

Patient Blood Management in the Netherlands: Between practice and evidence

Marian van Kraaij MD PhD hematologist – transfusion medicine specialist Department of Transfusion Medicine, Sanquin Blood Bank Radboud University Medical Center, Nijmegen The Netherlands

October 9, 2015 | 1



# Outline

- Introduction
- Blood use in the Netherlands
- What is patient blood management (PBM)?
- Practical implementation of PBM
- Evidence of PBM
- More opportunities for PBM?
- Conclusions



# Introduction



#### Inhabitants Estonia: 1,3 million Netherlands: 16,9 million



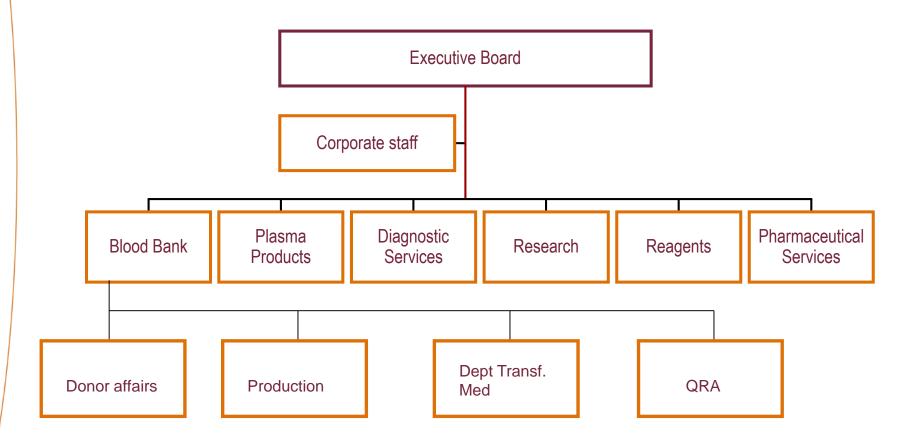


# Sanquin Blood Supply Foundation

- The only organization in the NL authorized to supply blood (products)
- Not-for-profit
- Approximately 3,000 employees; 5 divisions:
  - Blood Bank
  - Plasma Products
  - Diagnostic Services
  - Research Sanquin staff working with / partly employed at academic centers
  - Reagents



# Organization

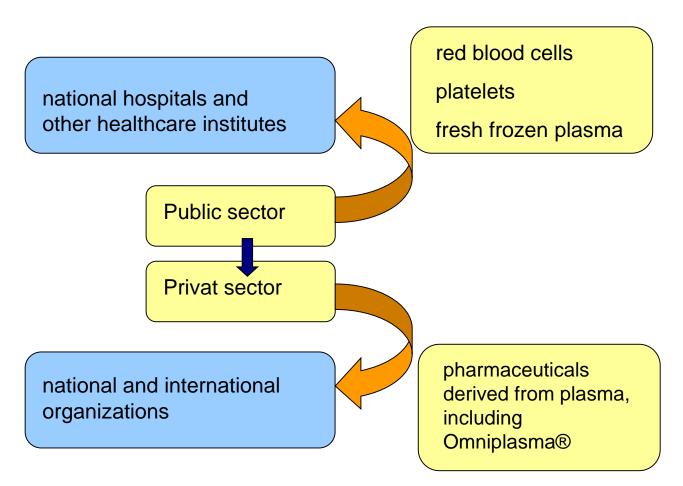








# Sanquin



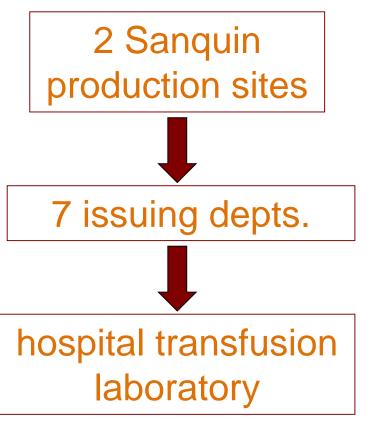
3000 employees; 400,000 donors



# Hospitals

- 90 hospitals
  - 8 university hospitals
- Each hospital has its own tranfusion laboratory and performs compatibility tests
- Sanquin: reference laboratory

