

Klinische effecten en mogelijke mechanismen van transfusion-related immunomodulation

Yavuz Bilgin, internist-hematoloog

Adrz

18 mei 2022

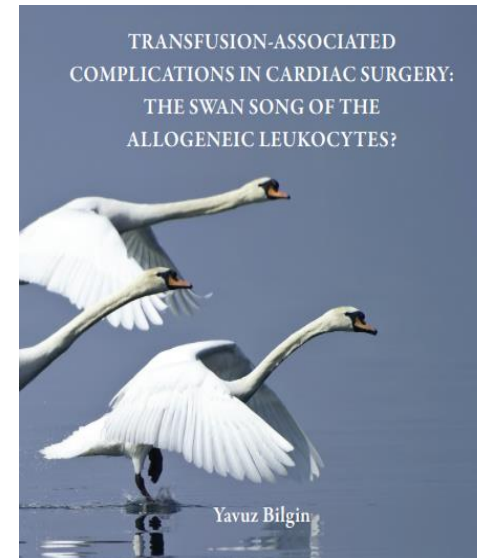
NVB-TRIP Symposium

Wat is transfusion-related immunomodulation (TRIM) ?

Effecten van bloedtransfusie op het immuunsysteem:

- In 1973: bloedtransfusie betere overleving niertransplantatie: **XX**
- Recidief kanker (gastro-intestinale maligniteiten): **XX**
- Postoperatieve infecties ??

→ Mogelijk rol van allogene leukocyten?



27 september 2011 Leiden

Leo/Anneke/Leiden (LAL studie)

Beneficial Effects of Leukocyte Depletion of Transfused Blood on Postoperative Complications in Patients Undergoing Cardiac Surgery A Randomized Clinical Trial

Leo M.G. van de Watering, MD; Jo Hermans, PhD; Jos G.A. Houbiers, PhD;
Pieter J. van den Broek, MD; Hens Bouter, MD; Fred Boer, MD; Mark S. Harvey, PhD;
Hans A. Huysmans, MD; Anneke Brand, MD

- N=914
- 48 (5.2%) patienten kregen geen transfusie
- Gemiddeld: 5.4 eenheden RBC

	PC	LD	PC	LD
			≥ 4 Units	
Sterfte 60-dagen (%)	7.8	3.5*	12.5	5.1*
Infecties (%)	23.5	17.9*	31.4	22*

* $p < 0.05$

PC=buffy-coat depleted RBC

LD=leukocytes-depleted RBC

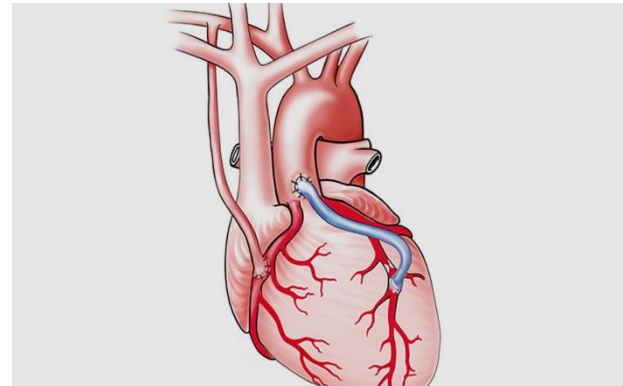
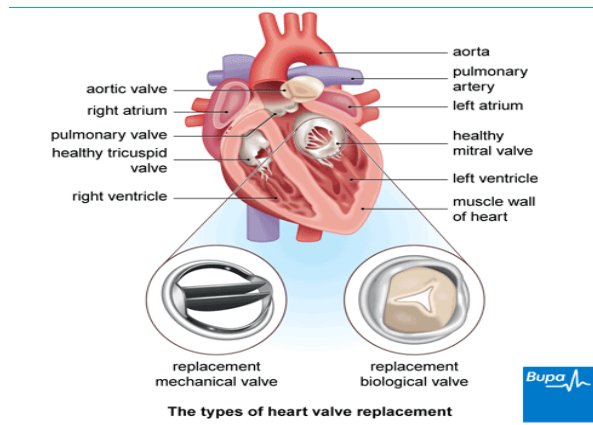
Zijn de bevindingen van LAL-studie toeval ?

