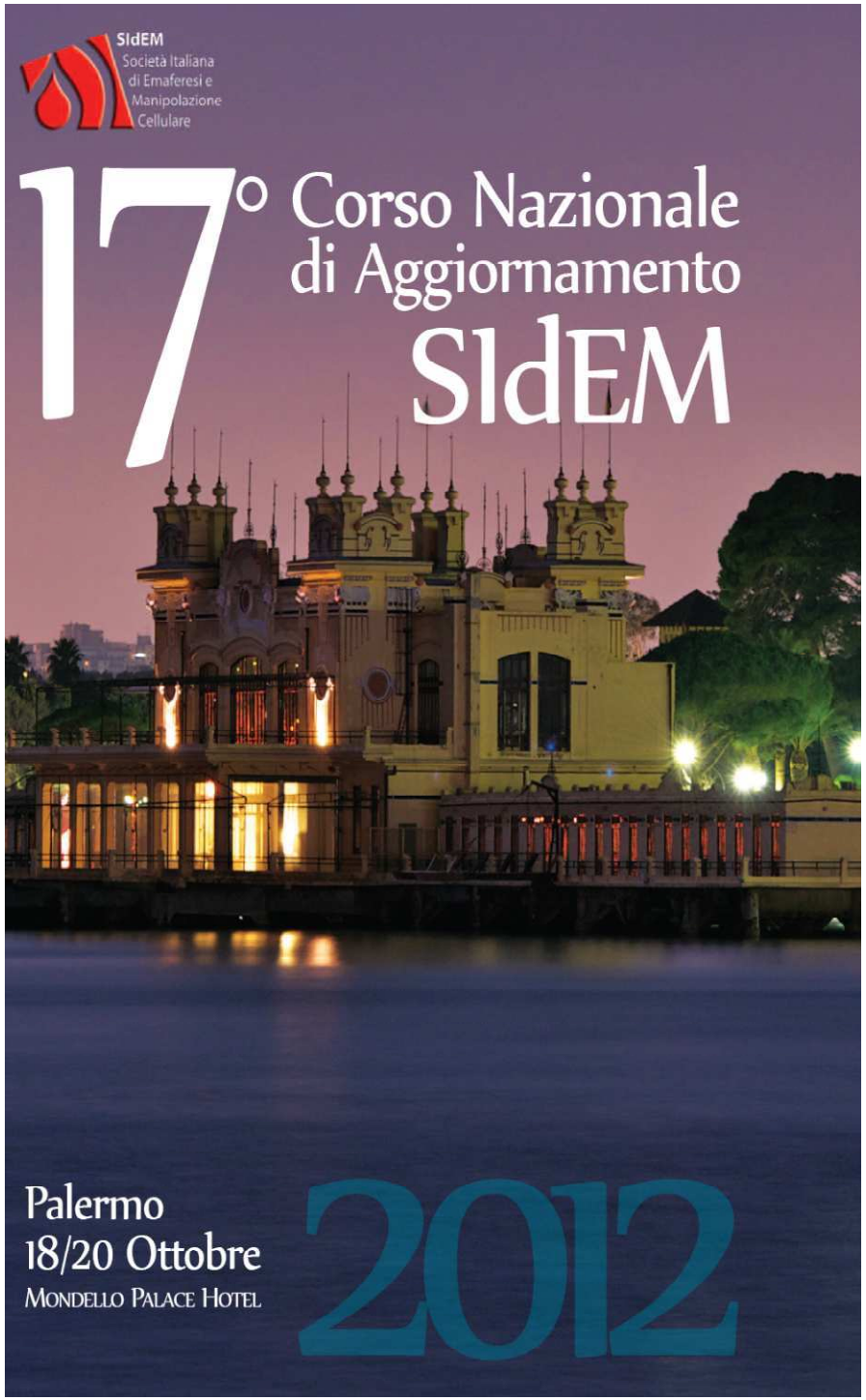

ANEMO
Consensus Group

Strategie di stimolazione ed espansione della eritropoiesi nel candidato alla chirurgia elettiva.

Giovanni Inghilleri

A.O. Fatebenefratelli e Oftalmico
Milano

Strategie di stimolazione ed espansione della eritropoiesi nel candidato alla chirurgia elettiva.

- Terapia Marziale
- Predeposito di sangue autologo
- Eritropoietina

Terapia marziale

Campi di impiego

- Correzione degli stati anemici;
- Somministrazione perioperatoria per accelerare il recupero dall'anemia indotta dall'intervento
- Terapia di supporto in corso di predeposito e terapia con EPO

Terapia marziale

10-20% dei pazienti candidati ad interventi di chirurgia maggiore presentano conclamata o borderline

Carenza marziale

Tutti i pazienti candidati ad intervento chirurgico per i quali sia prevedibile supporto trasfusionale e che presentano valori di Hb/Hct bassi o borderline devono essere valutati per definire la possibilità di correggere l'"anemia" con approprioata terapia.

Terapia marziale

Diagnosi di anemia sideropenica

Generalmente abbastanza semplice essendo facilmente identificabile mediante il riscontro di:

- **ridotto volume globulare (<80-84 fl)**
- **ferritinemia inferiori a 30ng/mL,**
- **sideremia inferiori a 40-60 µg/dL**
- **saturazione della transferrina < 15-20%**

Killip S et al. Iron deficiency anemia. Am Fam Physician ,2007;75:671-8

Vari autori raccomandano di inserire la determinazione di almeno una proteina della fase acuta (PCR)

Carenza Marziale

Potential role of MCV as a screening marker to detect iron deficient conditions in blood donors and surgical patients (evaluated donors n° = 2301)

	MCV value		
	< 80	< 84	<86
N° of cases	63 (2,7%)	227 (9.8%)	467 (20%)
Mean Ferritin value	32±47	48±60	62±77
Median ferritin val.	13	24	37
N° of cases with Ferritin <30 µg/mL	50 (79%)	132 (58%)	211 (45%)

Data from Niguarda Hospital and "AVIS Comunale Milano", unpublished

Iron deficiency anemia (IDA)

Treatment

- **Oral iron support**
  - **Iron is most easily given in the oral form**.
  - The least expensive form is ferrous sulfate.
  - Provide 65mg of iron per 325 mg tablet.
  - Dose: in adult 150-200 mg of elemental iron per day.
  - Better absorption in acidic gastric env (+ Ascorbic Ac avoid antacid).
  - Reticulocytosis in 7-10 days.
  - Increase of Hb by 1 g/dL every 2-3 weeks.
  - *Helicobacter Pylori* infection and chronic gastritis limit the efficacy

Diagnosis and management of iron-deficiency anaemia

Best Practice & Reserch Clinical Haematology 2005;18: 319-332

James D. Cook* MD, MSc (Med)

Table 2. Indications for parenteral iron therapy.

A. High iron requirements:
–gastrointestinal bleeding
–menorrhagia
–chronic haemodialysis
B. Iron malabsorption
–gastric resection, plication, or bypass
–atrophic gastritis
–coeliac disease
C. Failure of oral therapy
–gastrointestinal side-effects
–poor adherence

Treatment of iron deficiency

Chertow GM, et al.
Update on adverse drug events associated with parenteral iron.
Nephrol Dial Transplant (2006) 21: 378–382

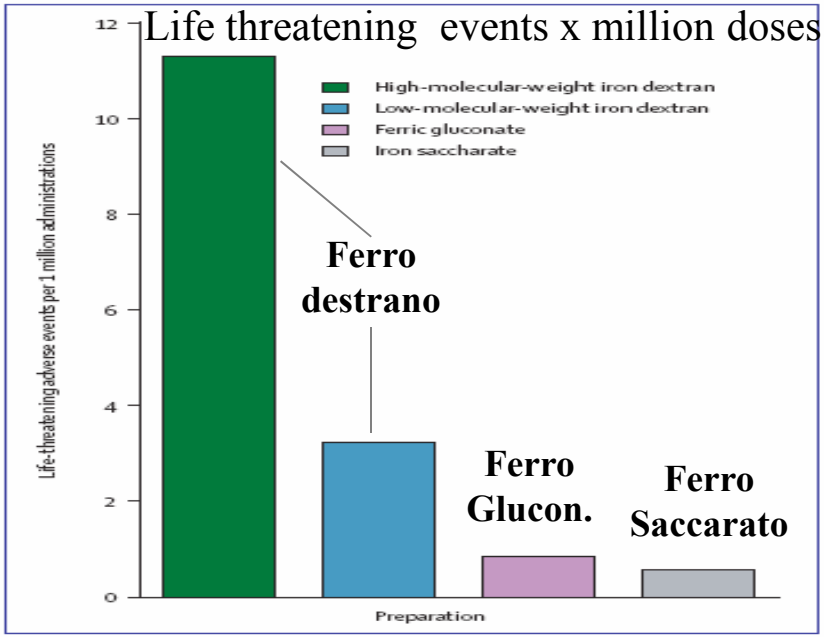

Figure: Relative rates of reported serious adverse events with the four different parenteral iron preparations[35]
From FDA Medwatch reports 2001–03, Chertow et al[15,16] reported that high-molecular-weight iron dextran was associated with 3·2-fold increase in odds

Table 1. Major ADEs by parenteral iron formulation 2001 through 2003

ADE	Ferrlecit® ($n = 11\,973\,800$)	Dexferrum® ($n = 2\,563\,000$)	InFed® ($n = 6\,690\,000$)	Venofer® ($n = 8\,837\,00$
Death	3	2	5	1
Cardiac arrest	3	8	5	0
Coma	1	13	6	4
Anaphylactoid reaction	4	6	6	0
Dyspnea[a]	9	44	28	10
Allergic reaction[b]	23	22	25	18
Abdominal pain	10	2	3	5
Back pain	7	28	8	4
Chest pain	8	32	16	9
Hypotension	20	26	12	12
Nausea	11	8	10	10
Vomiting	13	6	7	3
Sweating	4	15	4	3
Total	232	331	269	175
Life-threatening	11	29	22	5

[a]includes respiratory depression and bronchospasm.

Azienda Ospedaliera San Camillo-Forlanini

Dipartimento di Medicina Trasfusionale ROMA-OVEST

Servizio di Immunoematologia e Medicina Trasfusionale
Direttore Prof. L. Pierelli
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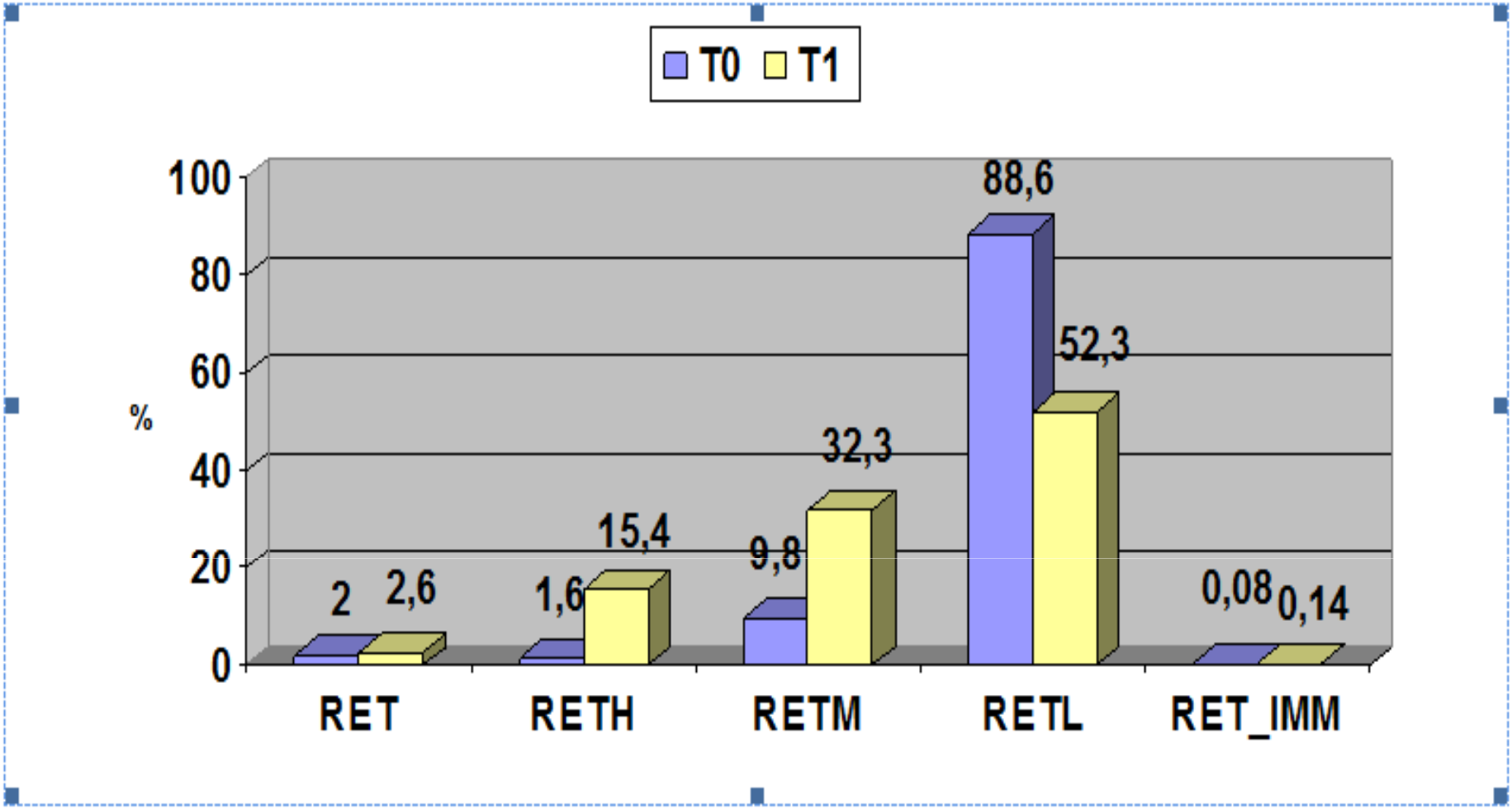
TEL. 06/ 58703558 FAX. 06/58704258

