



# Patient Blood Management: Treating Anemia

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# Disclosures

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- Research: Canadian Blood Services, Octapharma
- Consulting: Choosing wisely Canada

# Objectives

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1. Advocate for the importance of patient blood management
2. Diagnose and treat iron deficiency anemia
3. Decide which patients should receive preoperative erythropoietin

# Patient Blood Management

- PBM is a patient-centered and organized approach in which the entire health care team coordinates efforts to improve results by managing and preserving a patient's own blood.

Pre-op

Treat anemia

During surgery

Minimize blood loss

Post-op

Appropriate use of  
blood

# Patient Blood Management

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- PBM is a patient-centered and organized approach in which the entire health care team coordinates efforts to improve results by managing and preserving a patient's own blood.

Antenatal

Treat anemia

Peridelivery

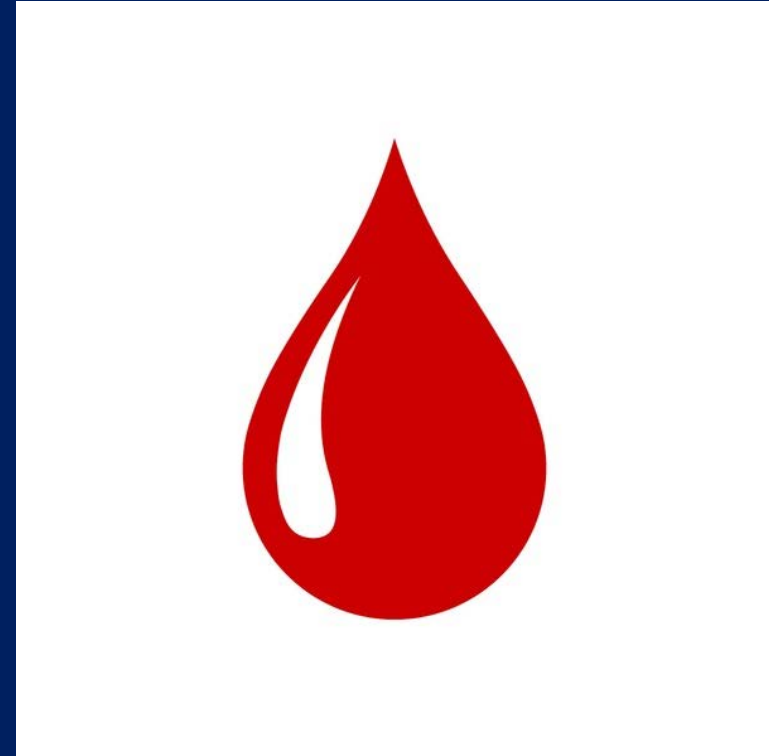
Minimize blood loss

Postpartum

Appropriate use of  
blood

**Learning objective 1:**

**Why is treating  
preoperative anemia  
so important?**



**#1 Preoperative anemia is associated with increased mortality**

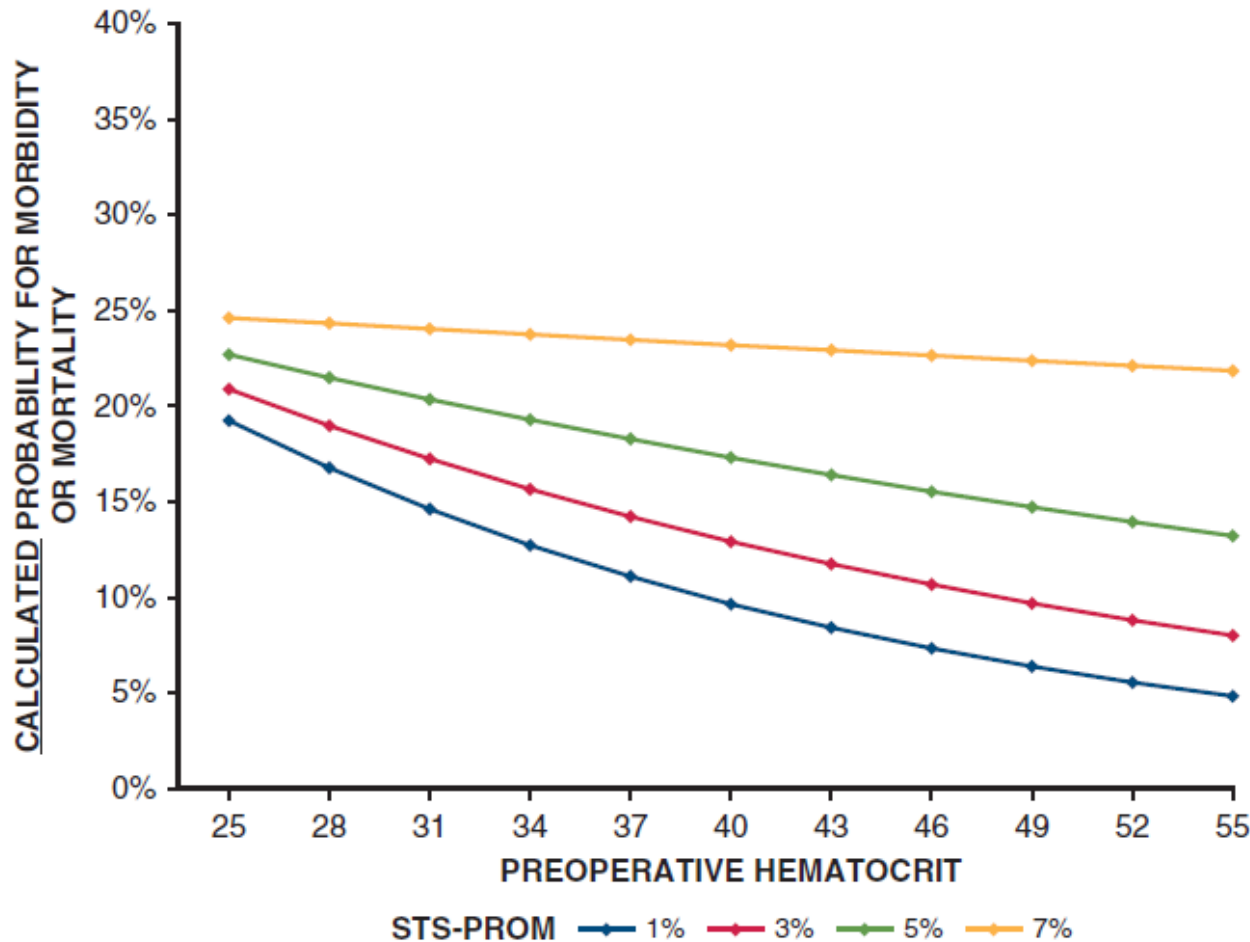
2019 CV Surgery Systematic Review  
**OR 2.74** (95%CI, 2.32-3.24)

2018 PBM Consensus Conference  
**OR 2.09** (95%CI, 1.48-2.95)

2014 Europe N= 39,309 pts  
**OR 1.99** (95%CI, 1.67-2.37)

2011 US NSQIP N= 227,425 pts  
**OR 1.42** (95% CI, 1.31-1.54)

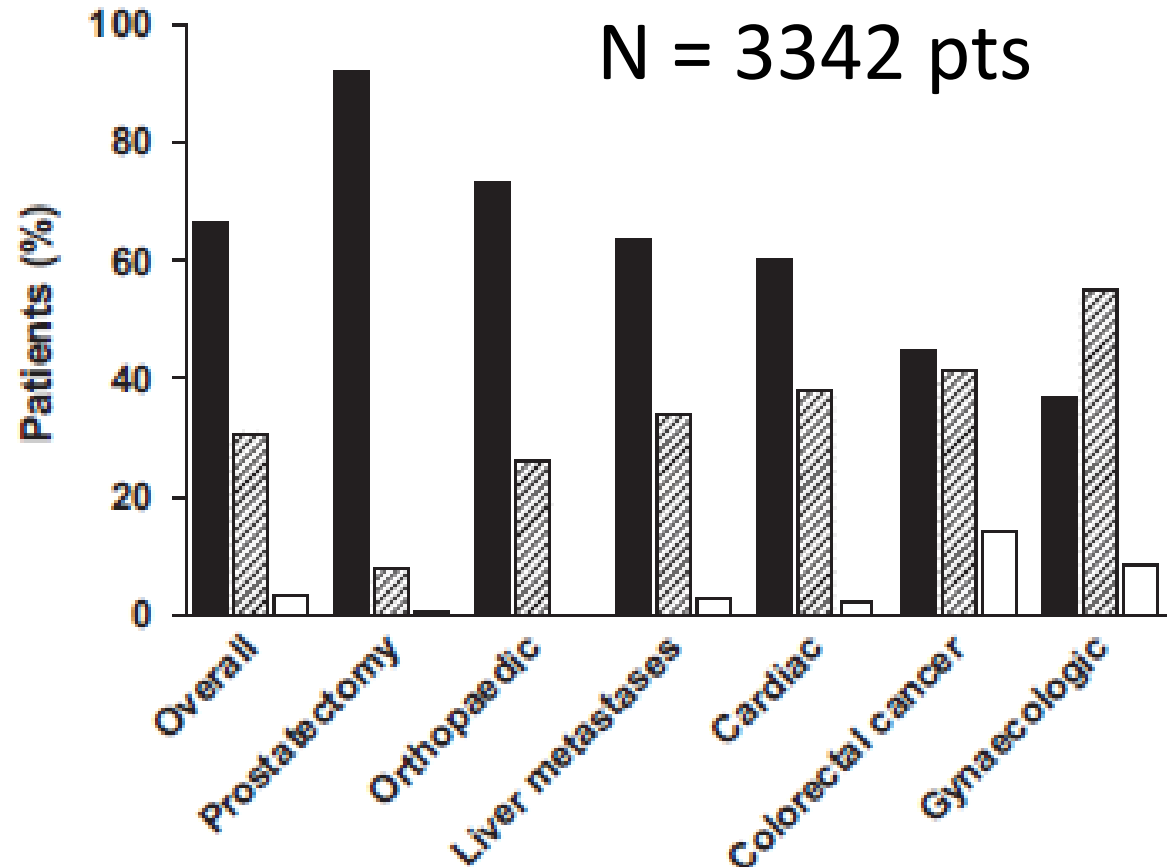
# Preop anemia may be even more important in low risk patients...