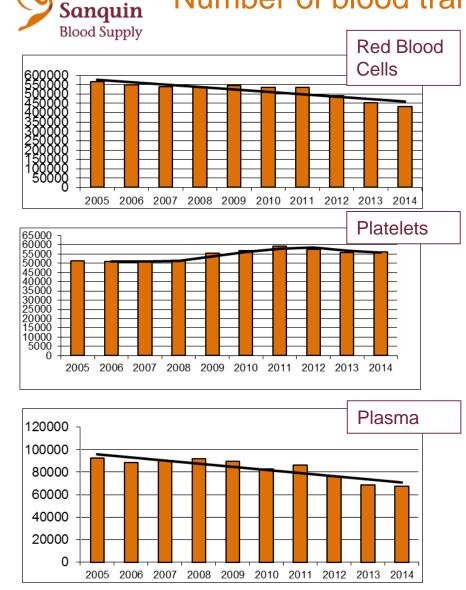






# Blood use in the Netherlands

#### Number of blood transfusions in the Netherlands



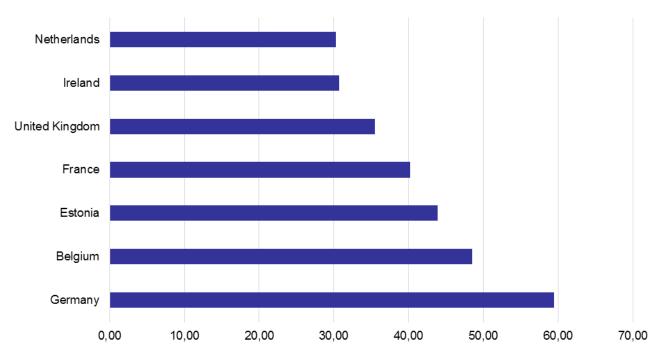
Blood products (2014)

- 433,500 red blood cells (↓ 26%)
- 56,000 platelets (10%)
- 67,600 plasma (↓ 27%)



# Benchmark Europe EDQM 2012

whole blood/ 1000 inhabitants



Survey 2012 European Directorate for the Quality of Medicines and Health Care

October 9, 2015 | 12



#### Possible reasons for declined (red) blood use

- National guideline "Blood Transfusion" (2004, 2011 revised version) including Patient Blood Management
- Quality Act for Health Care institutes and national hemovigilance office "TRIP" (<u>Transfusion and Transplantation Reactions In Patients</u>; founded 2001)
- Benchmark blood use between Dutch Hospitals organized by Sanquin
- Reimbursement system for blood products in the Netherlands
- Cost reduction health care -> hospitals have to economize (6%) and quality indicators Dutch Society of Surgeons -> concentration of care



# What is Patient Blood Management (PBM)?



## **Patient Blood Management defenition**

Patient Blood Management (PBM) is an evidence-based, multidisciplinary approach to optimising the care of patients who might or do need blood transfusion.



# Three pillars of Patient Blood Management (http:///www.health.wa.gov.au/bloodmanagement/)

- 1. optimising the patient's own blood
- 2. minimising surgical blood loss and bleeding
- 3. harnessing and optimising the patient-specific physiological reserve of anaemia (including restrictive transfusion thresholds)



