

# Recommandations ICC PBM: *Anémie préopératoire*

**Pr Sigismond LASOCKI**

Département Anesthésie-Réanimation

Pole ASUR

CHU Angers

UMR CNRS 6214 – INSERM 771

Université d'Angers



SFTS Juin 2019



# Conflits d'intérêts

- J'ai, et/ou mon institution, avons reçu des subventions des laboratoires:
  - Vifor Pharma
  - Pfizer
  - Masimo

# 3 questions « simples »

## Preoperative Anemia

**PICO 1—Adverse Events:** In patients undergoing elective surgery [population], is preoperative anemia [intervention/risk factor] a risk factor for adverse clinical or economic outcome [outcomes], compared with no preoperative anemia [comparison]?

**PICO 2—Definition:** In patients undergoing elective surgery [population], the question “Should a specific hemoglobin cutoff [index test] vs another hemoglobin cutoff [comparator test] be used to diagnose preoperative anemia [outcome]?” was not answered because of lack in evidence.

**PICO 3—Management:** In patients with preoperative anemia undergoing elective surgery [population], is the use of red blood cell transfusion or iron supplementation and/or erythrocyte-stimulating agents [intervention] effective to improve clinical and economic outcomes [outcomes], compared with no intervention, placebo, or standard of care [comparison]?

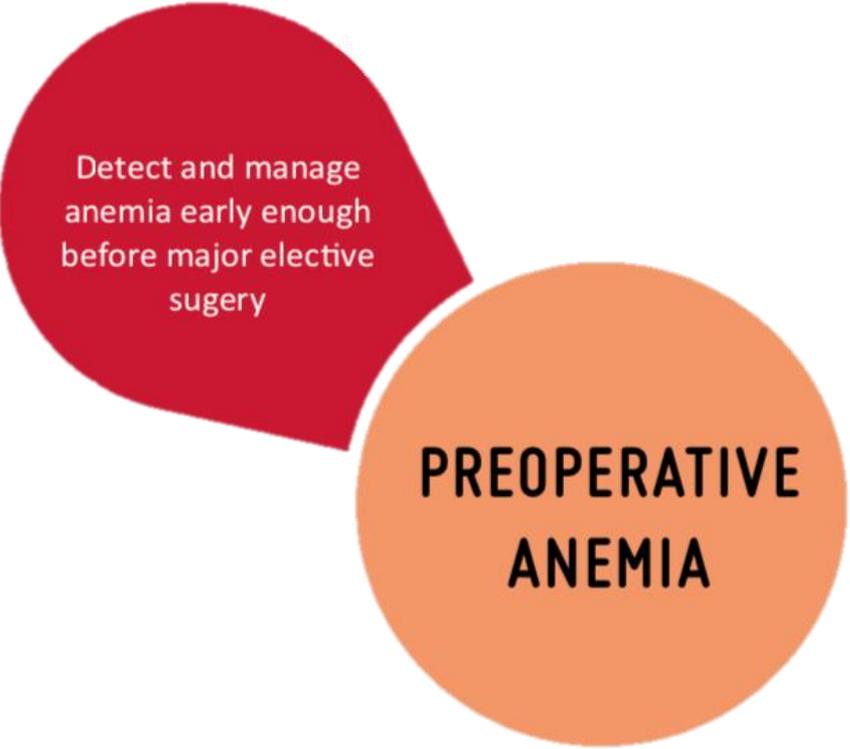
# 4 recommendations

Table 1. Clinical Recommendations: Preoperative Anemia

Clinical Recommendation	Level of Evidence
CR1–Detection and management of preoperative anemia early enough before major elective surgery	Strong recommendation, low certainty in the evidence of effects
CR2–Use of iron supplementation to reduce red blood cell transfusion rate in adult preoperative patients with iron-deficient anemia undergoing elective surgery	Conditional recommendation, moderate certainty in the evidence of effects
CR3– <i>Do not</i> use erythropoiesis-stimulating agents routinely in general for adult preoperative patients with anemia undergoing elective surgery	Conditional recommendation, low certainty in the evidence of effects
CR4–Consider short-acting erythropoietins in addition to iron supplementation to reduce transfusion rates in adult preoperative patients with hemoglobin concentrations <13 g/dL undergoing elective major orthopedic surgery	Conditional recommendation, low certainty in the evidence of effects



*Une seule forte...*



Detect and manage  
anemia early enough  
before major elective  
surgery

## **PREOPERATIVE ANEMIA**

# Evidence-to-Decision framework (PICO 1)

CRITERIA	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
1. DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?	 <b>EVIDENCE</b>	 <b>Rapporteurs</b>  <b>Audience</b>
2. UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?	 <b>EVIDENCE</b>	 <b>Rapporteurs</b>  <b>Audience</b>
3. CERTAINTY OF EVIDENCE	What is the overall quality of the evidence of effects?	 <b>EVIDENCE</b>	 <b>Rapporteurs</b>  <b>Audience</b>
4. VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?	 <b>OPINION POLL</b>	 <b>Rapporteurs</b>  <b>Audience</b>
5. BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	 <b>EVIDENCE</b>	 <b>Rapporteurs</b>  <b>Audience</b>
6. RESOURCES REQUIRED	How large are the resource requirements (costs)?	Not Applicable	
7. COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?	Not Applicable	
8. EQUITY	What would be the impact on health equity?	Not Applicable	
9. ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	Not Applicable	
10. FEASIBILITY	Is the intervention feasible to implement?	Not Applicable	



INTERNATIONAL  
CONGRESS  
**ICC-PBM**  
FRANKFURT  
2018

# 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)

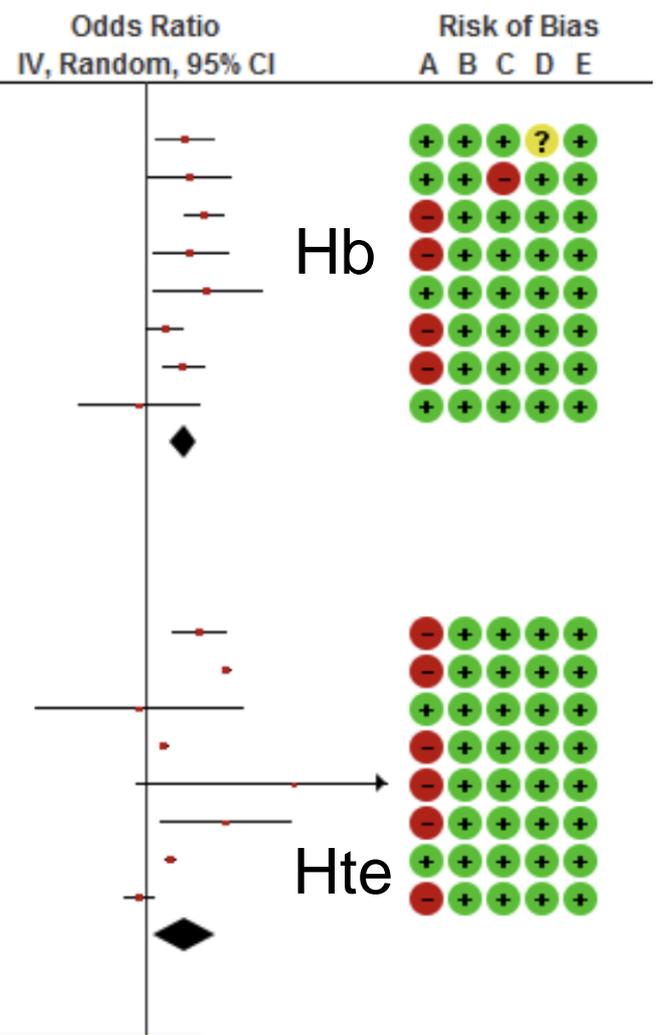
Outcomes	With no preoperative anaemia	With preoperative anaemia as a risk factor for adverse events	Difference	Relative effect (95% CI)
Hospital mortality	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 2.09</b> (1.48 to 2.95)
30-day mortality	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 2.20</b> (1.68 to 2.88)
30-day mortality (subgroup: severity of anaemia)	see Figure 3 (forest plot)			
Acute myocardial infarction	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 1.39</b> (0.99 to 1.96)
Acute ischaemic stroke or CNS complications	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 1.19</b> (1.02 to 1.38)
Acute kidney injury, renal failure/dysfunction or urinary complications	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 1.78</b> (1.35 to 2.34)
GI dysfunction	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 1.54</b> (0.50 to 4.79)
Acute peripheral vascular ischaemia	0 per 1.000	<b>0 per 1.000</b> (0 to 0)	<b>0 fewer per 1.000</b> (0 fewer to 0 fewer)	<b>OR 1.51</b> (0.20 to 11.52)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio	
				IV, Random, 95% CI	
<b>1.2.1 WHO definition (Hb &lt;13 g/dL for males and Hb &lt;12 g/dL for women)</b>					
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]
<b>Subtotal (95% CI)</b>			<b>37.7%</b>	<b>2.08</b>	<b>[1.62, 2.69]</b>

Heterogeneity: Tau<sup>2</sup> = 0.05; Chi<sup>2</sup> = 11.61, df = 7 (P = 0.11); I<sup>2</sup> = 40%  
 Test for overall effect: Z = 5.65 (P < 0.00001)

<b>1.2.2 HTC &lt;39% (males) or &lt;36% (females)</b>					
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]
<b>Subtotal (95% CI)</b>			<b>35.8%</b>	<b>2.13</b>	<b>[1.17, 3.91]</b>

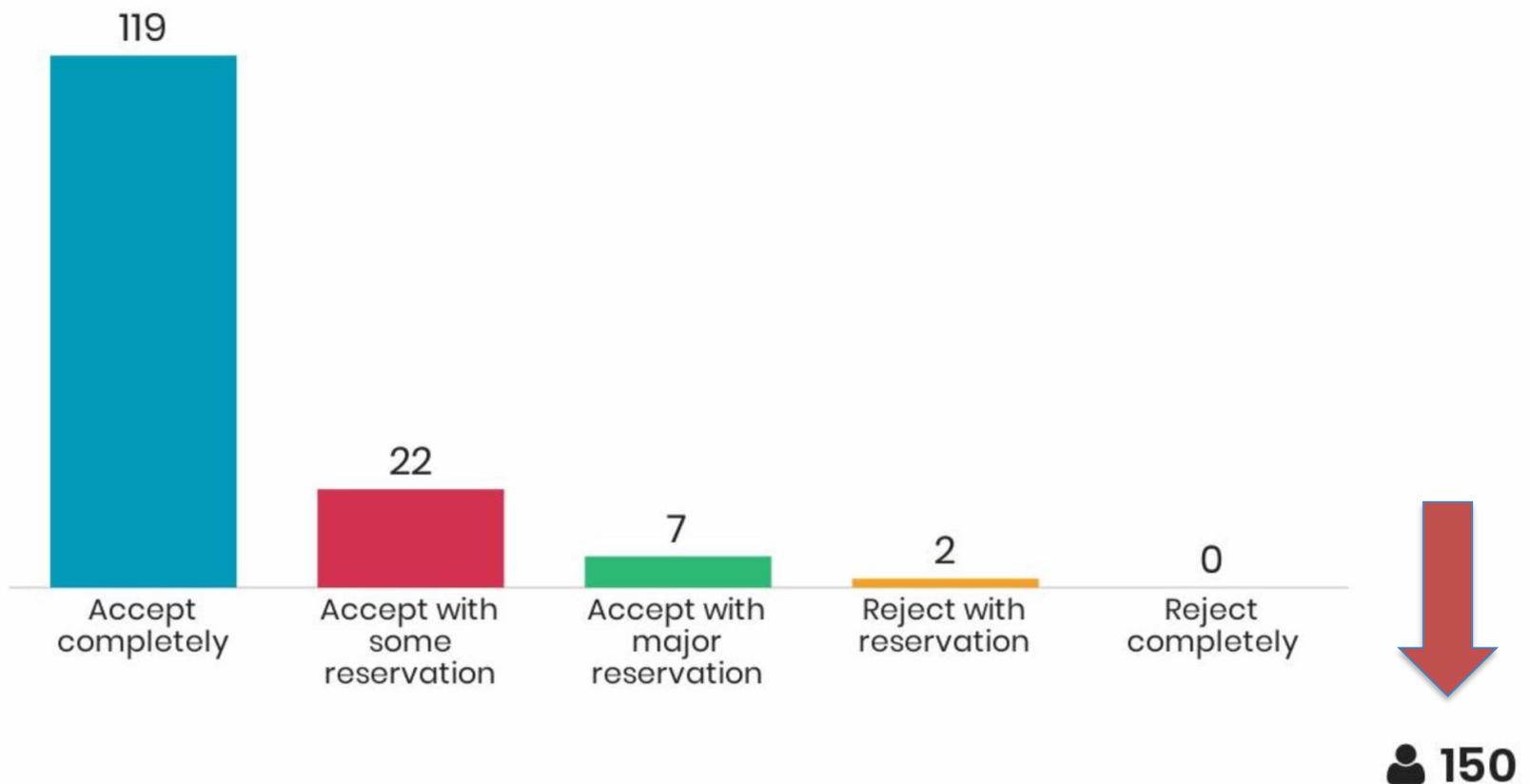
Heterogeneity: Tau<sup>2</sup> = 0.57; Chi<sup>2</sup> = 705.33, df = 7 (P < 0.00001); I<sup>2</sup> = 99%  
 Test for overall effect: Z = 2.46 (P = 0.01)



**X 2.2**

## detect and classify anaemia early before major elective surgery

Mentimeter



# Questions non résolues...

Detect and manage  
anemia early enough  
before major elective  
surgery

PREOPERATIVE  
ANEMIA

- Quelle définition?!
- Quel timing « **early enough** »?
- « **manage** »?

# « Nos » recommandations

**EJA**

*Eur J Anaesthesiol* 2017; **34**:332–395

## GUIDELINES

**Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology**

Société Française d'Anesthésie et de Réanimation

## Examens pré interventionnels systématiques

*We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. 1C*

*If anaemia is present, we recommend identifying the cause (iron deficiency, renal insufficiency or inflammation). 1C*

*We recommend treating iron deficiency with iron supplementation. 1B*

*We recommend the use of intravenous iron in preference to oral iron. 1C*

*If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. 2C*

*In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. 1C*

Lors d'une intervention à risque intermédiaire ou élevé, quel que soit l'âge, il est recommandé de prescrire un hémogramme avant l'acte pour son caractère pronostique ou d'aide à l'élaboration d'une stratégie transfusionnelle. (GRADE 1+)

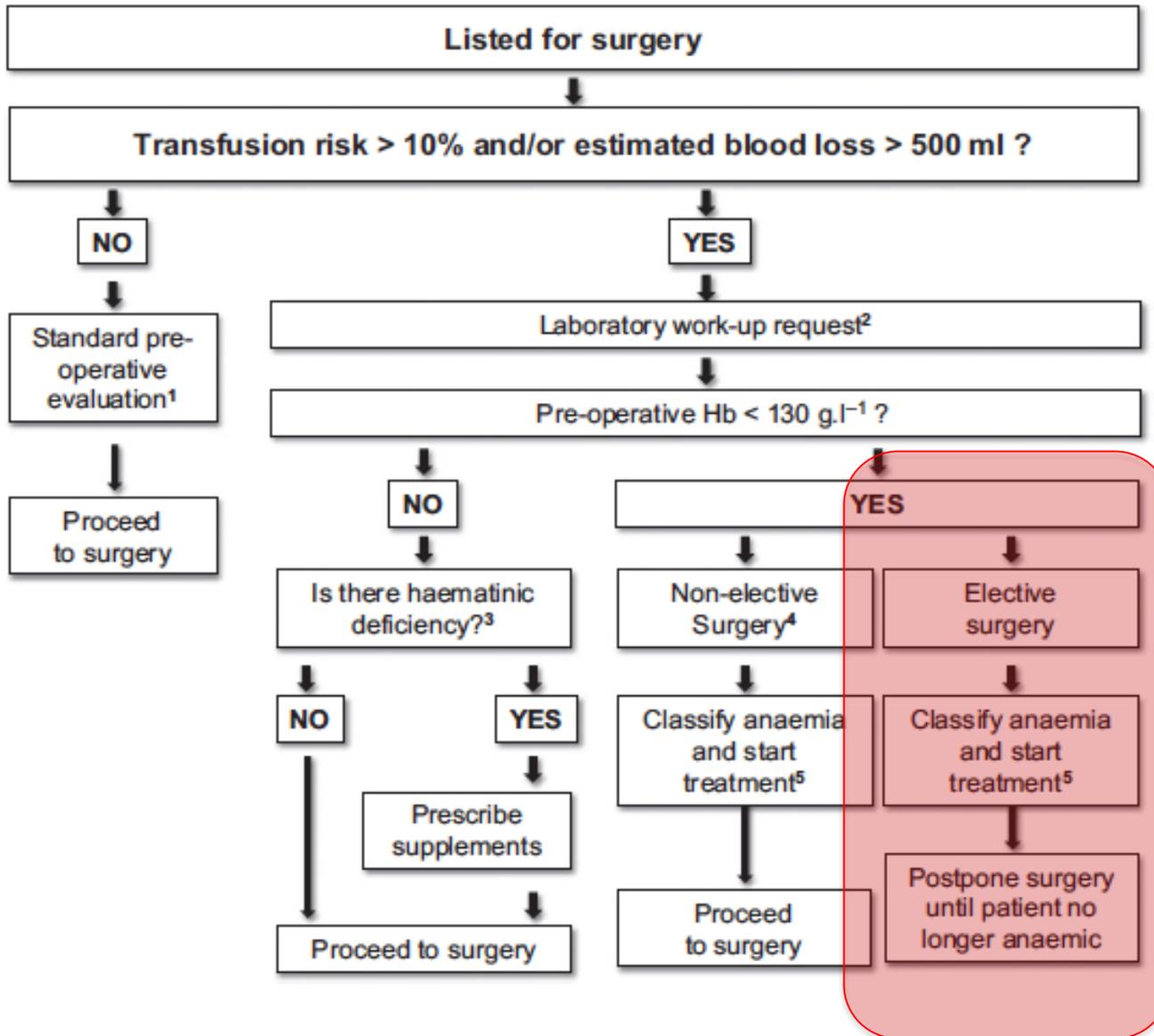


# Consensus Statement

---

## International consensus statement on the peri-operative management of anaemia and iron deficiency

M. Muñoz,<sup>1</sup> A. G. Acheson,<sup>2</sup> M. Auerbach,<sup>3</sup> M. Besser,<sup>4</sup> O. Habler,<sup>5</sup> H. Kehlet,<sup>6</sup> G. M. Liumbruno,<sup>7</sup> S. Lasocki,<sup>8</sup> P. Meybohm,<sup>9</sup> R. Rao Baikady,<sup>10</sup> T. Richards,<sup>11</sup> A. Shander,<sup>12</sup> C. So-Osman,<sup>13</sup> D. R. Spahn<sup>14</sup> and A. A. Klein<sup>15</sup>



