

# **Erythropoiesis: preventive actions**

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# **Disclaimer**

**Advisory board : Vifor, Pharmacosmos,  
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**Speakers' bureau : Vifor, Amgen**

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**SURGERY**

**Erythropoiesis**

# **SURGERY**

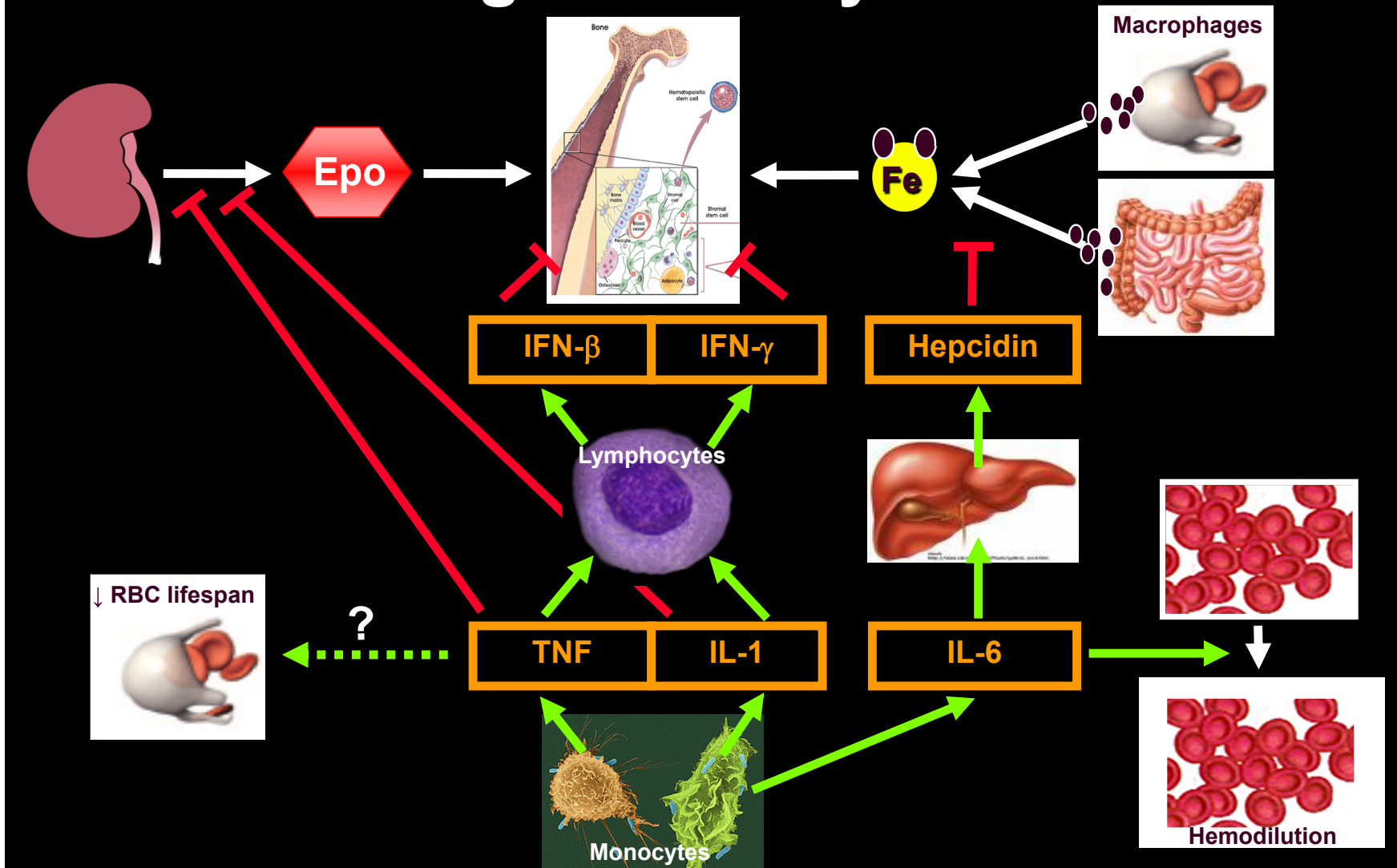
## **Effect on allogeneic transfusions**

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- **Preoperative red cell mass**
  - Weight/height, gender, **Hb**
- **Blood loss (pre-, per-, post-surgery)**
- **Transfusion trigger (Hb, clinical criteria)**
- **Volume transfused**