#### 2nd Pillar 1st Pillar **3rd Pillar** Minimize blood loss Optimize erythropoiesis Harness & optimize physiological & bleeding reserve of anemia Detect anemia Identify underlying disorder(s) Assess/optimize patient's Preoperative physiological reserve and risk causing anemia Manage disorder(s) Identify and manage bleeding risk factors Refer for further evaluation if Minimizing iatrogenic blood loss . Compare estimated blood loss with Procedure planning and rehearsal patient-specific tolerable blood loss necessary Preoperative autologous blood Formulate patient-specific Treat suboptimal iron stores/iron donation (in selected cases or when deficiency/anemia of chronic management plan using appropriate disease/iron-restricted patient choice) blood conservation modalities to Other minimize blood loss, optimize red erythropoiesis . Treat other hematinic deficiencies cell mass, and manage anemia Restrictive transfusion thresholds Note: Anemia is a contraindication for elective surgery Intraoperative Meticulous hemostasis and surgical techniques Optimize cardiac output Blood-sparing surgical techniques Timing surgery with hematological Optimize ventilation and Anesthetic blood conserving optimization oxygenation strategies Restrictive transfusion thresholds Autologous blood options Pharmacological/hemostatic agents Vigilant monitoring and management of post-operative bleeding Avoid secondary hemorrhage Postoperative Rapid warming/maintain . normothermia (unless hypothermia Optimize anemia reserve specifically indicated) Stimulate erythropoiesis Maximize oxygen delivery Autologous blood salvage Be aware of drug interactions that Minimize oxygen consumption Minimizing iatrogenic blood loss can increase anemia Avoid/treat infections promptly Hemostasis/anticoagulation Restrictive transfusion thresholds management Prophylaxis of upper gastrointestinal hemorrhage Avoid/treat infections promptly Be aware of adverse effects of medication

#### October 9, 2015 | 17



# Practical implementation of PBM in the Netherlands



### National Guideline "Blood Transfusion"

- Effective use of blood products
  - so-called 4-5-6 rule

(depending on the presence of co-morbidity, the threshold for RBC transfusion varies between 4.0 mmol/L (6.4 g/dL) and 6.0 mmol/L (9,7 g/dL)

- alternatives for red blood cell transfusion pharmaceuticals, cell savers
- improvement of operation techniques

Colofon: Richtlijn Bloedtransfusie



Transfusion Guideline 2011, Dutch Institute for Health Care Improvement CBO





4.0 mmol/l = 6.4 g/dl

5.0 mmol/l = 8.0 g/dl

6.0 mmol/l = 9.7 g/dl



## Alternatives for blood cell transfusion

- Iron (oral or IV) -> pre-operative anaemia
- Erytropoietin -> pre-operative anaemia
- Cell savers -> intra-operative/ post-operative



• Tranexamic acid (cheap)-> pre- and during operation, IV and topical



#### Iron in pre-operative anaemia

- No randomized controlled studies yet
- PREVENTT: preoperative intravenous iron to treat anaemia in major surgery: study protocol for a randomised controlled trial (Trials 2015, 16; 254)
- Litton et al: Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials (BMJ 2013; 347: f4822)
- Recommendations: A Kotze et al.: British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia. BJM 2015, September epub



# Fig 3 Risk of red blood cell transfusion in patients who received intravenous iron compared with oral iron and no iron.