**Chir à risque:**  
 Il faut avoir un bilan pré-op et éventuellement **décaler la chirurgie**

Detect and manage anemia early enough before major elective surgery

Optimal Hb thresholds for definition of preoperative anemia in different patient groups: further research needed

## PREOPERATIVE ANEMIA



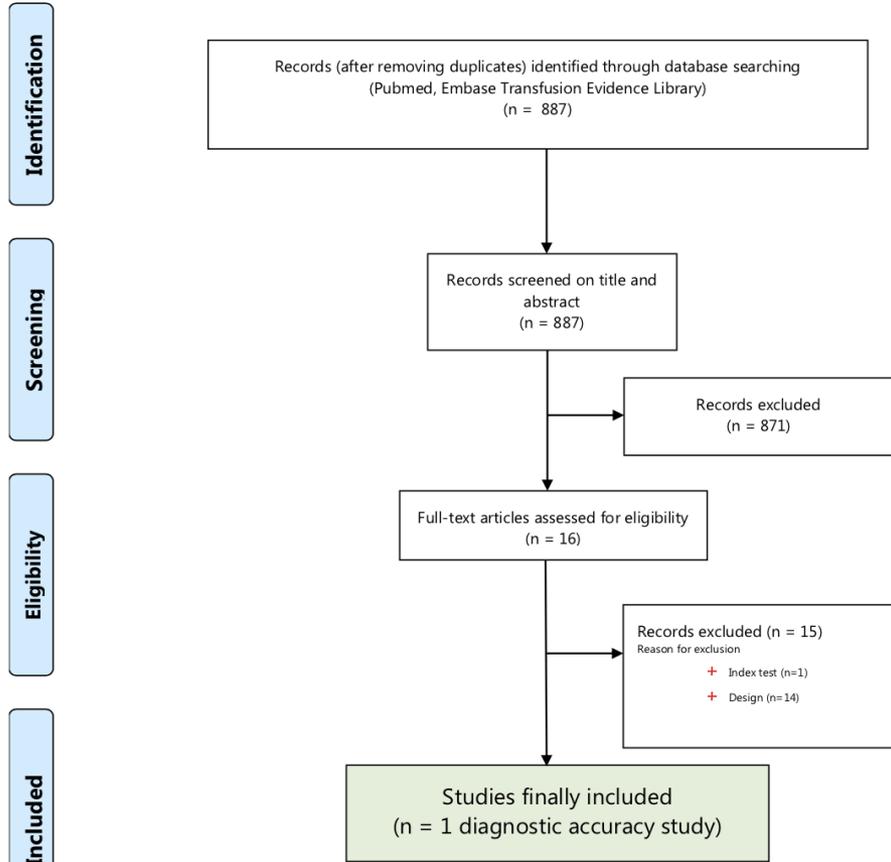
INTERNATIONAL  
CONGRESS OF PERIOPERATIVE MEDICINE  
ICC-PBM  
FRANKFURT  
2018

# 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**

Flow chart



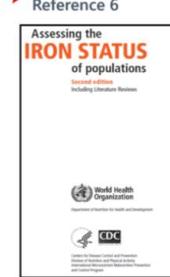
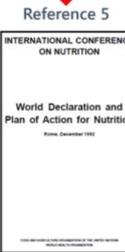
# Définition de l'anémie



Recommendations

Table 1  
Haemoglobin levels to diagnose anaemia at sea level (g/L)

Population	Anaemia*			
	Non-Anaemia*	Mild†	Moderate	Severe
Children 6–59 months of age	115 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



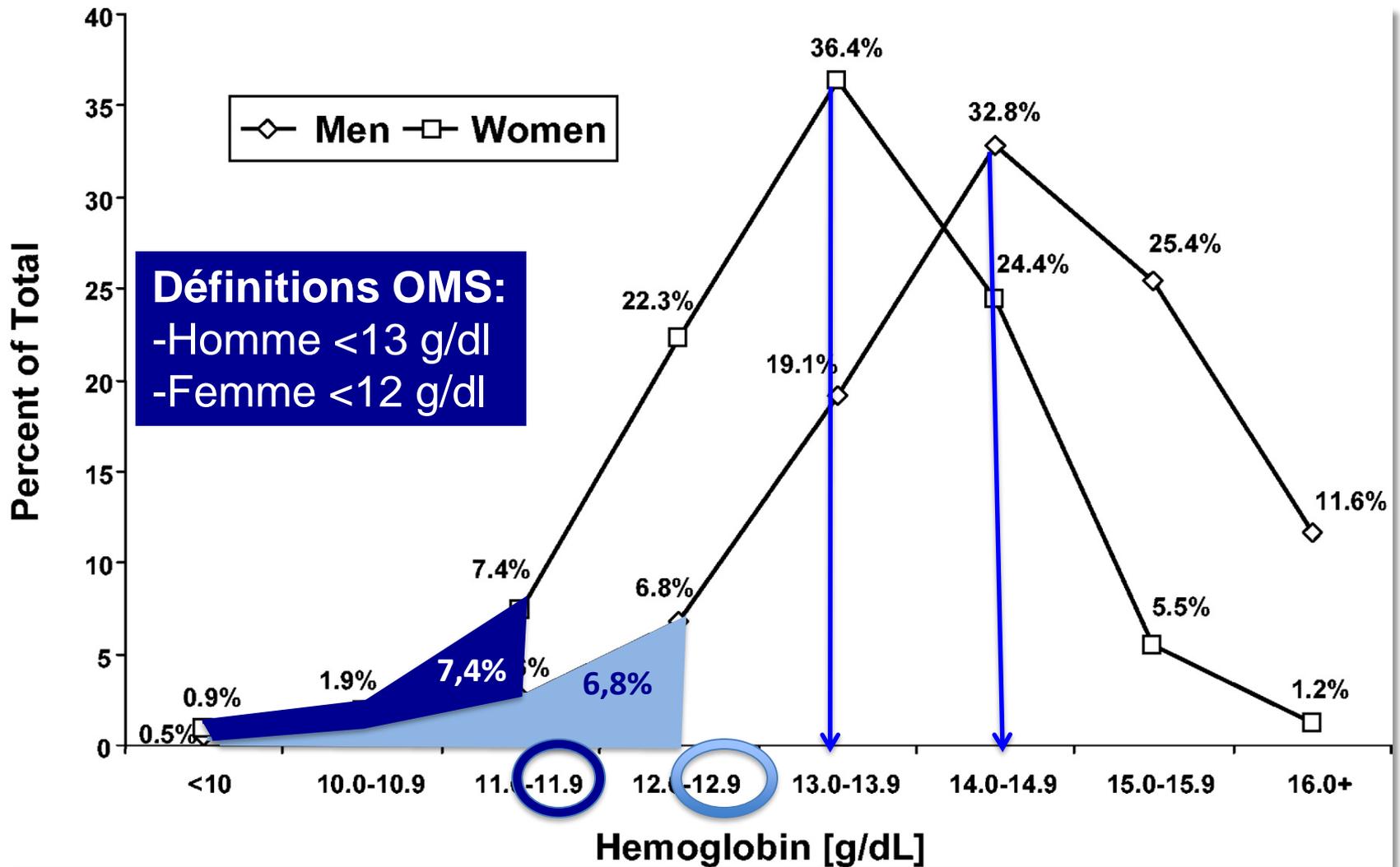
WHO recognized the public health importance of nutritional anaemia over 50 years ago (1) and haemoglobin threshold values to classify anaemia were first published in the report of a 1958 WHO Study Group (2). The thresholds were chosen arbitrarily. Revised thresholds were published in 1968 (3) based on a review of five earlier reports. The following text dealing with the recommendations is taken from the 1968 report: "The report (2) of the 1958 WHO Study Group recommended haemoglobin values below which anaemia could be considered to exist. These figures were chosen arbitrarily and it is still not possible to define normality precisely (4). However, more recent data (5–8) indicate that the values given previously should be modified. It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures given below (the values are given in g/100 ml of venous blood of persons residing at sea level):

children aged 6 months to 6 years:	11
children aged 6–14 years:	12
adult males:	13
adult females, non-pregnant:	12
adult females, pregnant:	11"

Five references were provided by WHO for the more recent data. Four referred to 1. Naving 1966

**Conclusion:** the WHO definition (Hb <130g/L (males) or Hb <120g/L (females)) to diagnose anaemia are not "evidence-based" but based on expert opinion and arbitrarily selected cut-offs 60 years ago.

# Distribution des concentrations d'Hb

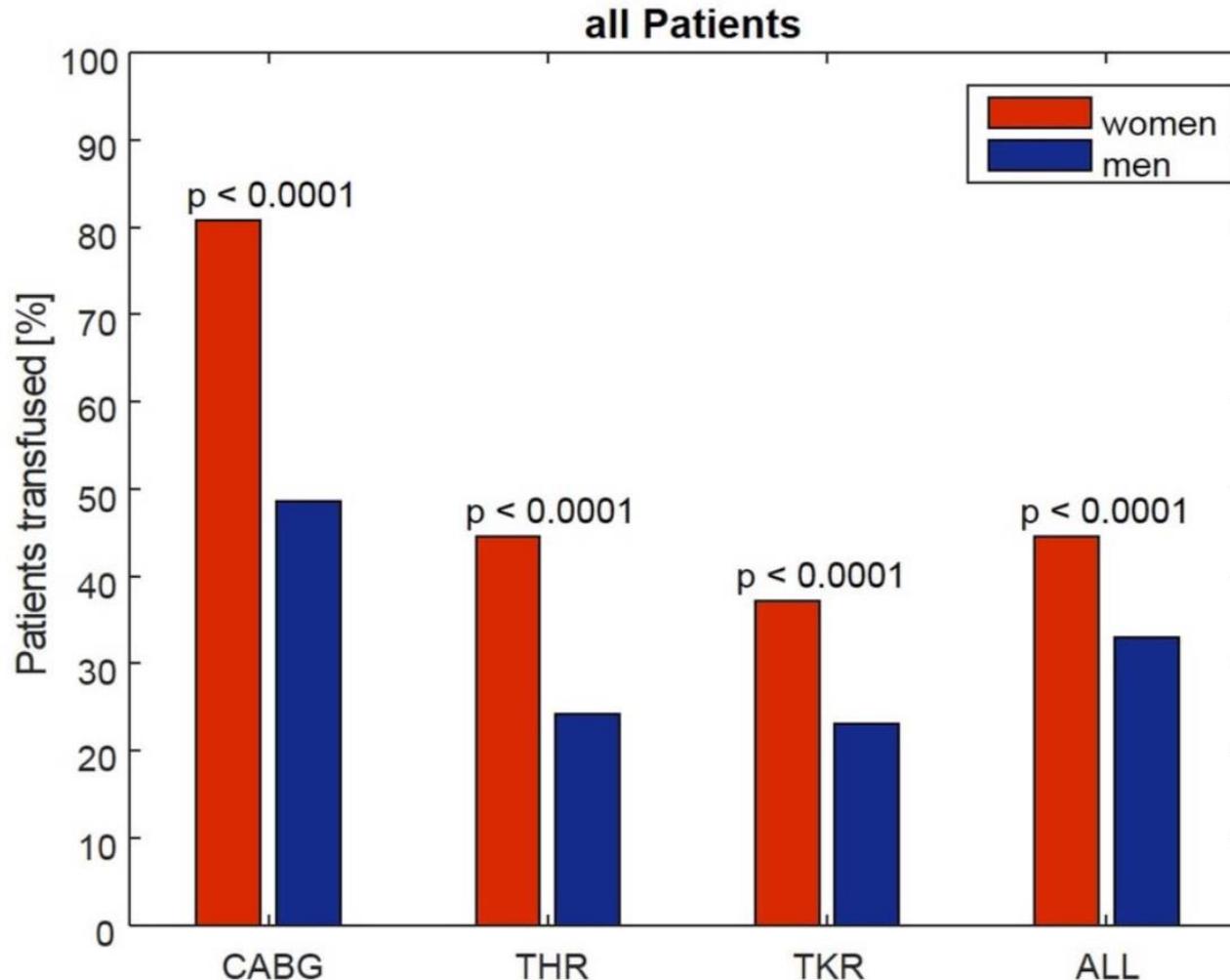


**n=26372**

# Non à la discrimination !



# Les femmes sont plus transfusées



- N=6530 pts, 23 centres
- Transfusion jusqu'à J5 post-op

**PREOPERATIVE  
ANEMIA**

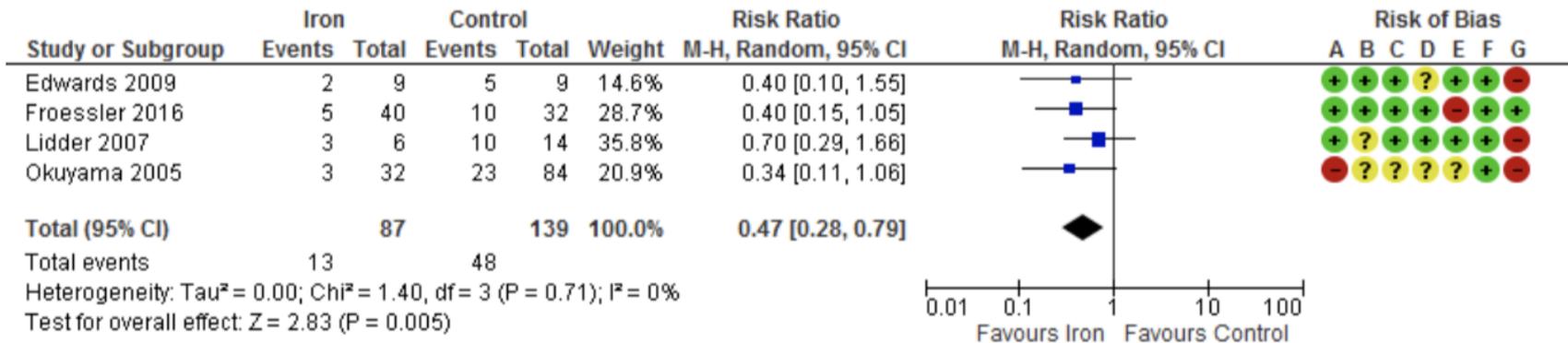
Detect and manage anemia early enough before major elective surgery

Optimal Hb thresholds for definition of preoperative anemia in different patient groups: further research needed

Use iron supplementation in adult preoperative elective surgery patients with iron-deficient anemia to reduce RBC transfusion rate\*