- Isolated CABG or valve surgery – Maryland
- N = 29,828 pts
- Looked at preop Hct and STS predicted risk of mortality
- Stronger association between preop Hct and morbidity/mortality at lower STS PROM



## #2 Preoperative anemia is common (25-40%)!



**Anemia in 36% (1/3)**

- Hb  $\geq$  130 g/L
- Hb 100-129 g/L
- Hb < 100 g/L

# #3 Pre-op anemia associated with ↑ transfusion

ONTraC: 20 Years of Patient Blood Management

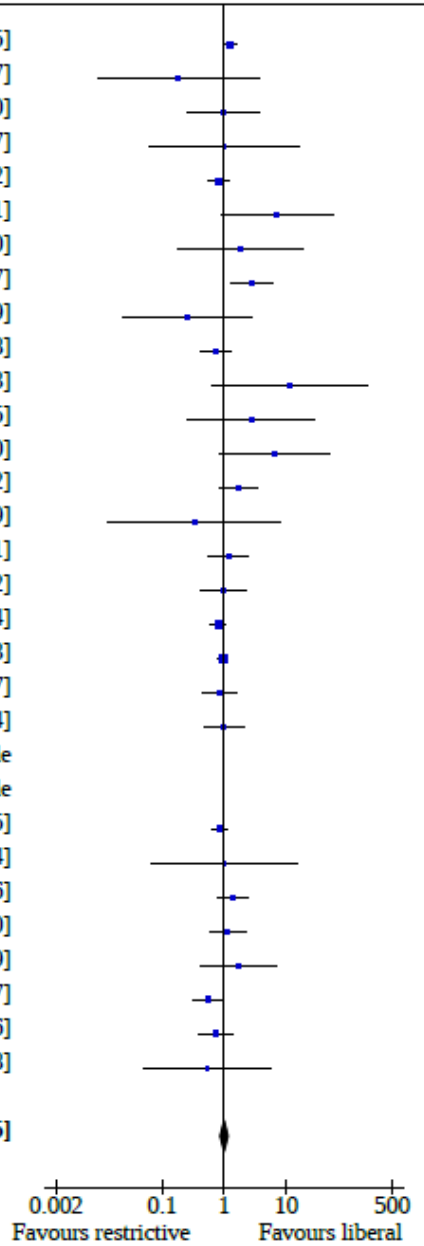
**Table. Relationship Between Preoperative Hemoglobin Concentration (Hb) and RBC Transfusion Rate.**

Preoperative Hb	Percentage of patients transfused during the 2021 data collection period				
	Knee arthroplasty Transfusion rate, % (n)	CABG surgery Transfusion rate, % (n)	Valve surgery Transfusion rate, % (n)	CABG + valve surgery Transfusion rate, % (n)	Gynecological surgery Transfusion rate, % (n)
Hb < 100 g/L	100 (3)	100 (9)	75.0 (8)	100 (4)	41.7 (24)
Hb < 110 g/L	5.0 (20)	100 (13)	70.6 (17)	100 (11)	28.8 (59)
Hb < 120 g/L	1.3 (76)	68.2 (44)	70.6 (34)	84.0 (25)	20.0 (115)
Hb < 130 g/L	0.8 (256)	61.2 (113)	67.8 (90)	78.4 (51)	11.8 (228)
Hb > 130 g/L	0.1 (884)	17.5 (456)	20.2 (273)	37.3 (153)	0.9 (216)
Hb > 140 g/L	0 (516)	15.4 (318)	13.1 (176)	30.3 (109)	0 (100)

Abbreviations: CABG, coronary artery bypass graft; Hb, hemoglobin.

Study or Subgroup	Restrictive		Liberal		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Bergamin 2017	84	151	67	149	11.8%	1.24 [0.99, 1.55]	
Blair 1986	0	26	2	24	0.2%	0.19 [0.01, 3.67]	
Bush 1997	4	50	4	49	1.1%	0.98 [0.26, 3.70]	
Carson 1998	1	42	1	42	0.3%	1.00 [0.06, 15.47]	
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56, 1.22]	
Carson 2013	7	55	1	55	0.5%	7.00 [0.89, 55.01]	
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18, 18.70]	
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30, 5.87]	
DeZem 2016	1	59	2	30	0.4%	0.25 [0.02, 2.69]	
Ducrocq 2021	19	342	25	324	4.6%	0.72 [0.40, 1.28]	
Foss 2009	5	60	0	60	0.2%	11.00 [0.62, 194.63]	
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26, 28.95]	
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86, 47.70]	
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87, 3.32]	
Grover 2006	0	109	1	109	0.2%	0.33 [0.01, 8.09]	
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57, 2.41]	
Hébert 1995	8	33	9	36	2.6%	0.97 [0.42, 2.22]	
Hébert 1999	78	418	98	420	10.7%	0.80 [0.61, 1.04]	
Holst 2014	168	502	175	496	13.5%	0.95 [0.80, 1.13]	
Jairath 2015	14	257	25	382	4.0%	0.83 [0.44, 1.57]	
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48, 2.04]	
Laine 2018	0	40	0	40		Not estimable	
Lotke 1999	0	62	0	65		Not estimable	
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63, 1.15]	
Møller 2019	1	29	1	29	0.3%	1.00 [0.07, 15.24]	
Murphy 2015	26	1000	19	1003	4.5%	1.37 [0.76, 2.46]	
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57, 2.20]	
Parker 2013	5	100	3	100	1.0%	1.67 [0.41, 6.79]	
Villanueva 2013	19	416	34	417	5.0%	0.56 [0.32, 0.97]	
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38, 1.36]	
Webert 2008	1	29	2	31	0.4%	0.53 [0.05, 5.58]	
<b>Total (95% CI)</b>		<b>8321</b>		<b>8408</b>	<b>100.0%</b>	<b>0.99 [0.86, 1.15]</b>	
Total events:	670		689				

Heterogeneity: Tau<sup>2</sup> = 0.03; Chi<sup>2</sup> = 40.06, df = 28 (P = 0.07); I<sup>2</sup> = 30%  
 Test for overall effect: Z = 0.07 (P = 0.94)  
 Test for subgroup differences: Not applicable



**31 trials (16,729 pts)**

**30 day mortality  
 OR 0.99  
 (95% CI 0.86-1.15)**

**Transfusion had no benefit  
 (with known risks)**

**\*Comparing hb thresholds,  
 not transfusion vs. no  
 transfusion**

# #4 Preoperative anemia is potentially modifiable

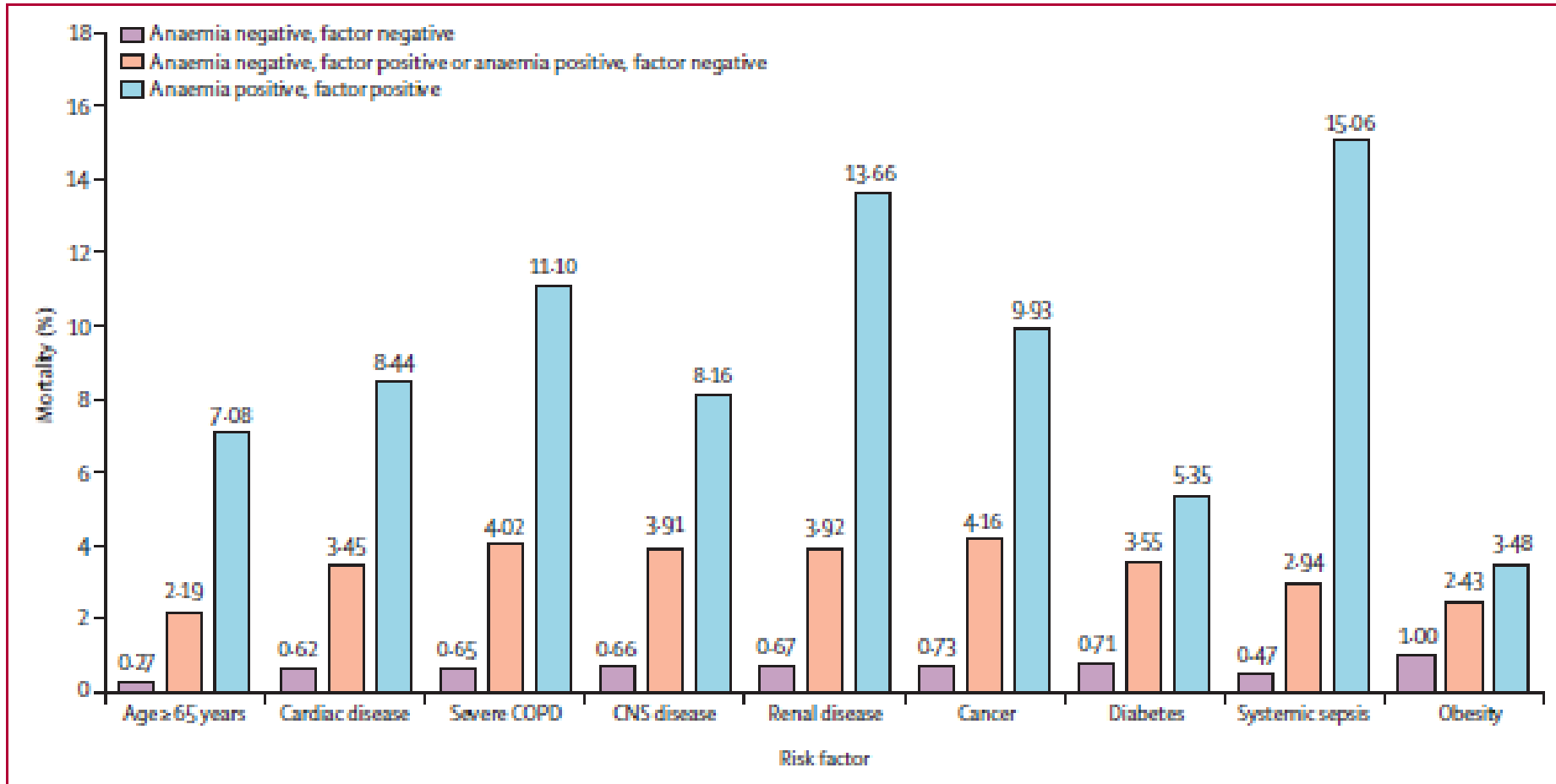


Figure 1: 30-day mortality, by anaemia and risk factor status  
COPD=chronic obstructive pulmonary disease.