STUDIO PILOTA SULL'UTILIZZO DEL FERRO BISGLICINATO NEI PAZIENTI CANDIDATI AD INTERVENTO DI CHIRURGIA ORTOPEDICA ELETTIVA (PROTESI D'ANCA E GINOCCHIO)

MODALITA' E SCOPO:

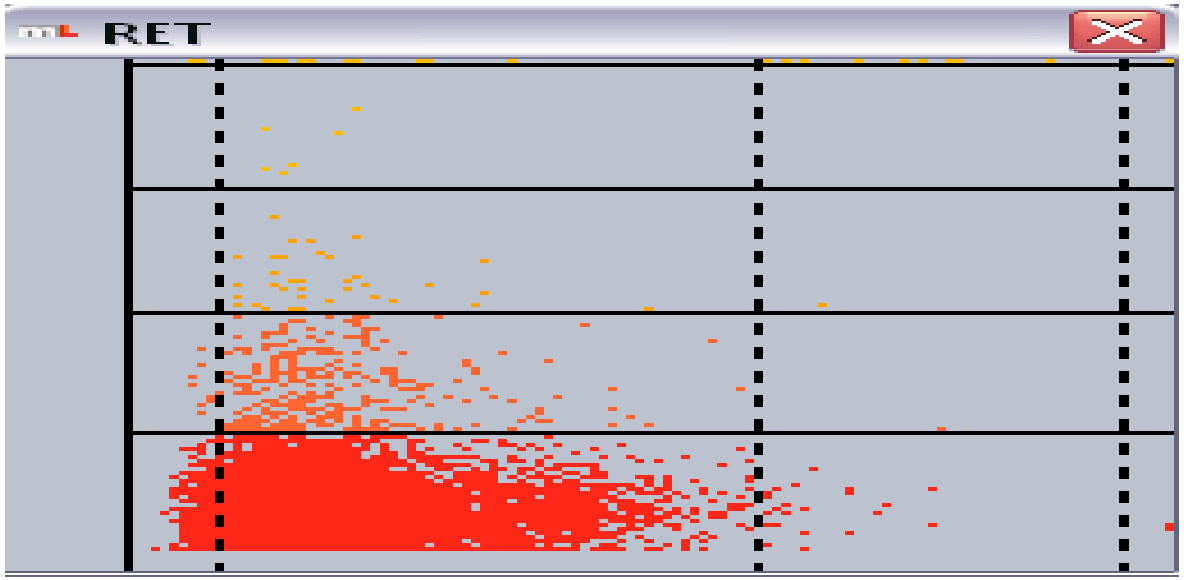
Lo scopo di questo studio pilota è di evitare o comunque limitare l'utilizzo di sangue omologo con l'obiettivo di tutelare la salute del paziente dai rischi trasfusionali, di correggere l'anemia nella fase preoperatoria, determinando un migliore compenso cardiovascolare e contribuendo così alla stabilizzazione delle condizioni emodinamiche del paziente con un miglior outcome assistenziale.
Questo percorso può essere applicato per:



T0 = Prima del trattamento

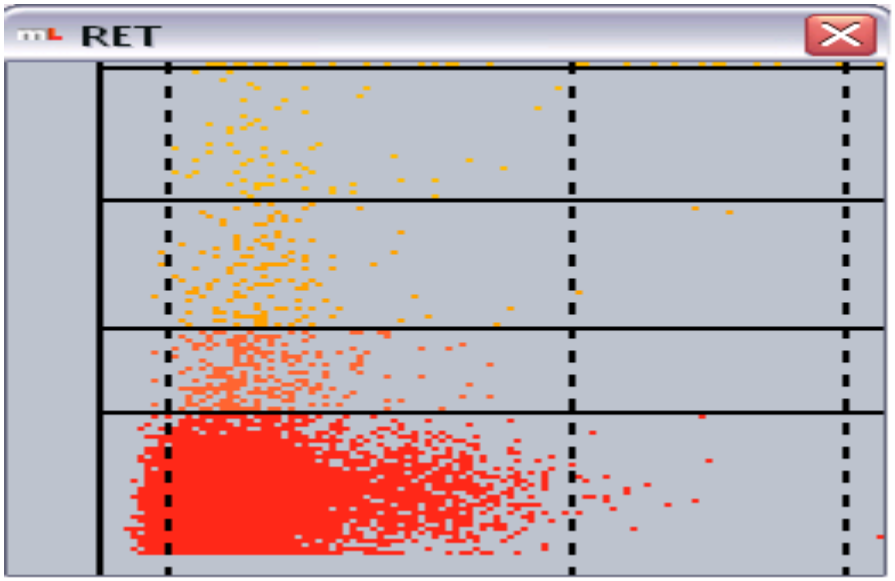
T1 = Dopo 20 giorni di terapia con Tecnofer

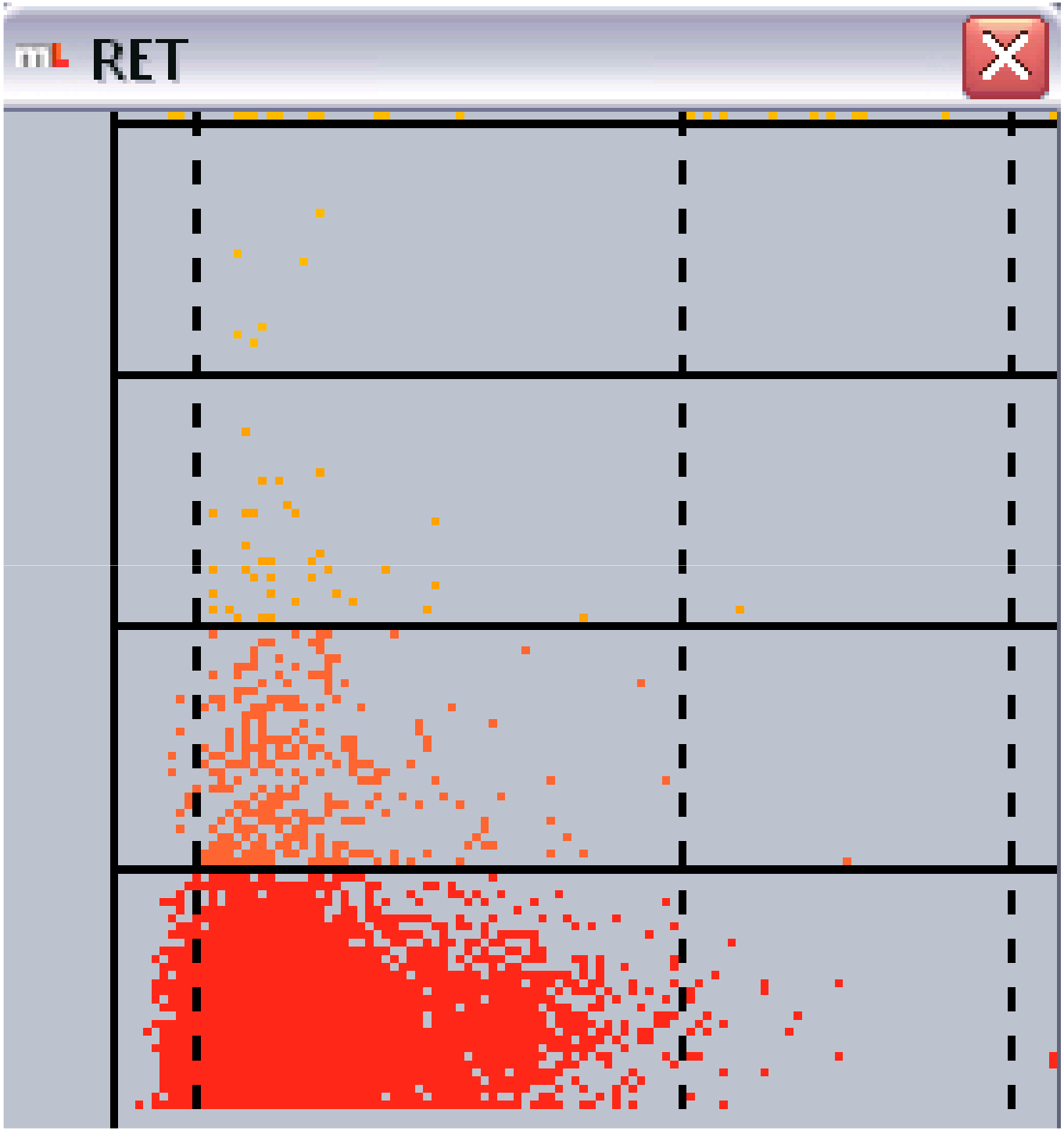
RET	4n	2.0	0.08	(_V)__		
RETH%		1.6		____		
RETM%		10.1		____		
RETL%		88.2		____		
MFI		15.2		____		
IRF		0.162		____		
CRC		1.51		____		
MRV		96		____		
RHCc		28.1		VC_		
PIC		--,--		____		
RET_IMM		0.08		____		



RET											
RETH%											
RETM%		32.3		V__							
RETL%											
MFI		29.8		V__							
IRF		0.534		V__							
CRC		1.87		V__							
MRV		100		V__							
RHCc		29.4		VC_							
PIC											
RET_IMM		0.14		V__							

An											
	2.6		0.10		(_V)__						
	15.4				____						
	32.3				V__						
	52.3				____						
	29.8				V__						
	0.534				V__						
	1.87				V__						
	100				V__						
	29.4				VC_						
	--,--				____						
	0.14				V__						

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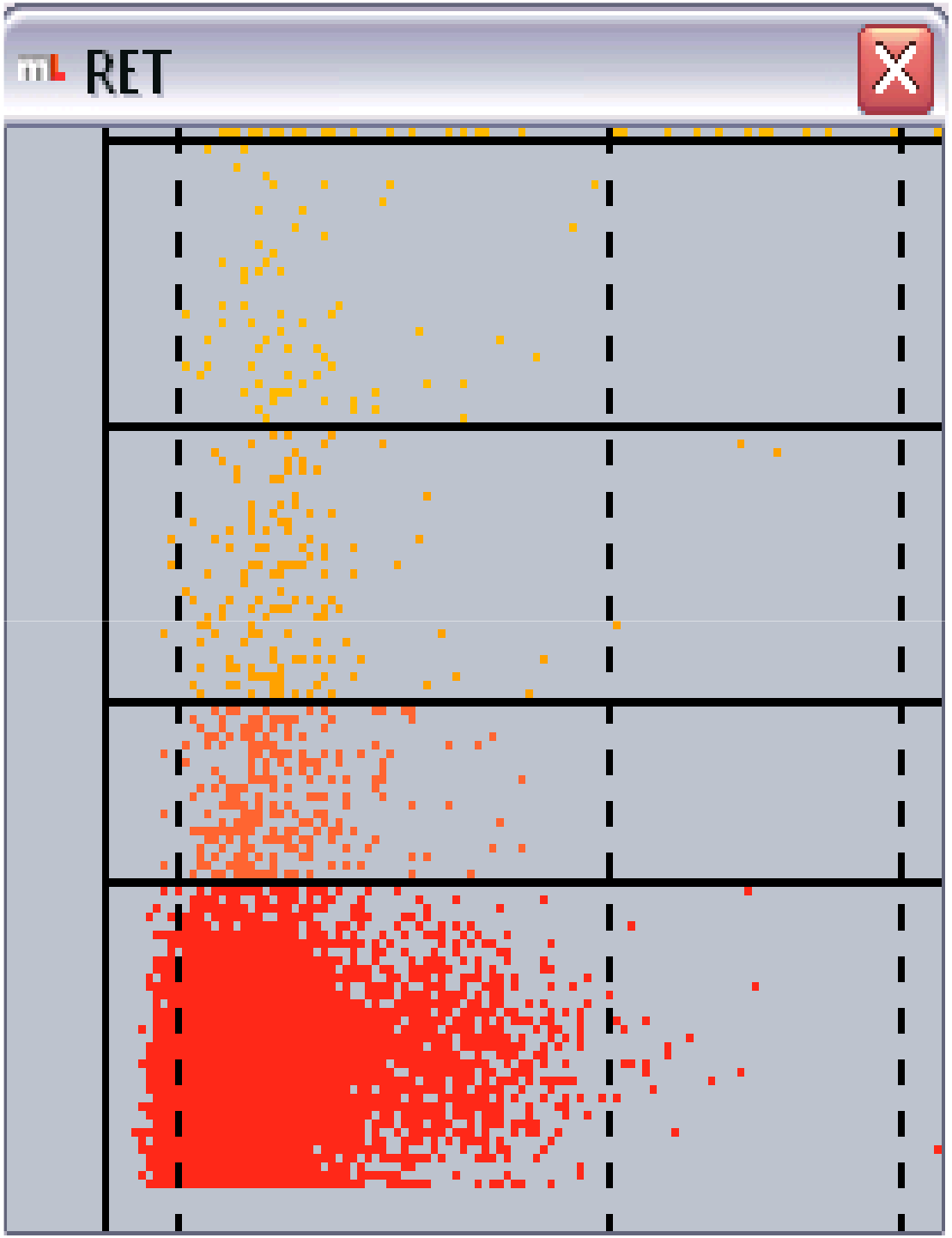

RET

Treatment of iron deficiency

Gaetano Pini Experience

Results obtained in ID Pts with low baseline Hct treated with IV iron

Pts evaluated	1186
IV iron treated pts	52 (4.4%)
Age (years)	44±15
Baseline Ferritin	24.2±17
Serum iron	62.4±24
MCV	82±8.5
Baseline Hct	36.2±2
Iron dosage (mg)	898±428
Hct after IV iron	38.9±2.7
RBC production (mL of RBCs)	157±87

Mercuriali F et al. Role of presurgery haematological patient's evaluation in transfusion practice. Haematologica 1999, 84 : 218

TRANSFUSION Volume 44, October 2004

Patients with pertrochanteric hip fracture may benefit from preoperative intravenous iron therapy: a pilot study

Jorge Cuenca, José A. García-Erce, Manuel Muñoz, Mónica Izuel, Angel A. Martínez, and Antorio Herrera

MATERIALS AND METHODS

Patients and treatment

Patients undergoing surgery for PHF repair between October 2002 and March 2003 (Group 2; n = 55) received 100 mg of IV iron sucrose (Venofer, Vifor, Saint Galene, Switzerland) at admission and before surgery and an additional 100-mg dose between admission and surgery if the Hb level was less than 12 g per dL. A previous series of PHF patients, operated on between January 2000 and December 2001 and who had not received IV iron, served as the control group (Group 1; n = 102).

