesirable effects favour the intervention or the comparison? (= what is the balance between the desirable and undesirable effects, taking into account how much individuals value the main outcomes, how substantial the desirable and undesirable effects are and the certainty of those estimates?)

- Favours the comparison
- Probably favours the comparison
- Does not favour either the intervention or the comparison
- Probably favours the intervention
- Favours the intervention

- Varies
- Don’t know

RBC Transfusion

Study characteristics

Author, year, country	Study design	Population	Intervention	Comparison
Karkouti, 2012, Canada	RCT	60 anaemic patients undergoing cardiac surgery with cardiopulmonary bypass	Prophylactic transfusion: 2 units of RBC transfused 1 to 2 days before surgery (same-day admit patients were transfused as outpatients in the medical day unit)	Standard of care: RBC 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.

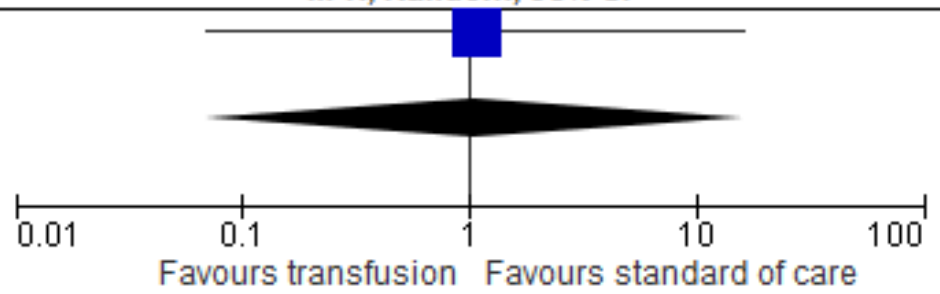
RBC Transfusion versus Standard of Care

CRITICAL OUTCOME: Mortality

Study or Subgroup	Transfusion Events	Transfusion Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
Karkouti 2012	1	29	1	31	100.0%	1.07 [0.07, 16.31]
Total (95% CI)		**29**		**31**	**100.0%**	**1.07 [0.07, 16.31]**
Total events	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.05 (P = 0.96)



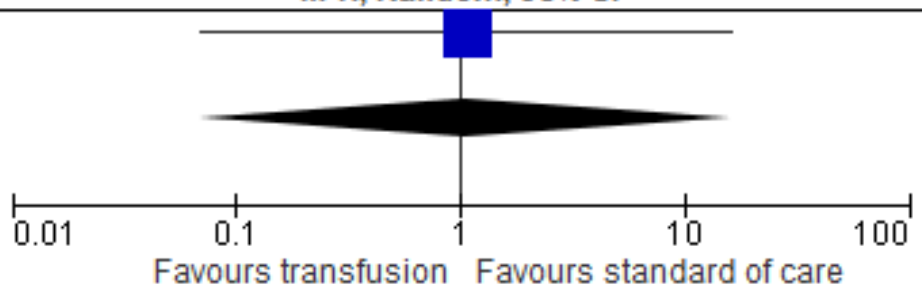
RBC Transfusion versus Standard of Care

CRITICAL OUTCOME: Acute Myocardial Infarction

Study or Subgroup	Transfusion Events	Transfusion Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
Karkouti 2012	1	29	1	31	100.0%	1.07 [0.07, 16.31]
Total (95% CI)		**29**		**31**	**100.0%**	**1.07 [0.07, 16.31]**
Total events	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.05 (P = 0.96)



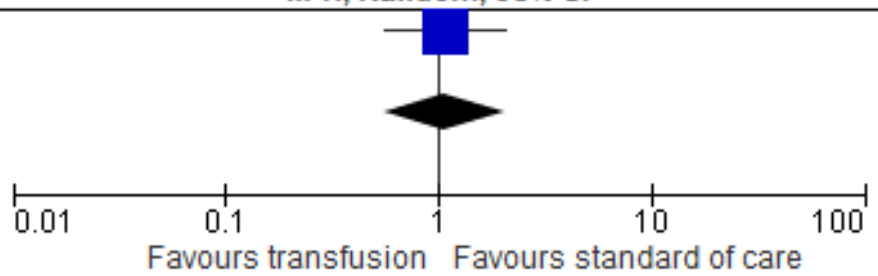
RBC Transfusion versus Standard of Care

CRITICAL OUTCOME: Acute Kidney Injury

Study or Subgroup	Transfusion Events	Transfusion Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
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 applicable

Test for overall effect: Z = 0.20 (P = 0.84)



RBC Transfusion versus Standard of Care

IMPORTANT OUTCOME: RBC Utilization

Outcomes	Difference (RBC transfusion versus standard of care)
RBC units transfused (pre-operative)	median **2 RBC units higher** (0 to 0)
RBC units transfused (intra-operative)	median **2 RBC units lower** (0 to 0)
RBC units transfused (total)	median **0 RBC units** (0 to 0)