Study	Treatment	Control	Relative risk	Weight	
IV iron v oral iron			(95% CI)	(%)	(95% CI)
Al 2005 <sup>18</sup>	0/45	1/45		0.3	0.33 (0.01 to 7.97)
Auerbach 2004 <sup>22</sup>	9/78	10/79		3.7	0.91 (0.39 to 2.12)
Auerbach 2010 <sup>23</sup>	41/116	48/122		17.6	0.90 (0.65 to 1.25)
Bayoumeu 2002 <sup>25</sup>	0/24	1/23		0.3	0.32 (0.01 to 7.48)
Breymann 2008 <sup>30</sup>	1/227	0/117		0.3	1.55 (0.06 to 37.82)
Dangsuwan 2010 <sup>33</sup>	5/22	14/22		3.8	0.36 (0.16 to 0.82)
Froessler 2013 <sup>37</sup>	1/101	3/97		0.6	0.32 (0.03 to 3.03)
Garrido-Martin 2012 <sup>38</sup>	20/54	27/53	-	11.7	0.73 (0.47 to 1.13)
Henry 2007 <sup>41</sup>	11/63	20/124		5.7	1.08 (0.55 to 2.12)
Kochhar 2012 <sup>48</sup>	0/50	1/50		0.3	0.33 (0.01 to 7.99)
Meyer 1996 <sup>59</sup>	0/21	2/21		0.3	0.20 (0.01 to 3.93)
Steensma 2011 <sup>78</sup>	20/164	43/326		9.5	0.92 (0.56 to 1.52)
Weisbach 1999 <sup>87</sup>	6/30	5/60	<b>—</b>	2.3	2.40 (0.80 to 7.23)
Westad 2008 <sup>88</sup>	4/59	11/70		2.3	0.43 (0.14 to 1.28)
Subtotal: P=0.45, I <sup>2</sup> =0%	118/1054	186/1209		58.6	0.82 (0.67 to 1.00)
IV iron v no iron					
Edwards 2009 <sup>34</sup>	0/34	2/26		0.3	0.15 (0.01 to 3.08)
Hedenus 2007 <sup>40</sup>	2/33	1/34		0.5	2.06 (0.20 to 21.65)
Karkouti 2006 <sup>43</sup>	4/21	4/10		2.0	0.48 (0.15 to 1.52)
Kim 2007 <sup>46</sup>	12/30	29/45		9.8	0.62 (0.38 to 1.01)
Madi-Jebara 2004 <sup>57</sup>	17/80	9/40		5.1	0.94 (0.46 to 1.93)
Na 2011 <sup>60</sup>	11/54	29/54		7.3	0.38 (0.21 to 0.68)
Pedrazzoli 2008 <sup>64</sup>	2/73	5/76		1.1	0.42 (0.08 to 2.08)
Serrano-Trenas 201172	33/100	41/100		15.3	0.80 (0.56 to 1.16)
Subtotal: P=0.33,   <sup>2</sup> =14%	81/425	120/385	<b>→</b>	41.4	0.64 (0.49 to 0.85)
Subtotal: P=0.34, I <sup>2</sup> =9%	199/1479	306/1594	÷	100.0	0.74 (0.62 to 0.88)
		0.0	008 1 1	29	

Edward Litton et al. BMJ 2013;347:bmj.f4822





# Evidence of erytropoietin and cellsavers – Dutch study in orthopaedic patients

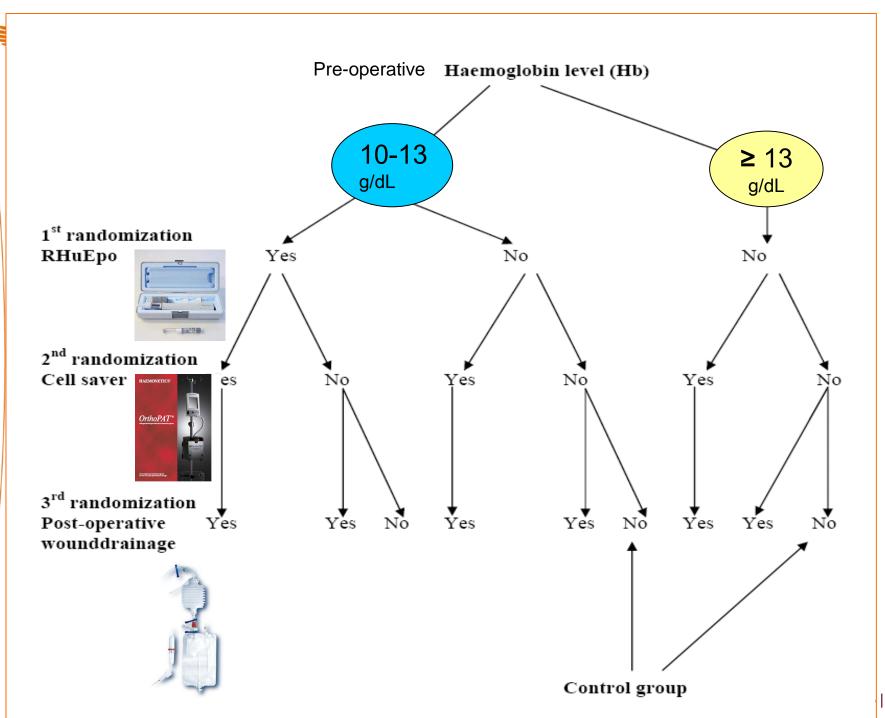
#### Dr Cynthia So-Osman





# Rationale

- Hip- and knee-replacement surgery result in large blood losses
- Ageing population will result in 3 fold increase of joint replacements in 2030 (> 100.000 per year)
- Blood sparing modalities are very popular and much investigated
- However:
- 1. NO evidence on combined effect of several modalities
- 2. NO evidence on effect of restrictive transfusion trigger
- 3. Most studies lack power, are methodologically poor