Patients with pertrochanteric hip fracture may benefit from preoperative intravenous iron therapy: a pilot study

TABLE 1. Demographic and clinical characteristics of patients undergoing surgery for PHF repair

	Group*	
	1 (n = 102)	2 (n = 55)
Age (years)	83 ± 9	86 ± 7
Sex (male/female, %)	27.4/72.6	30.9/69.1
Hb level (g/L)		
Admission	123 ± 18	124 ± 22
48 hr after surgery	96 ± 16	95 ± 17
Number (%) of patients transfused	57 (55.9)	24 (43.6)
Transfusion rate (units per patient)	1.27 ± 1.34	0.89 ± 1.22
Number (%) of infections	34 (33.3)	9 (16.4)†
Without ABT	8 (17.8)	2 (9.7)
With ABT	26 (45.6)‡	7 (29.2)
30-day mortality (n, %)	17 (16.7)	5 (8.9)
Length of hospital stay (days)	14.3 ± 3.6	12.6 ± 4.4

* Group 1, control; Group 2, 200 to 300 mg of IV iron sucrose.
† $p < 0.001$, Group 2 vs. Group 1.
‡ $p < 0.01$, no ABT vs. ABT.

Role of perioperative iron therapy in surgical patients

Author	Type of surgery	Type of study	Effect of iron
Karkouti K (2006)	Cardiac & Orthopedic	RCT	No effect
Madi-Jebara SN (2004)	Cardiac	RCT	No effect
Garcia –Erce 2005	Orthopedic (THR)	Observational	Beneficial
Hulin S (2005)	Cardiac pediatric	Observational	Beneficial
Bernière J (2004)	Orthopedic Pediatric (Spine)	Observational	Beneficial

British Journal of Anaesthesia **100** (5): 599–604 (2008)
doi:10.1093/bja/aen054 Advance Access publication March 27, 2008

BJA

REVIEW ARTICLE

Perioperative anaemia management: consensus statement on the role of intravenous iron

P. Beris[1*†], M. Muñoz[2], J. A. García-Erce[3], D. Thomas[4], A. Maniatis[5†] and P. Van der Linden[6]

- Non-anaemic patients with a serum ferritin level <100 ng ml^{-1} (or ferritin 100–300 ng ml^{-1} and transferrin saturation <20%) undergoing surgical procedures with an expected blood loss >1500 ml (haemoglobin drop of 3–5 g dl^{-1}) may benefit from preoperative oral or i.v. iron administration, depending on the presence of co-morbidities and on the timescale before surgery, as they may not have enough stored iron to replenish their perioperative haemoglobin loss and maintain normal iron stores (serum ferritin ≥30 ng ml^{-1}).[3 7 11 40]

Transfusion Medicine, 2007, **17**, 354–365

Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion

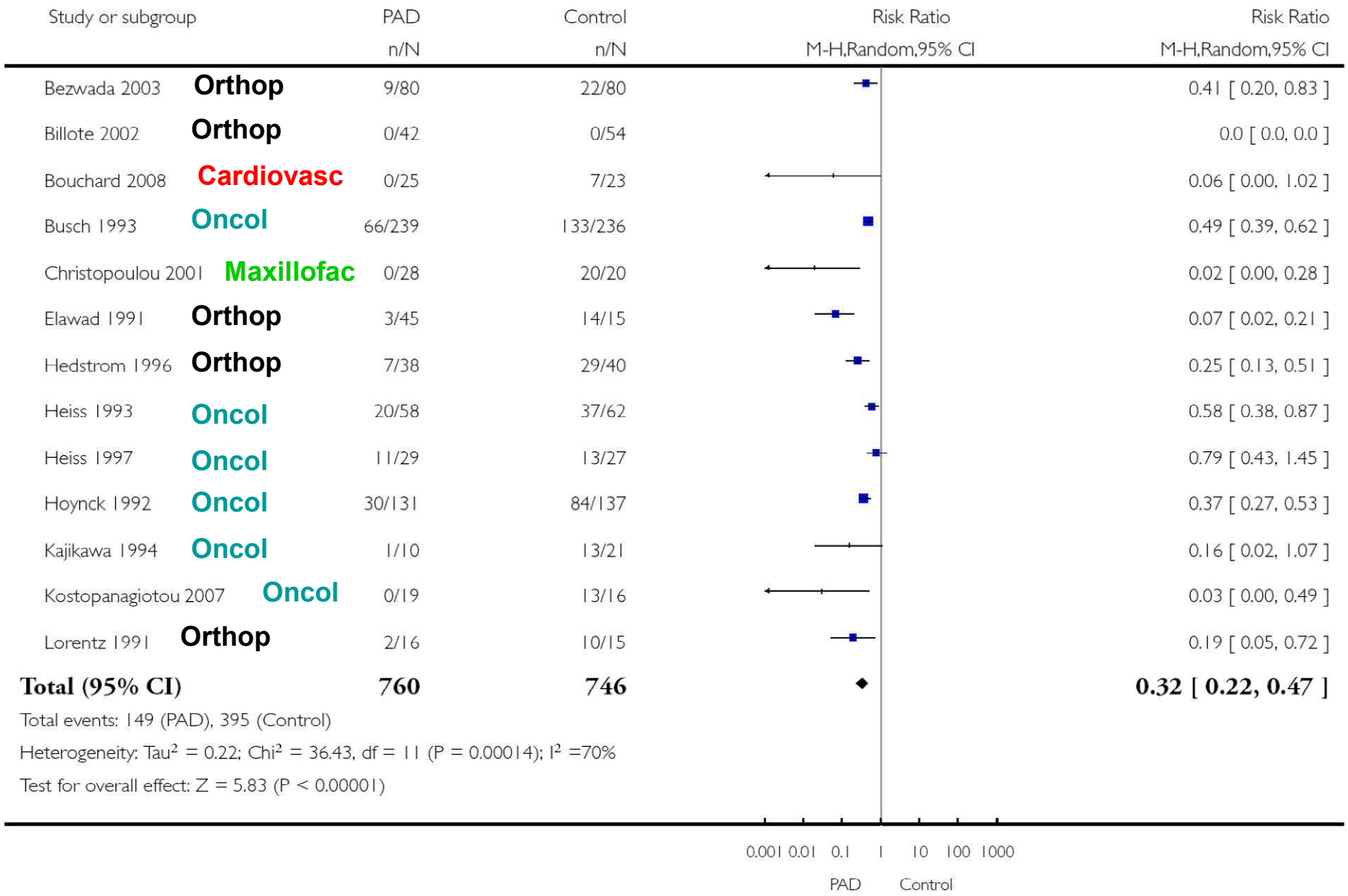
British Committee for Standards in Haematology, Transfusion Task Force

F. E. Boulton* & V. James† **National Blood Service, Southampton, and †National Blood service, Sheffield, UK*

PART 3. BCSH GUIDELINE RECOMMENDATIONS

- For each individual case, there should be a clear reason for preferring PAD to allogeneic blood as PAD is not indicated for most patients fulfilling the above criteria. Indeed, the clinical indications for collecting and using PAD are limited: for the majority of patients undergoing elective surgery of a nature likely to require transfusion to treat surgical and postoperative blood loss, allogeneic blood is the preferred option.

Henry DA, Carless PA, Moxey AJ, O'Connell D, Ker K, Fergusson DA. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Review content assessed as up-to-date: 31 July 2009



Autologous transfusion techniques: a systematic review of their efficacy

P. Carless,* A. Moxey,* D. O'Connell† and D. Henry* *Transfusion Medicine*, 2004, **14**, 123–144

Efficacy of PABD in reducing the exposure to allogeneic RBC transfusion in orthopaedic surgery: **Controlled cohort studies**

Study	PAD n/N	Control n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
02 Orthopaedic					
Bierbaum 1999	503 / 5741	1031 / 3741		4.1	0.32[0.29,0.35]
Biesma 1994	21 / 116	272 / 379		3.1	0.25[0.17,0.37]
Billote 2000	22 / 142	29 / 89		2.7	0.48[0.29,0.77]
Cha 2002	23 / 129	18 / 62		2.5	0.61[0.36,1.05]
Churchill 1994	41 / 302	116 / 267		3.4	0.31[0.23,0.43]
Churchill 1998	120 / 1268	324 / 660		3.9	0.19[0.16,0.23]
Feagan 2001	17 / 188	492 / 2042		2.8	0.38[0.24,0.59]
Goodnough 1990	38 / 276	128 / 315		3.4	0.34[0.25,0.47]
Goodnough 1992	30 / 162	55 / 119		3.1	0.40[0.27,0.58]
Hatzidakis 2000	23 / 264	59 / 225		2.8	0.33[0.21,0.52]
Julius 1994	30 / 134	102 / 102		3.4	0.22[0.16,0.31]
MacFarlane 1988	26 / 99	51 / 55		3.3	0.28[0.20,0.40]
Sculco 1999	93 / 1162	121 / 243		3.7	0.16[0.13,0.20]
Sharland 1995	14 / 149	78 / 85		2.6	0.10[0.06,0.17]
Thomson 1987	46 / 159	50 / 52		3.6	0.30[0.23,0.39]
Toy 1992	44 / 240	50 / 84		3.4	0.31[0.22,0.42]
Wasman 1987	17 / 44	44 / 44		3.2	0.39[0.27,0.56]
Woolson 1987	19 / 50	50 / 50		3.2	0.38[0.27,0.54]
Subtotal(95%CI)	1127 / 10625	3070 / 8614		58.2	0.29[0.25,0.34]
Test for heterogeneity chi-square=87.43 df=17 p<0.00001					
Test for overall effect z=-15.25 p<0.00001					

RR= 0.29,
95% CI 0.25-0.34

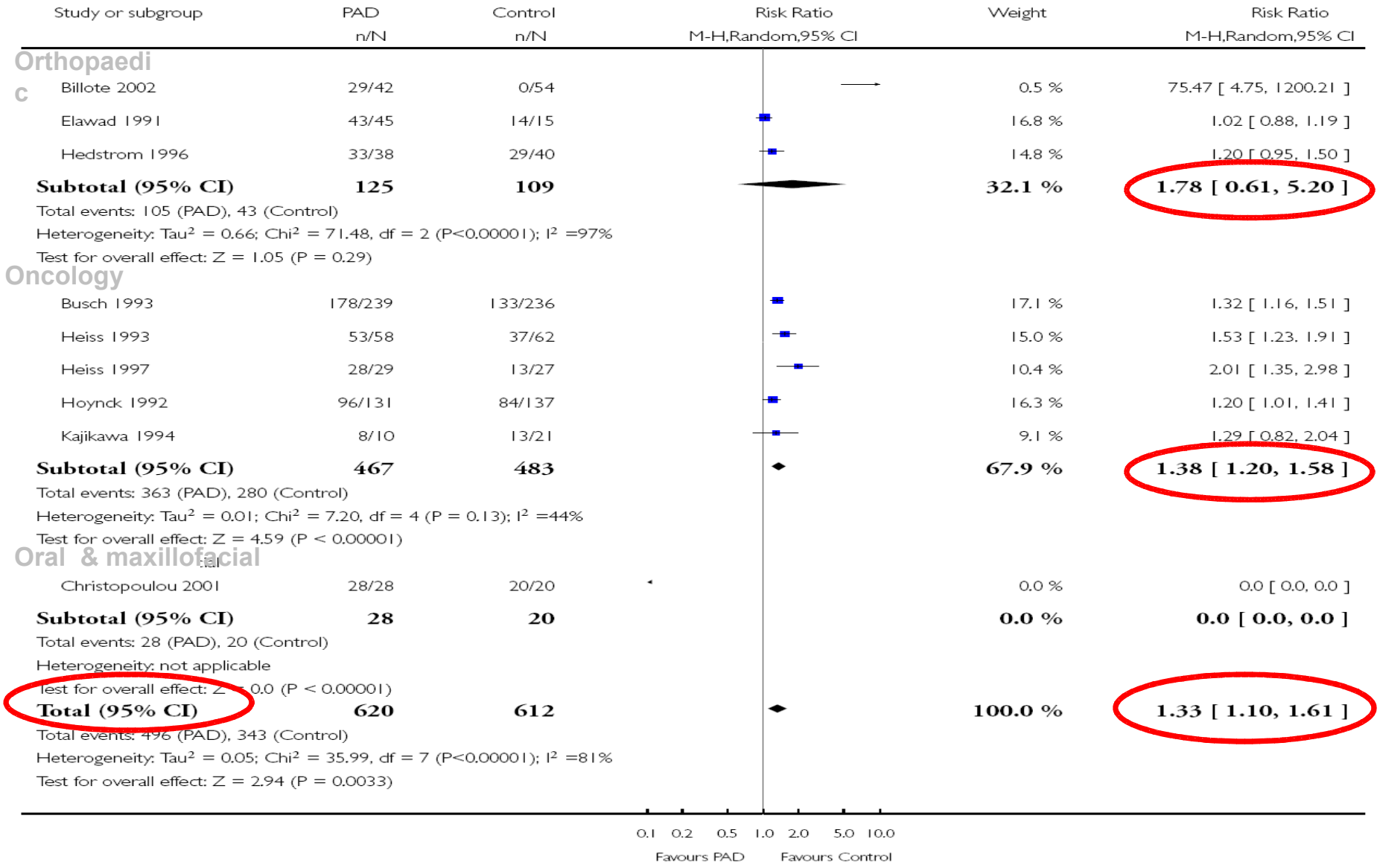
Predeposito di sangue autologo

Sicurezza

Il principale limite della tecnica del predeposito di sangue autologo è rappresentato dal fatto che i pazienti ricevono un maggior numero di trasfusioni (unità autologhe + omologhe)