RBC Transfusion versus Standard of Care

Quality of the body of evidence (critical outcomes)

Outcomes	Certainty of the evidence (GRADE)
Mortality	⨁◯◯◯ VERY LOW[a,b]
Acute myocardial infarction	⨁◯◯◯ VERY LOW[a,b]
Acute kidney injury	⨁◯◯◯ VERY LOW[a,b]

a. Risk of bias (-1): unblinded, pragmatic pilot study with postrandomization dropouts and important protocol deviations (i.e. delayed transfusions in the intervention arm)
b. Imprecision (-2): limited sample size/low number of events and large variability in results

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Iron Supplementation

Study characteristics

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Edwards, 2009, UK	RCT	62 patients undergoing bowel resection for suspected colorectal **cancer**	IV Iron: Iron sucrose 300 mg intravenously, two infusions (minimally 24 hours apart from each other, the second one completed within a minimum of 14 days before surgery)	Placebo: Placebo 250 mL intravenously, 2 infusions (minimally 24 hours apart from each other, the second one completed within a minimum of 14 days before surgery)	- Hb 8-10 g/dl: transfuse if * abnormal ECG * ischaemic heart disease * obstructive lung disease * consultant's discretion * unable to absorb oral iron - Hb <8 g/dl: transfuse to target 10 g/dl
Lidder, 2007, UK	RCT	49 patients with colorectal **cancer** scheduled for surgery	Oral iron: Oral ferrous sulphate 200 mg 3 times per day	Standard clinical management: not defined	
Muñoz, 2006, Spain	Cohort study	24 consecutive patients undergoing surgery for **total hip replacement**	IV iron: Iron sucrose 100 mg intravenously once per day for 3 days, starting after surgery	Control: no iron	Hb levels <8 g/dl (target Hb: 9 g/dl) and/or in the presence of symptoms of acute anaemia.
Okuyama, 2005, Japan	Non-RCT	116 patients undergoing colorectal **cancer** surgery	Oral iron: Oral sodium ferrous citrate 200 mg daily, after meals in the morning and evening, during at least 2 preoperative weeks	Control: no iron	intraoperative Hb levels of about 7 g/dl with unstable haemodynamics

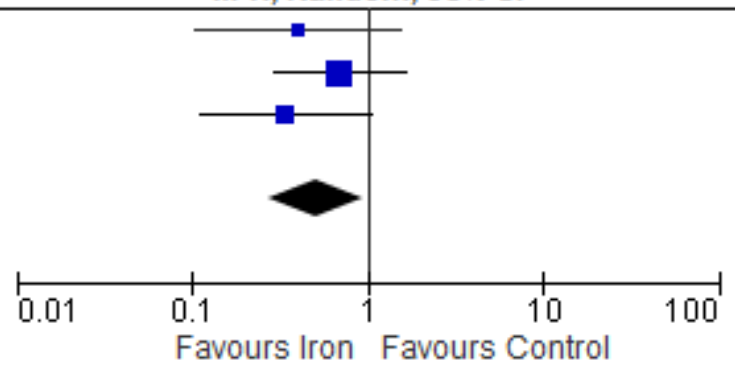
Iron versus Standard of Care/Placebo/No Intervention

IMPORTANT OUTCOME: RBC Utilization (number of patients transfused)

Study or Subgroup	Iron Events	Iron Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
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]
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: $Tau^2 = 0.00$; $Chi^2 = 1.28$, $df = 2$ ($P = 0.53$); $I^2 = 0\%$

Test for overall effect: $Z = 2.18$ ($P = 0.03$)



Iron versus Standard of Care/Placebo/No Intervention

Quality of the body of evidence

Outcomes	Importance	Certainty of the evidence (GRADE)
RBC utilization - Number of patients transfused	IMPORTANT	⨁⨁◯◯ LOW[a,b]

a. Risk of bias (-1): high risk of selection bias and unclear risk of selection, performance, detection and attrition bias
b. Imprecision (-1) low number of events

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Erythropoiesis Stimulating Agents (ESA)

Study characteristics

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Bedair, 2015, USA	Cohort study	80 patients scheduled to undergo unilateral primary **total hip or total knee arthroplasty**	Epoetin alpha: Received at least 1 dose (median 2 doses; range 2-4) of Epoetin alpha preoperatively	Control: no Epoetin alpha	Patients with postoperative Hb <10 g/dL who were also symptomatic (hypotension, tachycardia, dizziness, and/or an inability to participate in therapy) and whose symptoms were resistant to fluid boluses were transfused.
Weltert, 2010, Italy	RCT	320 patients with isolated coronary vessel disease undergoing off-pump **coronary artery bypass grafting surgery**	EPO: - 14 000 IU EPO subcutaneously on preoperative days 2 and 1 - 8 000 IU EPO subcutaneously on operative day and postoperative days 1 and 2.	Control: no treatment	Hb <8 g/dl and/or in the case of blood exsanguination, as estimated by saturation of venous blood <50%
Weltert, 2015, Italy	RCT	600 patients undergoing **heart surgery**	EPO: - 80 000 IU EPO subcutaneously on preoperative day 2	Control: no treatment	Hb <8 g/dl