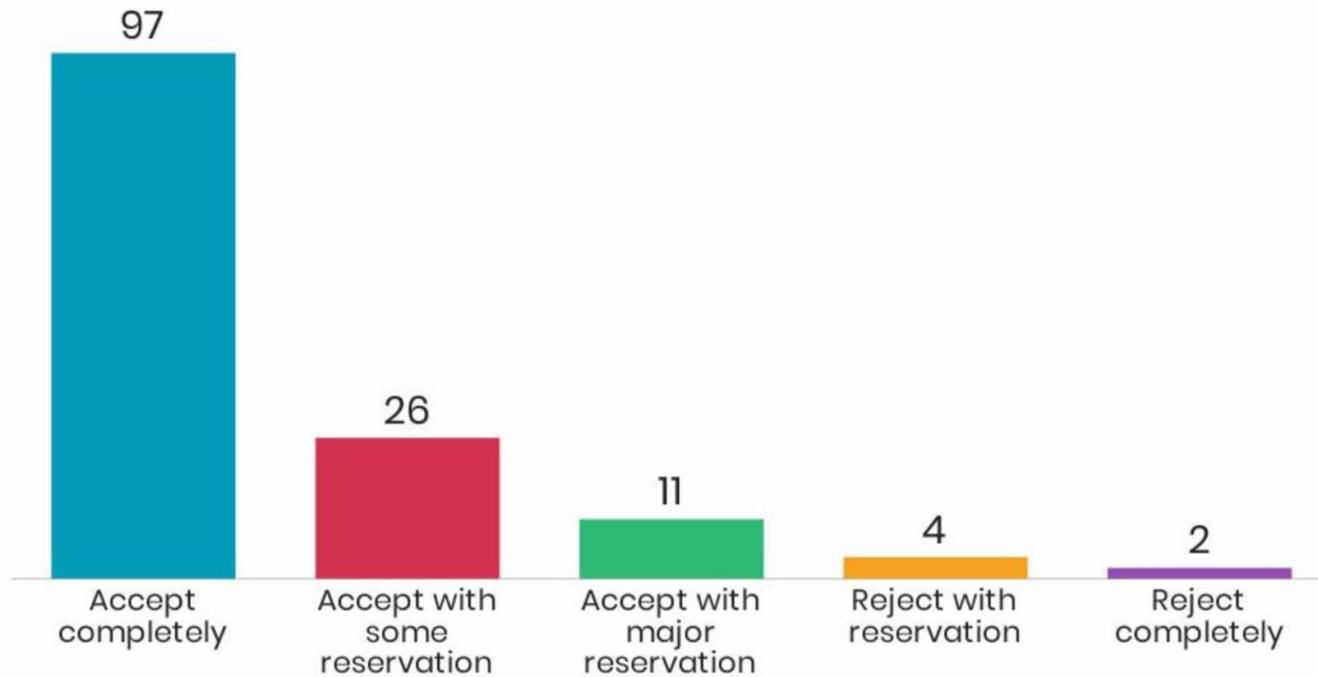
# Intérêt du traitement martial

**eFigure 4.** Study-Specific Risk Ratios Representing the Association Between Iron Supplementation (Compared to Placebo/Usual Care) and the Number of RBC Transfusions



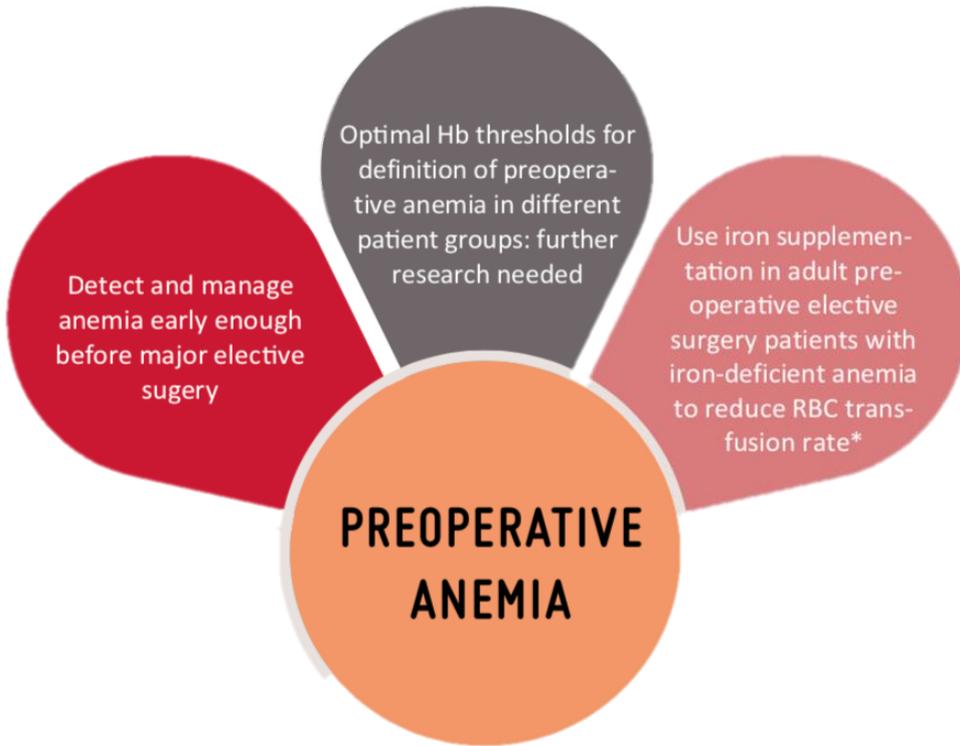
## iron supplementation in adult preoperative elective surgery patients with iron-deficiency anaemia to reduce red blood cell transfusion rate

Mentimeter



140

# Questions non résolues



- IV vs Oral?
- Diagnostic de la CM?

\* Choice of iron formulation and administration based on the degree of anemia, time to surgery procedure and the ability to absorb and tolerate oral iron

# Recommandations pour le diagnostic de la carence martiale: HAS 2011

*Prendre en compte le contexte clinique et réaliser préalablement l'hémogramme*

**Ferritinémie**

**OUI**

- En **première intention** lors d'une recherche de carence en fer
- Elle est témoin des réserves en fer
- Si son taux est diminué, inutile de rechercher un autre marqueur
- Son taux peut être augmenté dans les situations inflammatoires

**Coefficient de Saturation de la Transferrine (CST)**

**OUI DANS LES SITUATIONS COMPLEXES**

- **Pour aider au diagnostic dans les situations inflammatoires** (cancer, maladies inflammatoires chroniques intestinales), insuffisance rénale chronique, résultat de la ferritine sérique non contributif
- Il est calculé à partir du fer sérique et de la transferrine

**Fer seul**

**Fer + Ferritine**

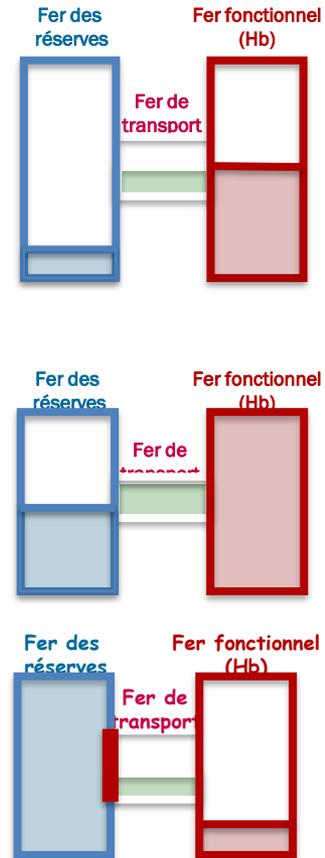
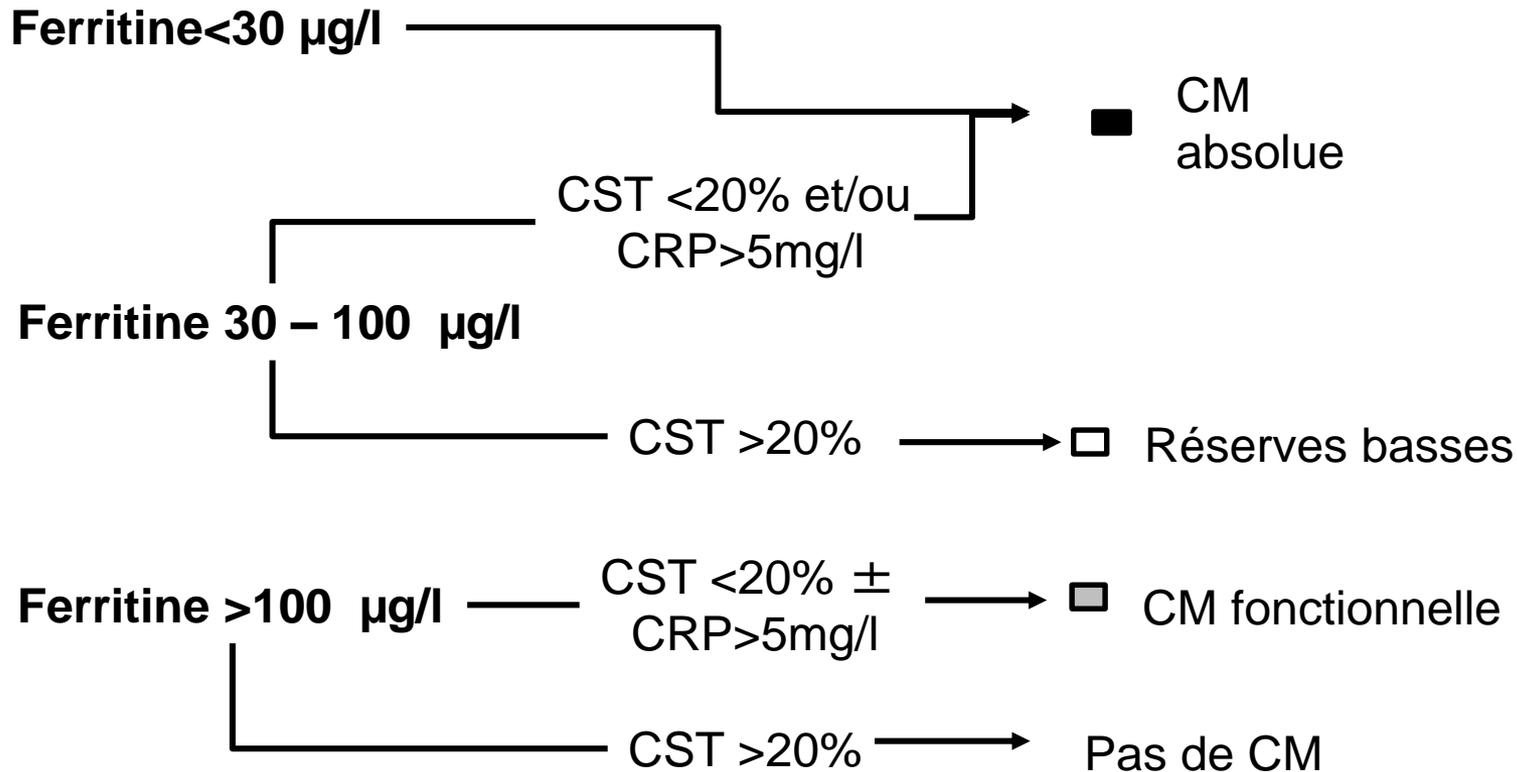
**NON**

- Le dosage du fer seul est **moins informatif** que celui de la ferritine (importante variabilité nyctémérale)
- Le dosage du fer en plus de celui de la ferritine n'apporte pas d'informations supplémentaires

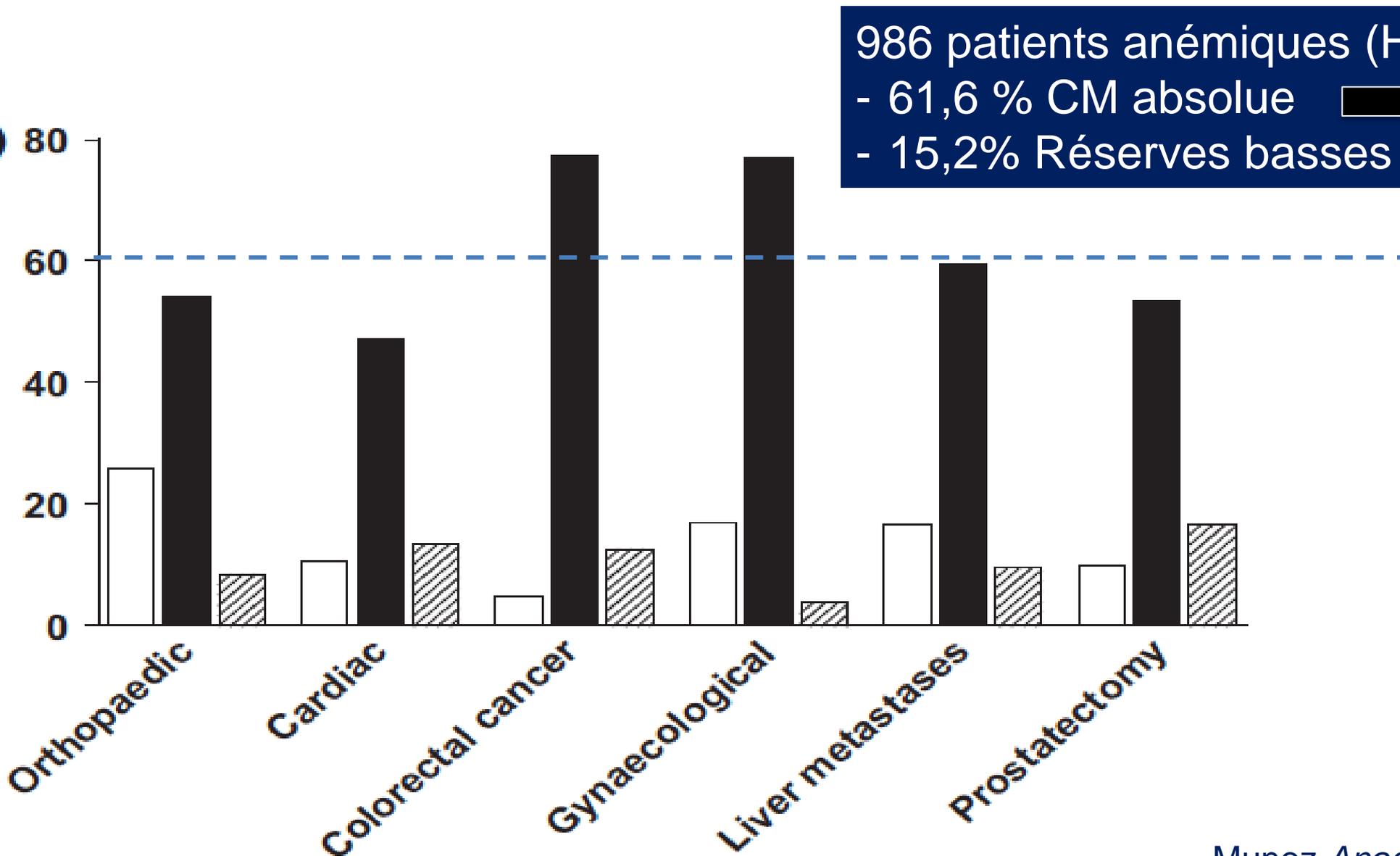
**Ferritine basse**  
=  
**Réserves basses**

**CST bas**  
=  
**Défaut d'apport**

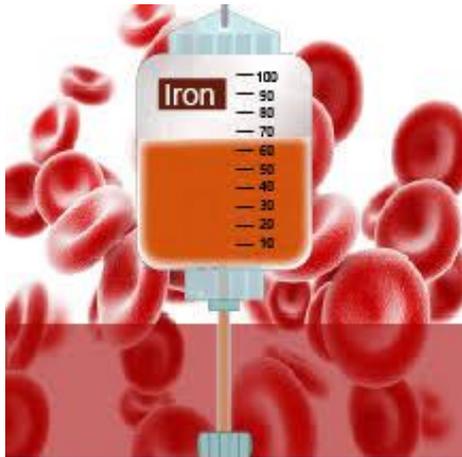
# Diagnostic Carence Martiale



# Prévalence de l'anémie par CM



# IV ou per OS ?



### GUIDELINES

#### **Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology**

*We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. 1C*

*If anaemia is present, we recommend identifying the cause (iron deficiency, renal insufficiency or inflammation). 1C*