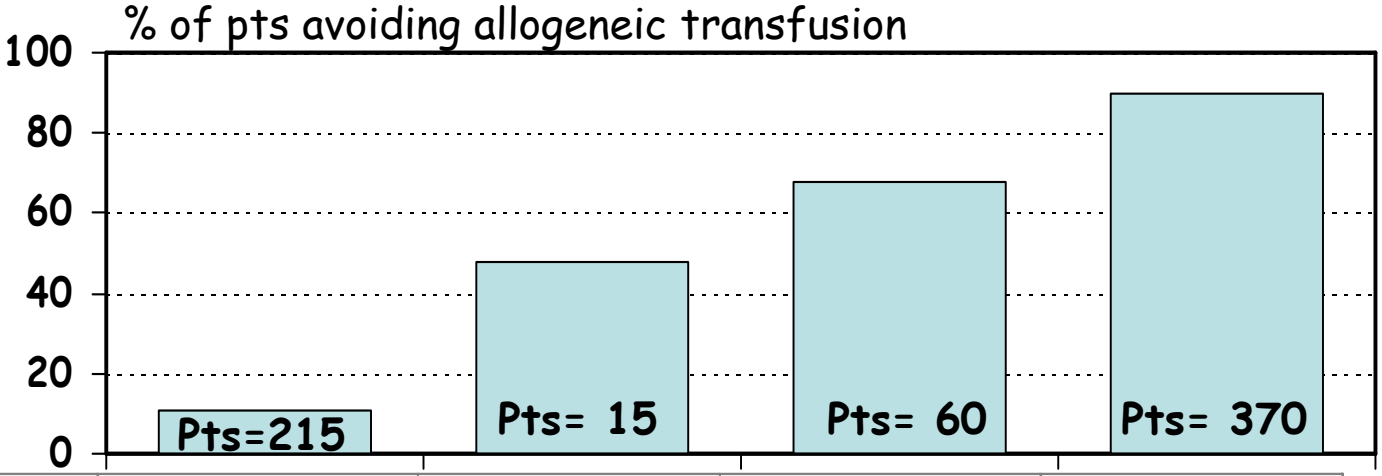
Henry DA et al. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews 2001, Issue 4.*
Review content assessed as up-to-date: 31 July 2009.

Exposure to allogeneic + autologous transfusion (PABD vs Control)



Preoperative autologous blood donation

Efficacy in Total Hip Replacement



* p < 0.05

	Salvage only	1 PABD	2 PABD	3 PABD
Blood loss (ml of RBC)	630	620	643	782
Allogen. units transf.	**2,48**	**1,23**	**0,43**	**0,22***
Baseline Hct	**39,3**	**40,5**	**40,1**	**41,1**
Hct 3 days postop.	28,2	26	28,3	28,3
Hcy 7 days. Postop.	29,9	28,9	27,8	29,2

From: Mercuriali F, Inghilleri G. Management of preoperative anemia. Br J Anaesth 1998; 81 (Suppl 1): 56-61 (modif.)

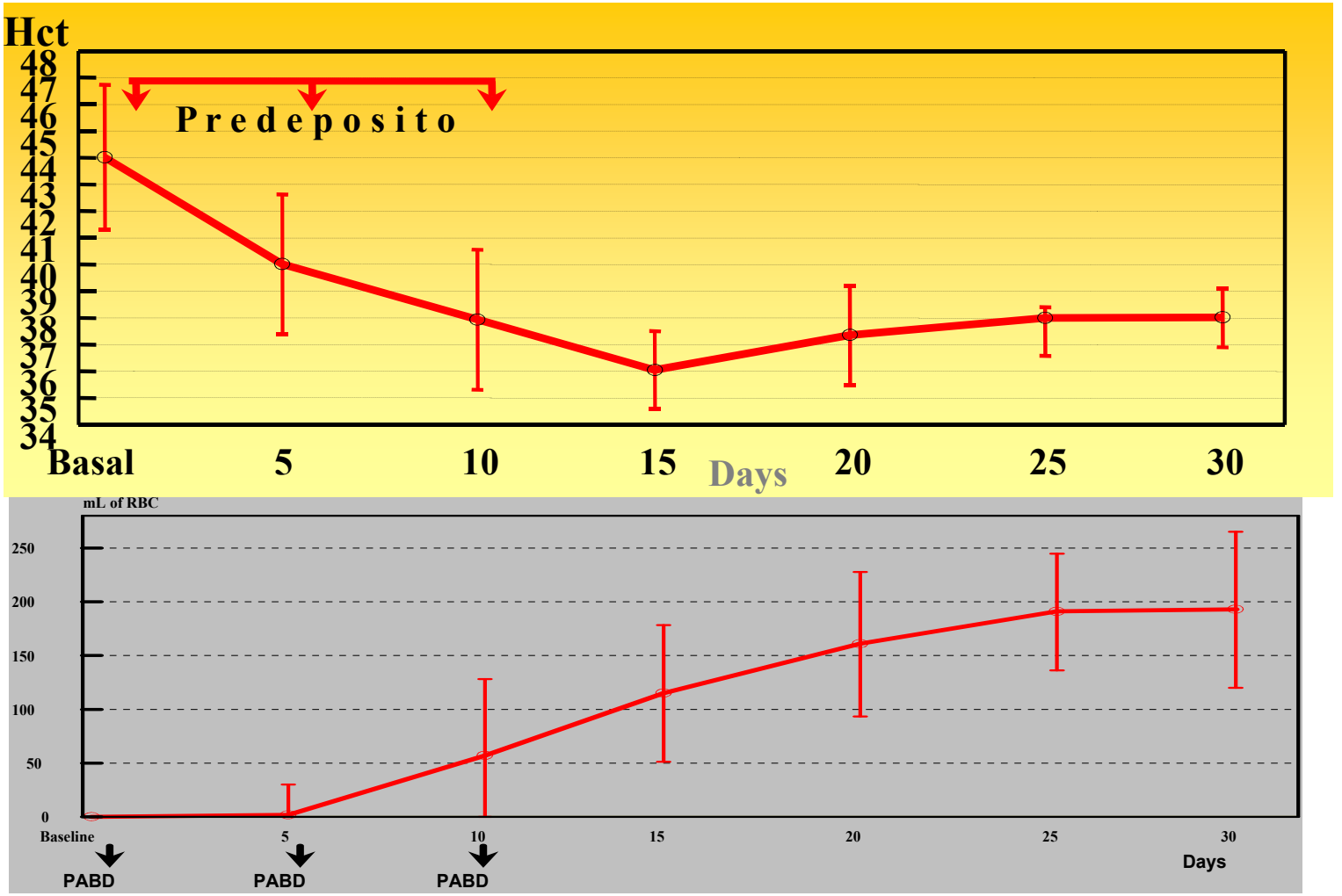
Predeposito di sangue autologo

Efficacia e sicurezza

- L'efficacia e la sicurezza della tecnica del predeposito è strettamente dipendente dalla capacità della metodica di indurre espansione della massa eritrocitaria.
- L'espansione della massa eritrocitaria indotta dal predeposito dipende dalle modalità di esecuzione del programma di predeposito

Predeposito di sangue autologo

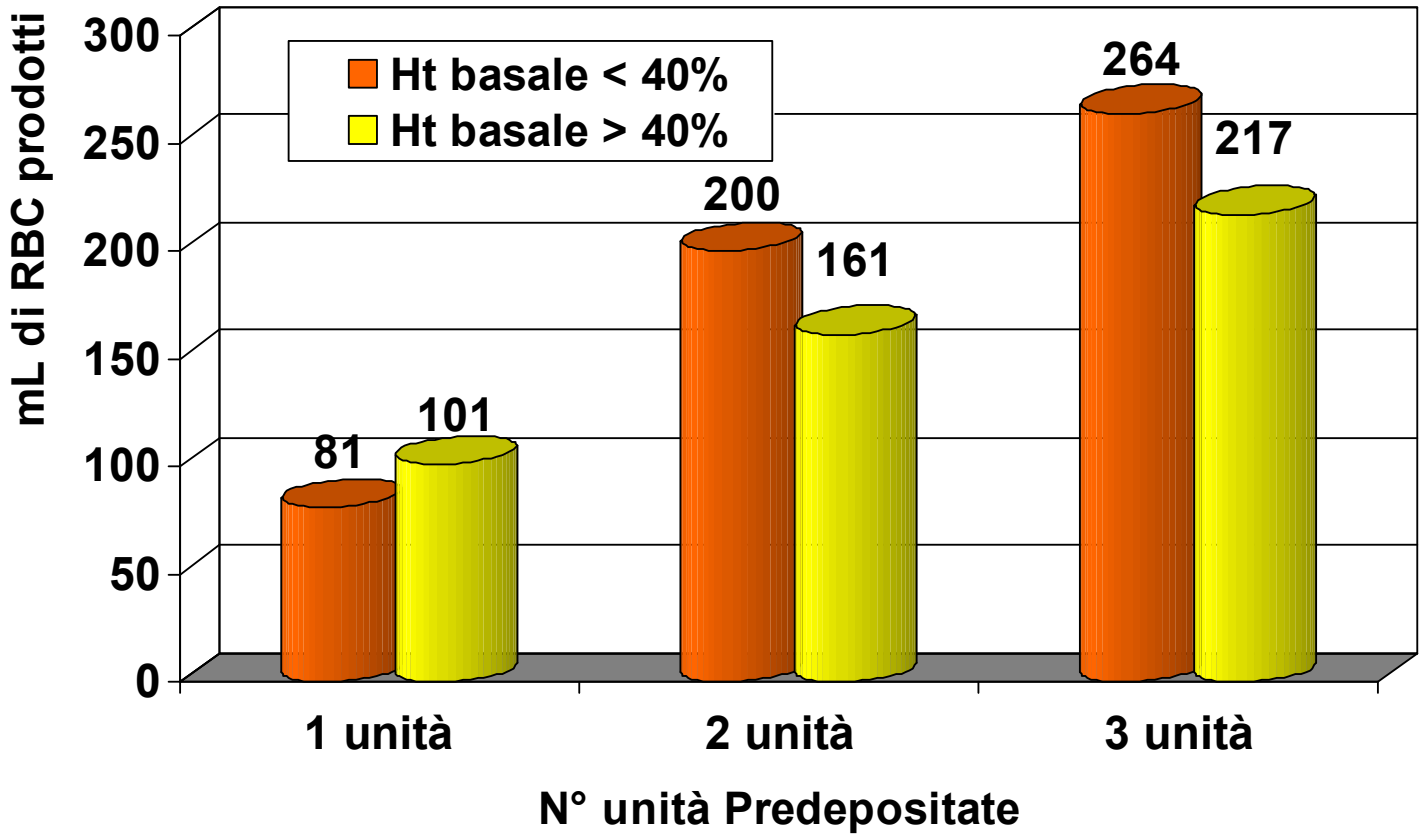
Variazione dei valori di Hct durante il programma di predeposito in 11 donne Prelievo di 3 unità di sangue (350ml) in 10 giorni



From: Mercuriali F, Inghilleri G. Curr Med Res Opin 1996; 13: 465-78 (modif.)

Predeposito di sangue autologo

Produzione di eritrociti (in mL) in pazienti inseriti in programma di predeposito suddivisa in base al n° di unità predepositate ed al hct basale



Da: Mercuriali F, Inghilleri G. Efficacy of preoperative autologous blood donation. Minerva Anestesiol 2000; 66 Suppl 1: 24-30 (modif)

Preoperative autologous blood donation - Part I

Only two clinical parameters determine efficacy of the autologous predeposit

MINERVA ANESTESIOL 2007;73:143-51

G. SINGBARTL

Methods. Prospective study in 704 patients scheduled for major orthopaedic surgery. Donation of either one or two separately collected RBC-units, and calculation of increase in RBC-mass by the HCT-method. Qualitative statistical analysis by multiple univariate analysis of variances, correlation analysis with Pearson, multiple linear regression analysis. Quantitative statistical analysis by t-/U-test; $P<0.01$ ($n \geq 100$), and $P<0.05$ ($n <100$), respectively.

Results. Two parameters were demonstrated of decisive impact to increase in RBC-mass to preopeative autologous blood donation (PABD) ($P<0.000$): first, time interval between preoperative autologous blood donation and surgery, that correlated positively with efficacy; second, haematocrit-level at predeposit-session that correlated negatively with efficacy. The highest level of RBC-regeneration reached was observed four weeks after last blood donation (one unit: 146.6±85.2 mL; two units: 297.4±78.6 mL). Patients with an anaemic initial haematocrit (females: ≤37%; males ≤40%) generated more RBC (*$P<0.05$) than non-anaemic patients (one unit: females, 148.3±67.6 *vs* 73.8±65.8 mL; males, 170.5±81.6 *vs* 77.0± 93.9 mL. Two units: females, 295.0±58.5 *vs* 226.0±79.7 mL; males, 299.9±82.5 *vs* 234.6± 107.5 mL).

Conclusion. To improve efficacy of preoperative autologous blood donation, a time interval between (last) autologous predeposit and surgery of at least 4 weeks should remain for efficacious RBC-regeneration; together with an acute and strong decline in haematocrit due to the autologous predeposit to push erythropoiesis as efficaciously as possible.

Predeposito di sangue autologo

Efficacia

Per ottimizzare l'efficacia del predeposito è necessario:

- Iniziare la raccolta di unità autologhe almeno 20 giorni prima dell'intervento.
- Prelevare almeno 2 unità di sangue autologo.
- Raccogliere l'ultima unità di sangue autologo almeno 7-10 giorni prima dell'intervento.
- Supplementazione marziale?