#### **Patients characteristics**

Parameter	Numbers (%) or mean (SD)
Evaluated patients	2442
Females	1699 (70%)
Mean age (years)	69 ( <u>+</u> 11)
THR Of which revision	1462 (60%) 130 (5%)
TKR Of which revision	980 (40%) 54 (2%)
Mean pre-operative Hb (mmol/L) Hb (g/dL)	8.6 ( <u>+</u> 0.8) 13.9 ( <u>+</u> 1.3)
Epo eligible patients	683 (28%)



# **General results**

- RBC transfusions in 11.6% of 2442 (n=284)
- If transfused: median of 2 RBC (range 1-27)
  - Intra-operatively n= 37 (range 1-12)
  - 0-14 days n= 246 (range 1-11)
  - 14 days-3 months n= 43 (range 1-27)
- Due to heterogeneity of revision patients, primary surgery group is separately reported in case of RBC use
- In case of cost analysis all patients were evaluated





# Significant reduction in % patients transfused: 2 times less

Non-significant mean RBC reduction: 29%



#### Autologous blood re-infusion effect

No reduction in mean RBC use AND in proportion transfused (with or without epo)

No difference between cell saver and drain



# Cost analysis Epo and autologous re-infusion devices

Costs ( in Euro' s) N=683	Total costs (in Euro)	Difference (95% CI)
Low Hb (stratum I)		
with epo (n=339)	5615	785
no epo (n=344)	4829	(262-1309)

Costs ( in Euro' s)	Total costs	Difference
N=2442	(in Euro)	(95% CI)
with autologous device (n=1481) without autologous device (n=691)	4399 4021	378 (161-595)



# **Conclusions**

- Significant red blood cell (RBC) reduction by Epo, however not cost-effective
- Neither red blood cell- nor cost-reduction by autologous blood reinfusion (i.e. cell saver or postoperative drain re-infusion)