*We recommend treating iron deficiency with iron supplementation. 1B*

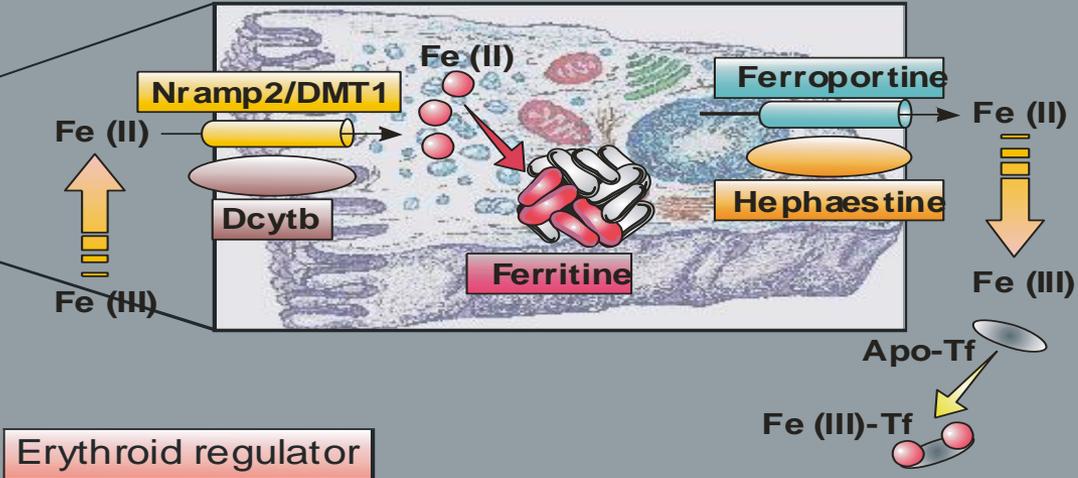
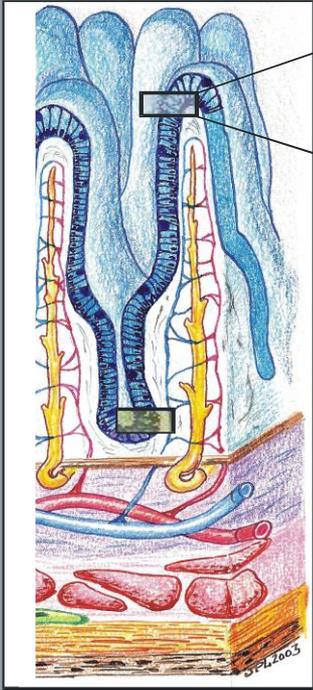
*We recommend the use of intravenous iron in preference to oral iron. 1C*

*If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. 2C*

*In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. 1C*

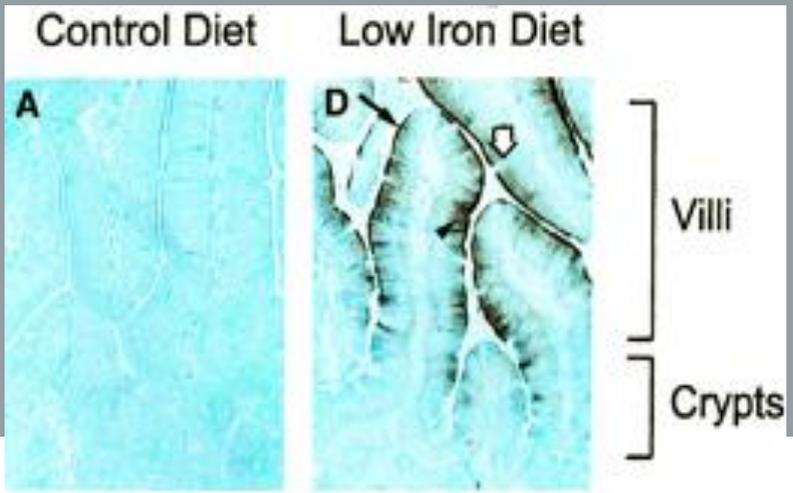
# Absorption intestinale du fer

Villosités duodénales



Erythroid regulator

Store regulator



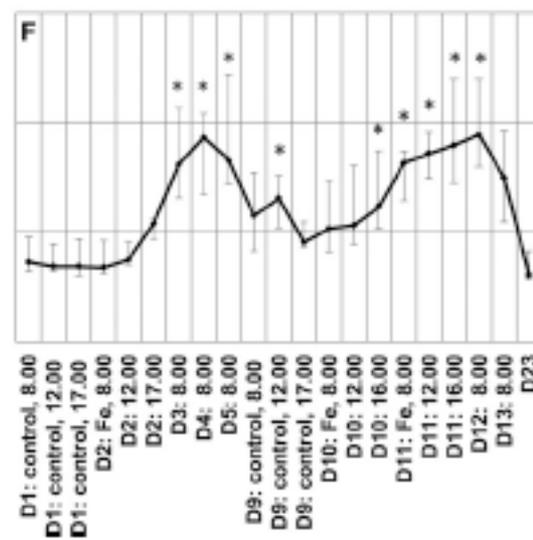
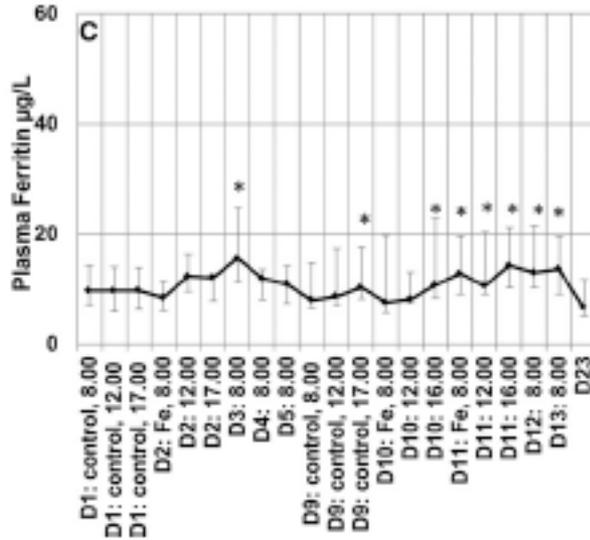
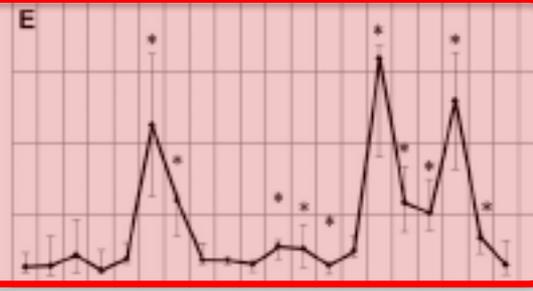
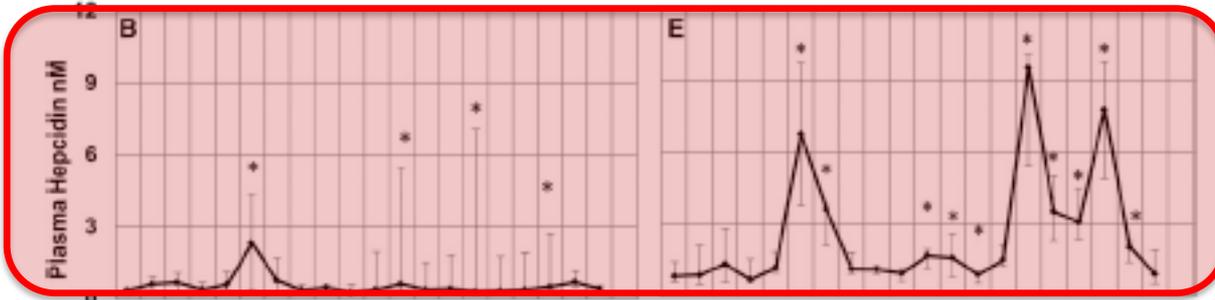
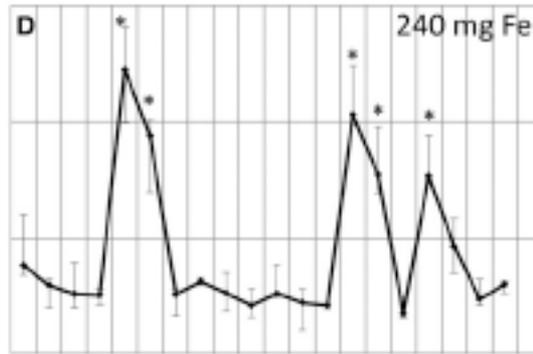
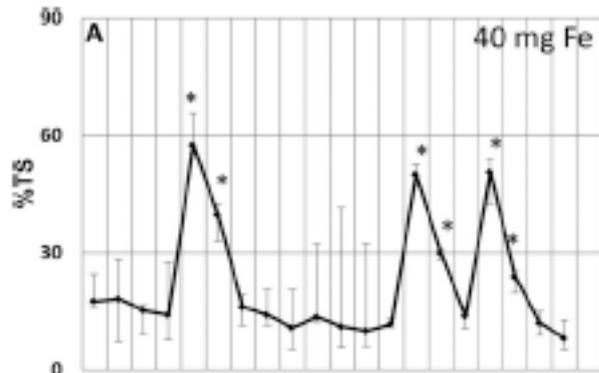
Nramp2/DMT1

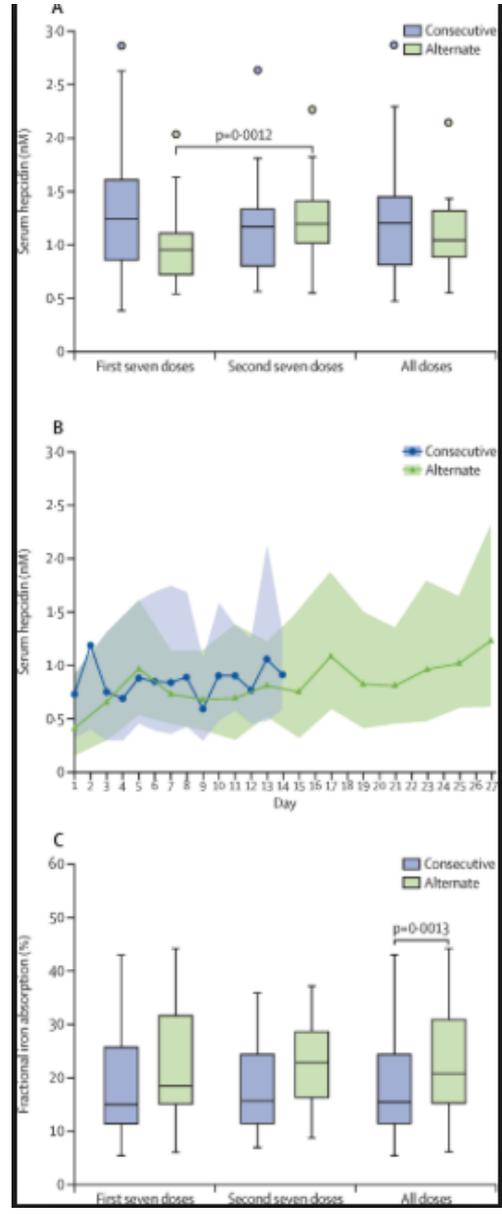
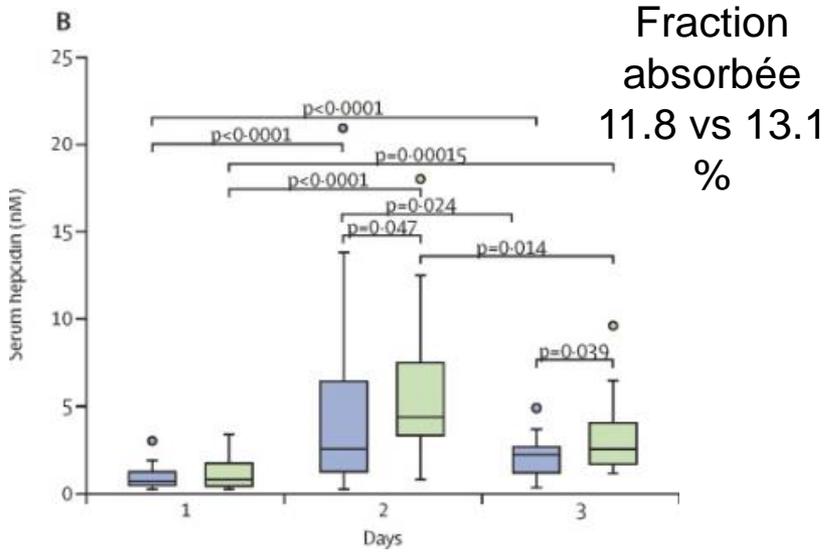
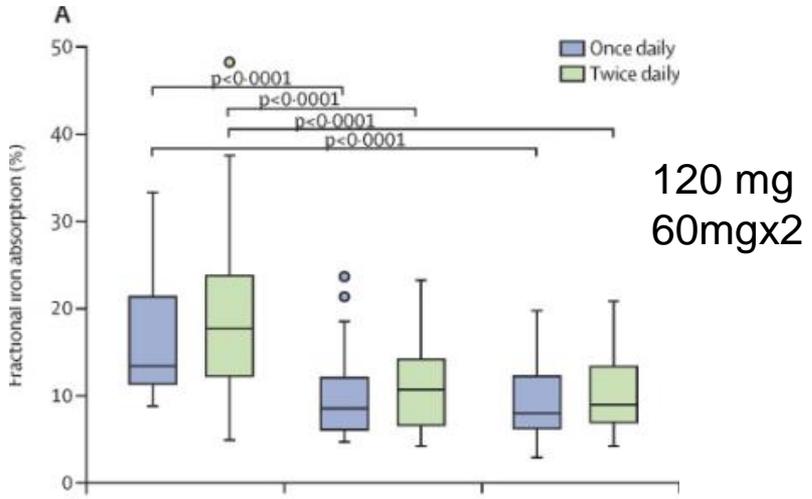
# L'absorption du FER oral est limitée

Table 1. Iron absorption and iron status markers with increasing oral doses of FeSO<sub>4</sub> in young women (study 1)

Fe dose (mg)	Day	Iron bioavailability		Iron status					
		Fractional Fe absorption (%)*	Fe absorbed (mg)*	PHep (nM)*	Plasma Fe (µg/mL)†	Transferrin saturation (%‡)	PF (µg/L)*	sTfR (mg/L)†	Body iron stores (mg/kg BW)†
10	1	NA	NA	0.30 (0.12-0.48)	0.63 (0.34)	20.9 (15.1)	10.0 (3.4-21.8)	8.2 (4.2)	-0.05 (3.7)
	2	22.7 (14.7-57.1)	9.1 (5.8-22.8)	0.35 (0.11-0.77)	0.55 (0.35)	16.5 (11.7)	9.1 (4.9-25.4)	8.4 (3.8)	-0.8 (3.7)
	9	19.4 (15.8-22.9)	7.8 (6.3-9.2)	0.59 (0.19-4.6)	0.67 (0.61)	21.3 (24.6)	10.3 (5.1-40.8)	7.1 (3.2)	0.11 (4.1)
	10	16.7 (11.8-20.7)‡	6.7 (4.7-8.3)‡	0.45 (0.05-4.3)	0.60 (0.4)	18.6 (16.3)	15 (8.4-51.6)	7.8 (3.5)	1.2 (3.6)
	23	NA	NA	ND	ND	ND	7.7 (4.2-20.1)	5.6 (1.9)	-0.64 (2.4)
30	1	NA	NA	0.93 (0.1-3.7)	1.2 (1.1)	29.8 (12.8)	19.4 (6.0-38.4)	4.8 (1.7)	3.5 (3.5)
	2	19.0 (10.5-30.9)	15.2 (8.4-24.7)	0.90 (0.40-2.2)	0.80 (0.40)	21.3 (8.4)	17.7 (6.0-43.6)	4.8 (1.6)	3.5 (3.4)
	9	18.2 (8.5-26.0)	14.6 (8.5-26.0)	1.1 (0.62-2.1)	0.75 (0.41)	20.9 (9.6)	17.7 (6.5-51.1)	4.5 (2.5)	3.6 (3.4)
	10	11.7 (8.4-24.7)§	9.3 (4.8-12.4)§	2.1 (0.98-5.1)¶	0.96 (0.60)	23.5 (12.5)	33 (24.1-55.0)	3.9 (1.7)	5.3 (2.7)
	23	NA	NA	ND	ND	ND	15.2 (7.2-68.3)	2.9 (1.5)	4.8 (3.7)

≈ 10 mg/jour





60 mg  
60 mg 1j/2

Dose absorbée  
après 14 doses  
(14 ou 28j=900  
mg)