## **Learning Objective #1:**

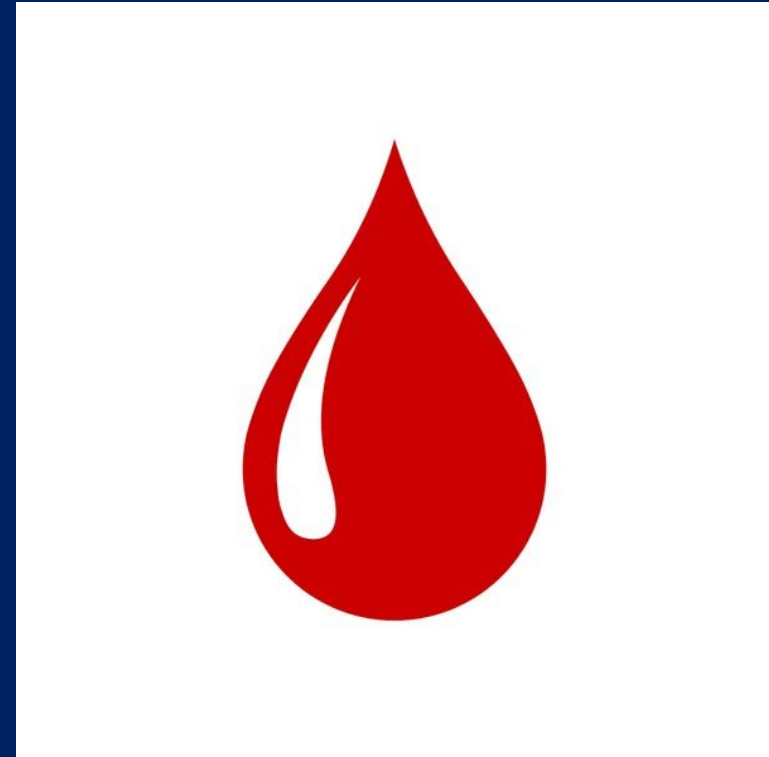
**Advocate for the  
importance of PBM**

Preoperative anemia is

1. Associated with mortality
2. Common
3. Associated with transfusion,  
with its inherent risks and  
scarcity
4. Potentially modifiable

**Learning objective 2:**

**How can we treat  
preoperative anemia?**



# Poll Question

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- When faced with a patient with preoperative anemia, which of the following have you done?
  - Proceeded with surgery
  - Referred to a blood conservation clinic
  - Arranged autologous blood
  - Prescribed oral iron
  - Prescribed intravenous iron
  - Prescribed erythropoiesis stimulating agent
  - None of the above



## Autologous Blood

- Patient donates own blood before surgery with sufficient time to allow patient to make up loss
- Goal: to provide additional RBC units for surgery (↑ red cell mass)





# Pitfalls of Autologous Donation

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- Takes at least 4 wks to re-generate autologous blood
- Preop Hb was **11 g/L lower** in autologous group (systematic review 14 RCTs)
- More expensive due to 50% wastage rate
  - 1 allogeneic unit costs \$446 (CBS 2020-21)

## Autologous Blood

- Preop autologous blood donation **NOT recommended**
- Exceptions
  - Patients with very rare blood type not easily met by donor base (e.g. unusual or multiple antibodies)
  - Contact the transfusion service in these cases!

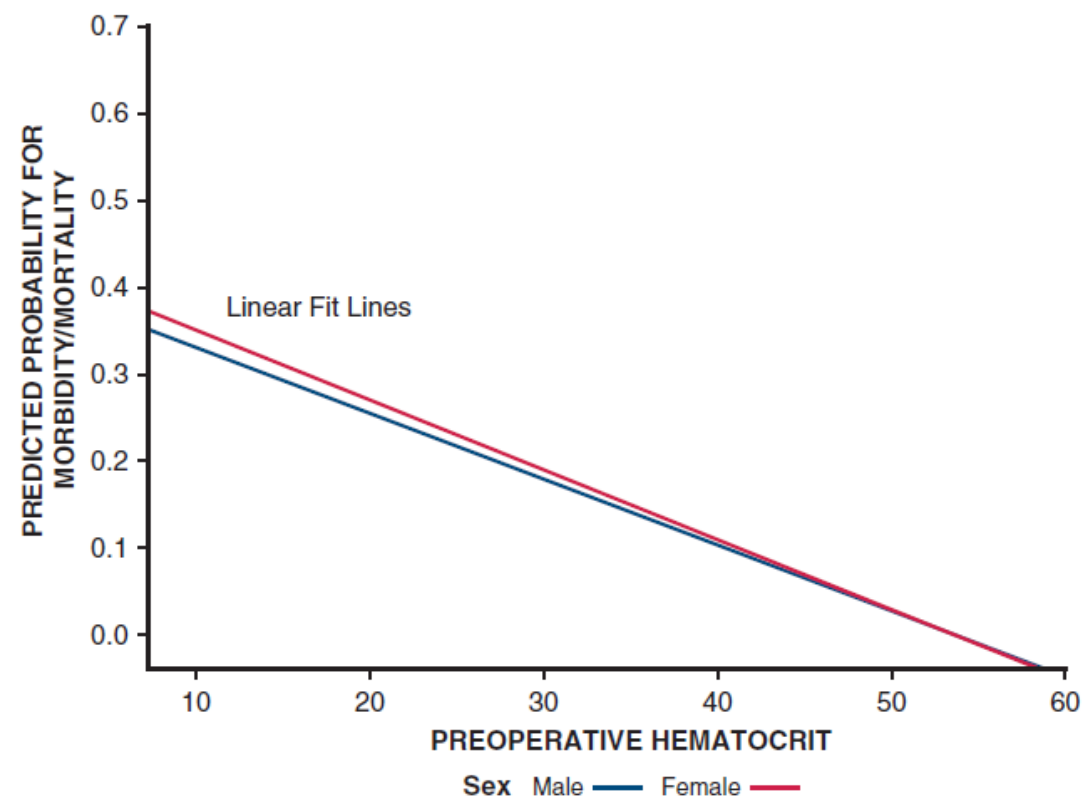
## Learning objective 2:

# Diagnose and treat iron deficiency anemia



# What is Preoperative Anemia?

- ~~• WHO: Hb < 130 g/L males; Hb < 120 g/L females~~
- **NEW:** Hb < 130 g/L used for all (high blood loss surgery)
  - Lower Hb in females may simply reflect iron deficiency
  - Similar impact of preop Hb and outcomes in both sexes
  - Accepting lower preop Hb for females ↑transfusion risk



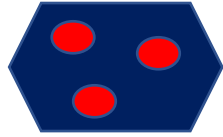
# Detection of Preop Anemia

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- Who should be screened?
  - High blood loss surgery (> 500 mL): ortho, cardiac, cancer
  - All high risk for severe anemia: colorectal, gyne surgery
- When?
  - At least 6 weeks before surgery
- How?
  - CBC, ferritin, TSAT, B12, creatinine
  - Focus on iron deficiency anemia (common & treatable)

# How to diagnose IDA?

- Ferritin



- Reflection of iron stores
- Ferritin < 30 ug/L = Iron deficiency

- Serum Fe

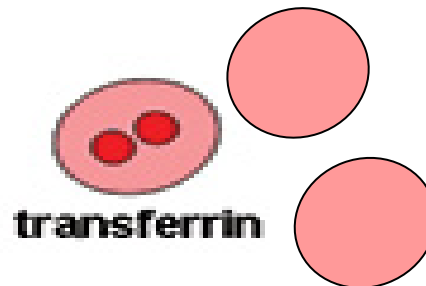
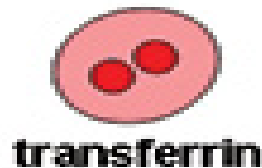


- Transferrin (TIBC)