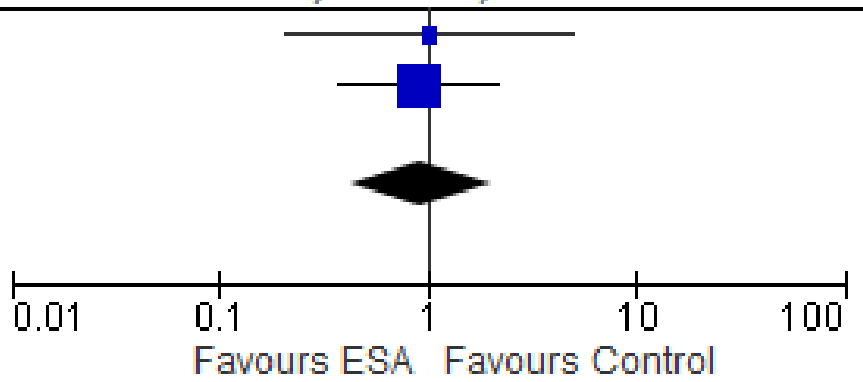
ESA versus No Treatment

CRITICAL OUTCOME: 45-day mortality

Study or Subgroup	ESA Events	ESA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Weltert 2010	3	158	3	162	23.8%	1.03 [0.21, 5.00]
Weltert 2015	9	300	10	300	76.2%	0.90 [0.37, 2.18]
Total (95% CI)		**458**		**462**	**100.0%**	**0.93 [0.43, 2.01]**
Total events	12		13			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$

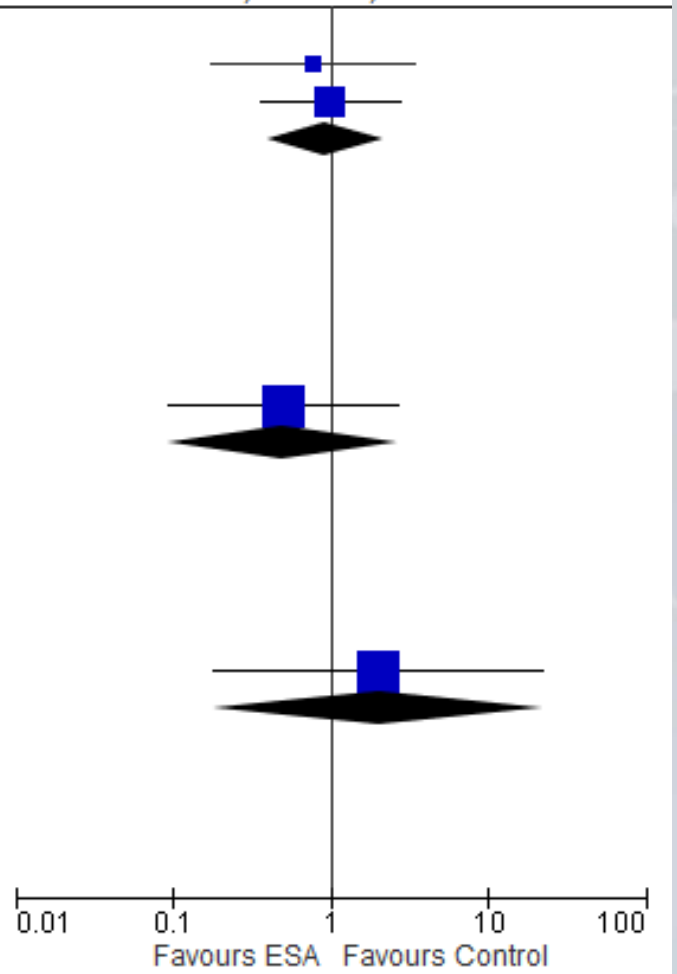
Test for overall effect: Z = 0.19 (P = 0.85)



ESA versus No Treatment

CRITICAL OUTCOME: Anaemia-associated ischaemic events

Study or Subgroup	ESA Events	ESA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Myocardial infarction						
Weltert 2010	3	158	4	162	32.8%	0.77 [0.17, 3.38]
Weltert 2015	7	300	7	300	67.2%	1.00 [0.36, 2.82]
Subtotal (95% CI)		**458**		**462**	**100.0%**	**0.92 [0.39, 2.14]**
Total events	10		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.2.2 Bowel Ischaemia						
Weltert 2010	0	158	0	162		Not estimable
Weltert 2015	2	300	4	300	100.0%	0.50 [0.09, 2.71]
Subtotal (95% CI)		**458**		**462**	**100.0%**	**0.50 [0.09, 2.71]**
Total events	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
3.2.3 Acute kidney injury						
Weltert 2015	2	300	1	300	100.0%	2.00 [0.18, 21.94]
Subtotal (95% CI)		**300**		**300**	**100.0%**	**2.00 [0.18, 21.94]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						