**131 mg** (71.4,  
240.5) versus  
**175.3 mg**  
(110.3, 278.5;  
 $p = 0.0010$ )

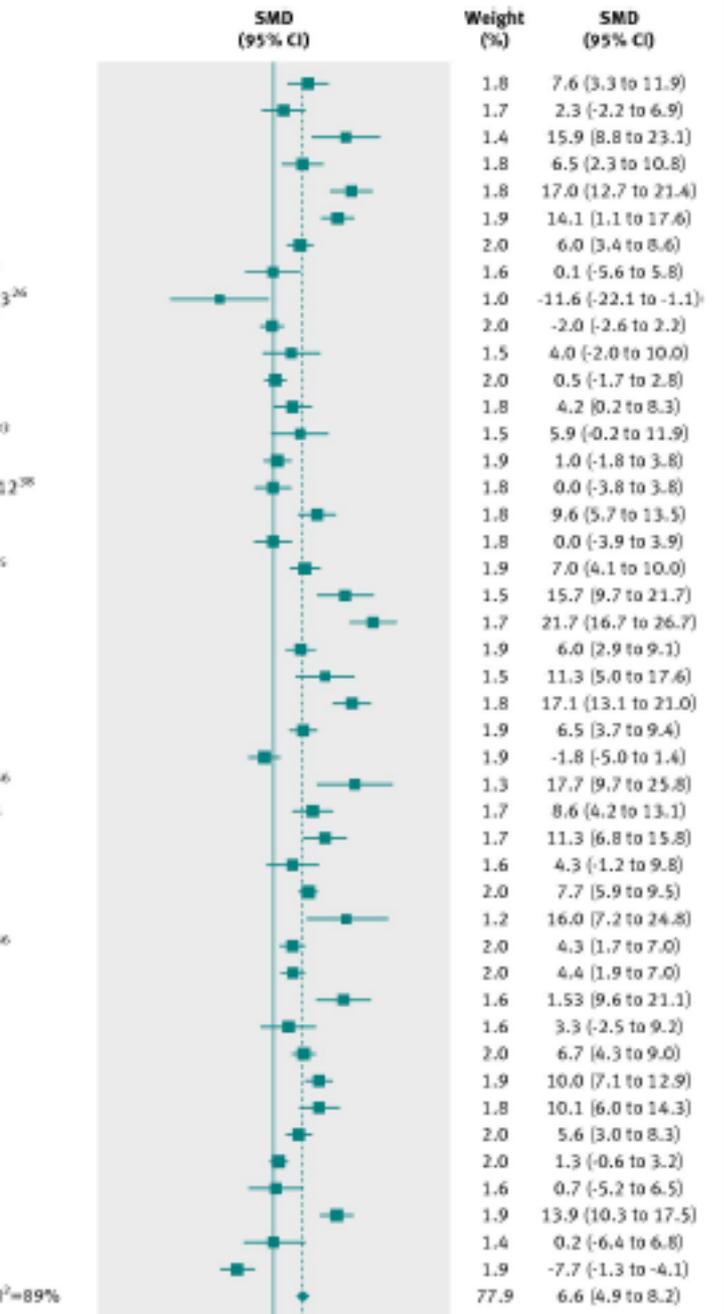
# Fer IV vs Oral

72 études

10.605 patients

-Delta Hb 6,5[4,9-8,2] g/L

-Transfusion 0,74[0,62-0,88]



# Dose moyenne efficace PRE-opératoire= 1 g

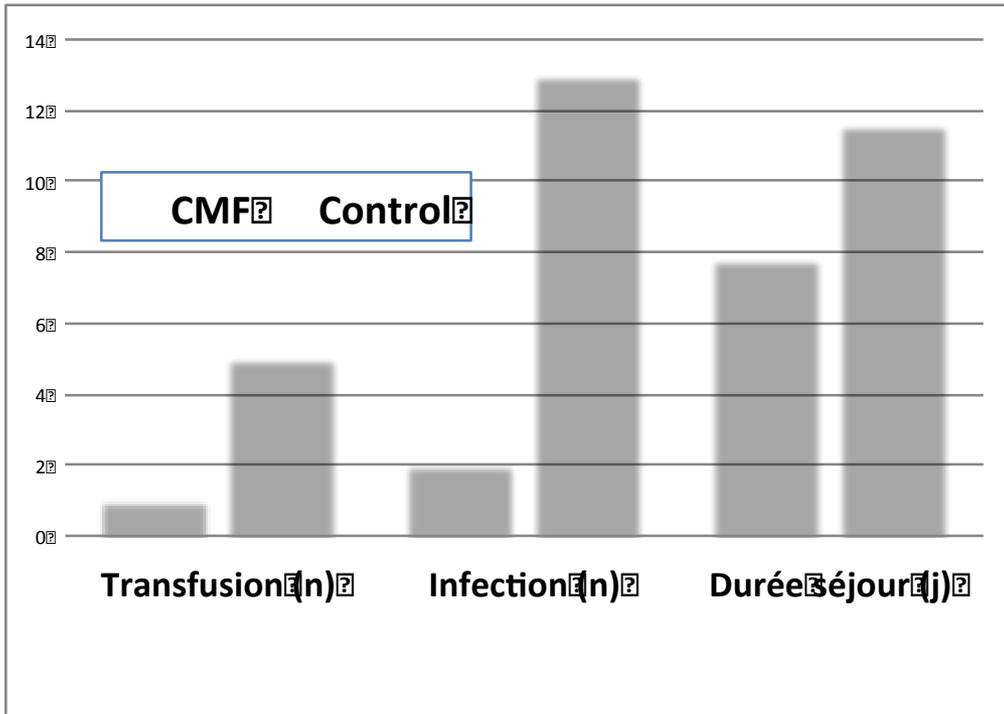
\* $P < 0.05$ ; \*\* $P < 0.001$ , IS vs FCM. †There were differences between groups with respect to patient distribution by surgical procedure ( $P < 0.001$ , IS vs FCM). ‡Final Hb=last Hb assessment before surgery. †Hb increment=final Hb – baseline Hb. §Response=Hb increment  $\geq 1.5$  g dl<sup>-1</sup> or final Hb  $\geq 13$  g dl<sup>-1</sup>. ||According to WHO definition: Hb  $\geq 12$  g dl<sup>-1</sup> in women, and Hb  $\geq 13$  g dl<sup>-1</sup> in men

	Iron sucrose				Ferric carboxymaltose			
	All	Colon cancer resection	Abdominal hysterectomy	Lower limb arthroplasty	All	Colon cancer resection	Abdominal hysterectomy	Lower limb arthroplasty
Patients (n) <sup>†</sup>	84	30	33	21	76	15	19	42
Gender (female/male)	59/25	8/22	33/0	17/4	66/10	5/10	19/0	37/5
Age (yr)	60 (32–88)	67 (36–83)	45 (32–55)	72 (53–88)	62 (36–87)	65 (36–87)	48 (36–75)	68 (46–82)
Weigh (kg)	72 (12)	74 (9)	68 (16)	76 (7)	71 (14)	68 (14)	62 (10)	75 (14)
Ferritin (ng ml <sup>-1</sup> )	18 (20)	15 (10)	12 (14)	33 (31)	21 (21)	16 (19)	20 (19)	23 (22)
C-reactive protein (mg dl <sup>-1</sup> )	1.0 (1.3)	1.6 (1.2)	0.5 (0.6)	1.5 (1.6)	0.8 (1.4)	1.1 (1.4)	0.3 (0.3)	1.0 (1.7)
Total iron deficiency (mg)	1000 (220)	1025 (240)	1050 (210)	920 (190)	950 (310)	1125 (230)	935 (210)	900 (350)
Total i.v. iron dose (mg)	1010 (440)	1140 (570)	1000 (350)	830 (270)	1120 (530)	1550 (650)*	1030 (330)	1000 (490)
Sessions (n)	5 (2)	6 (3)	5 (2)	4 (4)	2 (1)	3 (1)	2 (1)	2 (1)
Baseline Hb (g dl <sup>-1</sup> )	10.1 (1.3)	10.1 (1.2)	9.7 (1.2)	10.7 (1.1)	10.4 (1.6)	9.2 (1.0)*	10.6 (1.3)	10.9 (1.7)
Final Hb (g dl <sup>-1</sup> ) <sup>‡</sup>	12.1 (1.4)	11.0 (1.4)	12.7 (0.8)	12.6 (1.0)	12.5 (1.0)*	11.7 (0.8)**	12.4 (1.2)	12.8 (0.9)
Hb increment (g dl <sup>-1</sup> ) <sup>†</sup>	2.0 (1.6)	0.9 (1.5)	3.0 (1.2)	1.8 (1.1)	2.1 (1.4)	2.5 (1.3)*	2.3 (1.1)	1.8 (1.4)
Response rate [n (%)] <sup>§</sup>	56 (67)	10 (33)	32 (97)	14 (67)	53 (70)	11 (73)*	13 (68)*	29 (69)
Anaemia correction [n (%)] <sup>  </sup>	50 (59)	6 (20)	29 (88)	15 (71)	55 (72)	5 (33)	13 (68)	37 (88)
Allogeneic transfusion [n (%)]	20 (24)	12 (40)	2 (6)	6 (29)	7 (9)*	1 (7)*	0 (0)	6 (14)
Adverse events [n (%)]	6 (7)	0 (0)	5 (15)	1 (5)	4 (5)	1 (7)	1 (5)	3 (7)
Iron treatment costs (€)								
Acquisition costs	117 (51)				224 (106)			
Administration costs	190 (83)				21 (10)			
Total costs	307 (133)				244 (134)			

# Fer IV post-opératoire

- Etude randomisée, ouverte, bi-centrique
- J1 post op (ortho++, Visc, Uro, gyneco)
  - Chirurgie réglée
  - Séjour  $\geq 2$  nuits
  - Hb [7 – 12 g/dl]
  - CM= Ferritine  $< 100$  ou TSAT  $< 20\%$
- Randomisation CMF 1g vs standard of care

	Standard care (control; n=98)	Intravenous ferric carboxymaltose (intervention; n=103)	Treatment effect*	p value
<b>Haemoglobin (g/L)</b>				
Preoperative	134.40 (13.10)	134.50 (11.10)	-0.61 (-4.31 to 3.09)	0.094
Postoperative (day 1)	105.50 (13.80)	106.20 (11.90)	0.00	
4 weeks	121.50 (14.50)	130.10 (11.30)	7.84 (3.79 to 11.9)	<0.0001
12 weeks	133.60 (11.30)	137.50 (11.10)	3.07 (-0.99 to 7.14)	0.24
<b>Iron saturation (%)</b>				
Preoperative	22.60 (6.70)	22.30 (4.70)	0.01 (-2.82 to 2.83)	0.82
Postoperative (day 1)	12.00 (5.60)	11.70 (6.60)	0.00	
4 weeks	19.70 (10.70)	30.90 (11.70)	11.40 (8.33 to 14.50)	<0.0001
12 weeks	25.30 (13.10)	31.70 (9.50)	6.62 (2.78 to 10.50)	0.0026
<b>Serum ferritin (µg/L)</b>				
Preoperative	188.00 (103.00)	118.00 (185.00)	-45.20 (-148.00 to 57.50)	0.18
Postoperative (day 1)	329.00 (335.00)	304.00 (423.00)	0.00	
4 weeks	274.00 (296.00)	717.00 (410.00)	468.00 (355.00 to 582.00)	<0.0001
12 weeks	196.00 (231.00)	481.00 (611.00)	309.00 (159.00 to 460.00)	0.0026

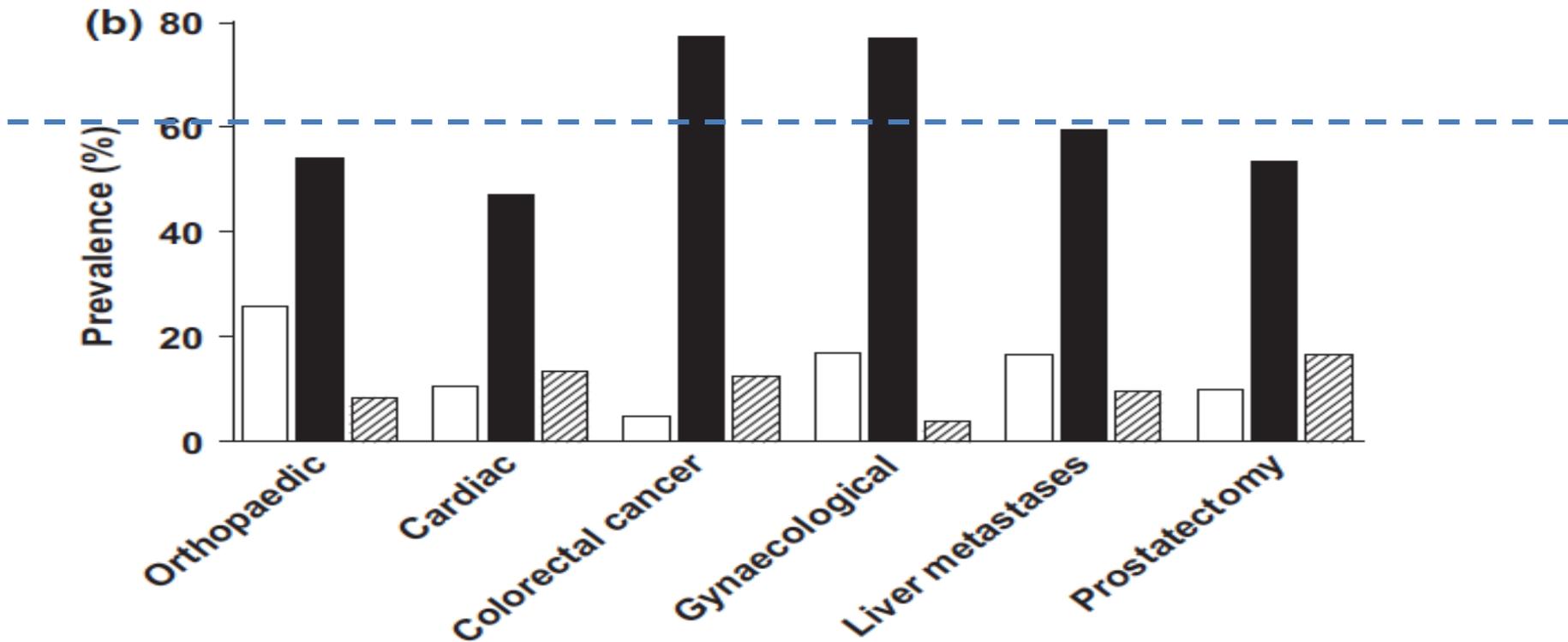


- ↓ Transfusion
- ↓ Infection
- ↓ Durée de séjour
- ↓ Fatigue

	Standard care (control; n=73)	Intravenous ferric carboxymaltose (intervention; n= 97)	Treatment effect*	p value
<b>Physical scales</b>				
<b>Physical functioning</b>				
Postoperative (day 1)	45.7 (31.4)	45.7 (29.6)	0.00	
4 weeks	33.6 (23.5)	42.1 (28.9)	8.47 (-3.50 to 20.40)	0.17
12 weeks	53.4 (27.6)	55.9 (26.7)	2.45 (-9.90 to 14.80)	0.70
<b>Role physical†</b>				
Postoperative (day 1)	52.8 (27.0)	41.2 (31.3)	0.00	
4 weeks	27.6 (25.6)	30.0 (26.8)	14.00 (0.18 to 27.80)	0.047
12 weeks	52.4 (28.6)	58.4 (27.5)	17.60 (4.37 to 30.90)	0.0092

# Prévalence de l'anémie par CM

986 patients anémiques (Hb<13 /dl)  
- 61,6 % CM absolue  
- 15,2% Réserves basses



# PREOPERATIVE ANEMIA

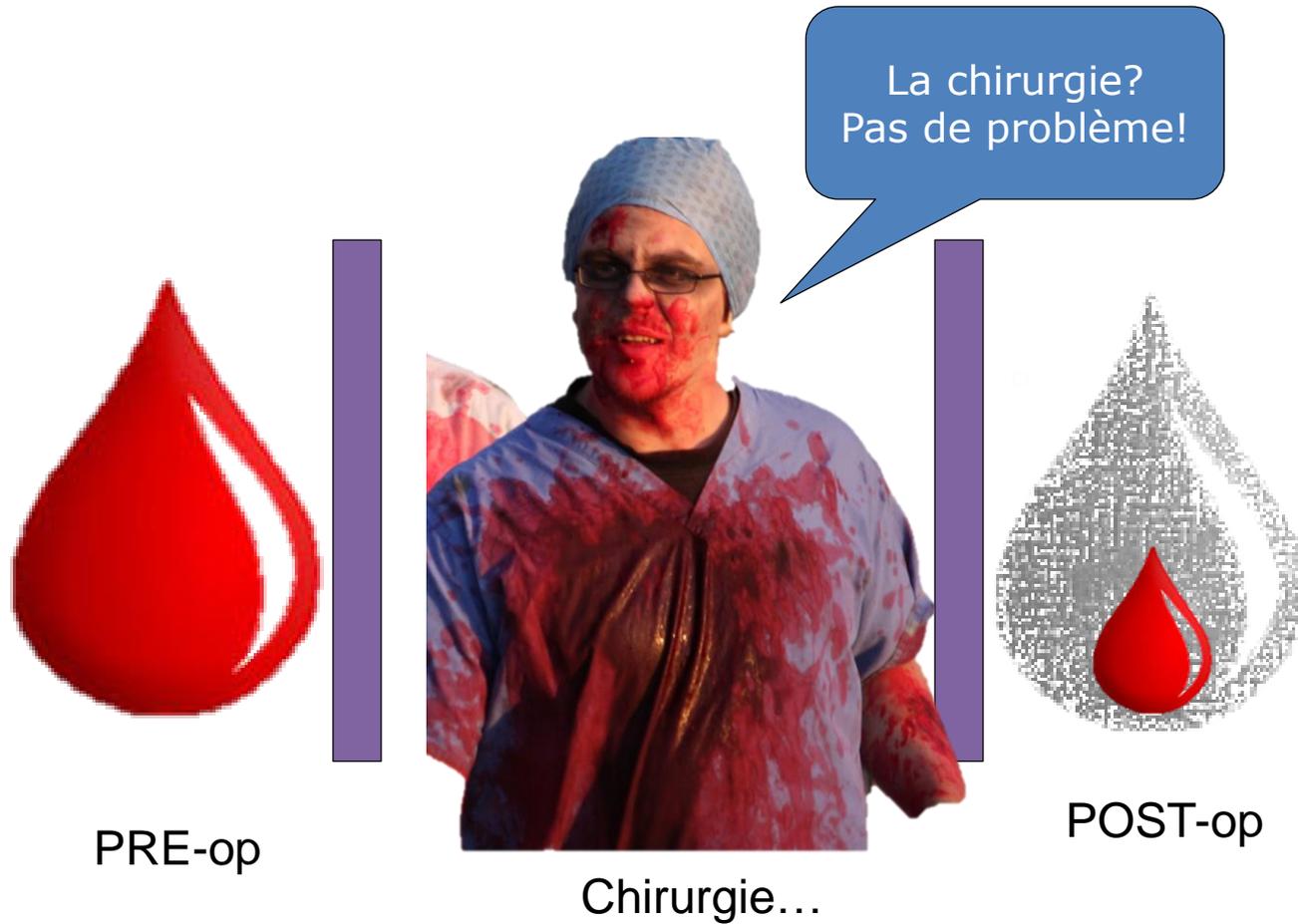
Detect and manage anemia early enough before major elective surgery