# ANEMIA OF INFLAMMATION

## Pathogenesis : cytokines



# IRON DEFICIENCY

## Absolute vs functional ID

- Absolute iron deficiency

= no iron stores : **ferritin** < 20  $\mu$ /L in N individual  
< 100  $\mu$ /L in cancer / infl  
CRF

- Functional iron deficiency

= iron stores present but ID in erythroid bone marrow  
**ferritin : normal or increased**

a) Iron sequestration in macrophages

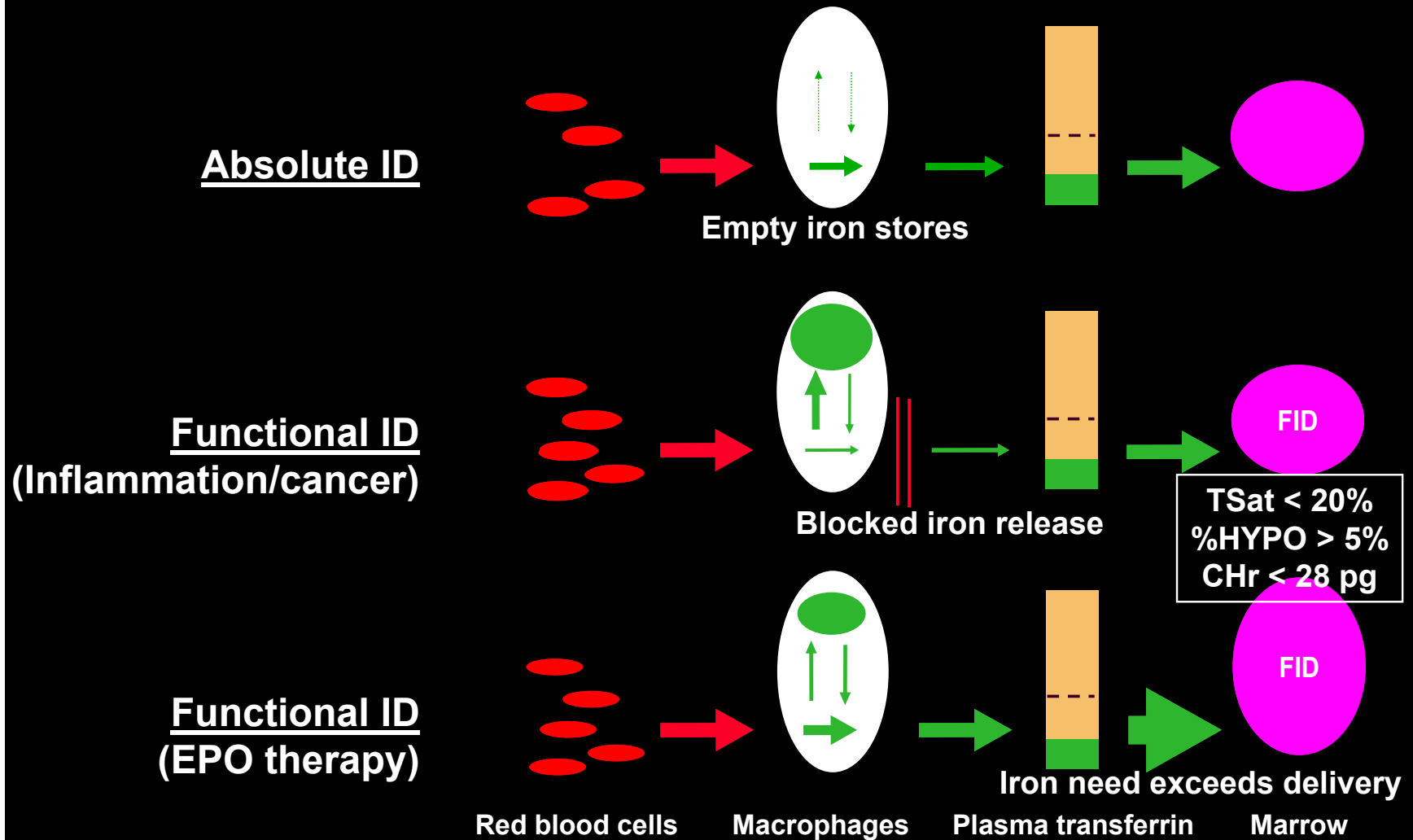
- **Inflammation (ACD, anemia of chronic disease)**