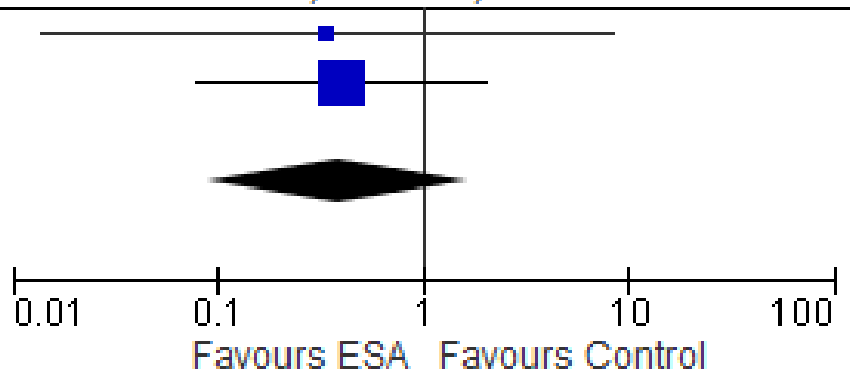
ESA versus No Treatment

CRITICAL OUTCOME: Thromboembolic Events

Study or Subgroup	ESA Events	ESA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
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)		**458**		**462**	**100.0%**	**0.39 [0.09, 1.66]**
Total events	2		6			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$

Test for overall effect: Z = 1.28 (P = 0.20)



ESA versus No Treatment

IMPORTANT OUTCOMES

Outcomes	Difference (ESA vs no treatment)	Relative effect (95% CI)
Length of hospital stay (experimental study: RCT)	In the RCT by Weltert et al. 2010 a statistically significant difference in the length of stay after the operation between patients receiving EPO subcutaneously and patients receiving no treatment could **not** be demonstrated (p=0.065).	
Length of hospital stay (observational cohort study)	MD **0.3 days fewer** (0.56 fewer to 0.04 fewer)	-
Infections	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.	
RBC utilization - Number of patients transfused (experimental study: RCT)	**211 fewer per 1.000** (267 fewer to 130 fewer)	**RR 0.43** (0.28 to 0.65)
RBC utilization - Number of patients transfused (observational cohort study)	**390 fewer per 1.000** (409 fewer to 94 fewer)	**RR 0.050** (0.003 to 0.770)
RBC utilization - Number of units transfused (experimental study: RCT)	In the RCT by Weltert et al 2010, **no** statistically significant decrease in the number of RBC 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).	
RBC utilization - Number of units transfused (observational cohort study)	For the observational cohort study by Bedair, 2005 in patients undergoing hip or knee arthroplasty, with Hb levels < 13 g/dl, the effect size was **not estimable** (Epoetin alpha vs control: 0 vs 0.41±0.07 units).	

ESA versus No Treatment

Quality of the body of evidence (critical outcomes)

Outcomes	Certainty of the evidence (GRADE)
45-day mortality	⊕⊕◯◯ LOW[a,b]
Anemia-associated ischaemic events	⊕⊕◯◯ LOW[a,b]
Thromboembolic events	⊕⊕◯◯ LOW[a,b]

a. High risk of performance bias (-1) (i.e. no blinding of participants and personnel).
b. Imprecision (-1): Low number of events and large variability of results

Iron + Erythropoiesis Stimulating Agents (ESA)

Study characteristics (1)

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Canadian Orthopedic Perioperative Erythropoietin Study Group (COPES), 1993, Canada	RCT	208 patients scheduled for elective unilateral **hip-joint replacement**	14 days EPO: - EPO 300 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 3 - Oral iron sulphate 300 mg, 3 times daily starting on preoperative day 21 until discharge 9 days EPO: - Placebo subcutaneously from preoperative day 10 to 6 - EPO 300 IU/kg/day subcutaneously from preoperative day 5 until postoperative day3 - 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 3 - Oral iron sulphate 300 mg, 3 times daily starting on preoperative day 21 until discharge	- Intraoperative: blood loss of more than 15% of the intravascular volume - Postoperative: Hb < 9 g/dl
Christodoulakis, 2005, Greece	RCT	223 patients undergoing elective colorectal surgery for resectable colorectal **cancer**	Epoetin alfa 150 IU: - Epoetin alfa 150 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 1 - Oral iron supplements 200 mg/day from preoperative day 10 until postoperative day 1 - In patients with iron deficiency: iron sulphate 40 mg intravenously daily until the day of discharge - Folic acid 15 mg/day for the first 10 days after randomization Epoetin alfa 300 IU: - Epoetin alfa 300 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 1 - Oral iron supplements 200 mg/day from preoperative day 10 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	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	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: - Hb <10 g/dl and poor prognostic features - Younger patients or patients in good health: Hb <8 g/dl

Study characteristics (2)