- Hartchirurgie (Klep-OK +/- CABG)
- AMC en LUMC (N= 496)
- Doel: Mortaliteit (90 dagen)
- 8.9% geen transfusie
- 58% \geq 4 eenheden RBC's
- Gemiddeld: 6.2 eenheden RBC's

Infecties

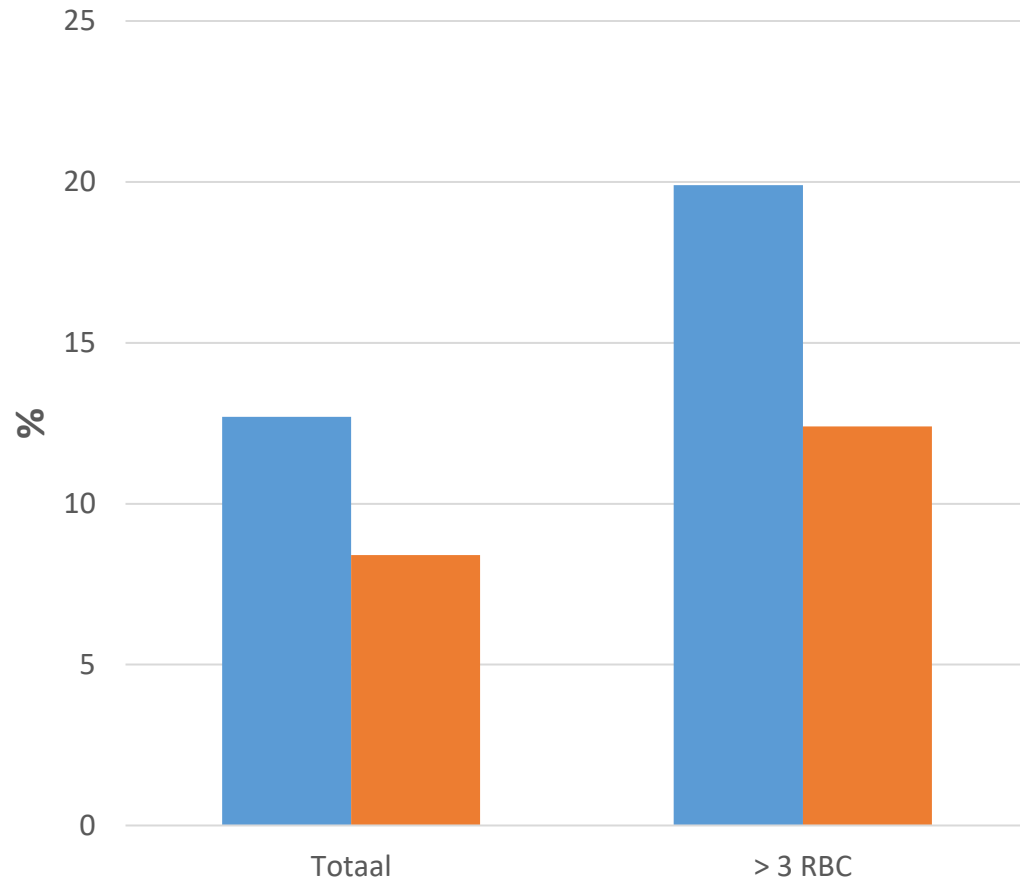
MODS (Multi-organ dysfunction syndrome)