PERGAMON

Transfusion Science 23 (2000) 69–73

TRANSFUSION SCIENCE

www.elsevier.com/locate/transci

Utility of red blood cell apheresis in autologous blood donation

J.M. Garcia Gala *, P. Rodriguez Vicente, S. Gonzalez Muñiz, M. Moran Alcala, J.M. Del Blanco Rodriguez

Materials and Methods. We studied 131 patients undergoing different types of surgery who entered the preoperative autologous blood donation program over a one year period. Apheresis was performed with the MCS 3p from Haemeonetics.

Results. We were able to collect 304 red blood cell units from 131 patients. The average yield per procedure was two units (88 cases, 67.2%). In 41 patients (31.3%), we collected 3 units and, in two cases, 4 units were collected. The mean volume of the units was 255 (191–280). 18 (13.7% patients had an adverse reaction. Most of these were mild. Only in one case was it necessary to stop the procedure. 202 units (66.4%) were transfused to 97 patients (74%). 12 (9.2%) patients also used allogeneic transfusions (mean units: 0.18 ± 0.05 with a range 1–5).

Preoperative autologous blood donation - Part II

Adapting the predeposit-concept to the physiological basics of erythropoiesis improves its efficacy

G. SINGBARTL [1], S. MALGORZATA [2], A. QUOSS [2]

Minerva Anestesiol
2007; 73; 153-60

Methods.

- Prospective study on the efficacy of two different ABD concepts.
- Osteoarthritis (n=160) and rheumatoid arthritis patients (n=74);
- **One RBC-unit each on two separate predeposit-sessions vs two RBC-units on one predeposit-session**.
- The increase in RBC-mass was calculated with the haematocrit-method.

Results.

- In either group of patients, **increase in RBC-mass was higher with the new than the conventional predeposit concept** (osteoarthritis: 261±114 vs 168±133 mL; P<0.000; rheumatoid arthritis: 239±112 vs 149±152 mL; P=0.039).
- Efficacy of either concept between osteoarthritis and rheumatoid arthritis patients was not different (new concept: 261±114 vs 238±112; P=0.765; conventional concept: 168±133 vs 149±152; P=0.941).

Transfusion Medicine, 2007, **17**, 354–365

Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion

British Committee for Standards in Haematology, Transfusion Task Force

F. E. Boulton* & V. James† *National Blood Service, Southampton, and †National Blood service, Sheffield, UK

Iron supplementation and PAD

The BSH Guidelines of 1993 recommend that 'oral iron should be prescribed to all patients who pre-deposit before the first donation and continued until surgery'. More recent studies cast doubt on the efficacy of oral iron alone, particularly in the absence of prior anaemia.

Cid *et al.* (2005) from Spain showed that neither oral iron nor folic acid supplements enhanced the accomplishment of their pre-operative autologous blood collection programme in patients with baseline Hb above 115 g L^{-1}.

Tseliou *et al.* (2002) from Greece concluded that oral iron therapy in non-iron-deficient patients undergoing a moderate programme of three autologous units is not necessary.

Transfusion Alternatives in Transfusion Medicine 2006;8:178–202 TATM

Spanish consensus statement on alternatives to allogeneic transfusions: the 'Seville document'

RAMÓN LEAL-NOVAL*[1], MD, PhD, MANUEL MUÑOZ[+2], MD, PhD, JOSÉ A PÁRAMO*, MD, PhD & JOSÉ A GARCÍA-ERCE[§], MD, PhD, FOR THE SPANISH EXPERT PANEL ON ALTERNATIVES TO ALLOGENEIC BLOOD TRANSFUSION

Iron supplements in preoperative autologous blood donation

Administration of oral or intravenous iron supplement without rHuEPO facilitates preoperative autologous blood donation (PABD) (Grade C recommendation). In one randomized trial, the yield of the PABD program for the group receiving high doses of oral iron was higher than that of the placebo group, although a beneficial effect of the addition of intravenous iron to the oral treatment was not observed.[51] Another randomized study did not find any benefit from the administration of oral or intravenous iron in patients without iron deficiency and not receiving rHuEPO.[52] In contrast, when four PABD units are requested for female patients, a higher yield is obtained with intravenous iron than with oral iron.[53]

- **Kasper SM, *et al.* Efficacy of oral iron supplementation is not enhanced by additional intravenous iron during autologous blood donation. *Transfusion 1998; 38: 764–70***
- **Weisbach V, *et al.* Oral or intravenous iron as an adjuvant to autologous blood donation in elective surgery: a randomized, controlled study. *Transfusion 1999; 39: 465–72.***
- **Gesemann M, et al. Intravenous vs. oral iron supplementation during autologous blood donation. *Beitr Infusionsther Transfusionsmed 1996; 33:***

Predeposito di sangue autologo

Ruolo della supplementazione marziale

Blood removed (donated)				*Blood produced*		
Patients (n)	Baseline RBCs (ml)	Requested/ donated units	RBCs (ml)	RBCs (ml)	Expansion (%)	Iron therapy
22	1936	3/2.8	590	**220**	11%	**None**
45	1991	3/2.9	621	**331**	17%	**PO**
41	1918	3/2.9	603	**315**	16%	**PO + IV**

Kasper SM, et al: Efficacy of oral iron supplementation is not enhanced by additional intravenous iron during autologous blood donation**.** ***Transfusion*** **1998, 38:764-770**.

Oral or intravenous iron as an adjuvant to autologous blood donation in elective surgery: a randomized, controlled study.

Weisbach V et al. Transfusion 1999; 39: 465-72

Net RBC production (mL) in the preoperative period according to the iron supplementation strategy

	Oral iron	IV iron	Controls
All patients	**473 ±178**	**436±170**	**397 ± 174**
Donors of 4 AB	**680 ± 272**	**636 ± 67**	**553 ± 164**
Donors of 3 AB	**430 ± 75**	**431 ± 107**	**391 ± 132**

p > 0.2

Treatment

Oral Iron: 3 x 100 mg of Fe^{2+} per day given orally for 5 weeks before sugery.

IV Iron: 200 mg of Fe^{3+} given IV after each AB donation.

Controls: No iron medication.

Oral or intravenous iron as an adjuvant to autologous blood donation in elective surgery: a randomized, controlled study.
Weisbach V et al. Transfusion 1999; 39: 465-72

Effect of PABD and Iron Supplementation Protocols on Iron Metabolism Parameters.

Ferritin

	1° PABD	2° PABD	3°PABD	At surg
Oral iron	**139±90**	113±87	98±79	**97±95**
IV iron	**217±135**	252±117	249±118	**224±114**
Controls	**164±139**	133±130	89±102	**109±176**

Transferrin Saturation

	1° PABD	2° PABD	3°PABD	At surg
Oral iron	**25.8±9.5**	21.9±9.3	23.3±10	**20.8±10**
IV iron	**28.9±10**	22.2±7.1	21.6±6.6	**19.3±7.2**
Controls	**25.6±4.7**	18.9±5.5	16.1±6.0	**10.2±5.9**

Predeposito di sangue autologo

Rapporto Costo-Efficacia

Strategie per rendere il rapporto costo-benefici più favorevole:

- Standardizzare la procedura di preaccertamento.
- Semplificare il processo di donazione ai salassi successivi al primo
- Evitare la separazione in emocomponenti
- **Consentire una ottimale ricostituzione degli eritrociti prelevati con i salassi;**
- Appropriata selezione dei pazienti ed evitare il prelievo di unità autologhe inutili

HSSJ (2011) 7: 141–144
DOI 10.1007/s11420-011-9200-9

ORIGINAL ARTICLE

Nonanemic Patients Do Not Benefit from Autologous Blood Donation Before Total Knee Replacement

Stephen Kim, MD · Eric Altneu, BS · Jad Bou Monsef · Elizabeth A. King, BS · Thomas P. Sculco, MD · Friedrich Boettner, MD

Table 1 Blood utilization in the two different treatment groups

	Number of patients	Number patients who received autologous blood transfusions	Number of patients who received allogenic blood transfusions	Total number of transfusions
Group A (1 unit autologous blood)	129 (100%)	98 (76%)	18 (14%)	0.93
Group B (no preoperative donation)	92 (100%)	0 (0%)	24 (25%)	0.33
Group A preop Hgb≤12.5 mg/dL	34 (26%)	31 (91%)	10 (29%)	1.29
Group B preop Hgb≤12.5 mg/dL	25 (27%)	0 (0%)	18 (72%)	0.96
Group A preop Hgb>12.5 mg/dL	95 (74%)	67 (71%)	8 (8%)	0.80
Group B preop Hgb>12.5 mg/dL	67 (73%)	0 (0%)	6 (9%)	0.09

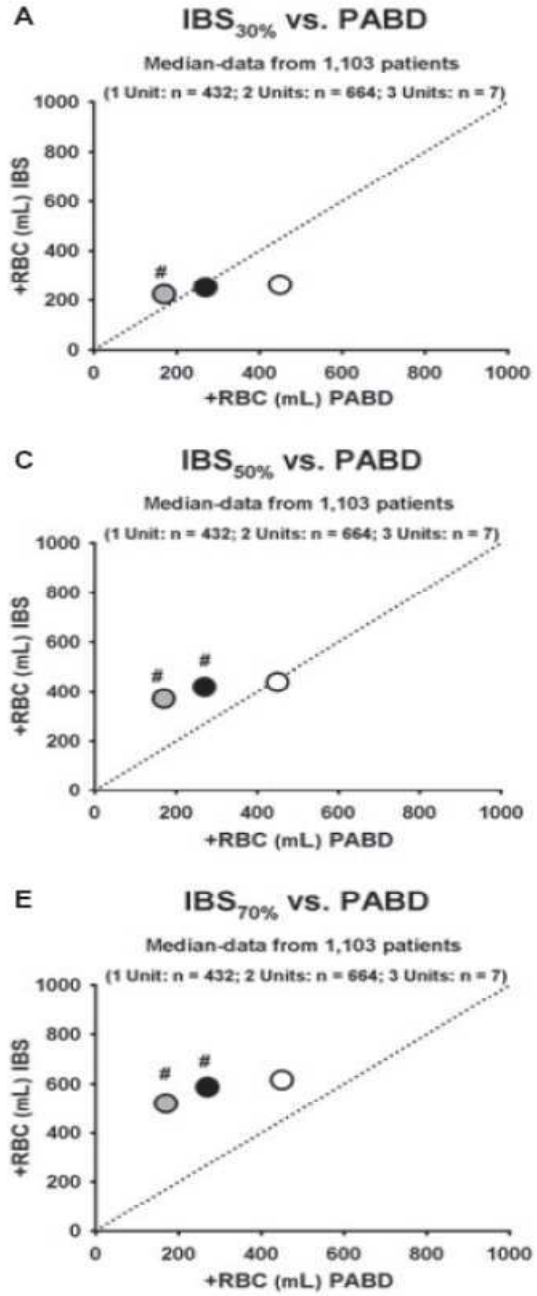
Preoperative autologous blood donation versus intraoperative blood salvage: intraindividual analyses and modeling of efficacy in 1103 patients

TRANSFUSION 2009;49:2374-2383.

Guenter Singbartl, Joerg Schreiber, and Kai Singbartl

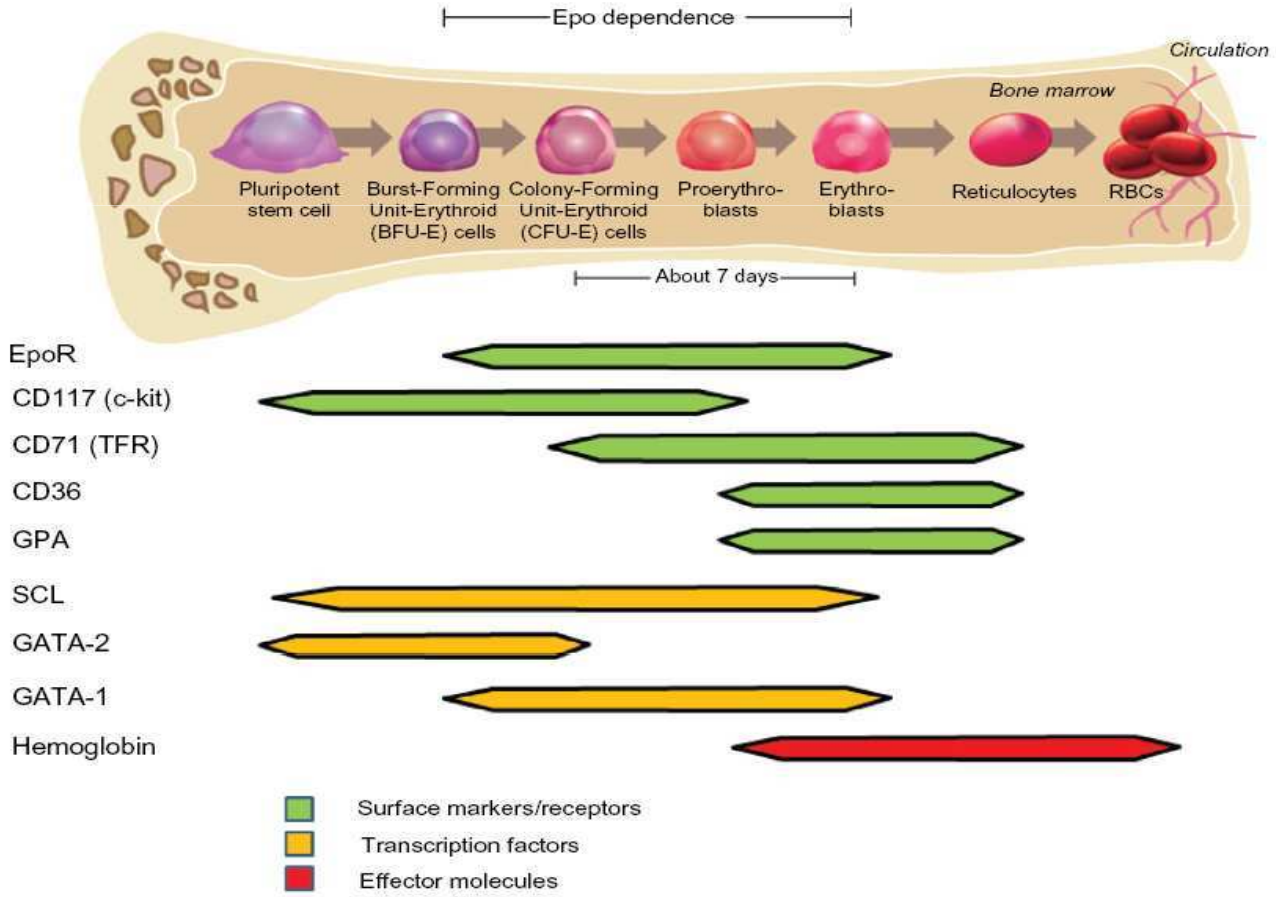
STUDY DESIGN AND METHODS: We analyzed data from 1103 patients undergoing PABD and subsequent major orthopedic surgery in one center. We then used a

RESULTS: The vast majority of patients would have tolerated greater MABLs if subjected to IBS rather than PABD (425 of 432 with 1 PABD unit, 580 of 664 patients with 2 PABD units, 3 of 7 patients with 3 PABD units). For a few patients, however, our model demonstrated greater MABL with PABD than with IBS. These patients were characterized by 1) lower initial hematocrit (Hct), 2) recovery from PABD with return to baseline Hct or above by the time of surgery, and 3) longer time between first PABD and surgery.