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Dousias, 2003, Greece	RCT	50 women with benign uterine leiomyomas scheduled for **abdominal total hysterectomy**	EPO + iron: - EPO 600 U/mL subcutaneously on preoperative days 14 and 7 and the morning before the operation - Iron supplementation 200 mg/day	Iron: - Normal saline subcutaneously on preoperative days 14 and 7 and the morning before the operation - Iron supplementation 200 mg/day	No information provided
Faris, 1996, USA	RCT	200 patients (67 men and 133 women, average age 66±13 years) scheduled for **major elective orthopaedic operation**	EPO 300 IU: - EPO 300 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 4 - Oral iron sulphate 325 mg, 3 times per day EPO 100 IU: - EPO 100 IU/kg/day subcutaneously from preoperative day 10 until postoperative day 4 - Oral iron sulphate 325 mg, 3 times per day	Placebo: - Placebo subcutaneously from preoperative day 10 until postoperative day 4 - Oral iron sulphate 325 mg, 3 times per day	Intraoperative and postoperative: at the discretion of the surgeon. However, every effort was made to avoid transfusion if Hct > 27%, unless the clinical situation warranted it. The use of intraoperative and postoperative reinfusion systems was allowed in all three groups.
Feagan, 2000, Canada	RCT	216 adult patients undergoing **total hip joint arthroplasty**	High-dose Epoetin alfa: - Oral iron 3 times per day from preoperative day 42 until hospital discharge - 40 000 IU subcutaneously weekly for 4 weeks before the operation Low-dose Epoetin alfa: - Oral iron 3 times per day from preoperative day 42 until hospital discharge - 20 000 IU subcutaneously weekly for 4 weeks before the operation	Placebo: - Oral iron 3 times per day from preoperative day 42 until hospital discharge - Placebo subcutaneously weekly for 4 weeks before the operation	according to usual practice of attending surgeons and anesthesiologists. Usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific Hb threshold

Study characteristics (3)

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Heiss, 1996, Germany	RCT	30 patients with primary diagnosis of resectable colorectal **cancer**	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	According to the patient's attending anesthesiologist or surgeon and recommended at Hb ≤9 g/dl, depending on the recorded blood loss.
Kettelhack, 1998, Germany	RCT	109 patients with colon **cancer** scheduled for right hemicolectomy	Epoetin beta: - 20 000 IU Epoetin beta subcutaneously for a minimum of 5 (maximum 10) preoperative days until postoperative day 4 - Oral iron in case of iron deficiency, and on postoperative day 1 (40 mg iron sulphate intravenously)	Placebo: - Placebo subcutaneously for a minimum of 5 (maximum 10) preoperative days until postoperative day 4 - Oral iron in case of iron deficiency, and on postoperative day 1 (40 mg iron sulphate intravenously)	Hb ≤7.5 g/dl
Kosmadakis, 2003, Greece	RCT	75 patients with non-metastatic gastrointestinal tract **cancer**	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	Control: - Placebo subcutaneously daily starting from preoperative day 7 until postoperative day 7 - Intravenous iron 100 mg daily	Hb ≤8.5 g/dl
Larson, 2001, Sweden	RCT	32 women with uterine myoma scheduled for **hysterectomy**	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	Oral iron: Oral iron succinate 100 mg twice per day during 4 preoperative weeks	No information

Study characteristics (4)

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Na, 2011, South Korea	RCT	113 women scheduled for bilateral **total knee replacement arthroplasty**	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	Control: no iron, no Epoetin beta	- Hb 6-6.9 g/dl: 1 unit of RBC - Hb 5-5.9 g/dl: 2 units of RBC - Hb < 5 g/dl or clinical symptoms of anemia and hypovolemia: immediate transfusion and exclusion from study
Qvist, 1999, Denmark	RCT	100 patients scheduled for colorectal surgery because of **cancer**	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 4 to preoperative day 1	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.
Scott, 2002, USA	RCT	60 patients scheduled for major head and neck **cancer** surgery	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 first dose of Epoetin alfa until the day of surgery.	Control: - 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.	At the discretion of the attending surgeon; however an effort was made not to transfuse patients with Hb levels ≥9 g/dl unless clinically indicated.

Study characteristics (5)

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
So-Osman, 2014, The Netherlands	RCT	730 patients scheduled for primary or revision **total hip- or knee-replacement surgery**	EPO: - 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.	Control: No intervention.	- Hb 6.4 g/dl (4.0 mmol/l) for younger than 60 yr of age and normal risk - Hb 8.1 g/dl (5.0 mmol/l) for age 60 yr or older and normal risk - Hb 9.7 g/dl (6.0 mmol/l) in case of high risk irrespective of age
Stowell, 2009, USA	RCT	681 patients scheduled for elective **spinal surgery**	Epoetin alfa: - 600 IU/kg Epoetin alfa subcutaneously on preoperative days 21, 14 and 7 and on the day of the operation - Standard of care treatment - Oral iron therapy from preoperative day 21 until the day of the operation	Standard of care: - No ESA, treated according to the institution's policy for blood conservation - Oral iron therapy from preoperative day 21 until the day of the operation	No information
Weber, 2005, The Netherlands	RCT	Patients scheduled for elective **major orthopaedic surgery**	Epoetin alfa: - 40 000 IU Epoetin alfa (Eprex®/Erypro®) subcutaneously once weekly for 3 weeks before surgery and on the day of the surgery - Oral iron daily for 3 weeks	No Epoetin alfa: - Could take oral or iv iron, if this was part of the usual standard of care in that hospital	Hb<8 g/dl
Wurnig, 2001, Austria	RCT	194 patients scheduled for elective surgery (mainly **orthopaedic and cardiac**)	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)	Control: Oral iron supplementation (200-300 mg/day)	Hb ≤8.5 g/dl