Optimal Hb thresholds for definition of preoperative anemia in different patient groups: further research needed

Use iron supplementation in adult preoperative elective surgery patients with iron-deficient anemia to reduce RBC transfusion rate\*

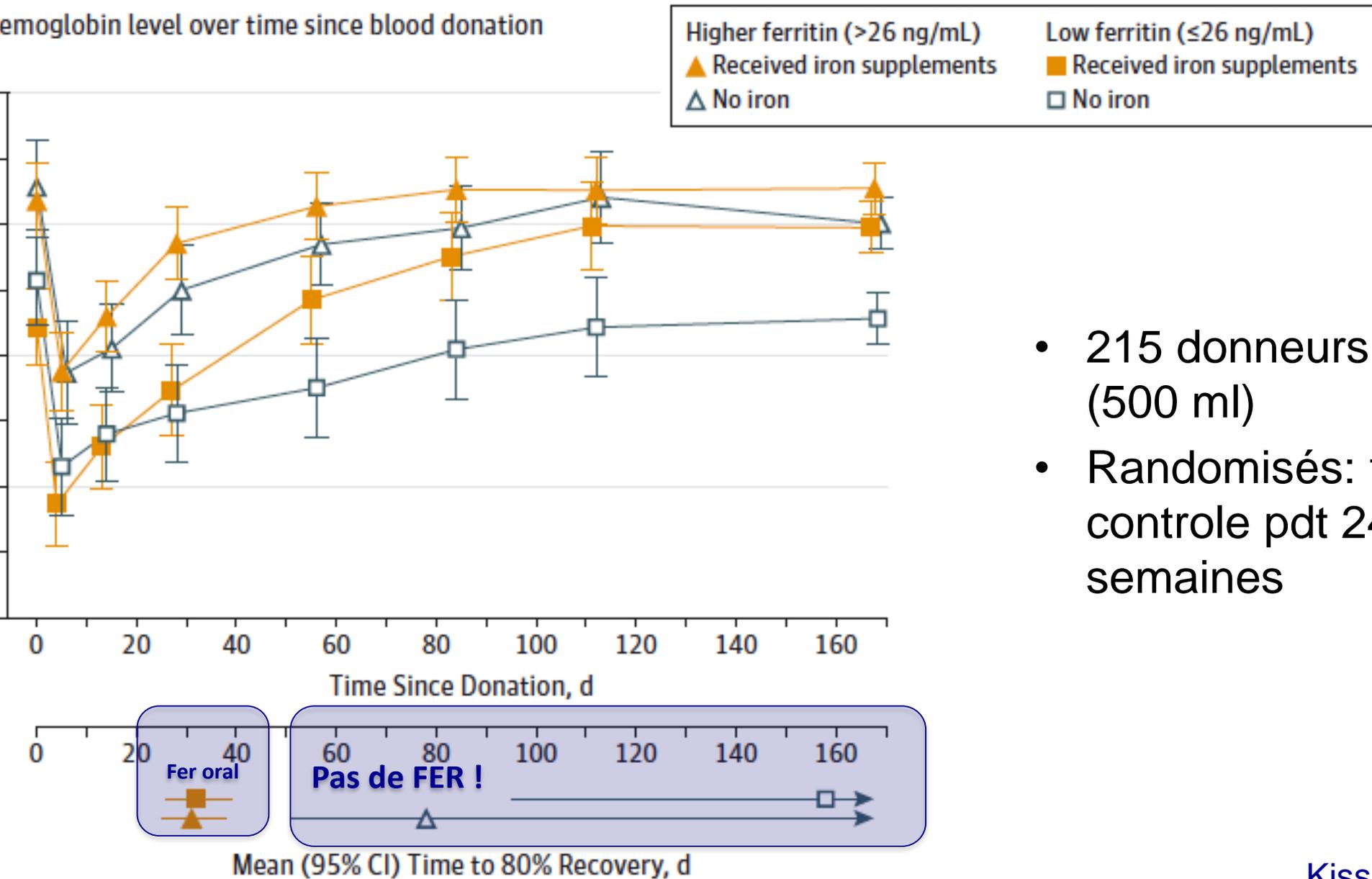
Iron supplementation in non-anemic, but iron-deficient patients scheduled for major surgery: further research needed

# Le saignement perop fait le lit de la Carence Martiale



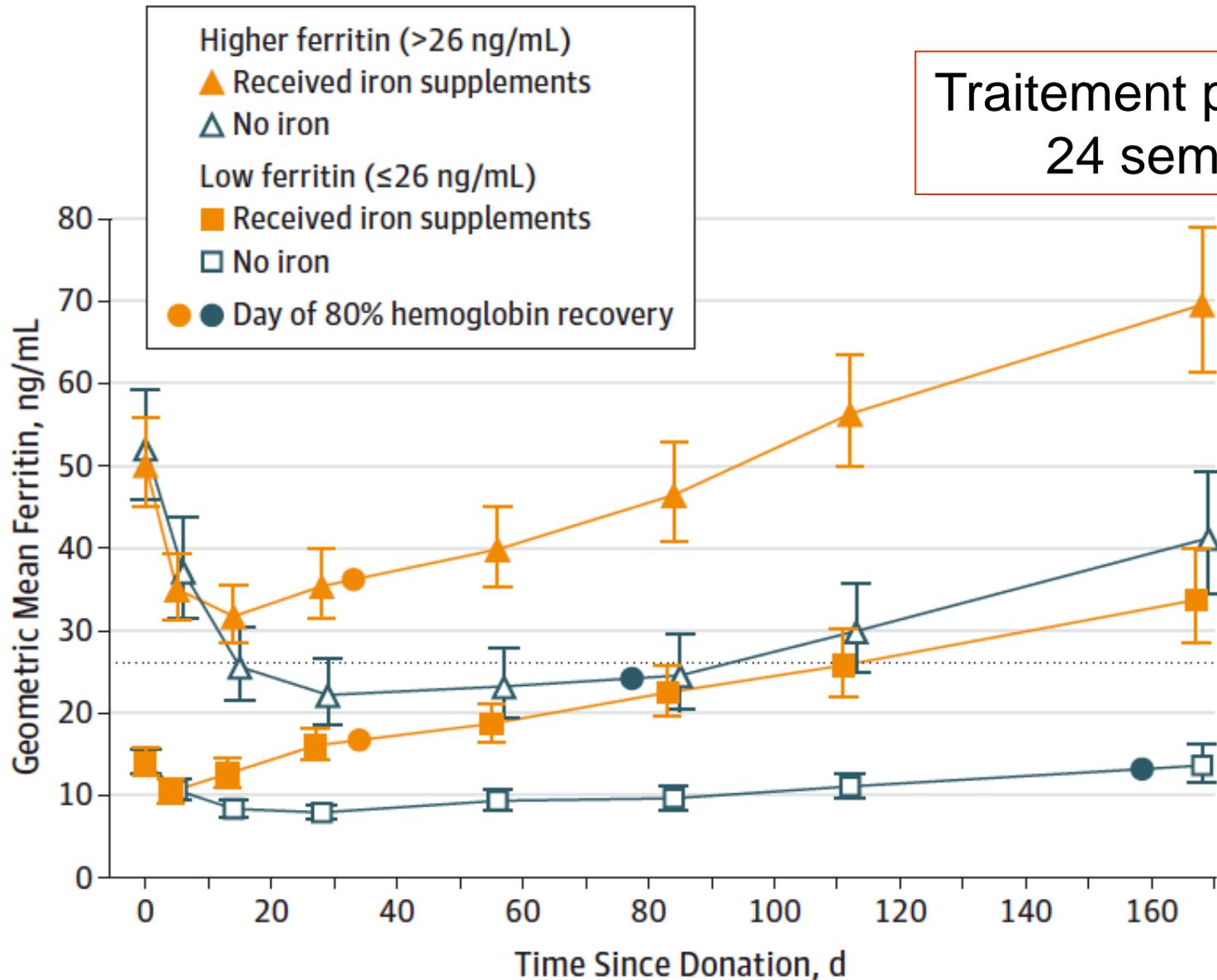
# Evolution de l'Hb après don de 500 ml de sang

hemoglobin level over time since blood donation



- 215 donneurs (500 ml)
- Randomisés: fe... controle pdt 24 semaines

# Mais pas de correction de la CM !



Traitement par fer oral  
24 semaines!

Detect and manage

Optimal Hb thresholds for definition of preoperative anemia in different patient groups: further research needed

Use iron supplementation in adult preoperative elective

\*\*

Take individual transfusion probability, etiology of anemia and thromboembolic risk into account

## ANEMIA

Iron supplementation in non-anemic, but iron-deficient patients scheduled for major surgery: further research needed

Consider short-acting erythropoietins + iron in adult preoperative elective major orthopedic surgery patients with Hb levels < 13 g/dL\*\*

Don't use ESA routinely in general adult preoperative elective surgery patients with anaemia

# EPO « seule »

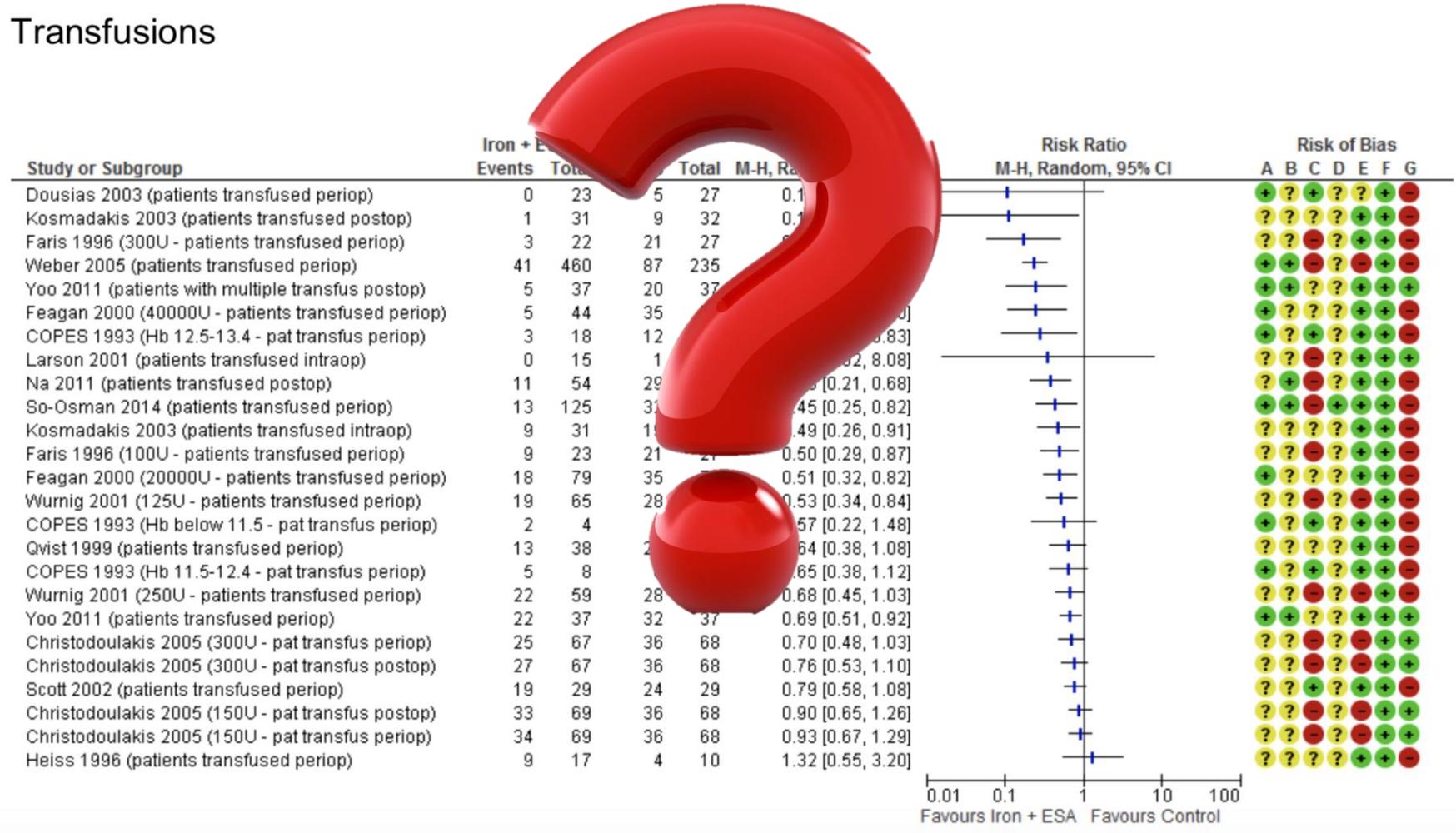
Outcomes	Difference (ESA vs no treatment)	Relative effect (95% CI)
Length of hospital stay (observational cohort study)	MD <b>0.3 days fewer</b> (0.56 fewer to 0.04 fewer)	-
RBC utilization - Number of patients transfused (experimental study: RCT)	<b>211 fewer per 1.000</b> (267 fewer to 130 fewer)	<b>RR 0.43</b> (0.28 to 0.65)
RBC utilization - Number of patients transfused (observational cohort study)	<b>390 fewer per 1.000</b> (409 fewer to 94 fewer)	<b>RR 0.050</b> (0.003 to 0.770)

DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial	Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High	No included studies		
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	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
RESOURCES REQUIRED	Large costs ◀◀	Moderate costs ◀	Negligible costs and savings ●	Moderate savings ▶	Large savings ▶▶	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison ◀◀	Probably favors the comparison ◀	Does not favor either the intervention or the comparison ●	Probably favors the intervention ▶	Favors the intervention ▶▶	Varies	No included studies
EQUITY	Reduced ◀◀	Probably reduced ◀	Probably no impact ●	Probably increased ▶	Increased ▶▶	Varies	Don't know