Eritropoietina (EPO)

L'EPO è un fattore di crescita obbligatorio che regola, con meccanismo ormonale, la proliferazione, la differenziazione e la maturazione dei precursori degli eritrociti nel midollo emopoietico in relazione alle condizioni di fabbisogno di ossigeno.



Eritropoietina Umana Ricombinante (rHuEPO)

Effetto biologico

Studi in soggetti sani ed atleti hanno dimostrato:

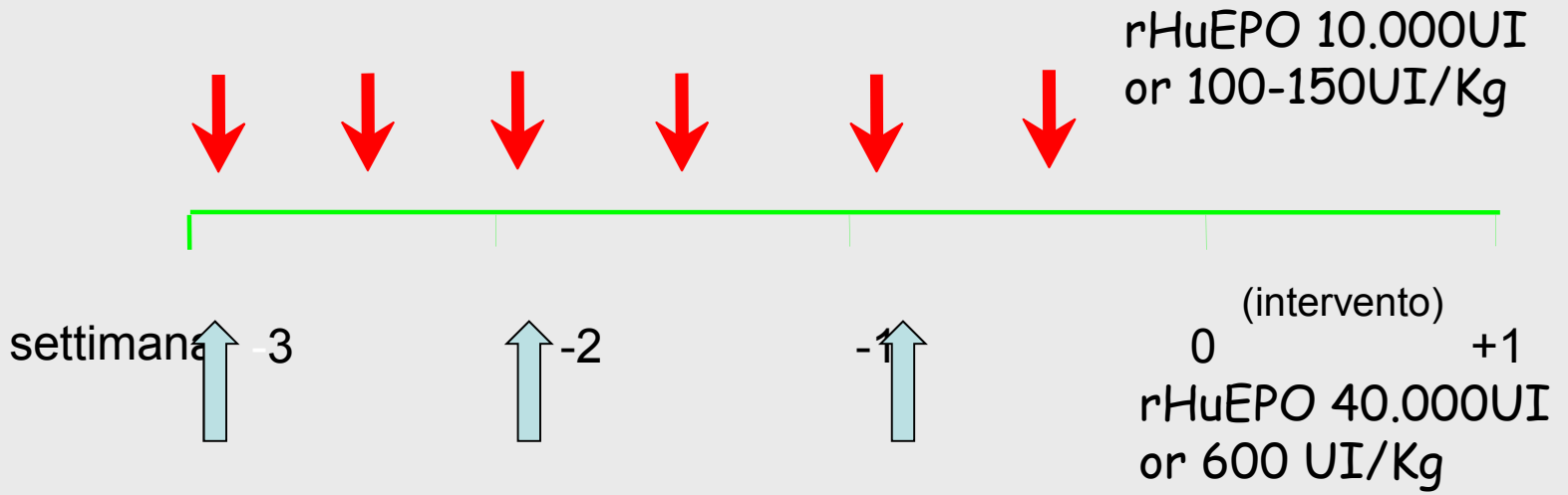
- Incremento del numero di reticolociti circolanti dopo circa 4-7 giorni dall'inizio dell'assunzione del farmaco, numero di reticolociti che si mantiene elevato fino a 7 giorni dopo la sospensione del farmaco.
- Incremento consistente del numeri degli eritrociti e della concentrazione dell'emoglobina dopo 7–10 giorni dall'inizio della terapia, incremento che si mantiene per alcune settimane dopo il termine del trattamento.

Eritropoietina (EPO)

rHuEPO in associazione a Predeposito

Protocolli

Ogni freccia indica una "visita" con somministrazione ed eventuale predeposito (rHuEPO x SC, Ferro EV e predeposito se hct >34%)



Laupacis A et al. Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. T*ransfusion Medicine*, 1998, 8, 309–317

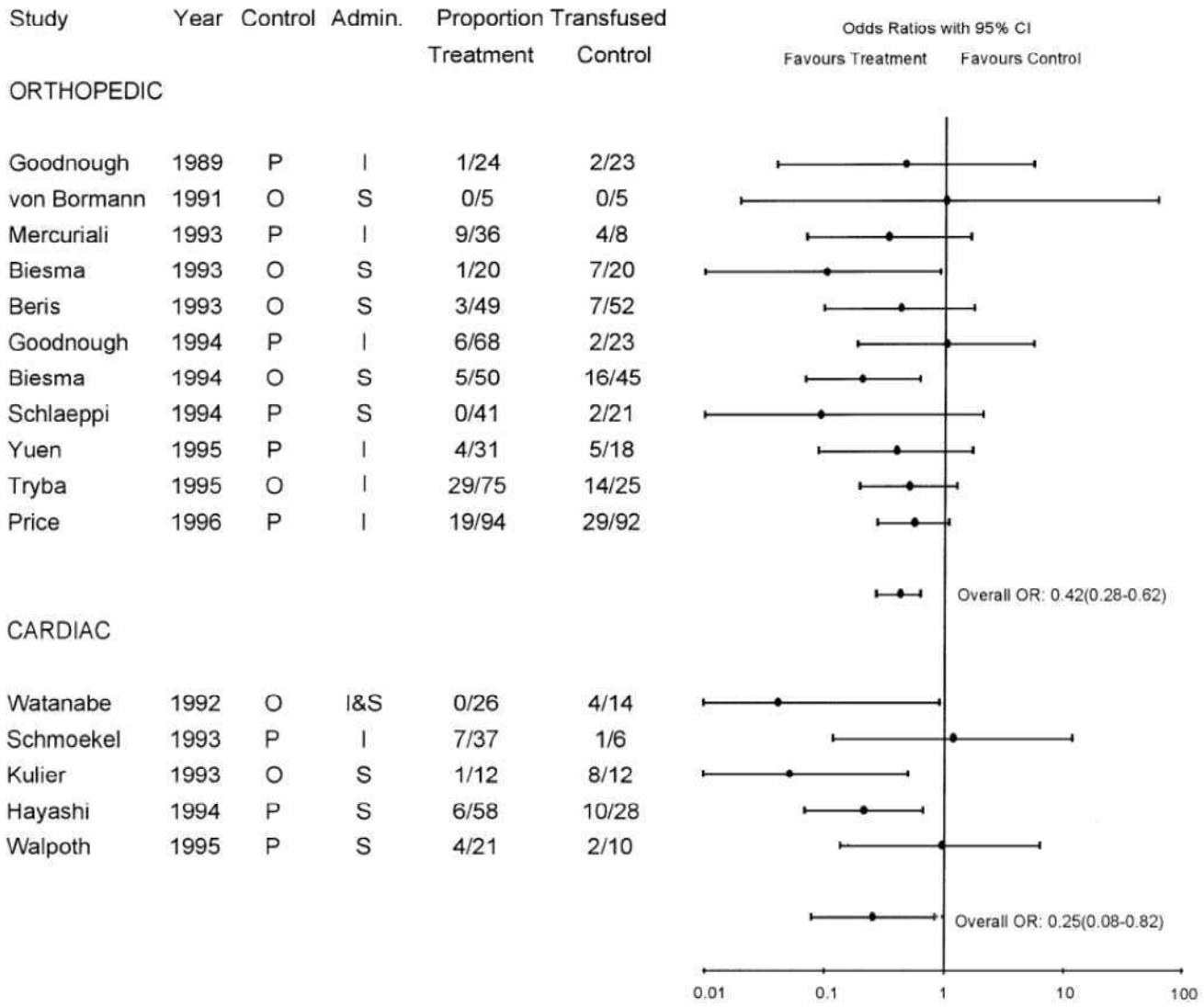


Fig. 1. Proportion of patients transfused in studies of erythropoietin to augment autologous donation in orthopaedic and cardiac surgery. Results expressed as odds ratios with 95% confidence intervals. P, placebo; O, open label control; I, intravenous; S, subcutaneous.

Eritropoietina Umana Ricombinante (rHuEPO)

rHuEPO Perioperatoria

Somministrazione di rHuEPO da sola (senza predeposito) per espandere la massa eritrocitaria circolante del paziente prima dell'intervento chirurgico, consentendo così al paziente di tollerare la perdita di sangue intra e postoperatoria conservando valori di Hct compatibili con le sue condizioni cliniche.

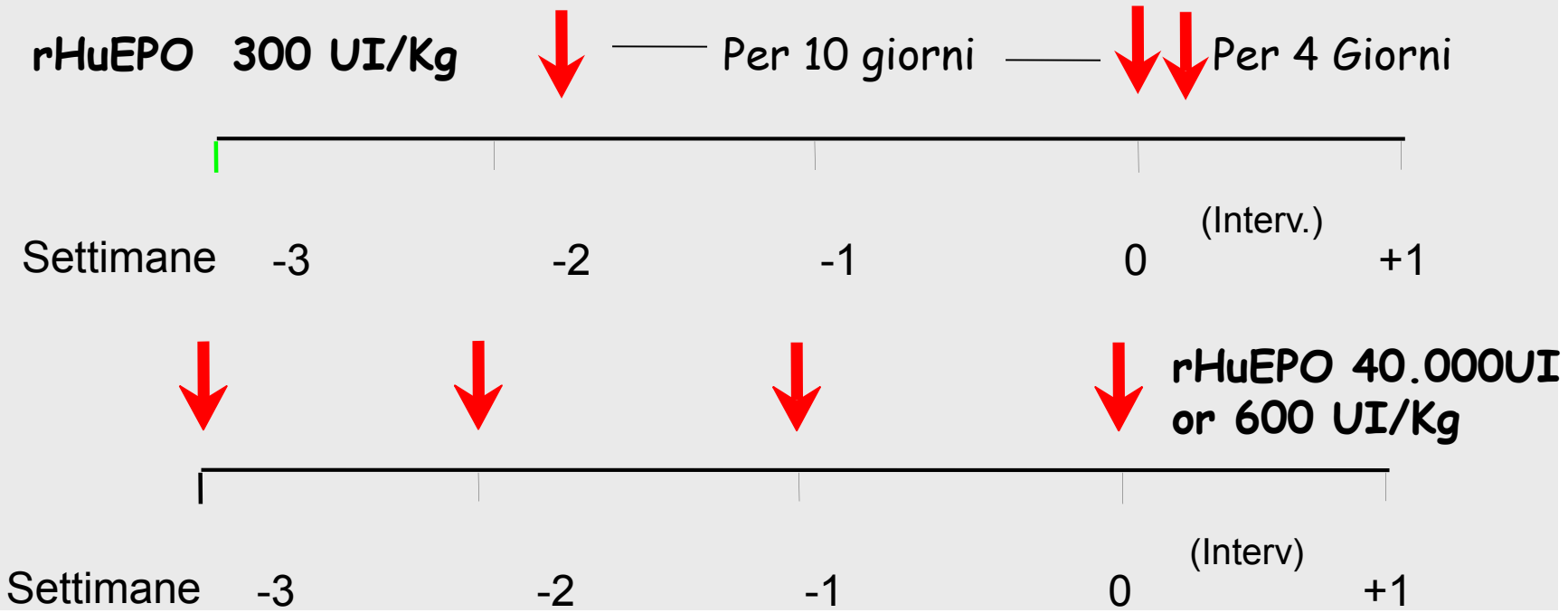
La somministrazione preoperatoria di rHuEPO inoltre fa si che il paziente al momento dell'intervento chirurgico presenti già un elevato grado di stimolazione dell'eritropoiesi così da poter rapidamente compensare la perdita degli eritrociti indotta dall'intervento chirurgico

Eritropoietina Umana Ricombinante (rHuEPO)

rHuEPO Perioperatoria

Protocolli approvati (in chir ortopedica)

rHuEPO perioperatoria: Ogni freccia indica rHuEPO SC raccomandata associazione con Ferro



Spahn DR. Anemia and Patient Blood Management in Hip and Knee Surgery. A Systematic Review of the Literature. Anestesiology 2010; 113: 482-95