Study characteristics (6)

Author, year, country	Study design	Population	Intervention	Comparison	Transfusion policy
Yoo, 2011, South Korea	RCT	74 patients scheduled for **valvular heart surgery**	EPO: 500 IU/kg EPO intravenously + iron sucrose 200 mg intravenously 16-24 hours before surgery	Control: Normal saline intravenously 16-24 hours before surgery	- Intraoperatively: Hb levels <7 mg/dl - Postoperatively: Hb levels <8 mg/dl

Study characteristics - summary

- Country
  - Europe: 10 studies
  - USA/Canada: 5 studies
  - Asia: 2 studies
- Setting
  - Orthopaedic surgery: 6 studies
  - Oncological surgery: 6 studies
  - Hysterectomy: 2 studies
  - Spinal surgery: 1 study
  - Orthopaedic + cardiac surgery: 1 study
  - Cardiac surgery: 1 study

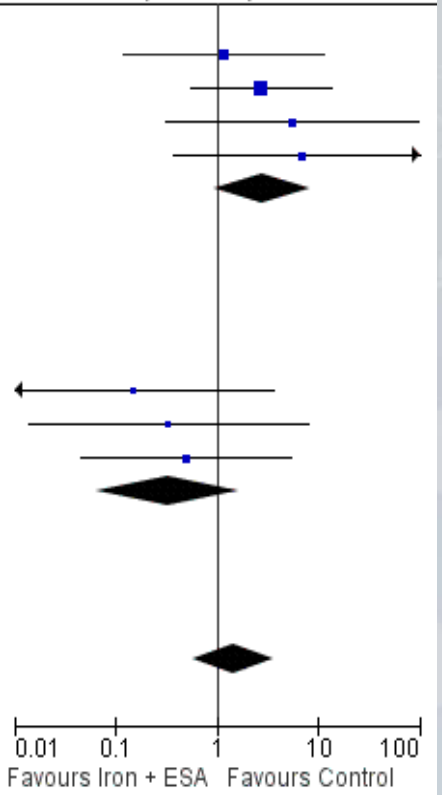
Study characteristics: Summary

- Intervention vs. comparison
  - ESA + oral iron vs. placebo/oral iron: 13 studies
  - ESA + IV iron vs. placebo/IV iron: 1 study
  - ESA + oral iron vs. no treatment: 1 study
  - ESA + IV iron vs. no treatment: 1 study
  - ESA + IV iron vs. normal saline IV: 1 study
- Transfusion policy for all patients: detailed information provided in 14/17 studies

ESA + Iron versus Placebo/No Treatment

CRITICAL OUTCOME: Mortality

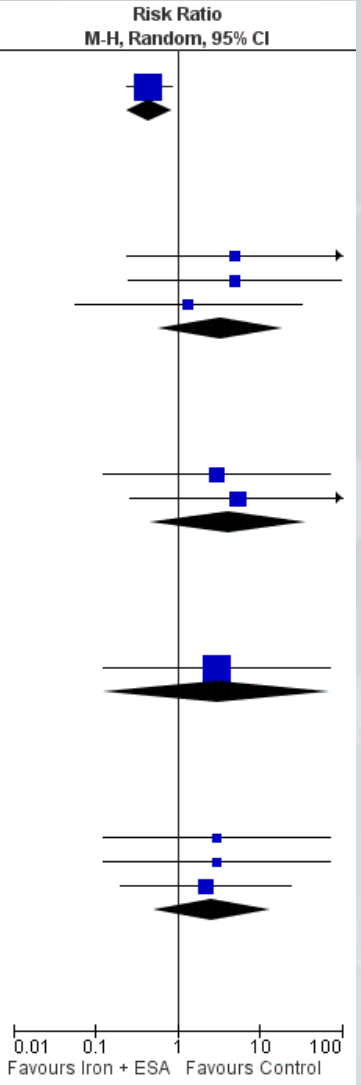
Study or Subgroup	Iron + ESA Events	Iron + ESA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Malignant disorders						
Heiss 1996 (postoperative death)	2	17	1	10	16.3%	1.18 [0.12, 11.39]
Kettelhack 1998 (death due to SAE)	5	52	2	57	32.0%	2.74 [0.56, 13.52]
Christodoulakis 2005 (150U+300U - postop death)	5	136	0	68	10.2%	5.54 [0.31, 98.75]
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: Tau² = 0.00; Chi² = 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: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 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: Tau² = 0.04; Chi² = 6.16, df = 6 (P = 0.41); I² = 3%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 4.62, df = 1 (P = 0.03), I² = 78.3%						