b) Increased iron requirements

- **EPO therapy**

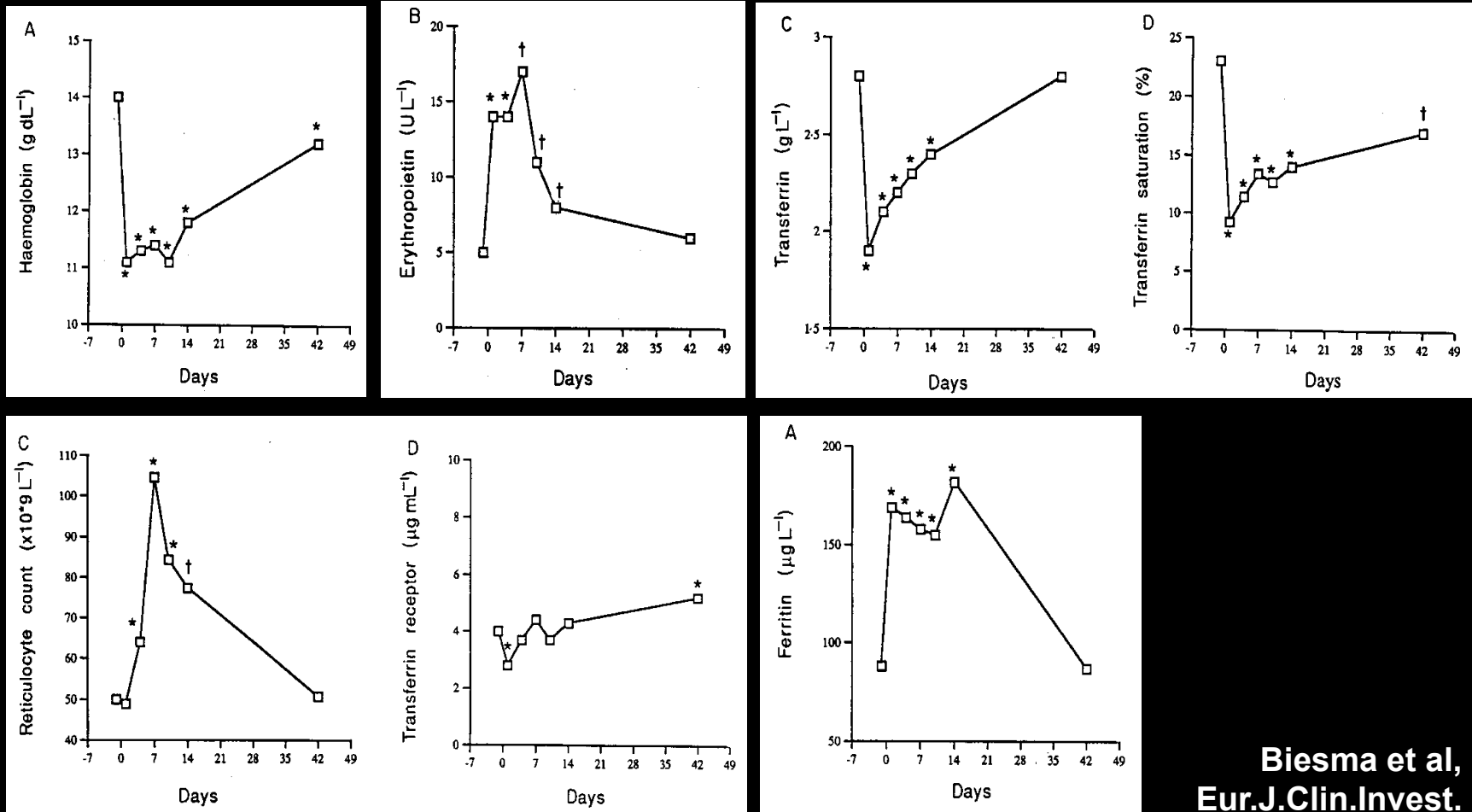
# TRANSFERRIN SATURATION

## Absolute vs functional ID



# SURGERY

## Iron metabolism and erythropoiesis





**SURGERY**

**EPO and/or iron**

**SURGERY**

**EPO**

# **PREOPERATIVE EPO**

## **Effect on allogeneic transfusions**

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### **Metaanalysis**

- **Cardiac surgery**
- **11 randomized trials, 708 patients**
- **EPO started 1-4 wks before surgery, dose very variable**
- **Autologous blood donation**
  - Yes : 7 trials
  - No : 4 trials
- **Iron supplements in all trials**

# PREOPERATIVE EPO

## Effect on allogeneic transfusions

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	Odds ratio (CI)	
• <b>rHuEpo and ABD</b>	0.28 (0.18-0.44)	347 patients
• <b>rHuEpo alone</b>	0.53 (0.32-0.88)	361 patients