- Transport protein of Fe

- Transferrin saturation

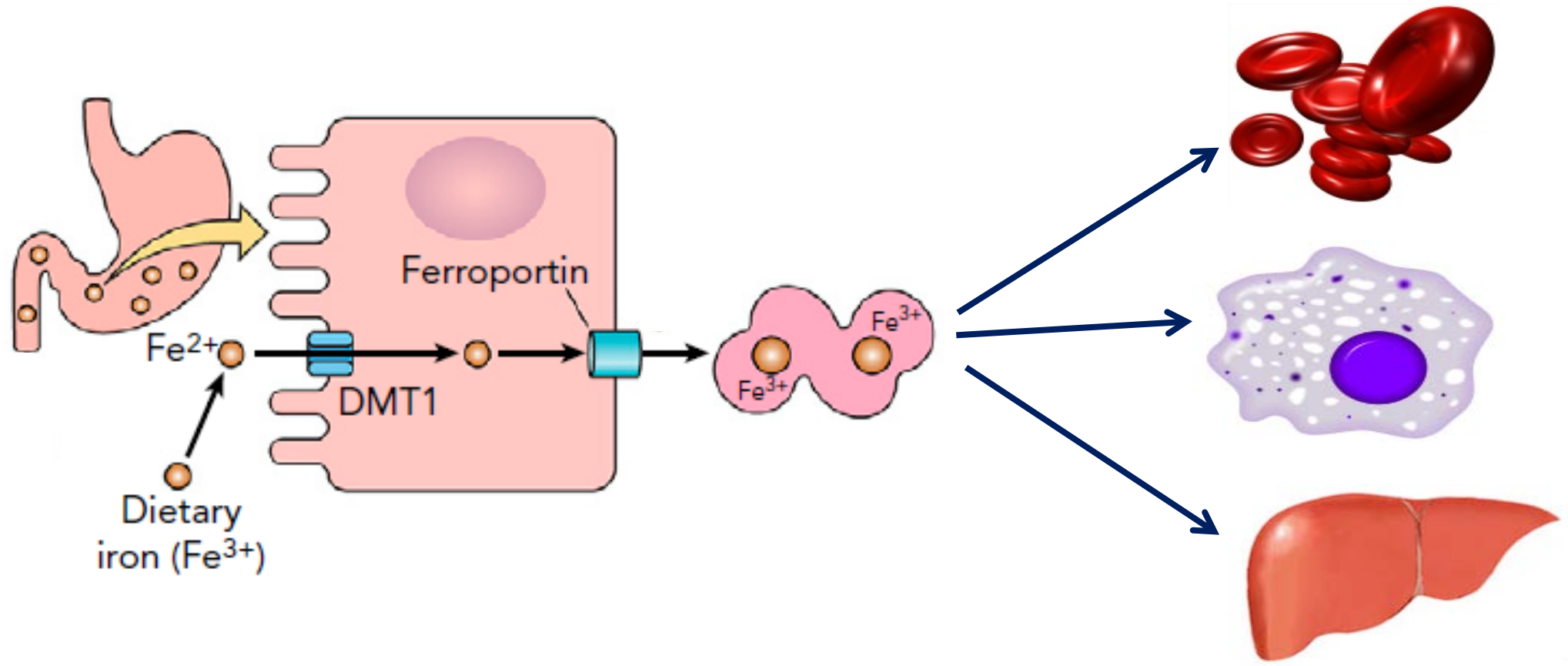
- Serum Fe / TIBC



Inflammation

↑ **Ferritin as acute phase reactant**

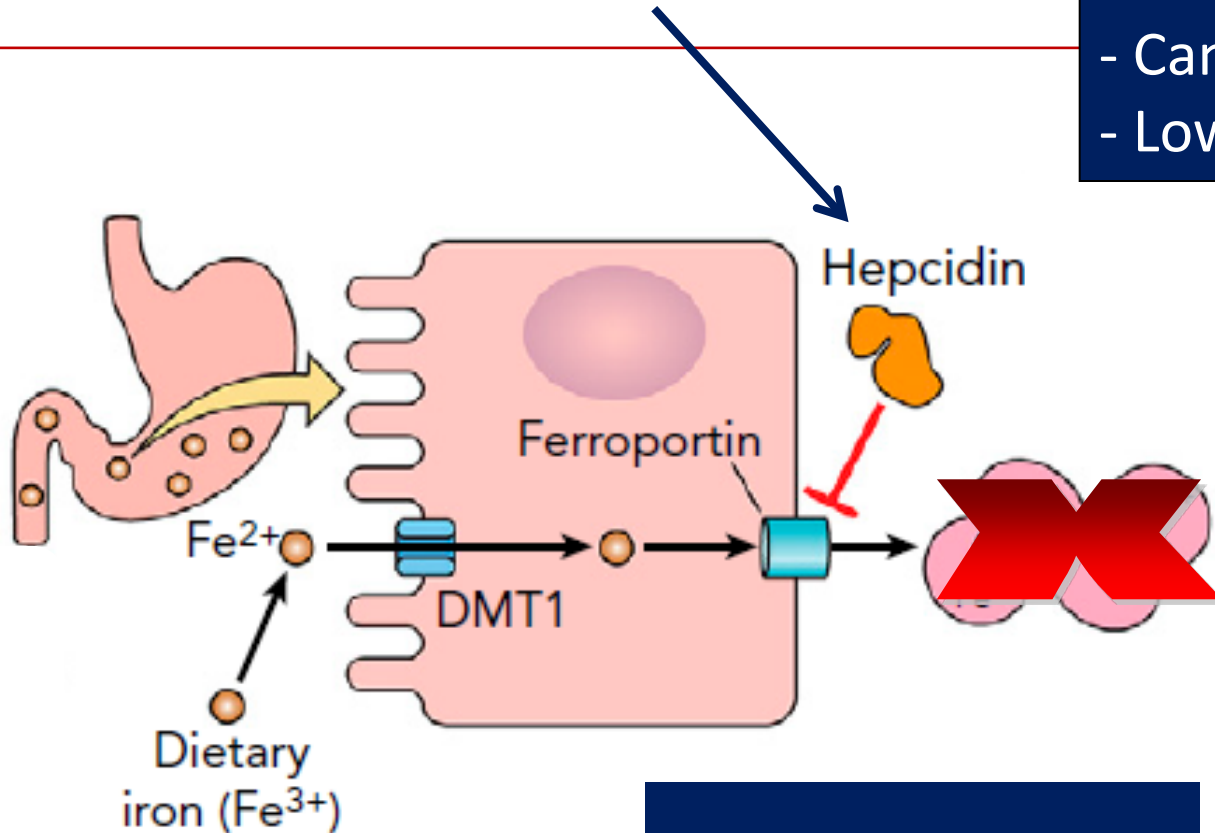
# Iron Pathway



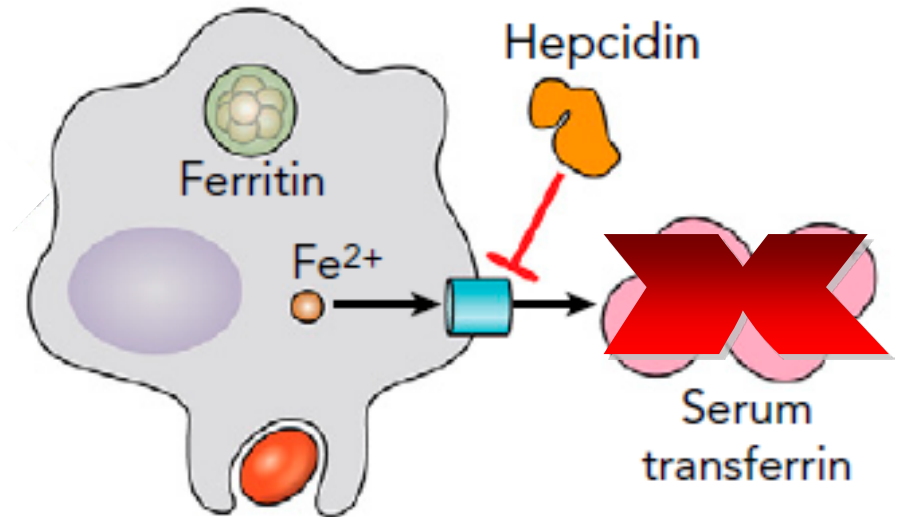
# Inflammation

Functional iron deficiency

- Adequate iron stores
- Cannot mobilize Fe for RBCs
- Low transferrin sat < 20%



↓ Oral absorption



Iron trapping  
within RES



# Defining iron deficiency anemia

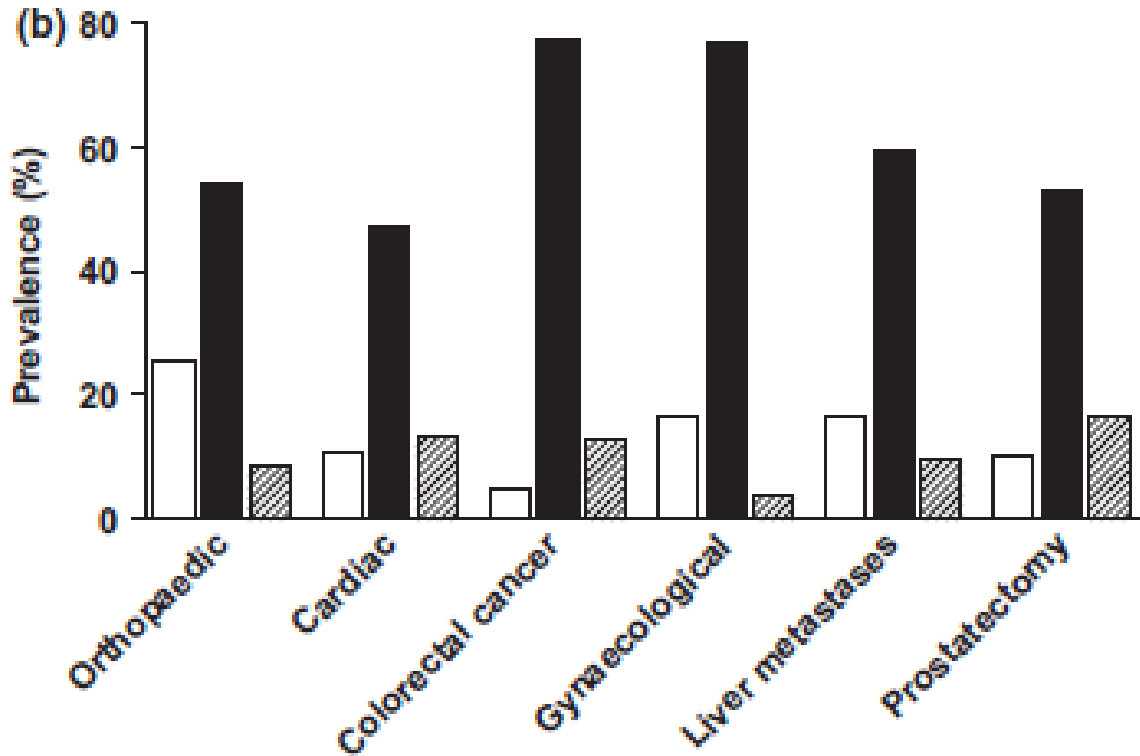
Absolute Iron Deficiency:

Ferritin < 30 mcg/L; or  
Ferritin < 100 + TSAT < 20% ± CRP > 5 mg/L

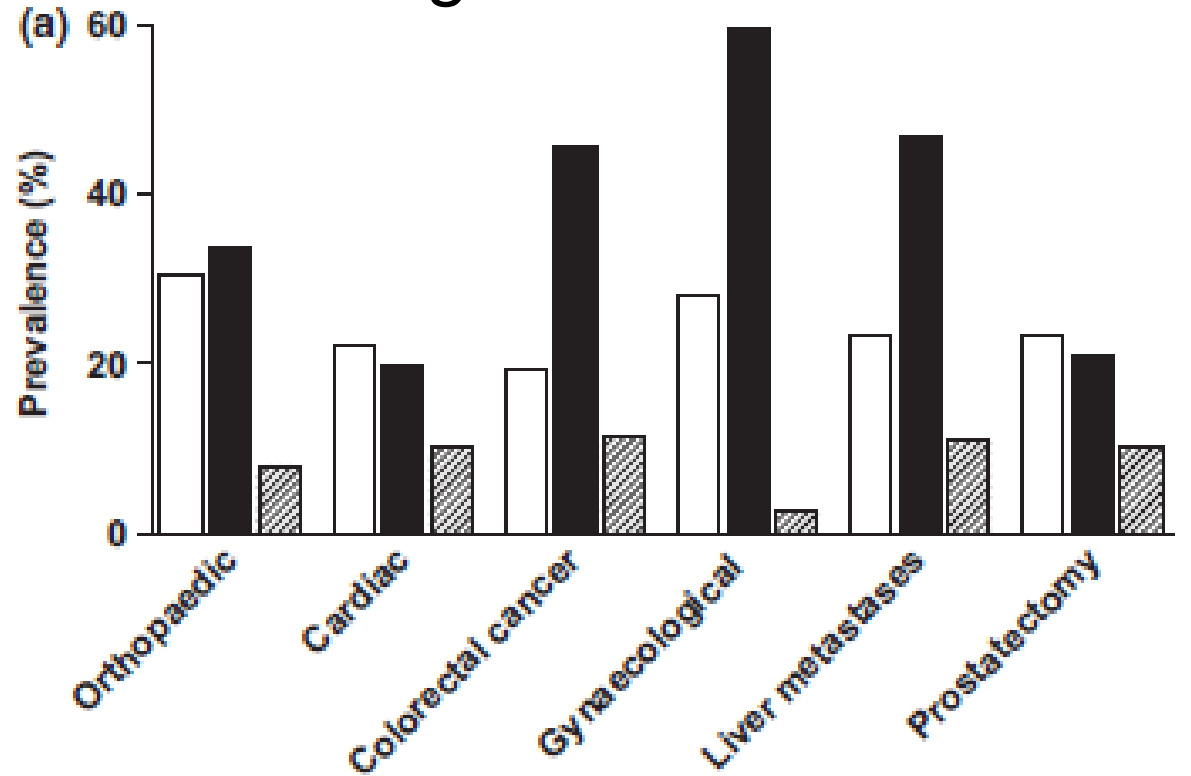
Low iron stores (major blood loss surgery): Ferritin 30-100 mcg/L + TSAT > 20%

Iron sequestration/Functional ID: Ferritin > 100 mcg/L + TSAT < 20%

Hb < 130 g/L



Hb ≥ 130 g/L



□ Low iron stores

■ Absolute ID

▨ Iron sequestration



## Treatment:

**#1 Investigate the cause of iron deficiency!**

**#2 Iron supplementation**

Table 1. Causes of iron-deficiency anemia in the preoperative setting

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### Causes of preoperative iron-deficiency anemia

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#### Too much iron OUT

##### Increased loss

- Blood loss, eg, gastrointestinal, gynecological bleeding
- Blood donation

##### Increased requirements

- Rapid growth in infants and children
- Pregnancy
- Use of ESAs

#### Too little iron IN

##### Decreased iron intake

- Iron-poor diet
- Vegetarian or vegan

##### Decreased absorption

- Celiac disease
- Gastrectomy, gastric bypass, gut resection
- *Helicobacter pylori*
- Inflammatory bowel disease
- Drugs: antacids, proton pump inhibitors
- Foods: calcium, tannins (tea, coffee), phytates



# Oral Iron

- Preoperative
  - Small studies: no difference (RCT) to small  $\uparrow$ Hb,  $\downarrow$ transfusion rate (observational)
  - Greater benefit if given for
    - Longer course ( $>14$  vs.  $<14$  days)
    - Patients with anemia (vs. no anemia)
- ~~Postoperative: no benefit due to postop inflammation~~

Guidelines recommend oral iron if at least 6-8 weeks preop

# Oral Iron Salts

	Dose mg	Elemental mg	Cost
Ferrous gluconate (ODB)	300	35	\$0.07-0.14
Ferrous sulfate	300	60	\$0.03-0.14
Ferrous fumarate (ODB)	300	100	\$0.14-0.67

- Give once a day (or every other day) on an empty stomach (with a glass of orange juice ~80mg ascorbic acid)
- Absorption only 10% of elemental Fe
- GI side effects: epigastric pain, heartburn, nausea, vomiting, constipation or diarrhea

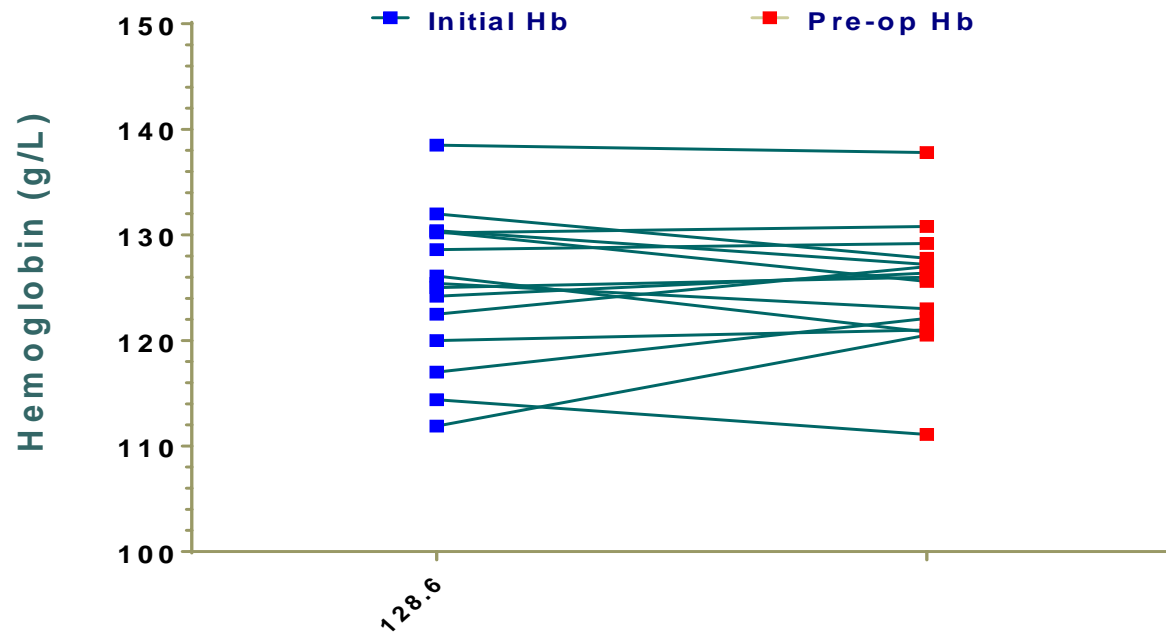


# Oral Iron

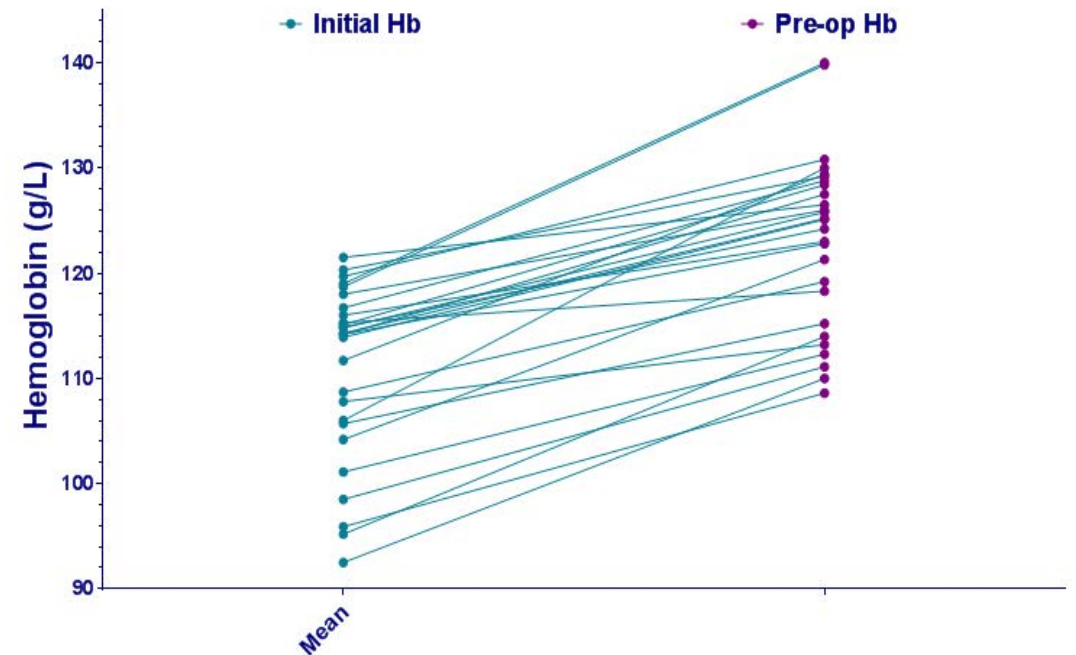
	Dose mg	Elemental mg	Cost
Polysaccharide (Odan, Triferexx, Feramax)	150	150	\$0.67-1.05
Heme iron (Optifer alpha, Proferrin)	398	11	\$0.86-1.03
Ferric asorbate (EBMfer)		100	\$1.05
Ferric pyrophosphate		30	\$2.00