#### Meta-analysis cell savers

	Cell Sa	ver	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
4.1. vears 1991-1999								
Majkowski 1991	7	20	19	20	5.3%	0.37 [0.20, 0.68]	1991	
Slagis 1991	9	27	14	25	5.2%	0.60 [0.31, 1.13]	1991	
Heddle 1992	10	39	27	40	5.4%	0.38 [0.21, 0.68]	1992	
Ritter 1994	23	137	30	138	5.8%	0.77 [0.47, 1.26]	1594	· · · · · · · · · · · · · · · · · · ·
Rosencher 1994	6	20	6	10	4.3%	0.50 [0.22, 1.15]	1994	
Mah 1995	9	44	26	55	5.1%	0.43 [0.2383]	1995	· · · · · · · · · · · · · · · · · · ·
Shenolikar 1997	2	50	40	50	5.1%	0.20 [0 10, 0.38]	1997	·
Newman 1997	3	35	28	35	3.4%	01 [0.04, 0.32]	1997	· •
Adalberth 1998	8	21	7	24	4.3%	1.14 [0.49, 2.65]	1998	
Sait 1999	1	60	35	60	1.6%	0.03 [0.00, 0.20]	1999	<b>←</b>
Subtotal (95% CI)		456		457	45.5%	0.38 [0.25, 0.60]		◆
Total events	84		232					
Heterogeneity: Tau² = 0	.36; Chi <b></b> *:	= 34.36	6, df = 9 (l	• < • •	u01); I² = I	74%		
Test for overall effect: Z	= 4.18 (P	< 0.00	01)					
				/				
4.1.2 years 2000-2009								
Thomas 2001	12	112	33	116	5.3%	0.37 [0.20, 0.67]		
Cheng 2005	4	26	13	34	3.7%	0.40 [0.15, 1.09]		
Dramis 2006	3	32	10	17	3.2%	0.16 [0.05, 0.50]		
So-Osman 2006	6	/ 12	6	11	4.5%	0.92 [042, 2.00]		
Abuzakuk 2007	13	52	12	52	5.0%	1.08 [0.55, 2.15]		
Zacharopoulos 2007	5	30	10	30	3.9%	0.50 [0.19, 1.29]		
Moonen 2007	1	45	5	32	1.4%	0.14 [0.02, 1.16]		
Amin 2006	12	92	13	86	4.8%	0.86 [0.42, 1.79]	2009	
Subtreal (95% C!)		404		378	31.7%	0.53 [0.33, 0.84]		
Total events	56		102					
Heterogeneity: Tau <sup>2</sup> = 0	•			- = 0.0	3); 1* = 54	%		•
Test for overall effect: Z	= 2.72 (P	= 0.00	0					
4.1.3 years 2010 - pres	ent							
Blatsoukas 2010	99	163	67	85	6.9%	0.77 [0.65, 0.91]	2010	
Atay 2010	1	20	8	21	1.5%	0.13 [0.02, 0.96]		
Dutton 2012	4	23	4	25	2.9%	1.09 [0.31, 3.85]		
Cip 2012	23	70	23	70	5.9%	1.00 [0.62, 1.61]		
So-Osman 2012	31	436	23	417	5.6%	1.35 [0.79, 2.29]		
Subtotal (95% CI)	51	712		618	22.8%	0.91 [0.63, 1.31]	2012	-
Total events	158		124					
Heterogeneity: Tau <sup>2</sup> = 0		= 8 63		= 0.07	r: I≧ = 54%	6		
Test for overall effect: Z	•		•	- 0.07,	/,1 = 34 /	,		
Cottor overan ellect. Z	- 0.01 (1	- 0.01	,					
Total (95% CI)		1572		1453	100.0%	0.51 [0.39, 0.68]		◆
Total events	298		458					
Heterogeneity: Tau <sup>2</sup> = 0	.28; Chi <b></b> *:	= 86.81	1, df = 22	(P < 0.)	00001); l <sup>a</sup>	'= 75%		
Test for overall effect: Z								0.1 0.2 0.5 1 2 5 10 Favours Cell Salvage Favours Control
Test for subgroup differ	ences: Cl	hi² = 8.	98, df = 2	(P = 0)	.01), I <sup>2</sup> = 7	7.7%		r avours Cen Daivage - Favours ContfOl

## **Outcome:**

Number of patients exposed to allogeneic RBC transfusion



### Conclusions meta-analysis cell saving

#### Cell Saving significantly reduces

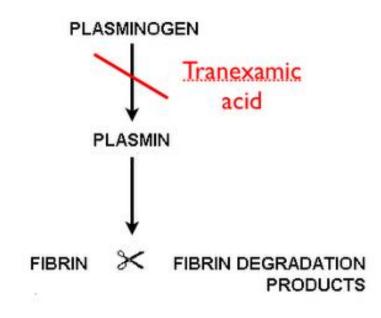
- the need for allogeneic RBC transfusion, and
- the volume of RBC transfused

However, in RCTs published more recently (2010-2012), Cell Saving does neither reduce the need for allogeneic RBC transfusion nor the volume of RBC transfused in both hip and knee surgery



## Tranexamic acid to prevent/ diminish bleeding

- TXA is a synthetic lysine analogue antifibrinolytic agent. It is an <u>antifibrinolytic</u> that competitively inhibits the activation of plasminogen to <u>plasmin</u>, by binding to specific sites of both plasminogen and plasmin, a molecule responsible for the degradation of <u>fibrin</u>.
- Oral, intravenous or topical administration





### Use of tranexamic acid

- in 2015 many randomized trials/ meta-analysis on tranexamic acid, i.e.:
  - Trauma
  - Postpartum haemorrhage
  - Orthopaedic surgery (total hip and knee, spine)
  - Upper gastro-intestinal bleeding
  - Open heart surgery