# PREOPERATIVE EPO

## Effect on allogeneic transfusions

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### Metaanalysis

- Orthopedic (knee or hip) surgery
- 26 randomized trials, 3,560 patients
- EPO started 0-4 (mostly 3) wks before surgery, dose very variable
- EPO with or without other interventions
  - EPO alone : 9 trials
  - EPO + ABD : 15 trials
  - EPO + acute normovolemic hemodilution : 2 trials
- Iron supplements in almost all trials : PO in 20, IV in 7, none in 1 trial

# PREOPERATIVE EPO

## Effect on transfusions, Hb & TEE

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- **Effect on allogeneic Tx**

RR 0.48 (0.38-0.60)

3,450 patients

p<0.00001

- **Effect on Hb at discharge**

+0.7 g/dL

3,093 patients

p<0.00001

- **Thrombo-embolic events**

RR 1.04 (0.65-1.67)

3,041 patients

NS

# PERIOPERATIVE EPO

## Effect on allogeneic transfusions

### Perioperative EPO : effect on allogeneic transfusions ?

- **Yes**

- Qvist, 1999
- Kosmadakis, 2003
- Weltert, 2010

Colorectal surgery  
Colorectal surgery  
Cardiac surgery

- **No**

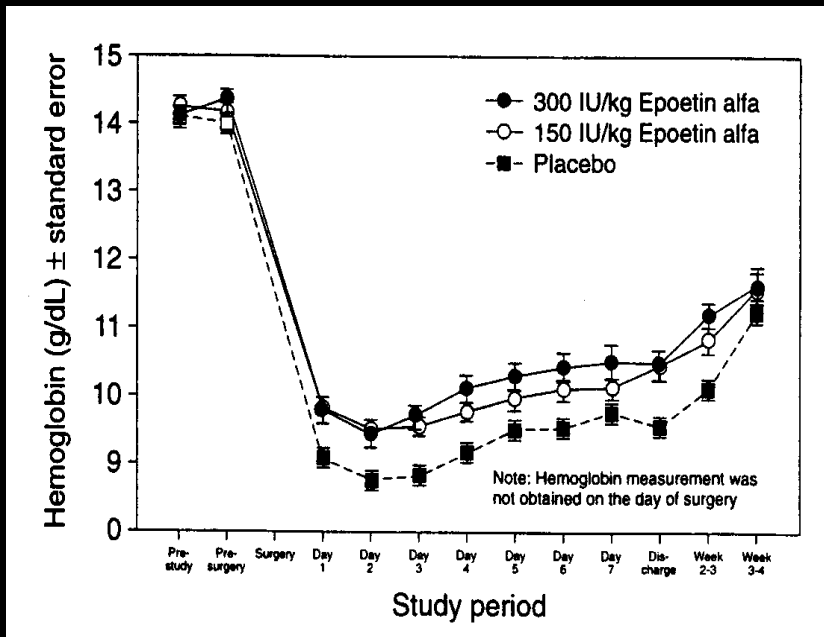
- Heiss, 1996
- Kettelhack, 1998
- Grobmyer, 2009