- More expensive, fewer side effects
- No evidence that more effective than oral iron salts

## Oral iron only



## IV iron only



2017 ONTraC data: Hb change 1 g/L vs. 13 g/L ( $p < 0.0001$ )

Lead time < 3 weeks in ~50%

# Oral vs. IV iron

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- Oral iron:
  - Pros: ease of administration, inexpensive and effective when tolerated
  - Cons: GI side effects, iron repletion takes 3-6 months
- Indications for IV iron
  - Oral iron not tolerated or effective (absorption, inflammation or ongoing bleeding)
  - Moderate/severe anemia, e.g. Hb < 100 g/L
  - Short time to surgery < 6-8 weeks



# RCT: IV Iron in Abdo Surgery

- 72 pts for major abdominal surgery **with IDA**
  - Ferritin < 300, TSAT < 25% (mean ferritin 19-37)
- Randomized to IV iron or usual care
  - Ferric carboxymaltose 15mg/kg up to 1000mg preop + postoperative 0.5 mg per mL blood loss
  - Usual care ~ no treatment
    - 3 patients prescribed oral iron in entire cohort
    - IV iron: 1 pt preop and 4 pts post-op

# RCT: IV Iron in Abdo Surgery

- Terminated early due to poor outcomes in usual care group! (target 268 pts)
  - ↑ Hb increment 8 g/L vs. 1 g/L pre-op ( $p=0.01$ )
  - ↓ transfusion 12.5% vs. 31.3% ( $p<0.0003$ )
  - ↓ length of stay 7.0 vs 9.7 days ( $p=0.026$ )
  - ↑ Hb at 4 wks 122 g/L vs. 111 g/L ( $p<0.001$ )
- *“Usual care failed the majority of participating patients, leaving them untreated with a treatable condition”*

# PREVENTT Trial

Elective major open abdominal surgery  
Hb < 120 g/L women  
Hb < 130 g/L men

N = 474 pts  
2014-2018  
46 UK sites

No specific criteria for IDA

Placebo

N = 243

Ferric carboxymaltose

N = 246

Blood Transfusion/Death:  
28% vs. 29%  
(RR 1.03; 95% CI 0.78-1.37)

Number of transfusions:  
111 vs. 105  
(RR 0.98; 95% CI 0.68-1.43)

Richards et al. Lancet 2020;396:1353-61



# PREVENTT Trial

- No baseline iron criteria; 5% had IBD; 29% had iron deficiency
- Intervention:
  - Median 15 days preop; Hb ↑ 5 g/L preop
  - Anemia corrected 21% vs. 10%
  - No specific transfusion protocol
- No difference in subgroups (Hb  $\leq$  100; ferritin  $\leq$  100)
- No difference in postop complications, LOS, QOL
- Decreased risk of readmission to hospital in IV iron group\*

# Preop IV iron systematic reviews...

- All surgery
  - Iron supplementation ↑ Hb but may not result in reduced # of pts transfused (N=700 pts)
  - Iron ± ESAs ↑ Hb and probably ↓ # of pts transfused (N=1500 pts)
- Colorectal cancer surgery (5 RCTs, 485 pts)
  - Preop iv iron ↓ transfusion, ↑Hb compared to controls (included oral iron)
  - No difference in mortality and postop complications
- Cardiac surgery (6 RCTs, 936 pts; 5 obs, 1350 pts)
  - Preop iv iron ↓ mortality (no difference if only RCTs included), no difference in transfusion



Intravenous iron	ferric derisomaltose	ferric gluconate	iron sucrose
Name	Monoferric	Ferrlcit	Venofer
Indication	IDA when oral iron cannot be used	IDA in HD epo	IDA in CKD
Max single dose	1500 mg	125 mg	300mg
Test dose	No	No	No
Infusion time @ SBK	30 min (500mg) 60 min (1000mg)	1 hour	2 hours
Costs @ SBK	\$47.48 per 100mg (LU code)	\$46.00 per 100mg	\$29.00 per 100mg (EAP)
Life threatening ADE	comparable	0.9 per 10 <sup>6</sup>	0.6 per 10 <sup>6</sup>

# How to give IV iron

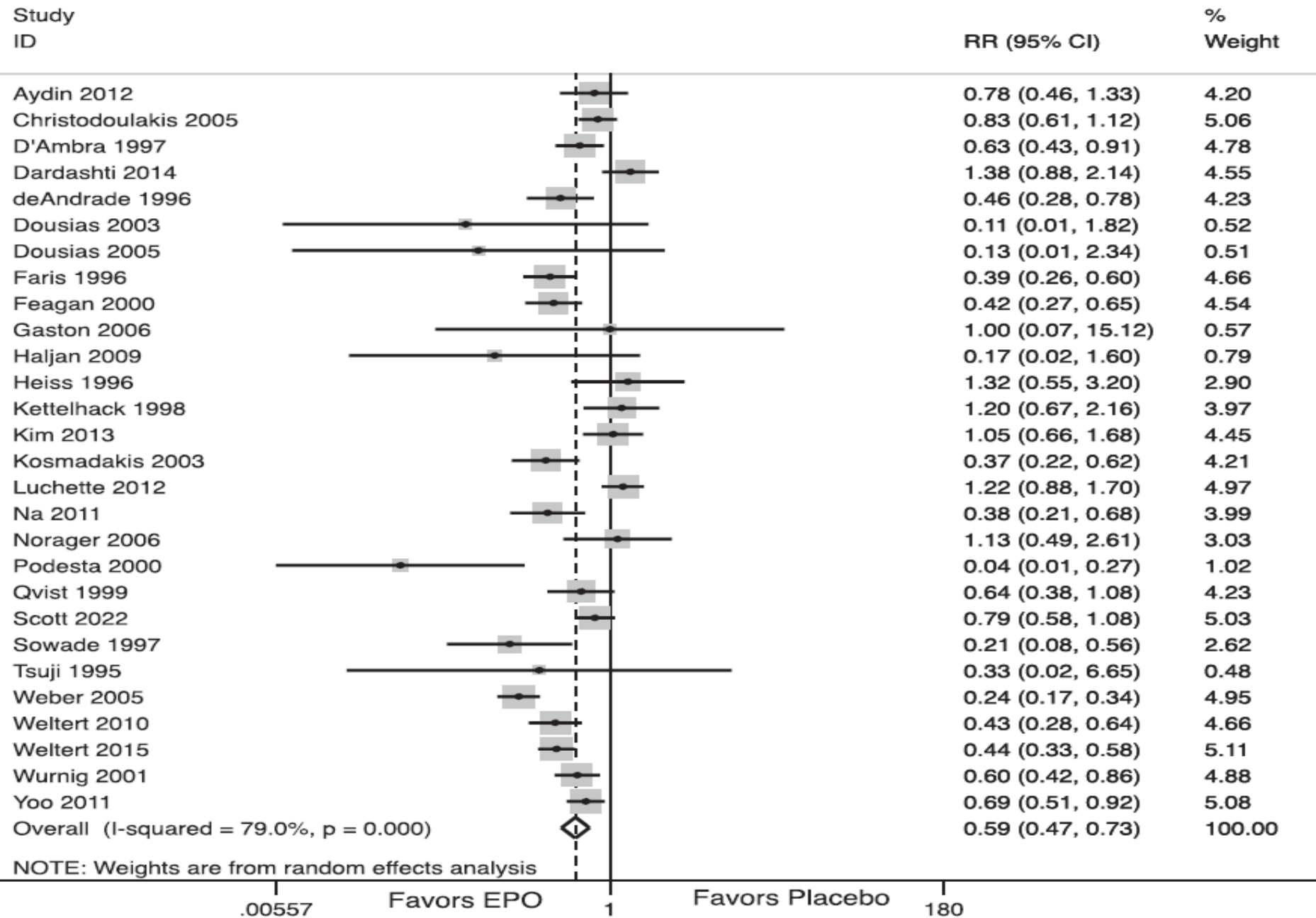
- Dose: Ganzoni formula
  - Dose =  $[\text{wt (kg)} \times (\text{target} - \text{initial Hb g/dL}) \times 2.4] + 500\text{mg}$
  - In practice, 1000 - 1500 mg
- Side effects
  - Serious allergic reactions are rare but include anaphylaxis
  - Fishbane reactions: flushing, chest tightness (encourage hydration before coming to appt)
  - Hypotension 1-2%, metallic taste, headache, muscle cramps, arthralgias
- Contraindications: active infection, previous allergy to IV iron