- Tevens: verzamelen van bloedmonsters

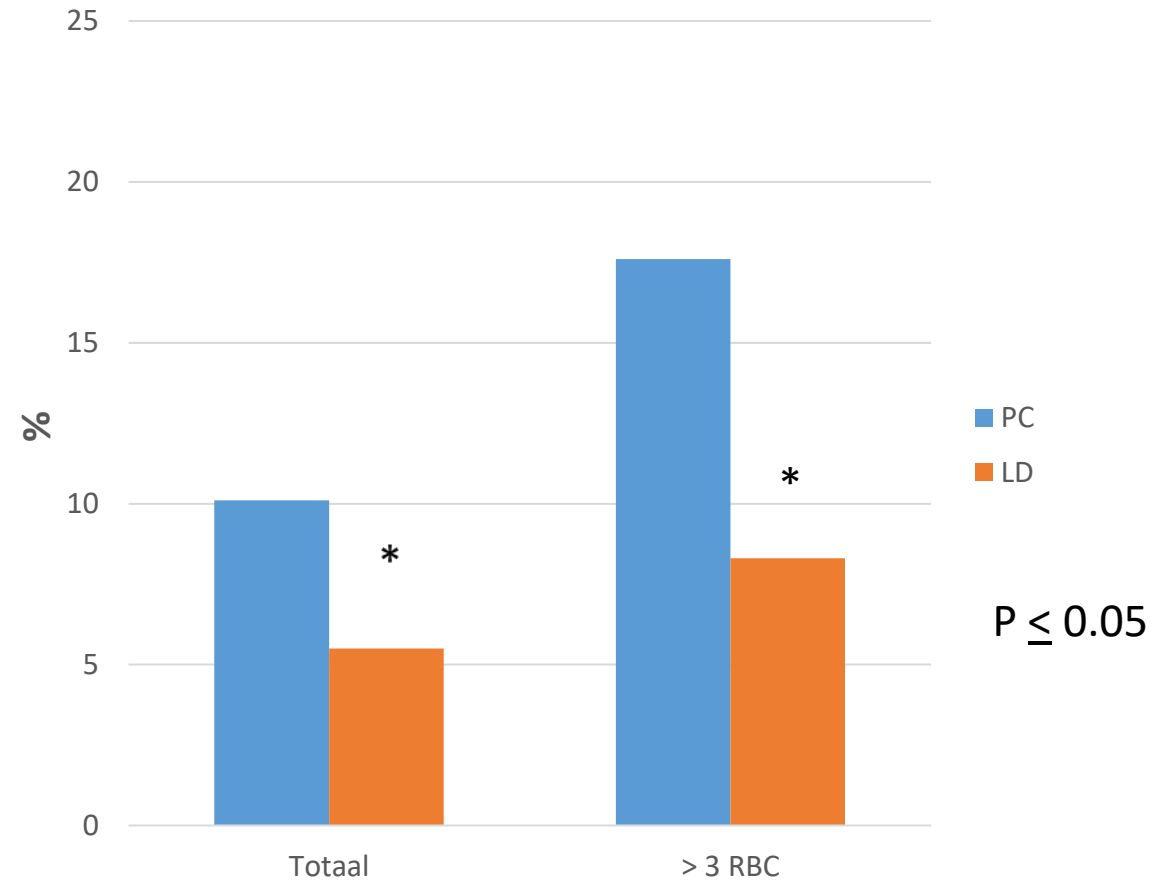


Mortaliteit na klep-chirurgie +/- CABG

Sterfte op dag 90

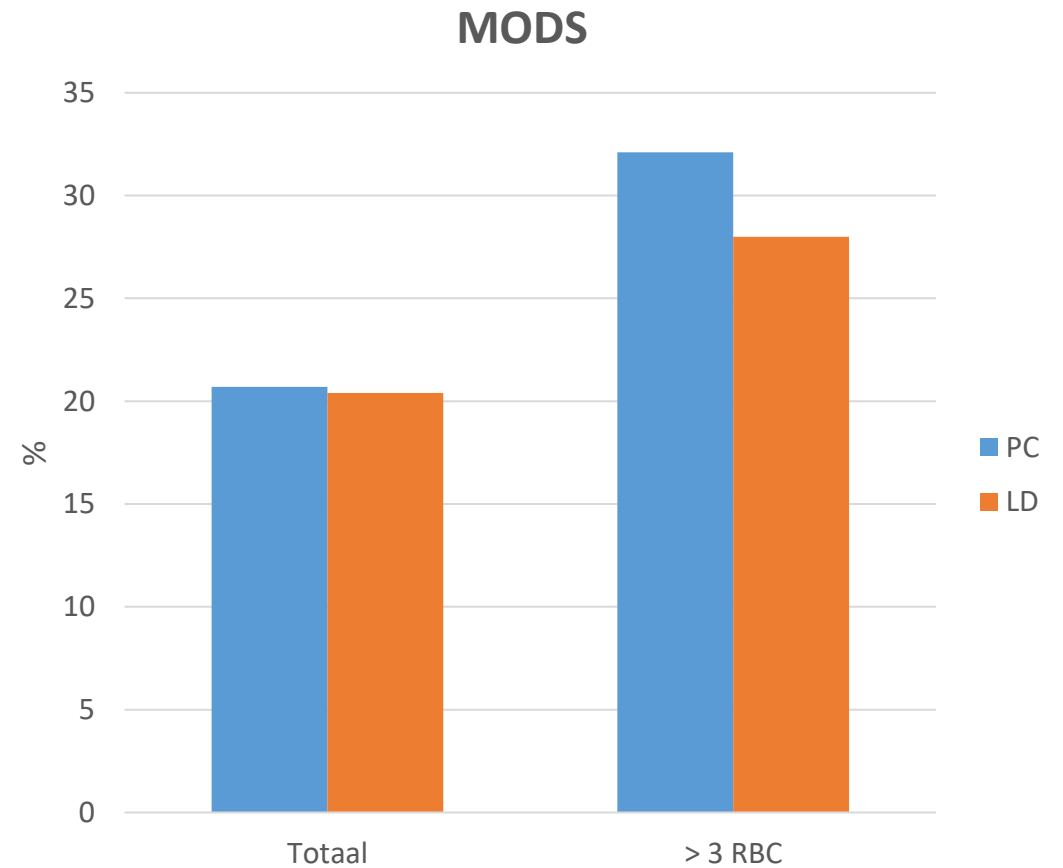