Colorectal surgery  
Colorectal surgery  
Colorectal surgery

# PREOPERATIVE EPO

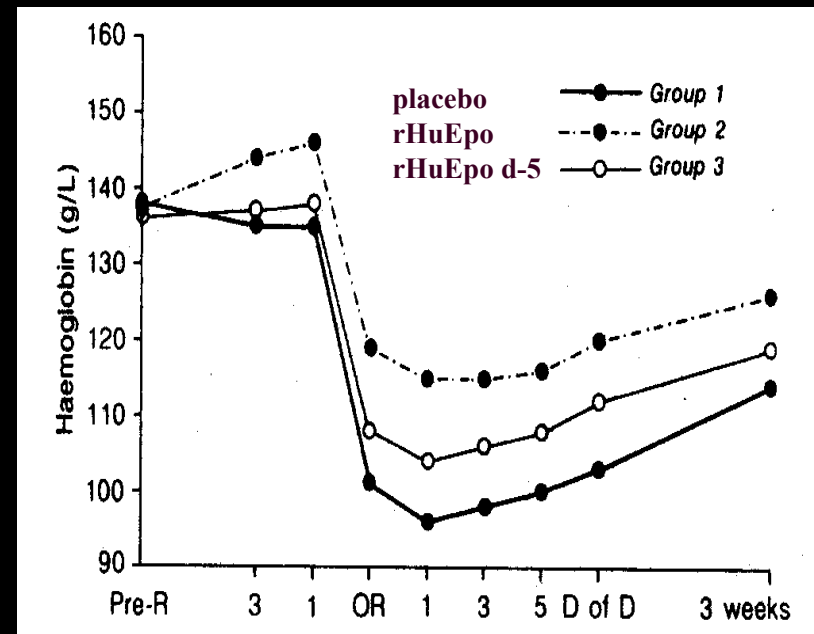
## Late EPO initiation

### Cardiac surgery Days -5 to +2



D'Ambra, Ann.Thorac.Surg. 1997, 64:1686

### Orthopedic surgery Days -10 or -5 to +3

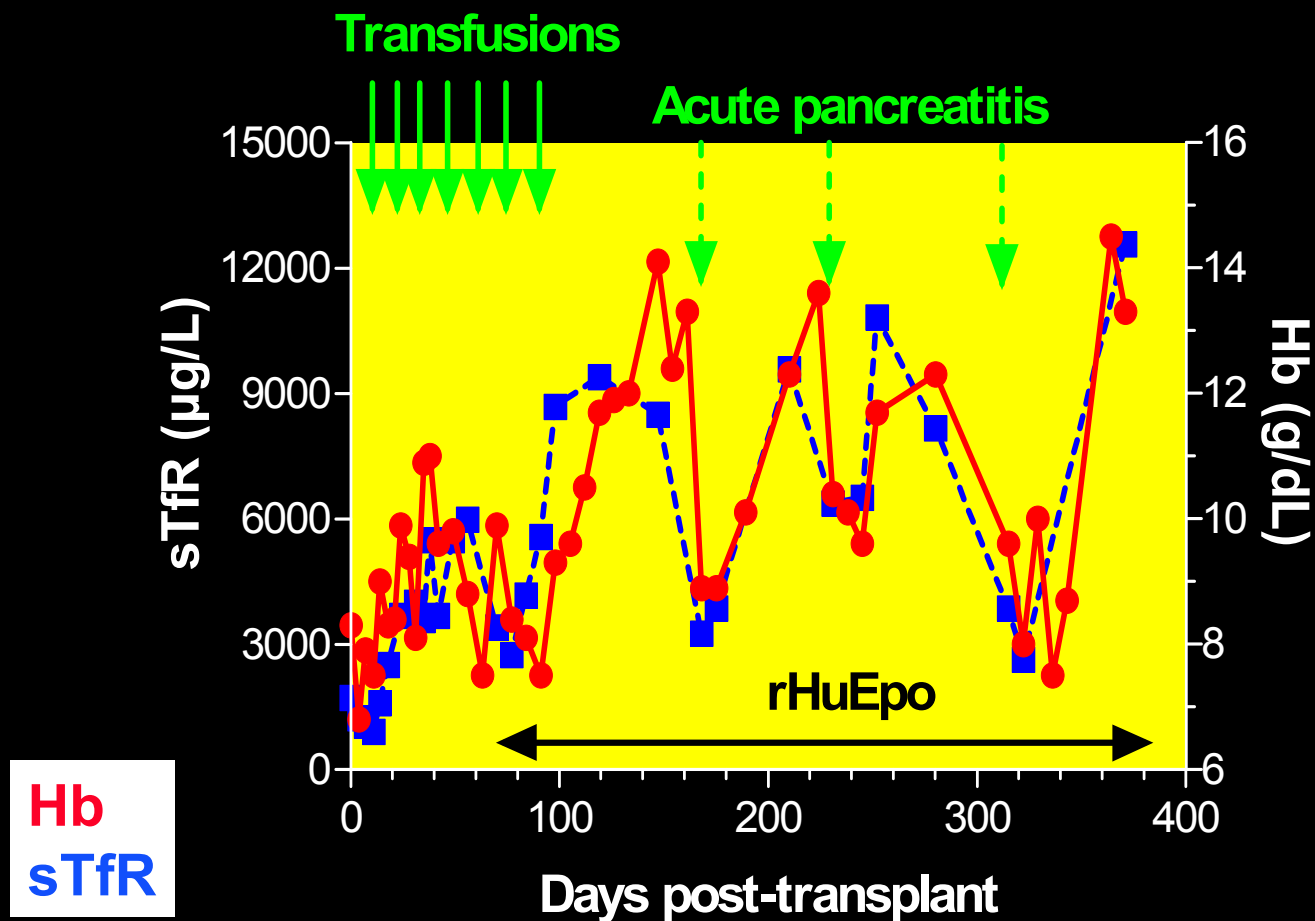


Laupacis, Lancet 1993, 341:1227



# EPO THERAPY IN CANCER

## Resistance : inflammation



**SURGERY**

**IRON**

# PREOPERATIVE IRON

## Effect on allogeneic transfusions

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### Few randomized studies

- **Kim 2009** : IV iron sucrose (up to 200 mg TIW for 3 wks) more effective than oral iron (only 80 mg/d) in correcting IDA due to menorrhagia; no effect on transfusions reported.
- **Braga 1995** : IV iron sucrose (12 x 200 mg/d) much less effective than EPO + iron for collecting ABD and avoiding allogeneic transfusions in anemic patients with GI cancer.
- **Rohling 2000 & Olijhoek 2001** : oral iron as effective as IV iron in supporting preoperative EPO-driven stimulation of erythropoiesis; no effect on transfusions reported.

# PERIOPERATIVE IRON

## Oral iron

### Several randomized studies

- **Compare :**
  - No iron
  - Oral iron for several weeks after surgery
- **No effect on :**
  - Hb values
  - Transfusion requirements

Zauber, 1992

Sutton, 2004

Weatherall, 2004

Mundy, 2005

Parker, 2010

# PERIOPERATIVE IRON

## IV iron

- **Orthopedic surgery**
- **Single center retrospective comparison**
  - 1,538 patients receiving IV iron (and EPO), most commonly
    - \* IV iron sucrose 200 mg on D0 and 48H later
    - \* rHuEPO 40,000 U once if preoperative Hb < 13 gr/dL
  - 1,009 historical controls
- **Results**
  - Transfusion rates reduced
    - \* Hip fracture repair : 12% vs 49%
    - \* Arthroplasty : 9% vs 30%
  - Length of stay ↓
  - Infection rate and D30 mortality ↓ in hip fracture repair only
- **Quality of evidence low**