RCT on perioperative EPO

Reference	Study Design	Duration of Observation	Type of Surgery	Study Groups		No. Included		Transfusion Trigger	Allogeneic Blood Transfusion Rate		
				Active	Control	Active	Control		Active	Control	*P* Value
Moonen *et al.*[37] **2008**	RCT	4 weeks	THA/TKA with pretreatment Hb level 10–13 g/dl	rHuEPO 40,000 IU weekly (4×) + ferrofumerate 200 mg tid during 3 weeks before surgery	Cell salvage	50	50	Hb < 8.1 or < 8.9 or < 9.7 g/dl depending on the ASA score	**4%**	**28%**	0.002
Keating *et al.*[38] **2007**	RCT	3 weeks	THA/TKA with pretreatment Hb level 11–14 g/dl	rHuEPO 45,000 IU weekly (4×) + polysaccharide iron complex or the equivalent of 300 mg elemental iron/day per os during 3 weeks before surgery	PAD + polysaccharide iron complex or the equivalent of 300 mg elemental iron/d per os during 3 weeks presurgery	146	132	Hb < 8 g/dl or higher if clinical symptoms	**3%**	**14%**	0.002
Weber *et al.*[41] **2005**	RCT	4–6 weeks	THA/TKA/spine surgery with pretreatment Hb level 10–13 g/dl	rHuEPO 40,000 IU weekly (4×) + oral iron (type and dose NA)	Usual care, including oral or IV iron (type and dose NA)	467	237	Hb < 8 g/dl	**9%**	**37%**	< 0.05
Faris *et al.*[43] **1996**	RCT	4 weeks	Major orthopedic surgery	rHuEPO 7,500 to 22,500 IU/d during 15 days + ferrous sulfate 325 mg tid per os	Placebo + ferrous sulfate 325 mg tid per os	131	69	NA	**21%**	**54%**	< 0.001
Canadian study group[44] **1993**	RCT	3 weeks	THA with pretreatment Hb level 11–16 g/dl	rHuEPO 7,500 to 22,500 IU/d during 14 days + iron sulfate 300 mg tid per os	Placebo + ferrous sulfate 300 mg tid per os	130	78	Hb < 9 g/dl	**27%**	**44%**	NA

Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: the European Epoetin Alfa Surgery Trial (EEST)

European Journal of Anaesthesiology 2005; 22: 249–257

E. W. G. Weber[*1], R. Slappendel[*], Y. Hémon[†], S. Mähler[¶], T. Dalén[‡], E. Rouwet[§], J. van Os[‖], A. Vosmaer[**], P. van der Ark[††]

- open randomized controlled multicentre trial in patients undergoing orthopaedic surgery with preop Hb 10-13g/dL.
- Preoperative epoetin alfa (40 000 IU SC/W for 3W before surgery and on the day of surgery + oral iron daily for 3 W) vs. routine care were compared in 6 Countries.
- **On-treatment population: epoetin *n*=460; control=235),**
- Epoetin-treated patients had higher Hb values from the day of surgery until discharge (*P* 0.001) and lower transfusion rates (12% vs. 46%; *P* 0.001). Epoetin treatment delivered no significant effect on postoperative recovery

A Restrictive Use of Both Autologous Donation and Recombinant Human Erythropoietin Is an Efficient Policy for Primary Total Hip or Knee Arthroplasty

Claude Couvret, MD*, Marc Laffon, MD*, Annick Baud, MD*, Valérie Payen, MD*, Philippe Burdin, MD†, and Jacques Fusciardi*

Departments of *Anesthesiology and Critical Care and †Orthopedic Surgery, Trousseau University Hospital, Tours, France

Study 1

- Indication for PABD was based on comparison of each patient's RBC reserve with mean estimated perioperative RBC loss:
- PABD indicated if RBC reserve was < 800 mL (THA) or <1000 mL (TKA), Hct > 33%, life expectancy of 10 yr, no medical contraindication, and consent of the patient.
- 2 AB units were collected preop.

Study 2

- EPO instead of PABD when Hct <37%, life expectancy > 10 yrs
- 3 weekly SC doses of 600 UI/kg .
- Oral ferrous sulfate 320 mg daily in association with EPO.
- No PABD in case of baseline Hct > 39%. PABD only in Pts with baseline hct between 37%-39%. Triggers for any transfusion (autologous or allogeneic) were identical

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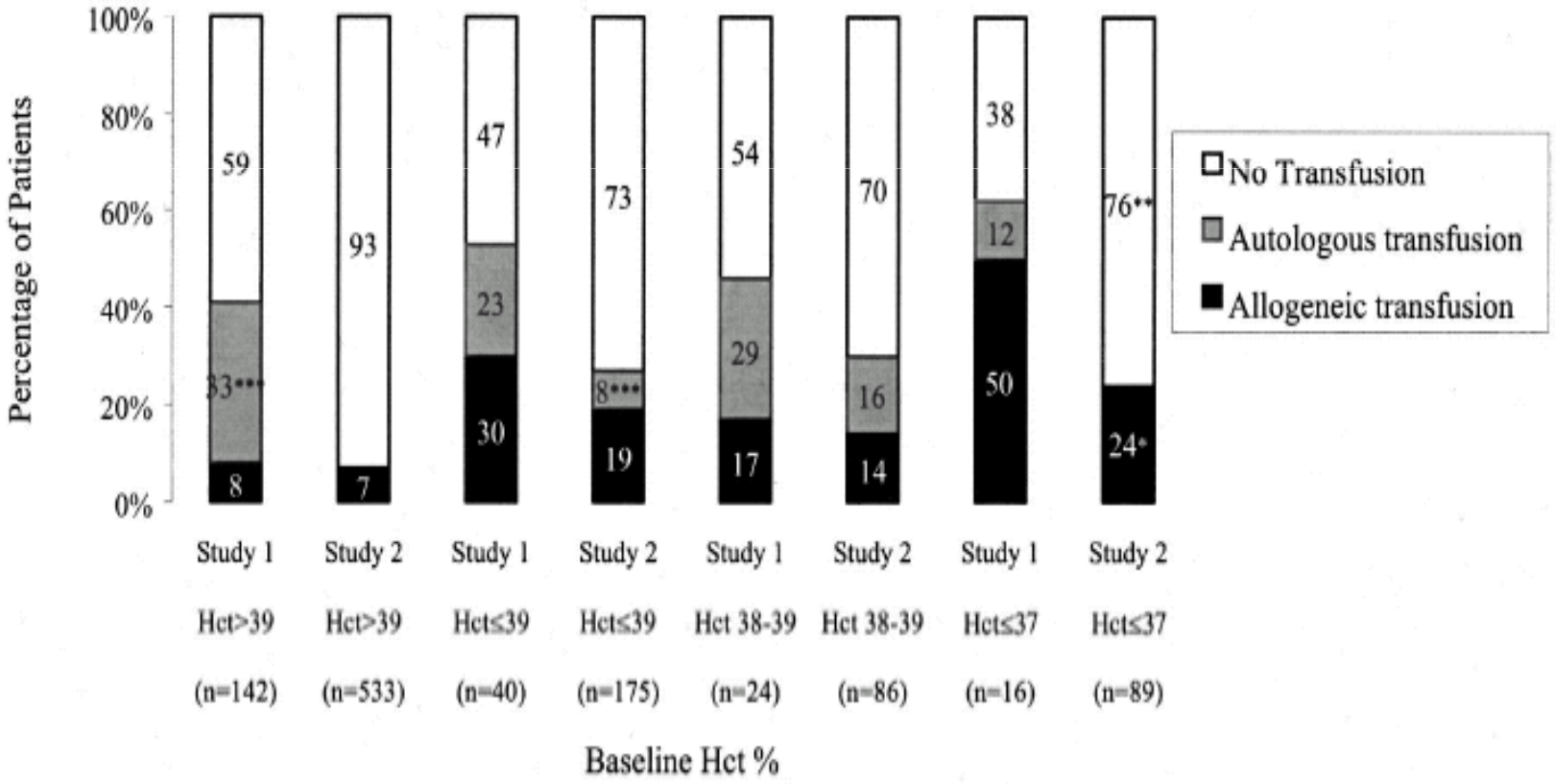


Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: A randomized blind controlled study

(J Thorac Cardiovasc Surg 2010;139:621-7)

Luca Weltert, MD, Stefano D'Alessandro, MD, Saverio Nardella, MD, Fabiana Girola, MD, Alessandro Bellisario, MD, Daniele Maselli, MD, and Ruggero De Paulis, MD

- 320 Patients randomized
- Pts randomized to the EPO group received 14,000 IU via subcutaneous administration 2 days before the operation, 14,000 IU on the next day, 8000 IU on the morning of the operation, 8000 IU 1 day after operation, and 8000 IU on postoperative day 2. The control group received no treatment.

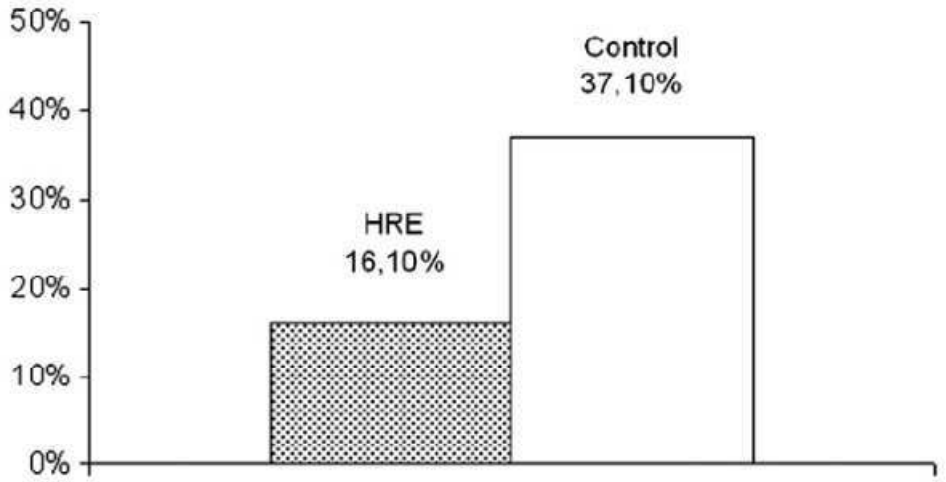


FIGURE 1. Risk of exposure to allogenic blood transfusion ($P = .007$). *HRE*, Human erythropoietin.

Effect of Single Recombinant Human Erythropoietin Injection on Transfusion Requirements in Preoperatively Anemic Patients Undergoing Valvular Heart Surgery

Anesthesiology 2011;115:929

Young-Chul Yoo, M.D.,* Jae-Kwang Shim, M.D., Ph.D.,† Jong-Chan Kim, M.D.,‡ Youn-Yi Jo, M.D.,* Jong-Hoon Lee, M.D.,§ Young-Lan Kwak, M.D., Ph.D.‖

Methods: In this prospective, single-site, single-blinded, randomized, and parallel-arm controlled trial, 74 patients with preoperative anemia were randomly allocated to either the erythropoietin or the control group. The erythropoietin group received 500 IU/kg erythropoietin and 200 mg iron sucrose intravenously 1 day before the surgery. The control group received an equivalent volume of normal saline. The primary endpoint was transfusion requirement assessed during the surgery and for 4 days postoperatively. Reticulocyte count and iron profiles were measured serially and compared preoperatively and on postoperative days 1, 2, 4, and 7.

Results: Transfusion occurred in 32 patients (86%) of the control group *versus* 22 patients (59%) of the erythropoietin group ($P = 0.009$). The mean number of units of packed erythrocytes transfused per patient during the surgery and for 4 postoperative days (mean ± SD) was also significantly decreased in the erythropoietin group compared with the control group (3.3 ± 2.2 *vs.* 1.0 ± 1.1 units/patient, $P = 0.001$). The reticulocyte count was significantly greater in the erythropoietin group at postoperative days 4 ($P = 0.001$) and 7 ($P = 0.001$).

Conclusions: A single intravenous administration of erythropoietin and an iron supplement 1 day before surgery significantly reduced the perioperative transfusion requirement in anemic patients undergoing valvular heart surgery, implicating its potential role as a blood conservation strategy.

Eritropoietina Umana Ricombinante (rHuEPO)

Sicurezza

La sicurezza del trattamento con EPO in pazienti chirurgici (non cardiovascolari) è stata dimostrata da una simile distribuzione degli eventi avversi nei pazienti trattati rispetto ai controlli in oltre 1000 pazienti inseriti in studi clinici.

Rischi potenziali

- **Anemia aplastica** (osservata solo in terapia cronica)
- **Effetto favorente la crescita tumorale**
- **Eventi tromboembolici**

rHuEPO in Surgical patients

Safety

Erithropoietin and tumour growth

- Epo-R mRNA and/or Epo-R protein found in breast, lung and renal carcinomas, tumours of the cervix and of other tumours.
- In vitro effects of Epo in tumour cells seen only with extremely high Epo concentrations, several orders of magnitude higher than those reached in therapy.
- Investigators failed to demonstrate any relationship between Epo-R expression and Epo signalling or tumour growth.

Eritropoietina Umana Ricombinante (rHuEPO)

rHuEPO e supplementazione marziale

1 Un adeguato supporto di ferro è indispensabile per ottenere l'effetto ottimale dalla terapia con rHuEPO

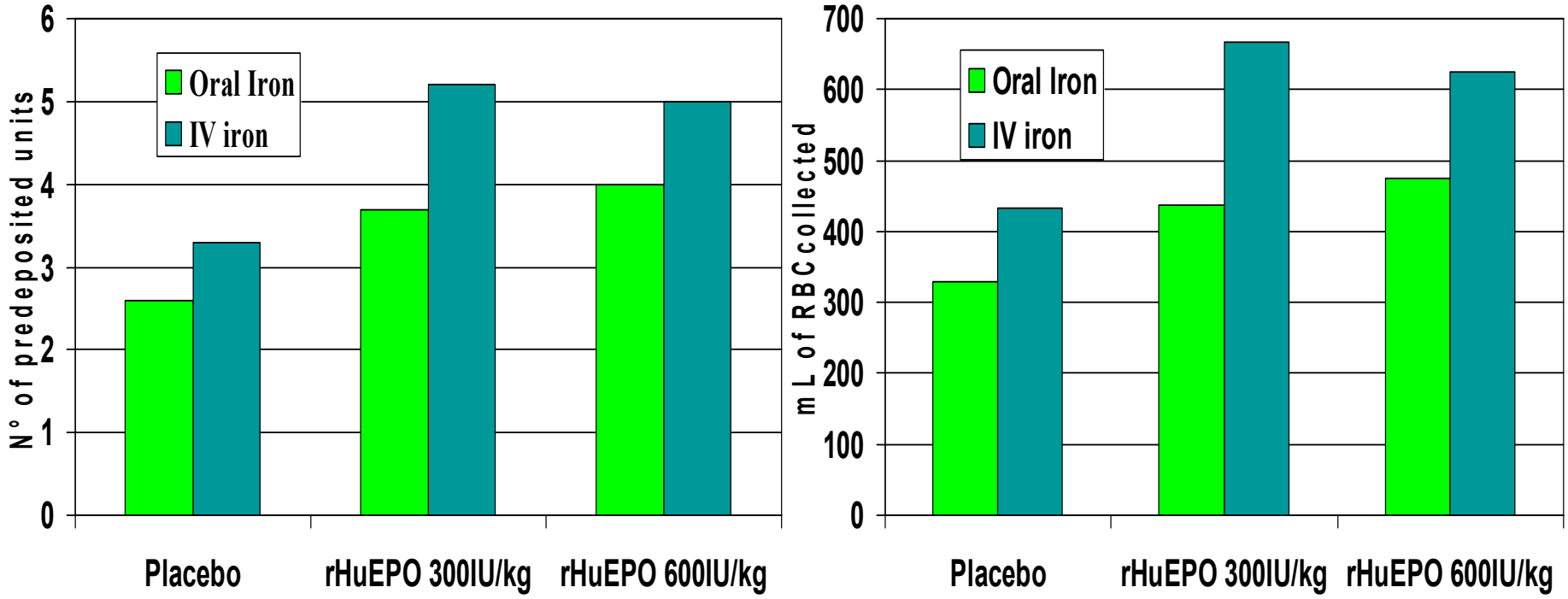
2 In pazienti trattati con rHuEPO si osserva un aumentata produzione di eritrociti ipocomici anche in presenza di adeguati depositi di ferro e di supplementazione marziale per os.