#### Sanquin Blood Supply Effect tranexamic acid in total knee arthroplasty in 34 randomized controlled trials

Study ID	SMD (95% CI)	% Weight	
intravenous			
Hiippala (1995)	-1.16 (-1.97, -0.35)	7.55	
Hiippala (1997)	-1.49 (-1.99, -0.98)	9.44	
Jansen (1999)	-0.81 (-1.44, -0.18)	8.67	
Tanaka (2001)	-2.67 (-3.26, -2.09)	8.96	_
Ellis (2001)	-1.36 (-2.34, -0.38)	6.51	E
Good (2003)	-1.01 (-1.60, -0.43)	8.95	k
Camarasa (2006)	-0.85 (-1.28, -0.41)	9.87	
Molloy (2007)	-0.30 (-0.69, 0.10)	10.09	t
Alvarez (2008)	-0.42 (-0.82, -0.01)	10.02	F
Charoencholva (2011)	-1.43 (-1.87, -0.99)	9.84	
Chareancholvanich (2012)	-1.27 (-1.67, -0.88)	10.10	
Engel (2001)	(Excluded)	0.00	
Veien (2002)	(Excluded)	0.00	
Subtotal (Lsquared = 83.8%, p = 0.000)	-1.14 (-1.53, -0.76)	100.00	
intraarticula			
Georgiadis (2013)	(Excluded)	0.00	
Subtotal (I-squared = .%, p = .)	. (., .)	0.00	
Overall (I-squared = 83.8%, p = 0.000)	-1.14 (-1.53, -0.76)	100.00	
NOTE: Weights are from random effects analysis			
-3.26 0	3.26		
-3.20 U	5.20		

Effect on blood units transfused per patient

Wu et al, Eur J Orthop Surg Traumatol 2015



# More indications for PBM than surgery?





#### Patient Blood Management in Europe (PaBloE)

Objectives of one of the working parties

- Data collection on current blood and blood component use and PBM practices
  - Survey of PBM practices among the PaBloE centres
  - Survey of top indications for red blood cell use



	Red (	Cell Issue Trace Audit Cycle 1, 2	2014
Box a) No of units:		Box c) Male 📃 Female 🗌	Audited Patient No.
Cardiothoracic Surgery		Vascular Surgery	
1 CABG (first)		23 Emergency AAA repair	
2 CABG (redo)		24 Elective open AAA repair	GI bleed
	_	25 Other (please state)	43 Upper acute
3 Valve replacement (+/- CABG	)		44 Lower acute
4 ECMO			45 Upper chronic
5 Congenital Heart Disease		Orthopaedics	46 Lower chronic
6 Other (please state)		26 THR (first)	47 Site of bleeding not known
		27 THR (redo)	
ENT		28 TKR (first)	Anaemia due to:
7 ENT		29 TKR (redo)	
Gastrointestinal Surgery		30 Other (please state)	48 Renal failure
8 Oesophageal			49 Cancer (non haem)
9 Gastric			50 Iron deficiency
			51 B12/folate def
10 Pancreatic		Plastic surgery	52 Chronic disorders e.g.

#### National Comparative Audit Program, NHS Blood & Transplant

nouroourgory				
14 Neurosurgery (including head injury)			Haematological	
Trauma	_	Obs & Gyn	56 AML (including APML)	
15 Blunt		34 Gynae (non malignant)	57 ALL	
16 Penetrating		35 Gynae oncology	58 Myeloma	
17 Fractured femur		36 Obstetric anaemia	59 Hodgkins/NHL/CLL	
18 Fractured pelvis		37 Obstetric haemorrhage	60 Acquired Haemolytic	
19 Other fracture		Neonatal/fetal	Anaemia	
20 Other (please state)		38 Neonatal top up	61 Thalassaemia	
		39 Neonatal exchange	62 Sickle cell disease	
Urology		40 Neonatal large volume	63 Other inherited anaemia	
21 Urology		transfusion	64 Myeloproliferative disease	e 🗌
Solid Organ Transplant		41 Intrauterine transfusion	65 CML	
22 Solid Organ Transplant		42 Other (please state)	66 Aplastic anaemia	
(State organ)			67 Other (please state)	
	1			