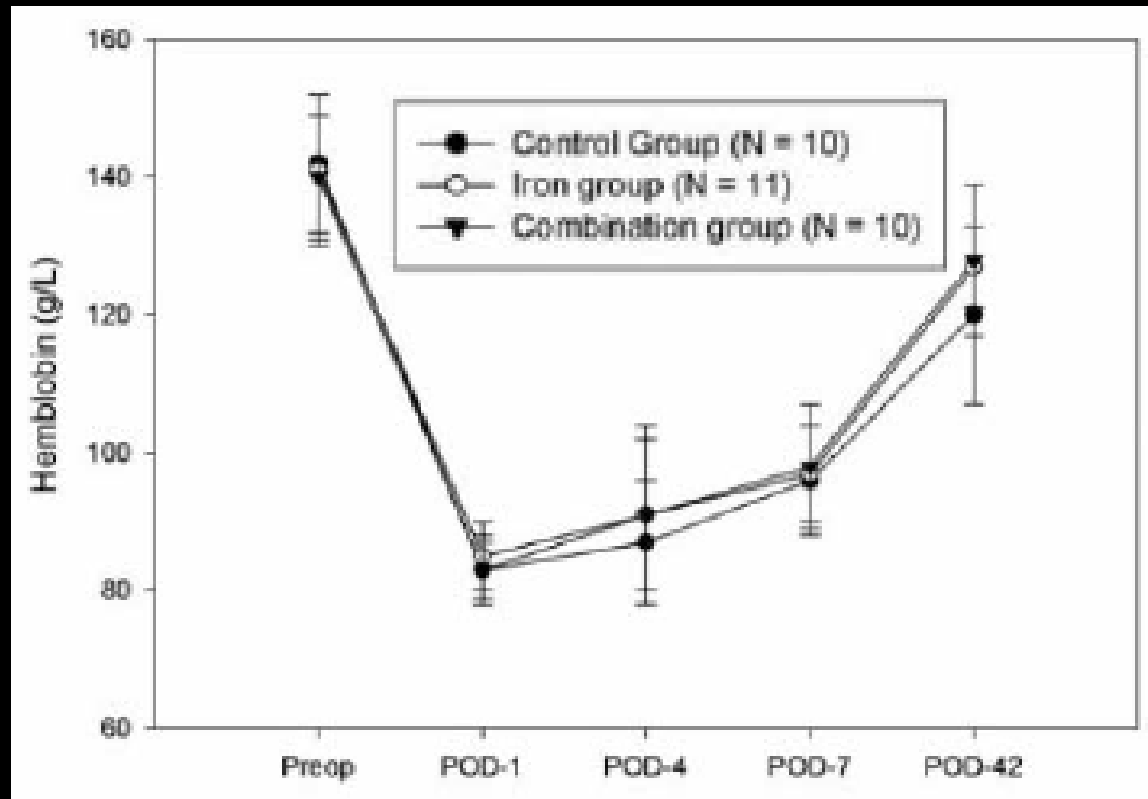
# PERIOPERATIVE IRON

## IV iron

- **Cardiac or orthopedic surgery**
- **38 patients (3,478 screened !)**
- **Post-operative Hb 7-9 gr/dL on D1**
- **Double-blind trial**
  - No treatment
  - IV iron sucrose 200 mg on D1-2-3
  - IV iron sucrose + rHuEPO 600 U/kg on D1 and D3
- **Hb values on day 7 and 6 weeks after surgery**

# PERIOPERATIVE IRON

## IV iron



**Transfusions not reported**  
**Trial stopped for futility**

Karkouti et al, Can.J.Anesth. 53:11, 2006

# PERIOPERATIVE IRON

## IV iron

- **Cardiac surgery**
- **120 patients**
- **Post-pump Hb 7-10 gr/dL**
- **Double-blind trial**
  - No treatment
  - IV iron sucrose 200 mg/d until reaching total iron deficit (TID)  
TID (mg) = 2.4 x BW (kg) x (target Hb [12 gr/dL]-lowest Hb)
  - IV iron sucrose + rHuEPO 300 U/kg on D1
- **Transfusions and hematologic parameters**



# PERIOPERATIVE IRON

## IV iron

**Table 2. Transfusion Requirements for the 120 Patients**

Group	No. of Pts Transfused	Mean No. of Blood Units/pt	Day of Transfusion		
			Day 2	Day 3	Day 4
I (n = 40)	9/40 = 22%	2.3	6/9	2/9	1/9
II (n = 40)	10/40 = 25%	2.3	6/10	3/10	1/10
III (n = 40)	7/40 = 17%	2.4	4/7	3/7	0/7
p	0.709				

Hb (g/dL) (Mean ± SD)	Gr I (n = 31)	Gr II (n = 30)	Gr III (n = 33)*
Day 0	14.37 ± 1.19	14.05 ± 1.12	14.18 ± 1.08
Day 1	10.81 ± 1.31	9.95 ± 1.06	10.20 ± 1.24
Day 2	9.70 ± 1.36	8.78 ± 0.88	9.12 ± 1.09
Day 3	9.38 ± 1.33	8.56 ± 0.89	8.86 ± 1.05
Day 4	9.31 ± 1.33	8.66 ± 0.98	8.91 ± 1.65
Day 5	9.46 ± 1.34	8.71 ± 0.93	9.05 ± 1.27‡
Day 15	10.33 ± 1.38	9.79 ± 0.95	10.18 ± 1.53§
Day 30†	11.87 ± 1.21	12.18 ± 1.04	12.42 ± 1.21

# PERIOPERATIVE IRON

## IV iron

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- **Hip fracture repair surgery**
- **200 patients**
- **Any Hb**
- **Open-label randomized trial**
  - No treatment
  - IV iron sucrose 200 mg/d x 3 : upon admission, 48 and 96H later (i.e. pre- or post-surgery)
- **Transfusions, mortality and hematologic parameters**

# PERIOPERATIVE IRON

## IV iron

Type of transfusion	Group A	Group B	p value
Timing of transfusion			
Intraoperatively	21 (21.6)	23 (23.2)	NS†
Early	8 (8.2)	4 (4)	
Late	12 (12.4)	6 (6.1)	
Compliance with the protocol			
Protocol-compliant	39 (95.1)	32 (97)	NS‡
Protocol-noncompliant	2 (2.1)	1 (1)	

Group	Group A*	Group B*	p value†
All patients (n = 196)	41 (41.3)	33 (33.3)	NS
Patients with intracapsular fracture (n = 70)	16 (45.7)	5 (14.3)	0.004
Patients with admission Hb $\geq$ 12 g/dL (n = 110)	18 (36)	11 (18.3)	0.049

\* Data are reported as number of patients (%).