# Learning objective 3:

## The role of erythropoiesis stimulating agents







**Preop EPO in  
Surgical Pts  
32 trials  
4,750 pts**

**Decreased  
transfusion  
OR 0.59  
(0.47, 0.73)**

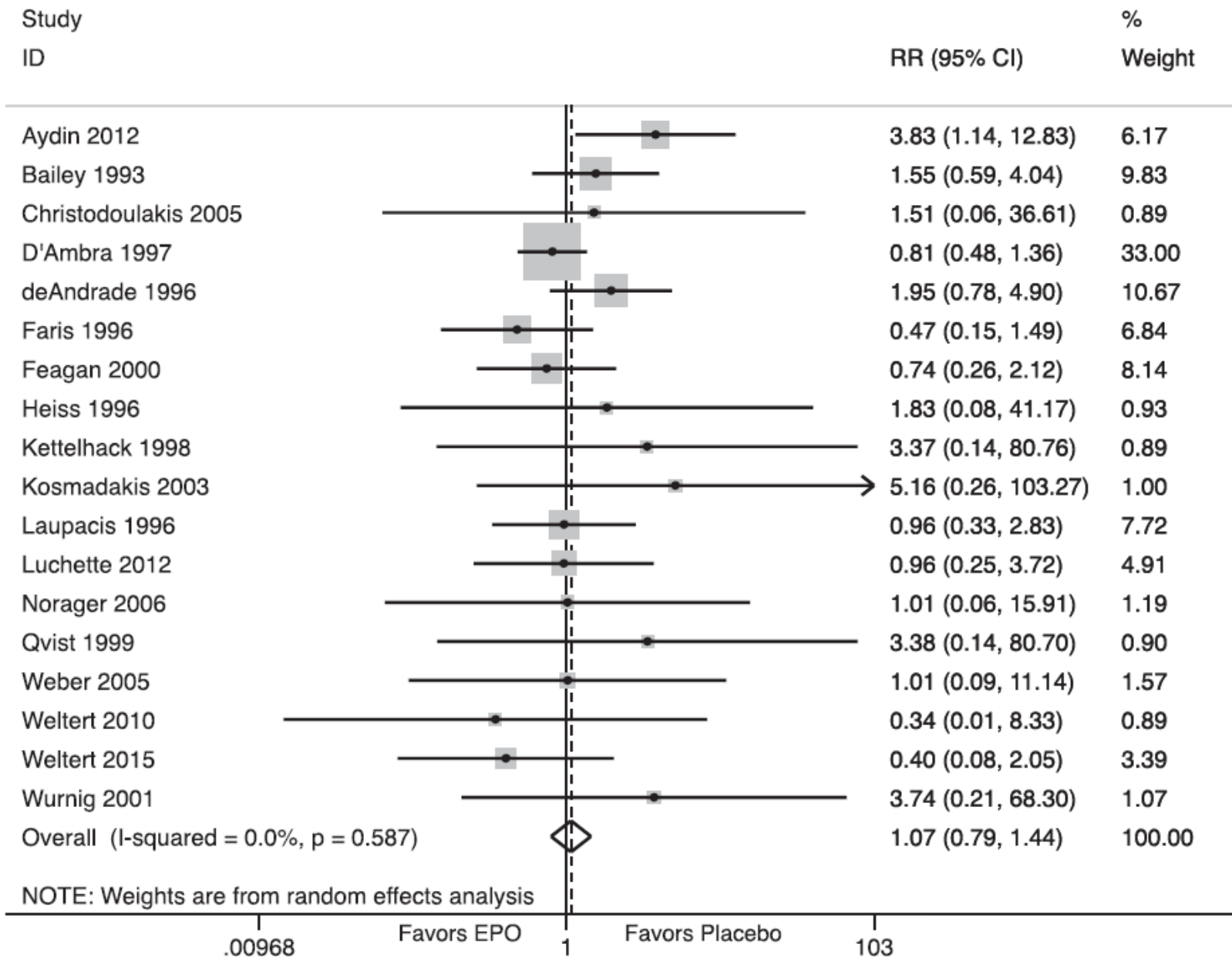
**Figure 2.** The weighted (pooled) estimate for the effect of preoperative erythropoietin (EPO) administration on incidence of whole hospitalization allogeneic transfusions (risk ratio [RR], 0.59; 95% CI, 0.47–0.73;  $P < .001$ ) compared to placebo administration.

# Concerns about ESA

- Chronic kidney disease
  - CHOIR: Epo to ↑ Hb to 135 g/L (vs. 113 g/L) associated with ↑ arterial TE events
  - CREATE: Epo to ↑ Hb to 130-150 g/L (vs. 105-115 g/L) – no difference
  - TREAT: Darbepoietin to ↑ Hb to 130 g/L (vs. placebo) – no difference in composite outcome, but ↑ stroke in darbepoietin group
  - ESA used for > 16 months

Singh et al. NEJM 2006;355:2085-98  
Druecke et al. NEJM 2006;255:2071-84  
Pfeffer et al. NEJM 2009;361:2019-32





**Preop EPO in Surgical Pts not associated with ↑ TE events**

**Overall rate 4.1%**

**2° outcome**

**Uncertainty (wide 95% CI)**

**Figure 3.** The weighted (pooled) estimate for effect of preoperative erythropoietin (EPO) administration on incidence of thromboembolic events (risk ratio [RR], 1.02; 95% CI, 0.78–1.33; *P* = .68) compared to placebo administration.

# ESA in Cancer

- Mortality effect RR 0.97 – 1.17 (2 SR ↑, 3 SR no difference)
  - Controversial: Mechanism? VTE related? Poor responders to ESAs = worse prognosis? Seen in trials that targeted high Hb > 120 g/L
- Concern about tumour progression
  - Not clear how as tumours have low/undetectable EpoR
  - Theories unproven: angiogenesis, ↑tissue oxygenation → tumour growth, contribution to chemo resistance
- ↑ Venous TE RR 1.48-1.67 (5 SR)
- Most studies in cancer used ESA > 8 weeks

# The role of ESAs

Guidelines: role of preop ESAs less clear

1. High blood loss surgery (> 10% transfusion)
  - cardiac, orthopedic, major abdominal surgery

CanJSurg

For patients with anemia who have no evidence of IDA or IDA refractory to iron supplementation, referral to a hematologist should be considered for treatment with erythropoietin and intravenous iron infusions.

Strong

High

10. In patients with inadequate response to IV iron or when iron sequestration or inflammation limits the bioavailability of iron, an ESA should be considered on a case-by-case basis.

NAC

11. In patients with anemia and evidence of inflammation or renal failure where an ESA is indicated, it should be combined with IV iron.

Greenberg et al. Can J Surg 2021;64:E491-509

Lett et al. NAC Statement on PBM 2022 June. <https://nacblood.ca/en/resource/nac-patient-blood-management-statement>



Figure 2. Leading pathophysiological mechanisms contributing to hypoferremia and AI in CKD, IBDs, autoimmune diseases, cancer, chronic lung diseases, CHF, infectious diseases, and ICUs.

# Anemia of inflammation



# The role of ESAs

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Guidelines: role of preop ESAs less clear

1. High blood loss surgery (> 10% transfusion)
  - cardiac, orthopedic, major abdominal surgery
2. Patients with anemia: Hb < 120-130 g/L
  - Religious objections to blood transfusion
  - Multiple alloantibodies → difficult to find blood

# Practical Aspects

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- Requires adequate lead time (3-4 weeks)
- Dose: 40,000 units s.c. q weekly x 2-4 doses ← short term use
- Lower Hb targets for pts with cancer and kidney disease (~120 g/L)
- Side effects: flu like symptoms with bone/muscle pain, hypertension (typically with longer term use)
- Iron supplementation
- Cost effectiveness uncertain
- Postop DVT prophylaxis

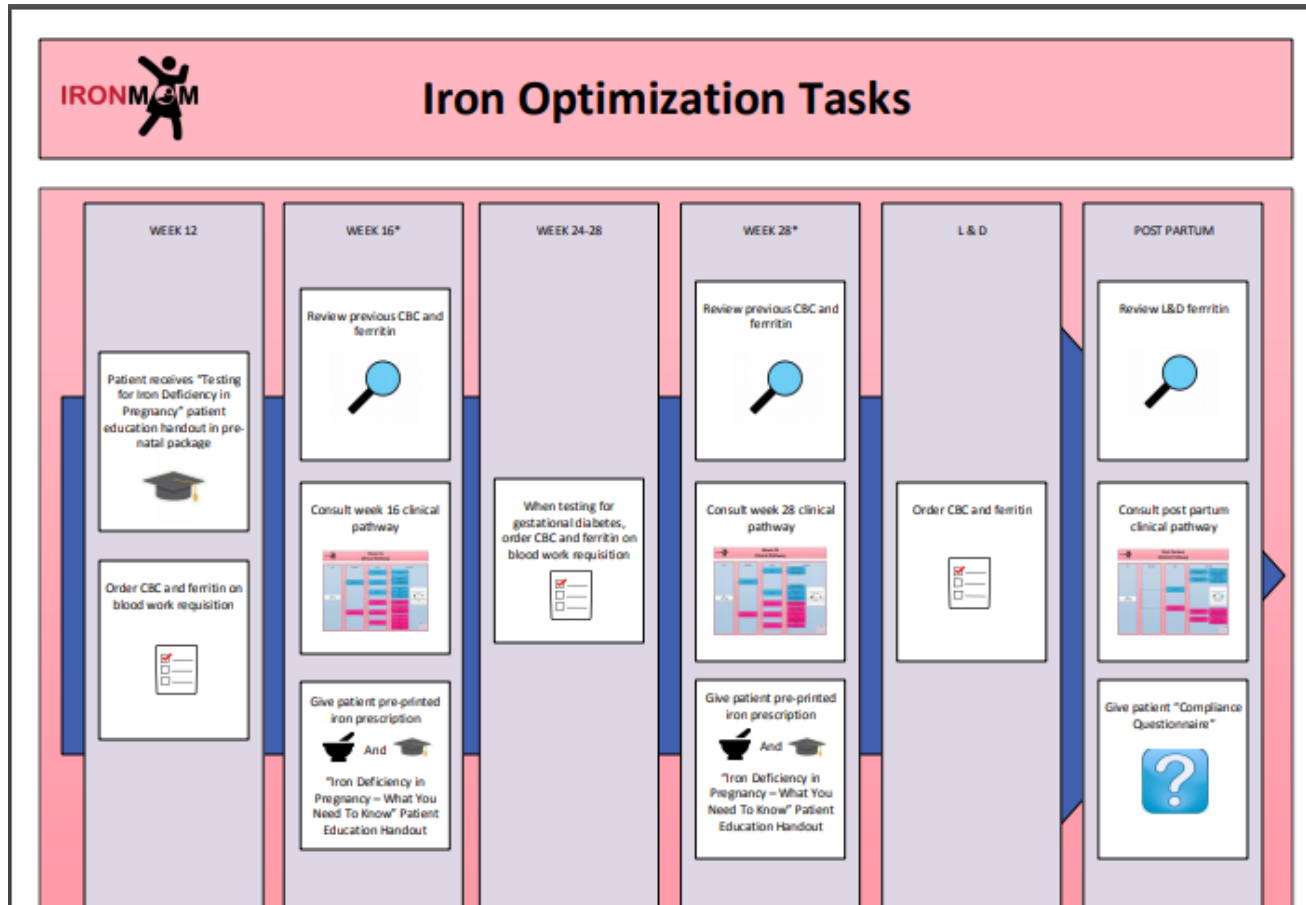


# PBM in Obstetrics

## Screen for Anemia

- ACOG
  - All pregnant women should be screened for anemia
  - Treat with iron if iron deficient
- BCH
  - Full blood count at booking (1<sup>st</sup> trimester) and at 28 wks
  - Anemic women with no other obvious cause: diagnostic trial of oral iron with CBC repeat at 2-3 wks