ESA + Iron versus Placebo/No Treatment

CRITICAL OUTCOME: Anaemia-associated ischaemic events

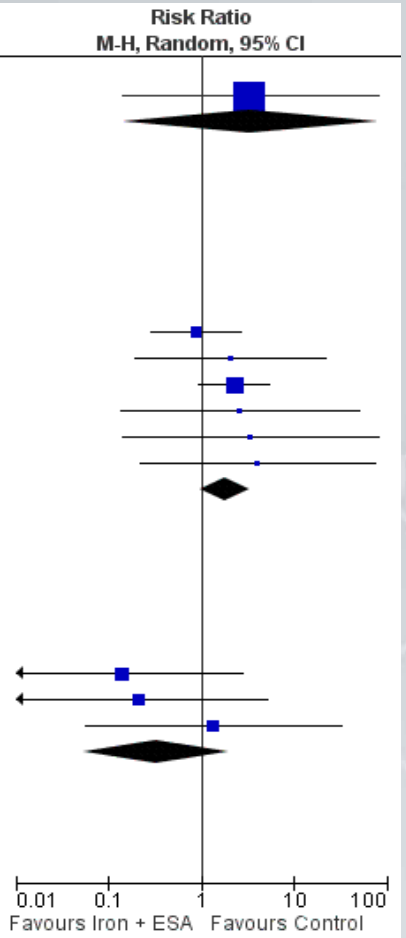
Study or Subgroup	Iron + ESA Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Acute kidney injury						
Yoo 2011 (postoperative acute kidney injury)	9	37	19	35	100.0%	0.45 [0.24, 0.85]
Subtotal (95% CI)		**37**		**35**	**100.0%**	**0.45 [0.24, 0.85]**
Total events	9		19			
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]
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: $Tau^2 = 0.00$; $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0\%$						
Test for overall effect: Z = 1.33 (P = 0.18)						
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]
Subtotal (95% CI)		**465**		**478**	**100.0%**	**4.14 [0.46, 37.25]**
Total events	3		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0\%$						
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: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 2 (P = 0.98); $I^2 = 0\%$						
Test for overall effect: Z = 1.14 (P = 0.25)						



ESA + iron versus Placebo/No Treatment

CRITICAL OUTCOME: Thromboembolic events

Study or Subgroup	Iron + ESA Events	Iron + ESA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Arterial thrombosis						
Kettelhack 1998 (arterial thrombosis)	1	48	0	54	100.0%	3.37 [0.14, 80.76]
Subtotal (95% CI)		**48**		**54**	**100.0%**	**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
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]
Stowell 2009 (DVT)	16	340	7	340	49.7%	2.29 [0.95, 5.49]
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: $Tau^2 = 0.00$; $Chi^2 = 2.39$, df = 5 (P = 0.79); $I^2 = 0\%$						
Test for overall effect: Z = 1.83 (P = 0.07)						
4.7.3 Pulmonary embolism						
So-Osman 2014 (PE)	0	125	0	138		Not estimable
Stowell 2009 (PE)	0	340	3	340	36.7%	0.14 [0.01, 2.76]
Feagan 2000 (20000U+40000U - PE)	0	123	1	78	31.6%	0.21 [0.01, 5.15]
Wurnig 2001 (125+250U - PE)	1	134	0	60	31.7%	1.36 [0.06, 32.80]
Subtotal (95% CI)		**722**		**616**	**100.0%**	**0.33 [0.05, 1.98]**
Total events	1		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.15$, df = 2 (P = 0.56); $I^2 = 0\%$						
Test for overall effect: Z = 1.21 (P = 0.23)						