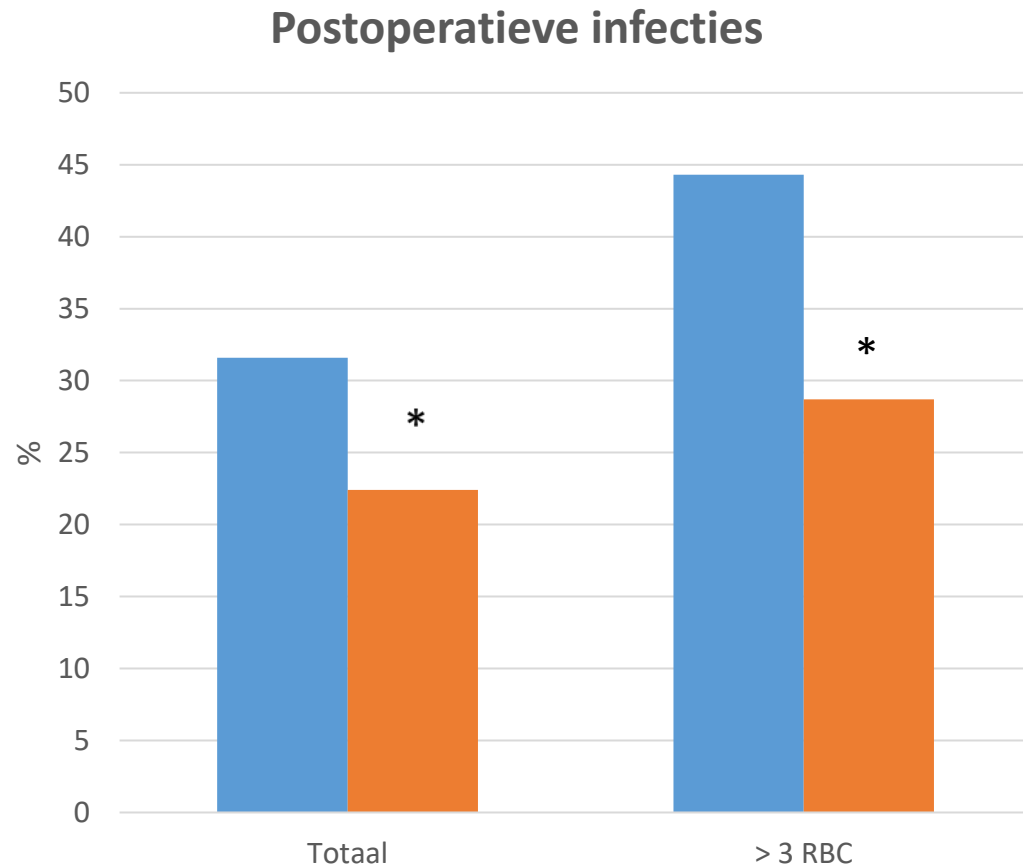


Sterfte in ziekenhuis



Circulation 2004

Infecties en MODS na klep-chirurgie +/- CABG



Waarom is er een verschil in complicaties?