**Hb levels on days +1 or +7 : identical**  
**Length of stay, morbidity and mortality : NS**

Serrano-Trenas et al, Transfusion 51:97, 2011

# PERIOPERATIVE IRON

## IV iron

- **Cardiac bypass surgery**
- **159 patients**
- **Any Hb**
- **Double-blind randomized trial**
  - IV iron sucrose 100 mg/d x 3 (pre- & post-surgery) + oral placebo
  - IV placebo + oral iron 105 mg/d periop. & 1 mo after discharge
  - IV placebo + oral placebo
- **Transfusions and hematologic parameters**

# PERIOPERATIVE IRON IV iron

	Group I (n = 54)	Group II (n = 53)	Group III (n = 52)	P-value
Transfusions <sup>a</sup> (blood units per patient)				0.84
In the operating room	0 (0-0)	0 (0-0)	0 (0-0)	0.18
In the ICU	0 (0-1)	0 (0-1)	0 (0-1)	0.56
In the cardiac ward	0 (0-0)	0 (0-0)	0 (0-0)	0.38

	Group I (n = 54)	Group II (n = 53)	Group III (n = 52)	P-value
Global blood transfusions (units/patients)—no. (%)				
0	34 (63)	26 (49.1)	26 (50.0)	0.7
1	11 (20.4)	18 (34.0)	16 (35.6)	
2	5 (9.3)	4 (7.5)	7 (13.5)	
3	2 (3.7)	3 (5.7)	2 (3.8)	
4	2 (3.7)	1 (1.9)	0 (0.0)	
5	0 (0)	1 (1.9)	1 (1.9)	
Number of patients transfused—no. (%)	20 (37)	27 (51)	26 (50)	0.18
In the operating room	8 (14.8)	6 (11.3)	6 (11.5)	
In the ICU	14 (26)	23 (43.4)	21 (40.4)	
In the cardiac ward	3 (5.6)	5 (9.4)	6 (11.5)	

	Group I (n = 54)	Group II (n = 53)	Group III (n = 52)	P-value
Haemoglobin (g/dl)				
Baseline	14.0 ± 1.63	13.7 ± 1.46	14 ± 1.35	0.62
Entry operating room	12.7 ± 1.64	12.6 ± 1.70	12.8 ± 1.29	0.82
Exit operating room	10.5 ± 1.39	10.7 ± 1.41	10.5 ± 1.56	0.22
ICU admission	10.8 ± 1.53	10.6 ± 1.57	10.5 ± 1.50	0.74
ICU discharge	10.0 ± 1.23	10.0 ± 1.01	10.2 ± 1.34	0.59
At hospital discharge	11.1 ± 1.52	11.0 ± 1.28	11.0 ± 1.44	0.96
One month after discharge	12.7 ± 1.40	12.4 ± 1.27	12.3 ± 1.15	0.32

**SURGERY**

**Conclusions**

# CONCLUSIONS

## Standardized approach in surgery

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- **Network for Advancement of Transfusion Alternatives (NATA)**
- **Diagnosis**
  - Measure Hb 28 days before elective (orthopedic) surgery
  - Target normal Hb before surgery
  - Laboratory testing for nutritional deficiencies, CRF and chronic inflammatory disease
- **Treatment**
  - Correct nutritional deficiencies, including iron
  - EPO after exclusion/correction of nutritional deficiencies

# IRON DEFICIENCY

## Absolute vs functional

**Iron deficiency anemia**

**Absolute ID (no iron stores)**

Ferritin < 20 µg/L  
(< 100 µg/L in cancer / infl)

**Functional ID (stores +/-)**

Ferritin > 20 µg/L  
(> 100 µg/L in cancer / infl)

**TSAT < 20%**

**Microcytic/hypochromic A**

**Microcytic/hypochromic A  
(chronic inflammation)  
Normocytic/normochromic A  
(acute inflammation)**



# CONCLUSIONS

## EPO in surgery

- **Pre-operative EPO therapy in anemic subjects**
  - **rHuEPO 300-600 U/kg/wk SC for 3-4 wks**  
(no evidence that higher doses are more efficient : 5 trials)
  - **Oral iron support : 200 mg/d ferrous iron**  
(no evidence that IV iron is more efficient)  
**IV iron in patients with inflammatory disorders / cancer**  
(evidence only from other settings)
  - **Adequate thromboprophylaxis**  
(not well studied in surgery, strong evidence in other settings such as cancer...)
  - **Cost-effectiveness questioned** (old studies)
- **Peri- and post-operative EPO therapy : unclear benefit**



# CONCLUSIONS

## Further research needs

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- **EPO**
  - Identify subgroups of anemic patients most likely to benefit
  - Compare oral with IV iron supplementation  
Particularly when EPO and ABD combined
  - Cost-effectiveness in 2013
- **Iron**
  - Compare oral with IV iron supplementation in preoperative setting with or without inflammation
  - Large placebo-controlled trial of perioperative IV iron

**THANK YOU !**