# IRON MOM Canada (QI project)

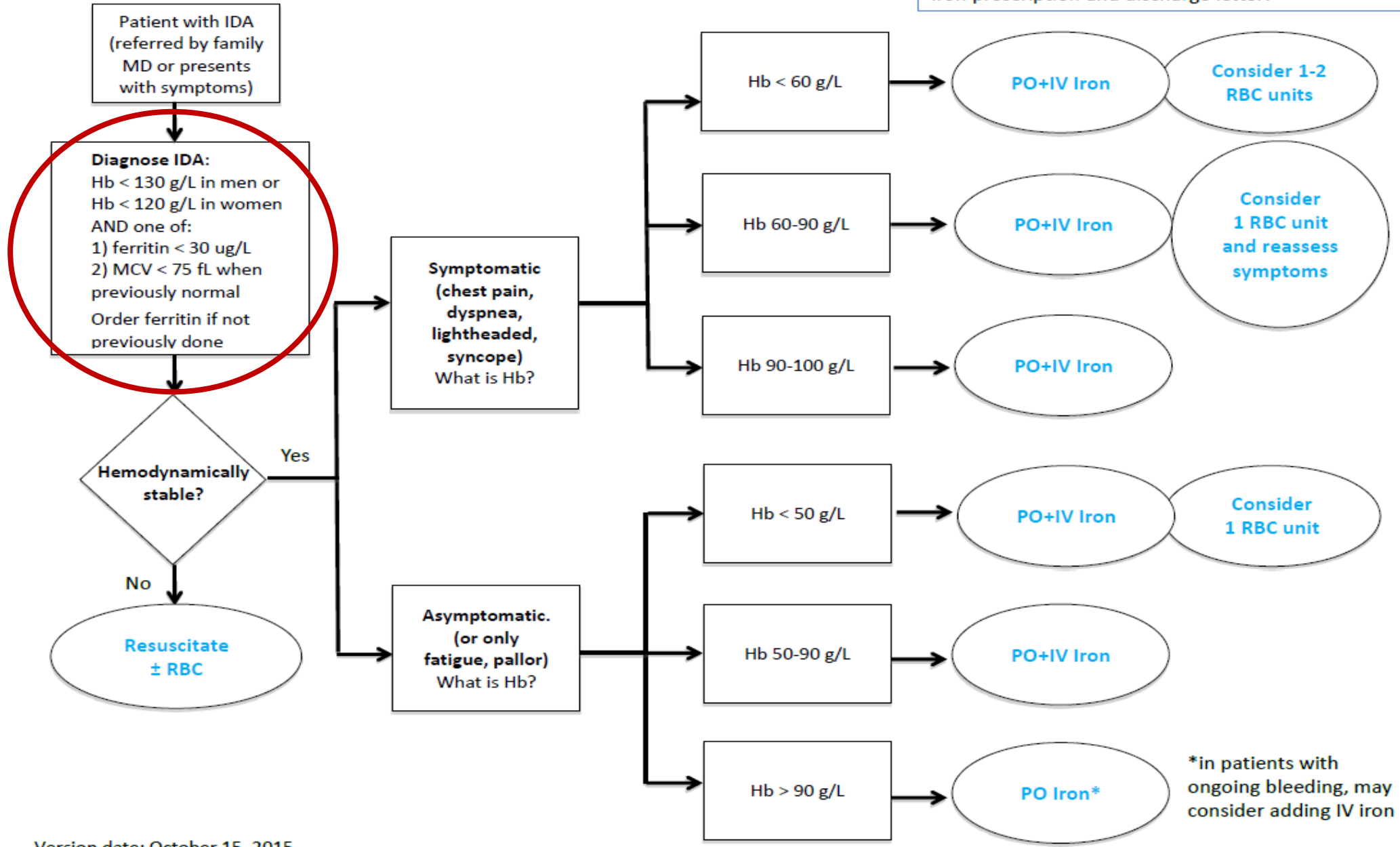


## Outcomes:

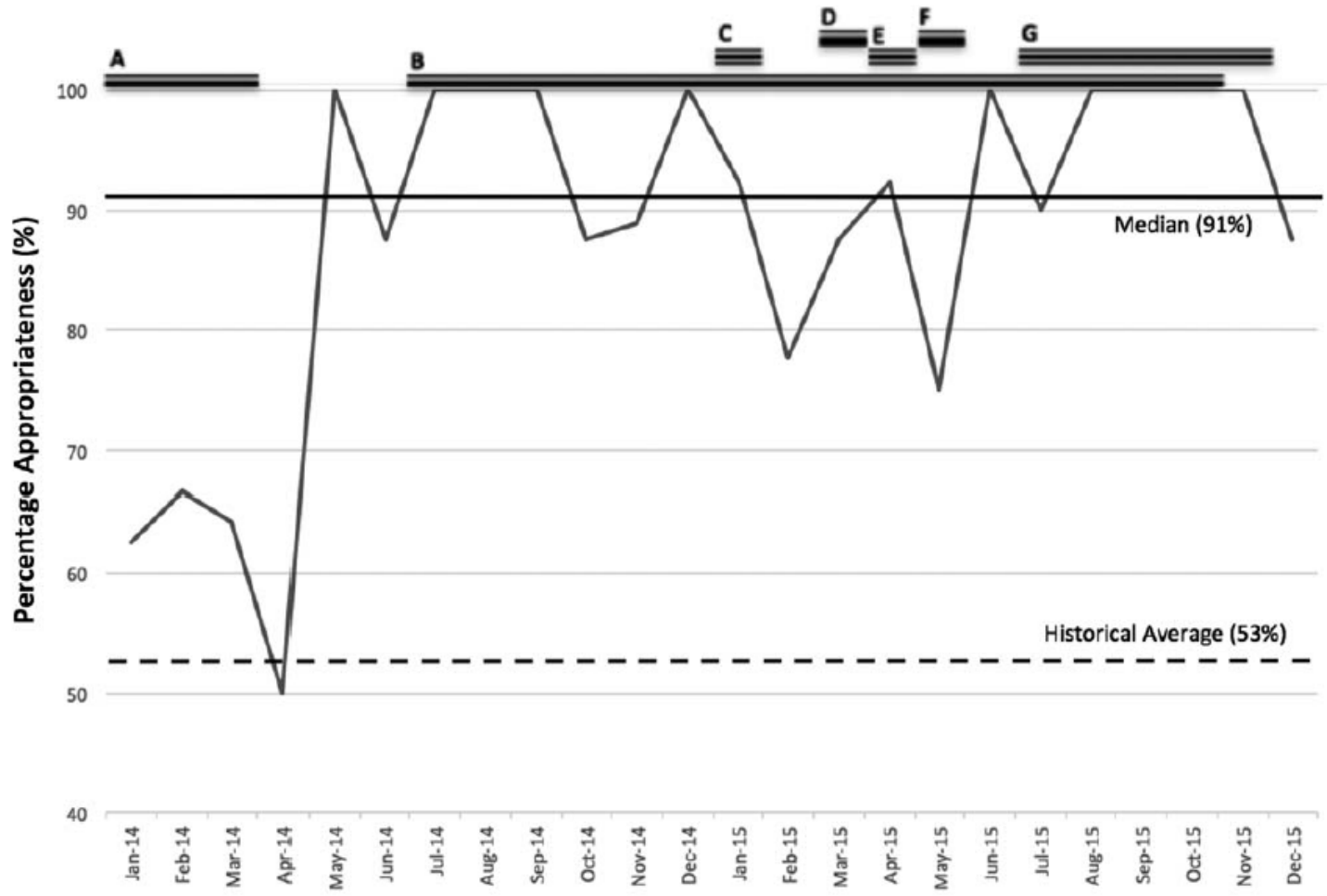
- ↑ ferritin tests
- ↓ anemia at delivery (13.5% to 10.6%,  $p>0.001$ )
- ↓ transfusions (1.2% vs. 0.8%,  $p=0.049$ )

# Guideline for Iron Deficiency Anemia Management in the ED

Note: Please refer to WebER for patient pamphlet, IV iron orders (written consent not required), oral iron prescription and discharge letter.



# ED: ↑ appropriate transfusion for IDA



- A. IV iron avail. in ED
- B. IV iron guideline
- C. Stakeholder feedback
- D. Grand rounds
- E. Access to TM MD
- F. Podcast release
- G. ED IDA toolkit

# Key learnings – Treat anemia

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- Preoperative anemia & transfusion are associated with bad perioperative outcomes
- Look for treatable anemia (Do CBC EARLY!)
- Look for iron deficiency anemia (common)
  - Ferritin < 30 ug/L; Ferritin < 100 ug/L + TSAT<20%
  - Make sure the underlying cause is identified in IDA
- Consider preop erythropoietin in high blood loss surgery especially in pts with religious objections or rare blood needs

# Thank you.