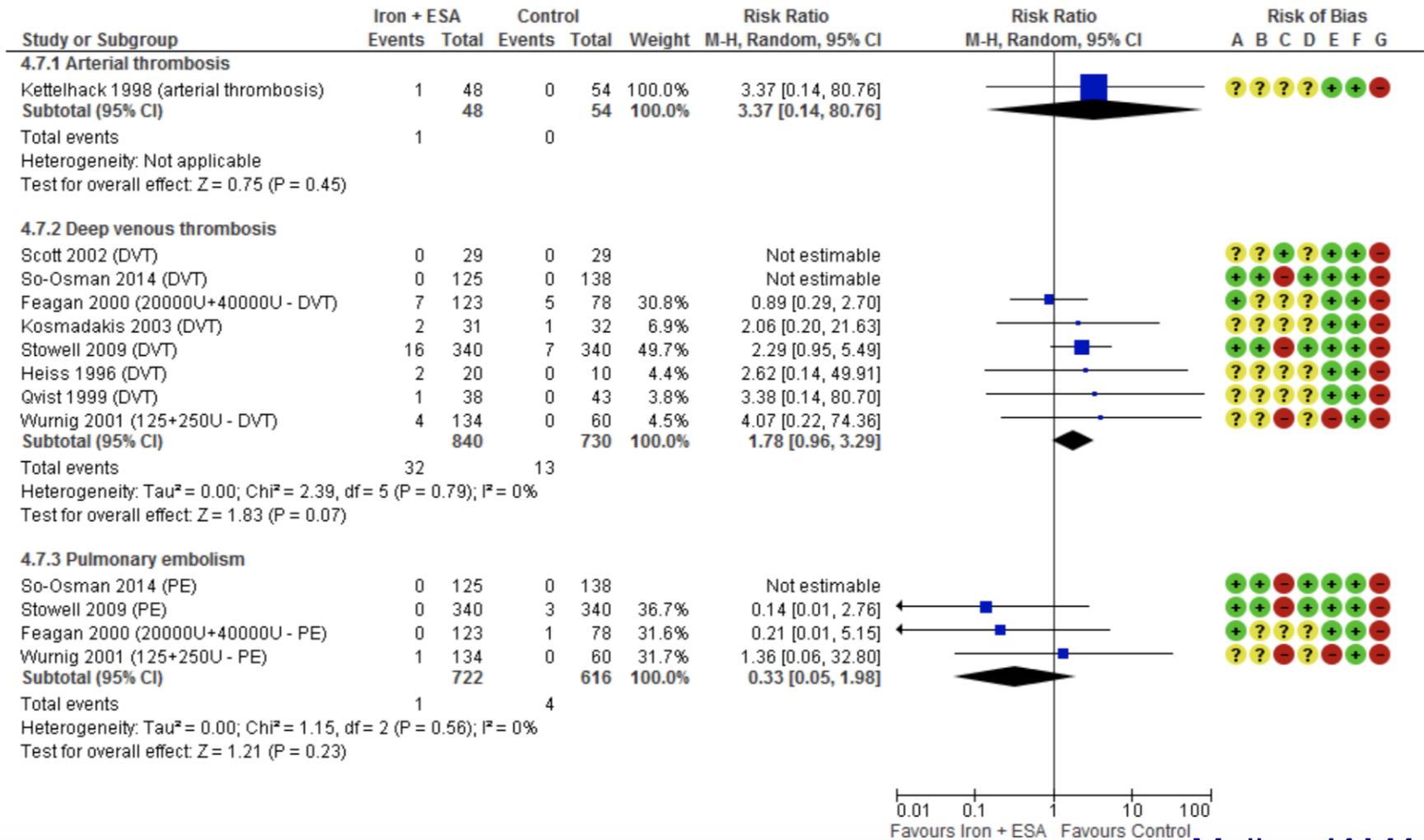
# Recommendation 4

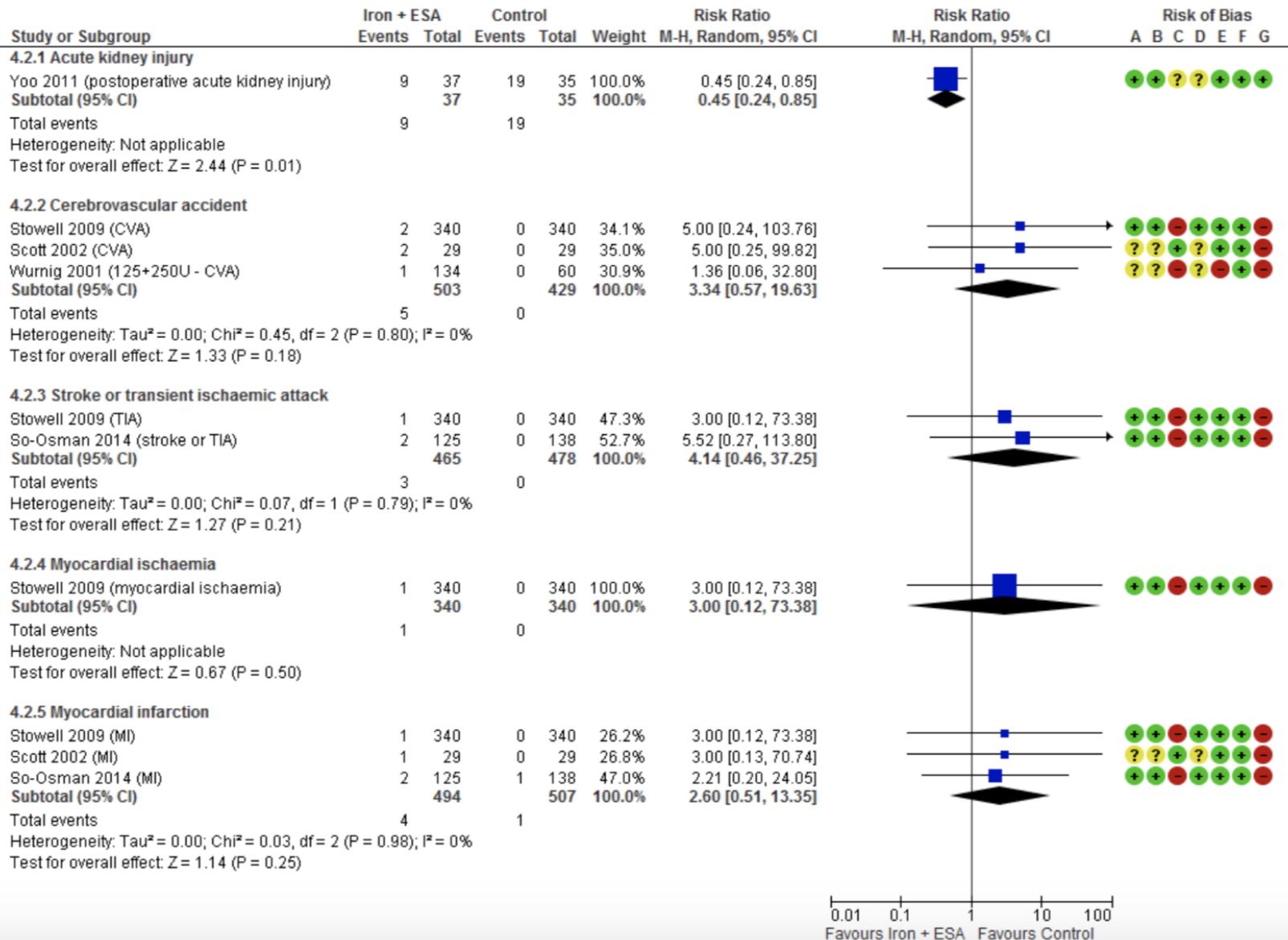
- The ICC-PBM multi-disciplinary panel decided to formulate no recommendation on the use of ESA's alone in adult preoperative **elective cardiac surgery patients.**

**eFigure 5.** Study-Specific Risk Ratios Representing the Association Between Iron+ESA Supplementation (Compared to Placebo/No Treatment/Usual Care) and the Number of RBC Transfusions



# Pas plus de complications





Moins d'insuffisance rénale...

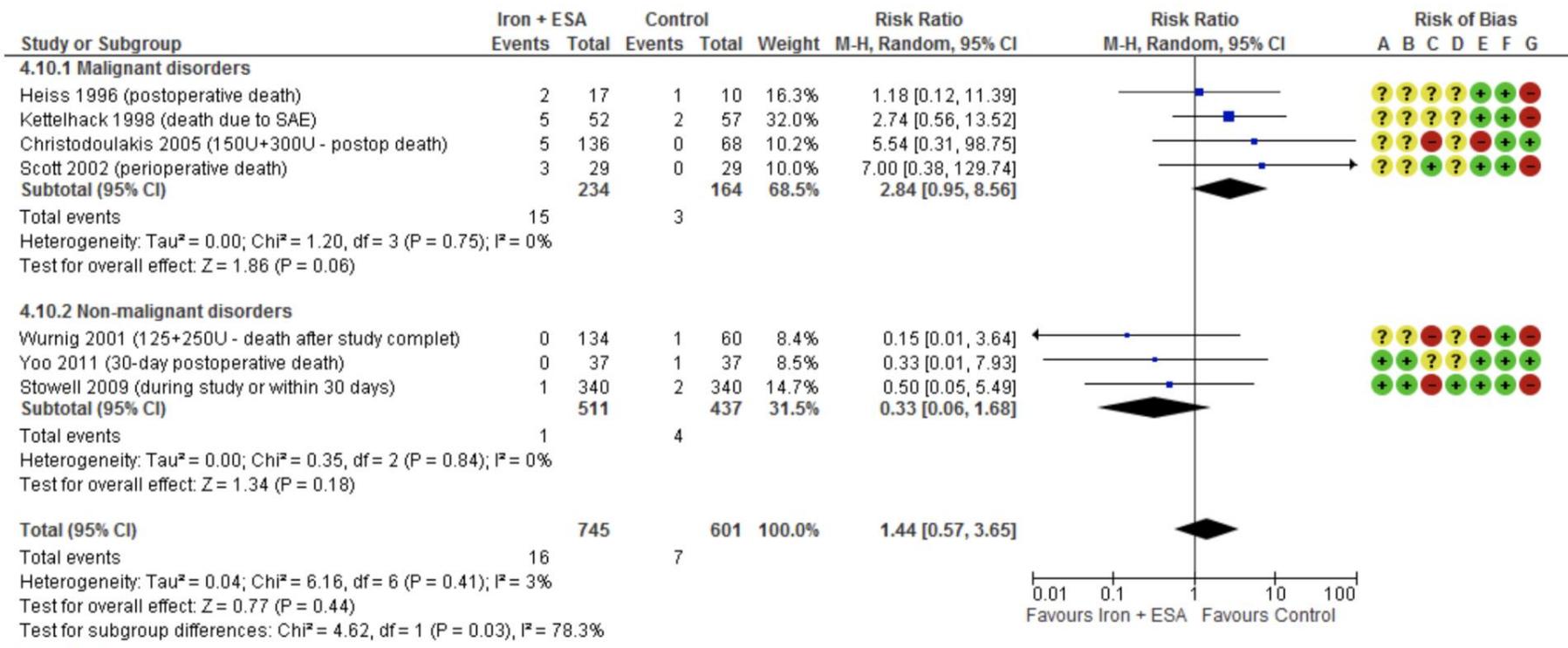
# 1. How substantial are the desirable anticipated effects?

Outcomes	Risk Ratio (ESA+iron vs placebo/no treatment)
Acute kidney injury	0.45, 95%CI [0.24, 0.85]
Pulmonary embolism	0.33, 95%CI [0.05, 1.98]

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

## 2. How substantial are the undesirable anticipated effects?

Outcomes	Risk Ratio (ESA+iron vs placebo/no treatment)
Mortality	1.44, 95%CI [0.57, 3.65]
Cerebrovascular accident	3.34, 95%CI [0.57, 19.63]
Stroke or transient ischaemic attack	4.14, 95%CI [0.46, 37.25]
Myocardial ischaemia	3.00, 95%CI [0.12, 73.38]
Myocardial infarction	2.60, 95%CI [0.51, 13.35]
Arterial thrombosis	3.37, 95%CI [0.14, 80.76]
<b>Deep venous thrombosis</b>	1.78, 95%CI [0.96, 3.29]





INTERNATIONAL  
CANCER CONFERENCE  
ICC-PBM  
FRANKFURT  
2018

# Conclusions

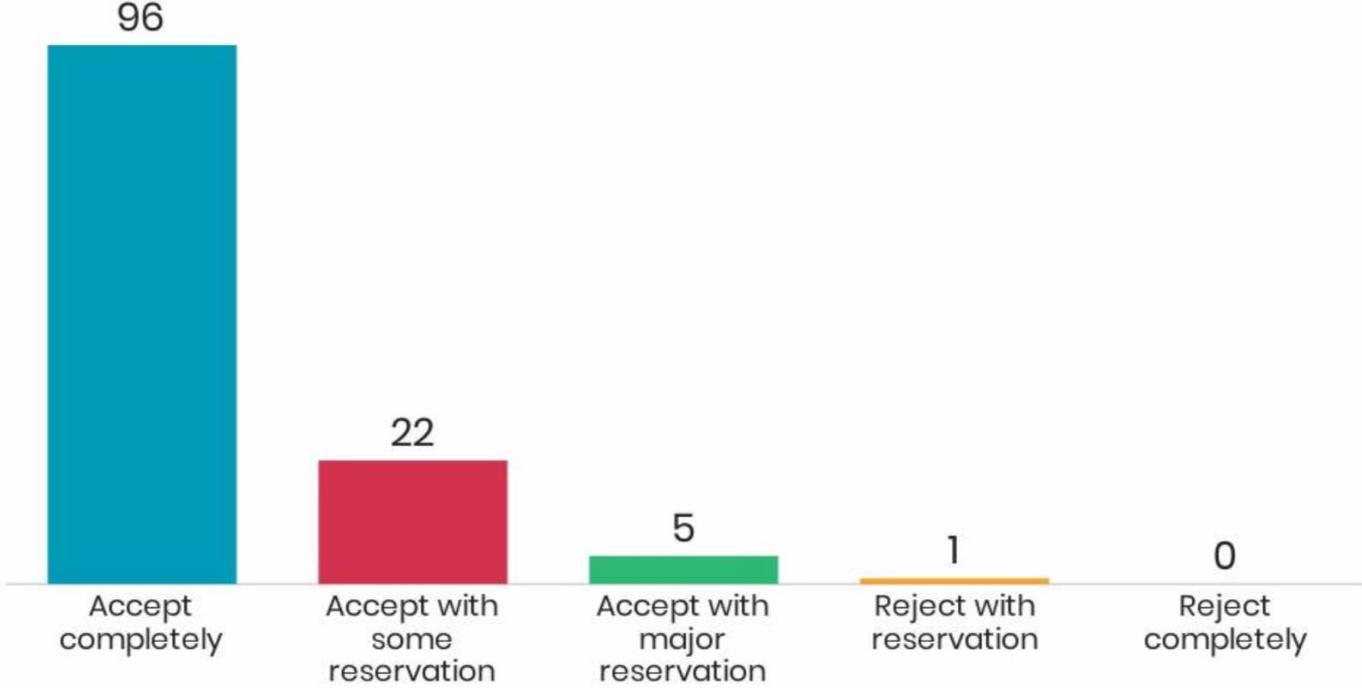
- Pre-operative ESA + iron:
  - Significant variation in treatment regimens (drugs, timing, dose, frequency, number of doses)
  - No information on final pre-operative Hb (was target set too high?)
  - Cannot demonstrate a difference in outcomes (mortality, anemia associated ischemic events, arterial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

# Recommendation 5



- The ICC-PBM multi-disciplinary suggests not to use ESAs **routinely** in general adult preoperative elective surgery patients anaemia (conditional recommendation, low quality evidence).
- The panel suggests to use ESAs in addition to iron supplementation in adult preoperative elective **major orthopedic surgery** patients with haemoglobin levels < 13 g/dL as desirable effects (reduced RBC transfusion rate) may outweigh potential undesirable effects for this subgroup of patients (conditional recommendation, low quality evidence).
- The panel decided to formulate a recommendation for **further research** on the use of ESAs + iron supplementation in adult preoperative elective surgery patients with focus on long term (un)desirable effects, optimal dose, type of surgery (particular in cancer surgery), co-presence of iron deficiency and cost effectiveness.