ESA + Iron versus Placebo/No Treatment

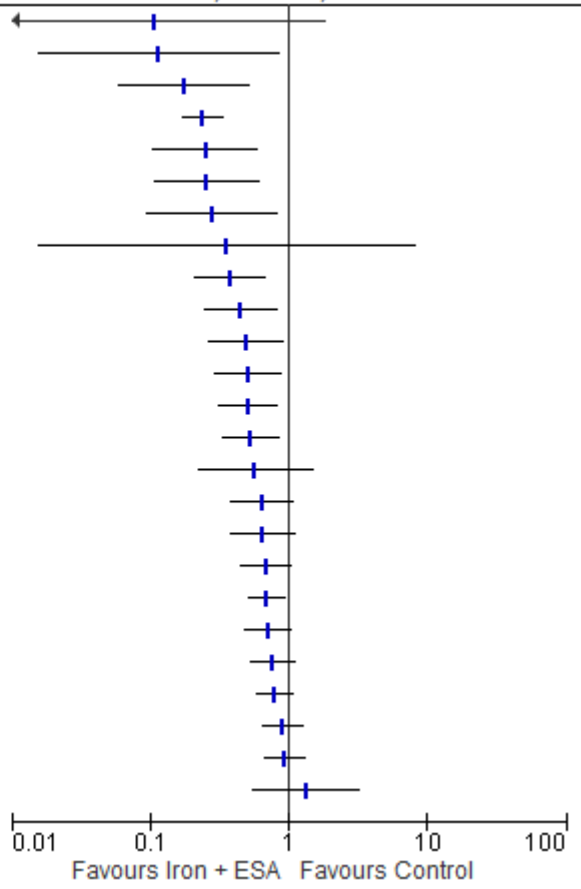
IMPORTANT OUTCOMES

Outcomes	Difference (ESA+iron vs placebo/no treatment)
Length of hospital stay	MD **1.54 days fewer** (3.29 fewer to 0.21 more)
Infections	A statistically significant effect on infections could **not** be demonstrated due to imprecise results (low number of events and/or large variability in results)

ESA + Iron versus Placebo/No Treatment

IMPORTANT OUTCOMES: RBC utilization (Proportion of patients receiving RBC transfusion)

Study or Subgroup	Iron + ESA Events	Iron + ESA Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI
Dousias 2003 (patients transfused periop)	0	23	5	27	0.11 [0.01, 1.82]
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]
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]
Feagan 2000 (40000U - patients transfused periop)	5	44	35	78	0.25 [0.11, 0.60]
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]
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]



ESA + iron versus Placebo/No Treatment

Quality of the body of evidence (critical outcomes)

Outcomes	Certainty of the evidence (GRADE)
(All-cause) mortality	⨁⨁◯◯ LOW[a,b]
Anemia-associated ischaemic events	⨁⨁◯◯ LOW[b,c]
Thromboembolic events	⨁⨁◯◯ LOW[a,b]

a. Risk of bias (-1): Performance bias, potential selection bias, attrition bias
b. Imprecision: low number of events
c. Risk of bias (-1): potential selection bias and detection bias (i.e. blinding of outcome assessors).

6. How large are the resource requirements (costs)? (= how large is the cost of the difference in resource use between the intervention and comparison?)

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings

- Varies
- Don’t know

Resource use

Outcome	Absolute Cost (intervention versus control) in euros	Author, year, country
Iron versus standard of care		
Direct cost (iron + transfusion units)	-3,583€	Lidder, 2007, UK
ESA versus no treatment		
Direct cost (EPO + transfusion units)	-280€	Bedair, 2015, USA
Direct cost (EPO + transfusion units)	Cost protocol expense intervention group (EPO): 241€ per patient Cost of 1 unit of blood = 268€ -> Saving of approximately half a unit of blood per patient was not cost-effective. -> The increased length of stay of 0.57 days per patient would increase the cost of the control group by 453€ per patient, thus making the protocol eventually convenient.	Weltert, 2010, Italy
Direct cost (EPO + transfusion units)	Cost protocol expense intervention group (EPO): 316€ per patient Cost of 1 RBC transfusion = 614€ -> a cost increase of 108€ per patient in the EPO group -> this additional cost might be balanced by reduction in hospital length of stay of approximately 0.57 days in the EPO group (6.92 days vs. 7.49 days) and by a related cost reduction of approximately 181€	Weltert, 2015, Italy
ESA+iron versus placebo/no treatment		
Direct cost (EPO)	The retail cost of epoetin alfa is 174€ per 20.000-U vial and 343€ per 40.000-U vial.	Feagan, 2000, Canada
Direct cost (EPO + iron + transfusion units)	EPO: 178€/day Iron: 20€/day RBC unit: 397€	Kosmadakis, 2003, Greece
Direct cost (EPO + transfusion units)	EPO: 998€/patient RBC unit: 133€	Qvist, 1999, Denmark
Direct cost (EPO + transfusion units)	EPO: 779€/patient RBC unit: 822€ (~4 times product price)	So-Osman, 2014, The Netherlands

Conclusions

- Pre-operative RBC transfusion vs. standard of care: cannot demonstrate a difference in outcomes and RBC utilization
- Pre-operative iron: less RBC utilization (number of patients transfused)
- Pre-operative ESA:
  - Cannot demonstrate a difference in outcomes (favourable and adverse)
  - Less RBC utilization (proportion of patients transfused)

Conclusions

- Pre-operative ESA + iron:
  - Significant variation in treatment regimens (drugs, timing, dose, frequency, number of doses)
  - No information on final pre-operative Hb (was target set too high?)
  - Cannot demonstrate a difference in outcomes (mortality, anemia associated ischemic events, arterial and venous thrombosis)
    - ?Trends
      - increased mortality in cancer surgery
      - decreased AKI
  - Less RBC utilization (proportion of patients receiving RBC transfusion)