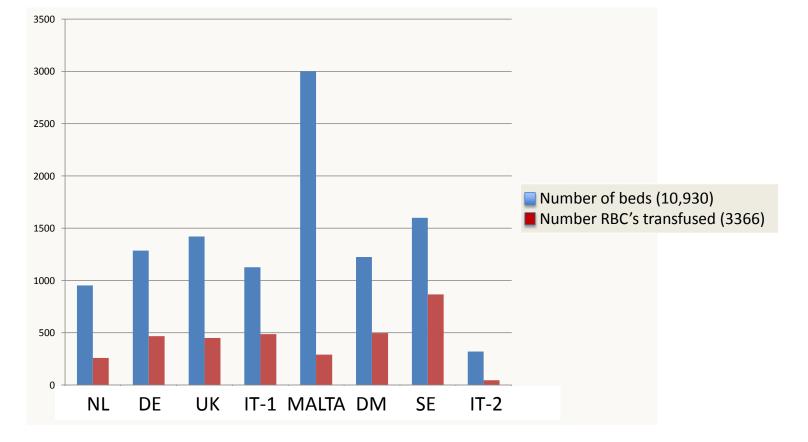


- Cardiothoracic Surgery
- ENT
- Gastrointestinal Surgery
- Neurosurgery
- Trauma
- Urology
- Solid Organ Transplant
- Vascular Surgery
- Orthopaedics
- Plastic Surgery
- Other Surgery
- Obstetrics & Gynaecology
- Neonatal/fetal
- GI Bleed
- Haematological
- Anaemia due to other causes



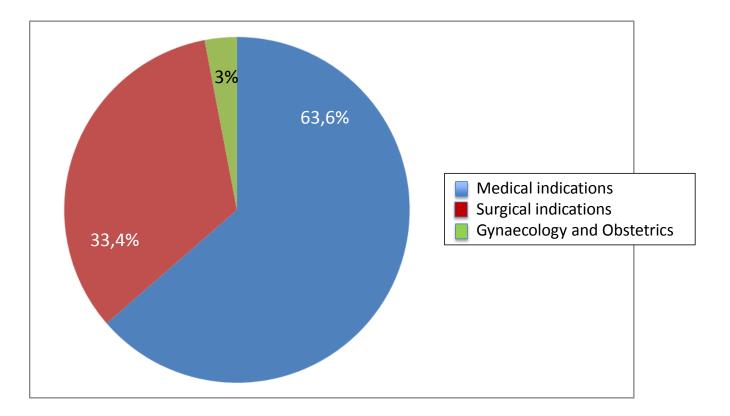
### **8 European Hospitals**

EUROPEAN BLOOD



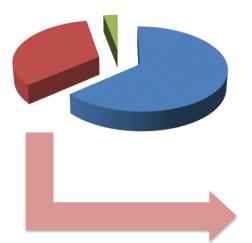


# Where did red cells go to?





# Top Surgical Indications



Indication	Number of red cell units transfused	Percentage of total (3366)
Cardiothoracic	324	9.6%
Gastrointestinal	193	5.7%
Trauma	133	4%
Orthopaedics	118	3.5%
Vascular	101	3%



# Top Medical Indications





Indication	Number of red cell units transfused	Percentage of total (3366)
Haematological	1013	30.1%
Gastro-intestinal bleeding	239	7.1%
Critical Care	147	6.8%
Cancer non- haematological	144	6.7%
Neonatal	99	2.9%



# Conclusions

- Patient Blood Management = Good Clinical Practice
- A simple rule (4-5-6) may safe blood use
- Alternatives for blood transfusion may be useful, but
- Evidence is needed to implement PBM properly
- PBM had been investigated particularly in surgical patients, but
- Most red blood cells go to medical indications

More research is needed on the topic of PBM





#### <u>m.vankraaij@sanquin.nl</u>

#### www.sanquin.nl

October 9, 2015 | 46