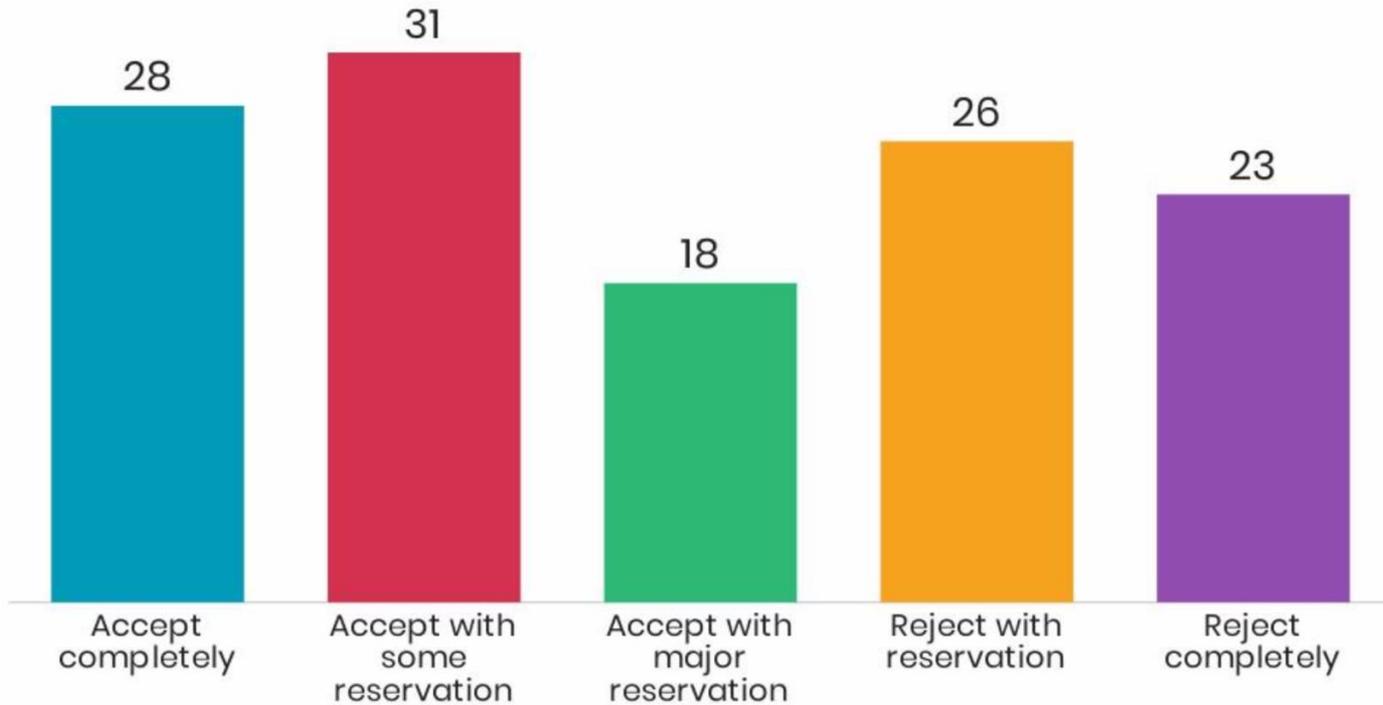
# suggests not to use ESAs routinely in general adult preoperative elective surgery patients anaemia



124

suggests to use ESAs in addition to iron supplementation in adult preoperative elective major orthopedic surgery patients with haemoglobin levels < 13

Mentimeter



126

# ESA pour ESA !

**EJA**

*Eur J Anaesthesiol* 2017; **34**:332–395

## **GUIDELINES**

### **Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology**

*We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. 1C*

*If anaemia is present, we recommend identifying the cause (iron deficiency, renal insufficiency or inflammation). 1C*

*We recommend treating iron deficiency with iron supplementation. 1B*

*We recommend the use of intravenous iron in preference to oral iron. 1C*

*If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. 2C*

*In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. 1C*

# Practice Guidelines for Perioperative Blood Management

*An Updated Report by the American Society of Anesthesiologists  
Task Force on Perioperative Blood Management\**

## *Recommendations for Preadmission Patient Preparation*

- Erythropoietin with or without iron may be administered when possible to reduce the need for allogeneic blood in selected patient populations (*e.g.*, renal insufficiency, anemia of chronic disease, refusal of transfusion).‡‡
- Administer iron to patients with iron deficiency anemia if time permits.

**A**

L'utilisation de l'EPO est recommandée en préopératoire de la chirurgie orthopédique hémorragique chez les patients modérément anémiques. L'utilisation devra être réservée aux patients ayant une anémie modérée (par exemple Hb : 10 à 13 g/dl), et chez lesquels on s'attend à des pertes de sang modérées (900 à 1 800 ml).

**B**

L'utilisation d'EPO dans le cadre péri-opératoire de la chirurgie colorectale carcinologique n'est pas recommandée, en raison de l'insuffisance de données sur la preuve de son efficacité.

# EPO Pre-opératoire: métaanalyse en orthopédie

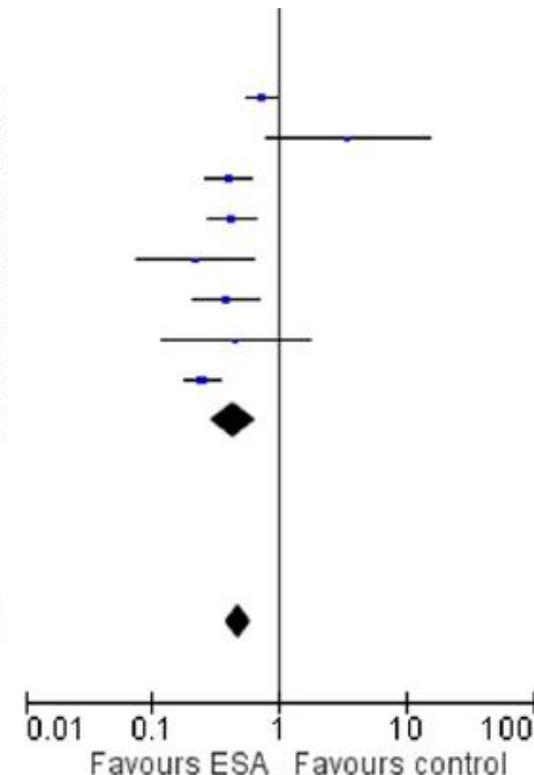
## 1.3.2 ESA Alone

Canadian group 1993	53	130	44	78	8.0%	0.72 [0.54, 0.96]
Deutsch 2006	7	25	2	25	1.8%	3.50 [0.80, 15.23]
Faris 1996	25	118	36	67	7.0%	0.39 [0.26, 0.60]
Feagan 2000	23	123	35	78	6.7%	0.42 [0.27, 0.65]
Keating 2007	4	130	17	121	2.9%	0.22 [0.08, 0.63]
Na 2011	11	54	29	54	5.6%	0.38 [0.21, 0.68]
Rosencher 2005	3	45	6	41	2.1%	0.46 [0.12, 1.70]
Weber 2005	42	460	87	235	7.6%	0.25 [0.18, 0.34]
<b>Subtotal (95% CI)</b>		<b>1085</b>		<b>699</b>	<b>41.8%</b>	<b>0.44 [0.29, 0.67]</b>

Total events 168 256  
 Heterogeneity:  $\text{Tau}^2 = 0.24$ ;  $\text{Chi}^2 = 33.81$ ,  $\text{df} = 7$  ( $P < 0.0001$ );  $I^2 = 79\%$   
 Test for overall effect:  $Z = 3.85$  ( $P = 0.0001$ )

**Total (95% CI)** 2059 1391 100.0% 0.48 [0.38, 0.60]

Total events 307 445  
 Heterogeneity:  $\text{Tau}^2 = 0.14$ ;  $\text{Chi}^2 = 52.83$ ,  $\text{df} = 23$  ( $P = 0.0004$ );  $I^2 = 56\%$   
 Test for overall effect:  $Z = 6.57$  ( $P < 0.00001$ )  
 Test for subgroup differences:  $\text{Chi}^2 = 0.61$ ,  $\text{df} = 1$  ( $P = 0.44$ ),  $I^2 = 0\%$



**RR de transfusion = 0,44**  
**(15 vs 37% de patients transfusés)**

# EPO en chirurgie cardiaque

- *Yoo Anesthesiology 2011*
  - RCT, simple aveugle, n=74,
  - 59 vs 86% (p=0.009) de transfusion ( $-1 \pm 1.1$  CG)
- *Welter Transfusion 2015:*
  - RCT, simple aveugle, n=600,
  - RR 0.43 [0.33-0.57]
- *Spahn Lancet 2019*
  - RCT + control, n=1006
  - OR 0,7[0.5-0.98],

Focus on long term (un-)desirable effects, optimal dose, type of surgery (particular in cancer surgery), co-presence of iron-deficiency, and cost-effectiveness

## PREOPERATIVE ANEMIA

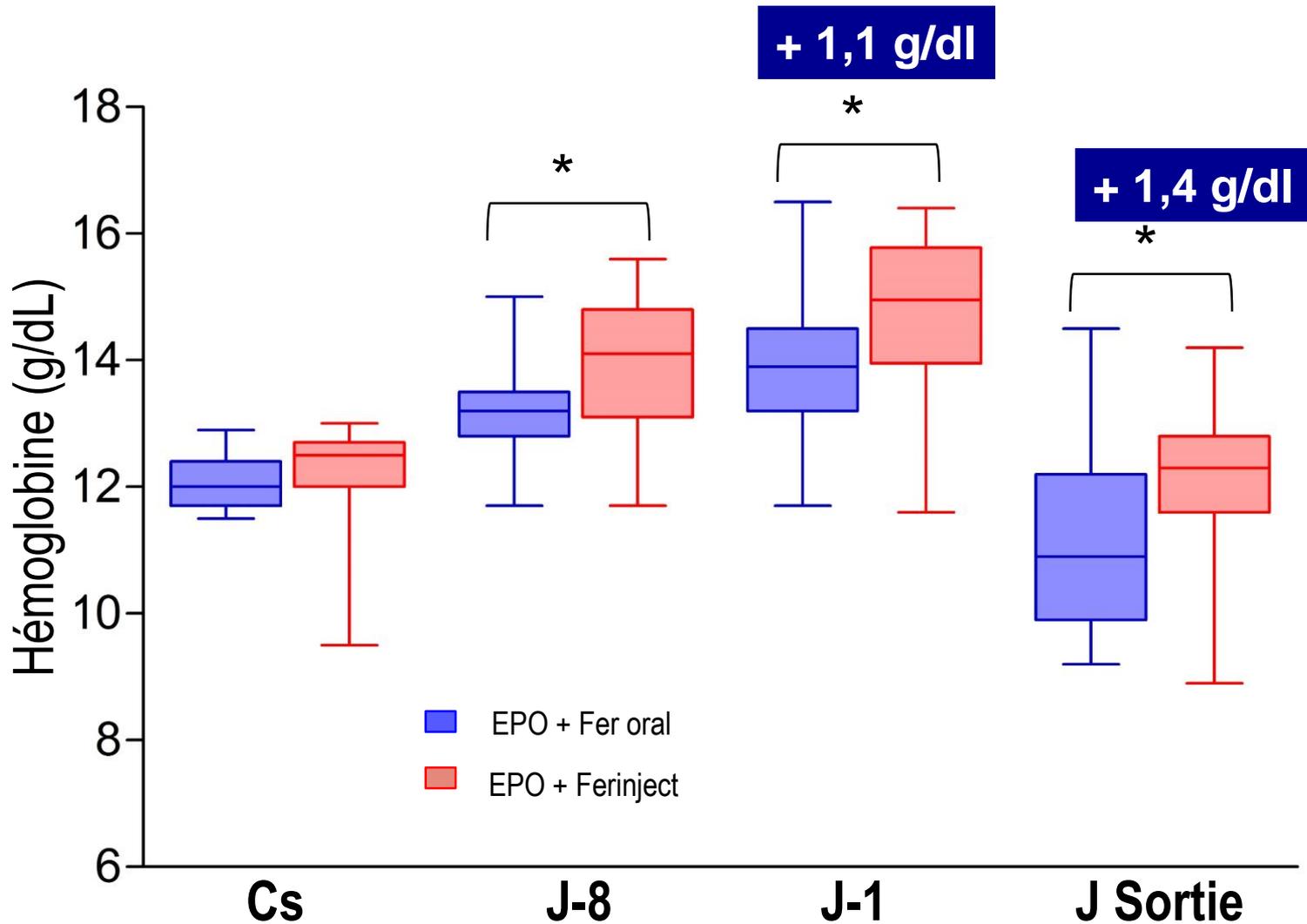
Short-acting erythropoietins + iron in preoperative elective major orthopedic surgery patients with Hb levels < 13 g/dL\*\*  
Further research needed\*\*\*

Consider short-acting erythropoietins + iron in adult preoperative elective major orthopedic surgery patients with Hb levels < 13 g/dL\*\*

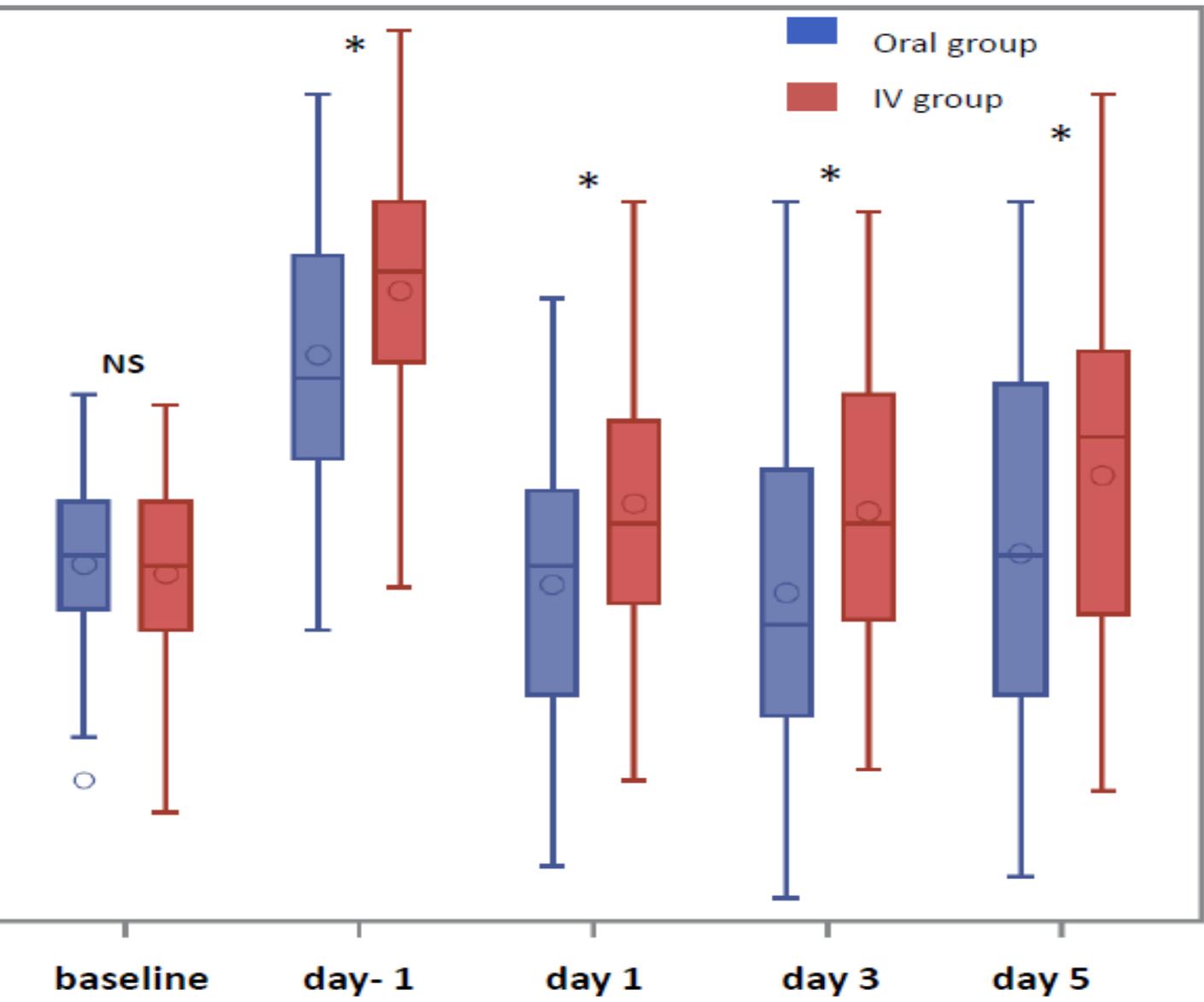
Don't use ESA routinely in general adult preoperative elective surgery patients with anaemia

Iron supplementation in non-anemic, but iron-deficient patients scheduled for major surgery: further research needed

# Meilleure réponse à l'EPO



+ 0,7 g/dl



# Intérêt de FER IV avec EPO

- Effets secondaires  
digestifs ( $p < 0,0001$ )
- IV 2%
  - Per os 52%

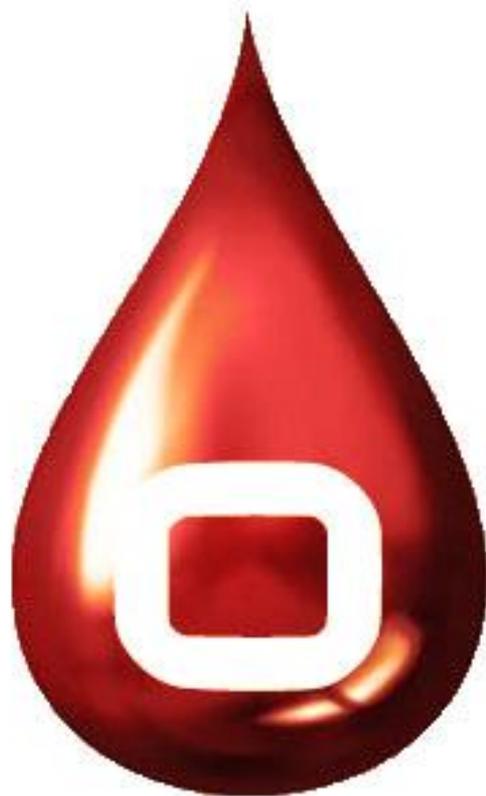
# Conclusions

- Diagnostiquer et traiter l'anémie pré-opératoire
- Traiter l'anémie par carence martiale EPO pour chirurgie orthopédique majeure... pas dans les autres chirurgies



**Il est urgent de rajouter des pétales rouges à la fleur !**

*Merci*



**ZET**

*Objectif ZERO transfusion*