3 La somministrazione marziale per via endovenosa è stato dimostrato garantire una supplementazione più adeguata al grado di stimolazione dell'eritropoiesi, permettendo di ottenere a parità di dosi totali di rHuEPO una maggior produzione di nuovi eritrociti o di ridurre il dosaggio di rHuEPO richiesto

rHuEPO in Surgical patients

Iron Supplementation

Oral vs IV iron in rHuEPO treatment



Mercuriali F, Zanella A, Barosi G, et al Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. Transfusion 1993; 33: 55-60

Strategie alternative alla trasfusione di sangue allogenico

Le strategie attualmente disponibili per coprire il fabbisogno trasfusionale di un paziente chirurgico hanno, così come ogni procedura sanitaria, dei costi e dei rischi associati.

Tali **strategie devono essere utilizzate solo** quando necessario, ossia **quando sussista una reale probabilità** che il paziente necessiti di supporto trasfusionale.

E' pertanto necessario che ciascun paziente venga valutato da un esperto di medicina trasfusionale al fine di definirne il suo specifico fabbisogno trasfusionale previsto.

Una continua analisi dei dati provenienti dalla pratica clinica è fondamentale per dare risposta ai molti quesiti aperti.

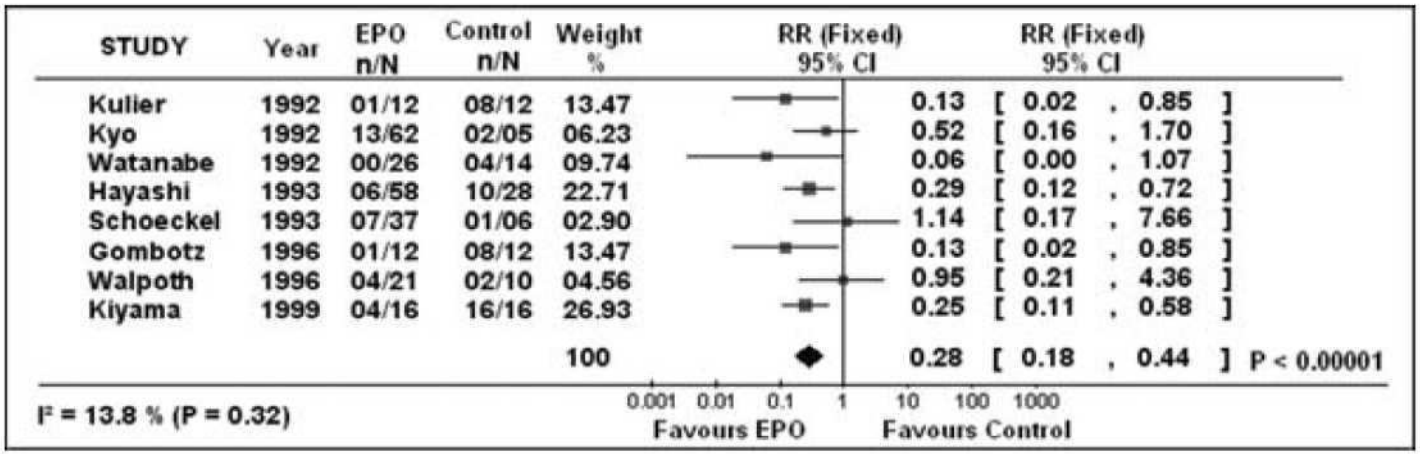
Conclusioni

- L'applicazione accurata delle differenti strategie disponibili per coprire il fabbisogno trasfusionale nel paziente chirurgico offre al paziente la possibilità di ricevere il miglior trattamento ad un costo accettabile
- La decisione di utilizzare una specifica strategie o una combinazione di esse si deve basare sulle caratteristiche cliniche dello specifico paziente e su valutazioni di carattere logistico-organizzativo

Does the Use of Erythropoietin Reduce the Risk of Exposure to Allogeneic Blood Transfusion in Cardiac Surgery? A Systematic Review and Meta-Analysis

J Card Surg 2006;21:320-326

PABD



NO PABD

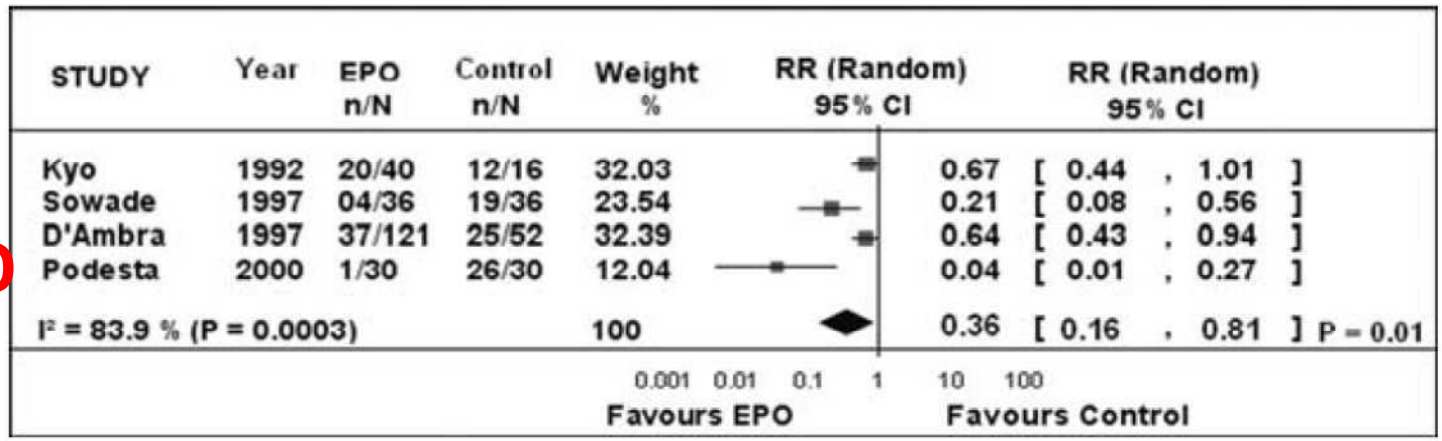


Figure 3. *Meta-analysis of all studies that did not include PABD. RR = relative risk; CI = confidence interval; Random = random effect model statistics; n = number of patients exposed to allogeneic blood; N = total number of patients in a given arm; I^2 = I square test for heterogeneity.*

Eritropoietina Umana Ricombinante (rHuEPO)

The efficacy of rhEPO administration in reducing transfusion requirement has been proven in:

- Orthopaedic surgery
- Cardiovascular surgery (not approved in US)

A Cochrane review (2009) in colorectal cancer surgery has shown no statistically significant differences in the proportion of patients transfused between the EPO group and control group.

rHuEPO in surgery

Safety

Pure red-cell aplasia

An upsurge was associated with the SC use of one product only (epoetin alfa distributed outside the USA).

.... caused by the introduction of a new buffer (polysorbate 80) in 1998, which replaced human serum albumin, and which can induce the release of organic compounds with adjuvant properties from the rubber stoppers of prefilled syringes.

Sharma B, et al Technical investigations into the cause of the increased incidence of antibody-mediated pure red cell aplasia associated with Eprex. *Eur J Hosp Pharm* 2004; **5:** 86–91.
Boven K et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney Int* 2005; **67:** 2346–53.

rHuEPO in surgery

Perisurgical use of rHuEPO

Protocol

Erythropoietin

rHuEPO 200 IU/kg IV at first donation (3-4 days before surgery)

rHuEPO 100 IU/kg SC from 3-4 days before to 3 days after surgery

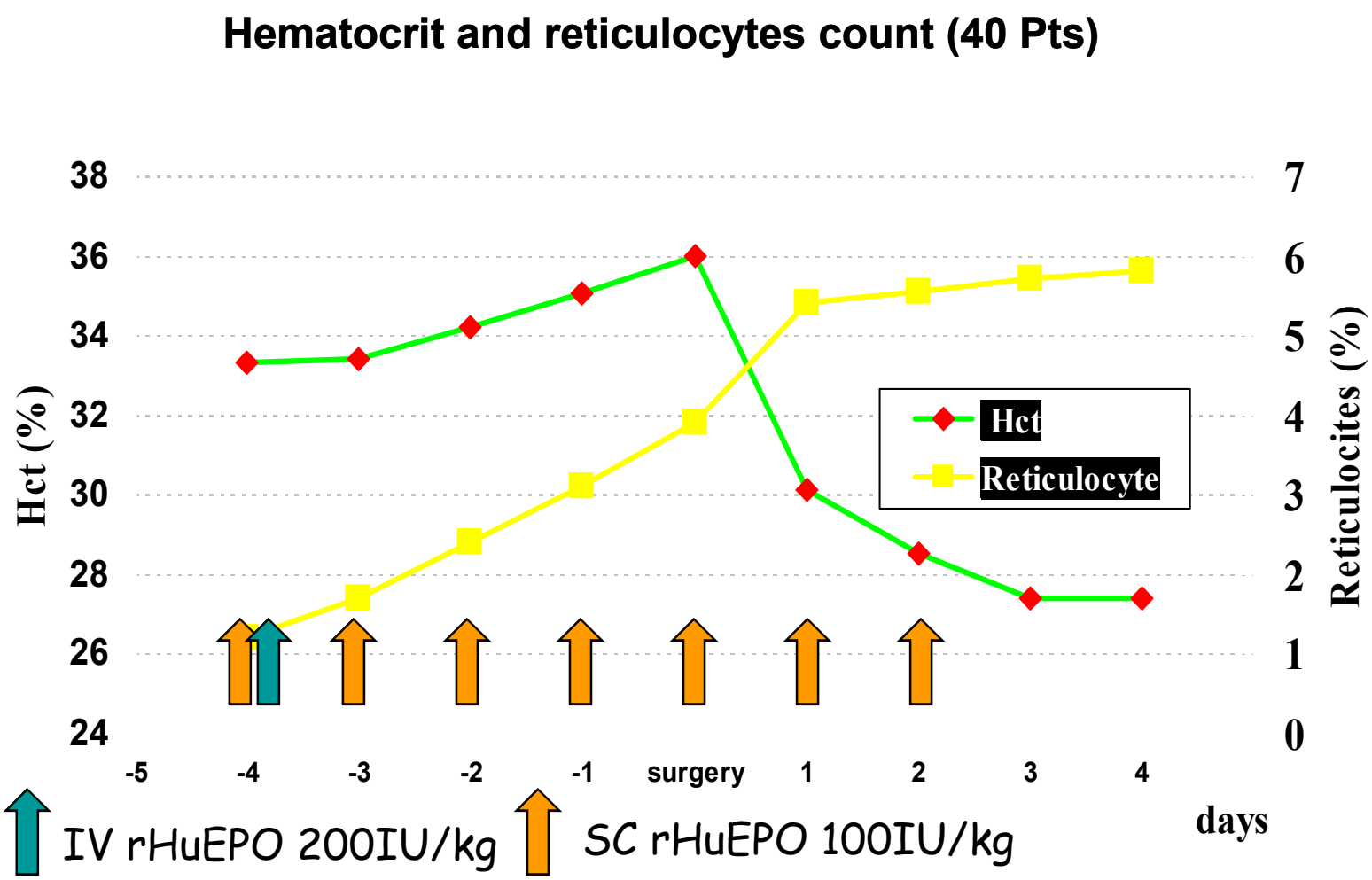
Iron Supplementation

Iron suchrose 100-200 mg IV at each rHuEPO dose

Perioperative Salvage during surgery

rHuEPO in surgery

rHuEPO Perisurgical



rHuEPO in surgery

rHuEPO perisurgical in elective surgery

Transfusion Treatment

34 out of 40 patients (85%) completely avoided allogeneic transfusion

Allogeneic blood transfused:
20 units to 6 patients

rHuEPO in surgery

Safety

The FDA has recently stated that the use of ESAs may increase the risk for thrombotic events in the peri-surgical setting

Jerkins JK. 2007 Erythropoiesis stimulating agents

http://www.fda.gov/ola/2007/esa062607.htlm

However, this occurred mostly in pts with preoperative Hb > 13 g/dl

rHuEPO in Surgical patients

Safety

FDA Public Health Advisory

- A higher chance of death and an increased rate of tumor growth were reported in pts with advanced head and neck cancer receiving radiation therapy and in pts with metastatic breast cancer receiving chemotherapy, when ESAs were given to maintain hemoglobin levels of more than 12 g/dL.
- A higher chance of death was reported and no fewer blood transfusions were received when ESAs were given to Pts with cancer and anemia not receiving chemotherapy.

No evidence for EPO therapy in surgical cancer Pts