- Beide studies (LAL+Klep)
- N= 1085 patienten
- Soort infecties
- Doodsoorzaken

Transfusion Medicine, 2007, 17, 304–311

doi: 10.1111/j.1365-3148.2007.00746.x

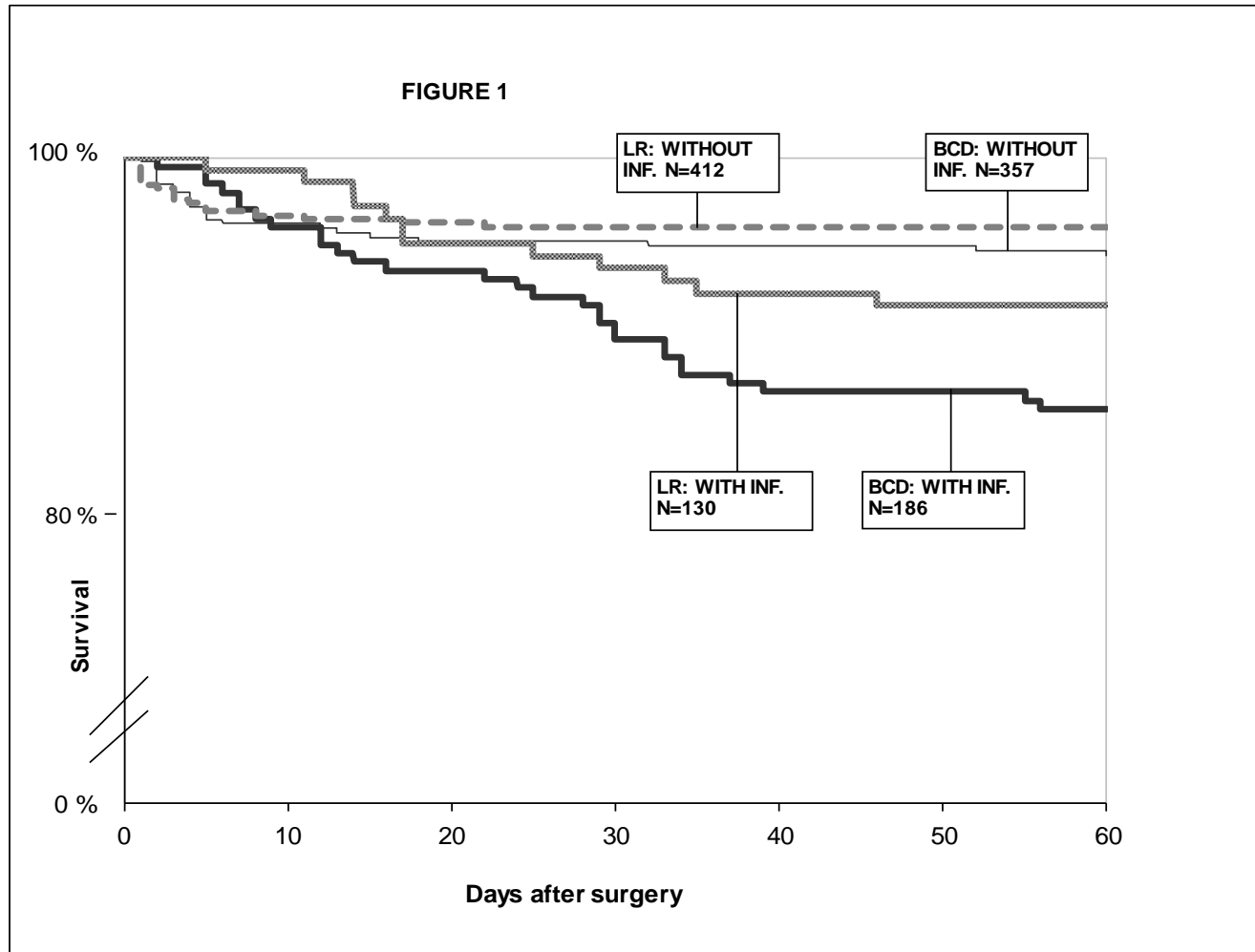
ORIGINAL ARTICLE

Is increased mortality associated with post-operative infections after leukocytes containing red blood cell transfusions in cardiac surgery? An extended analysis

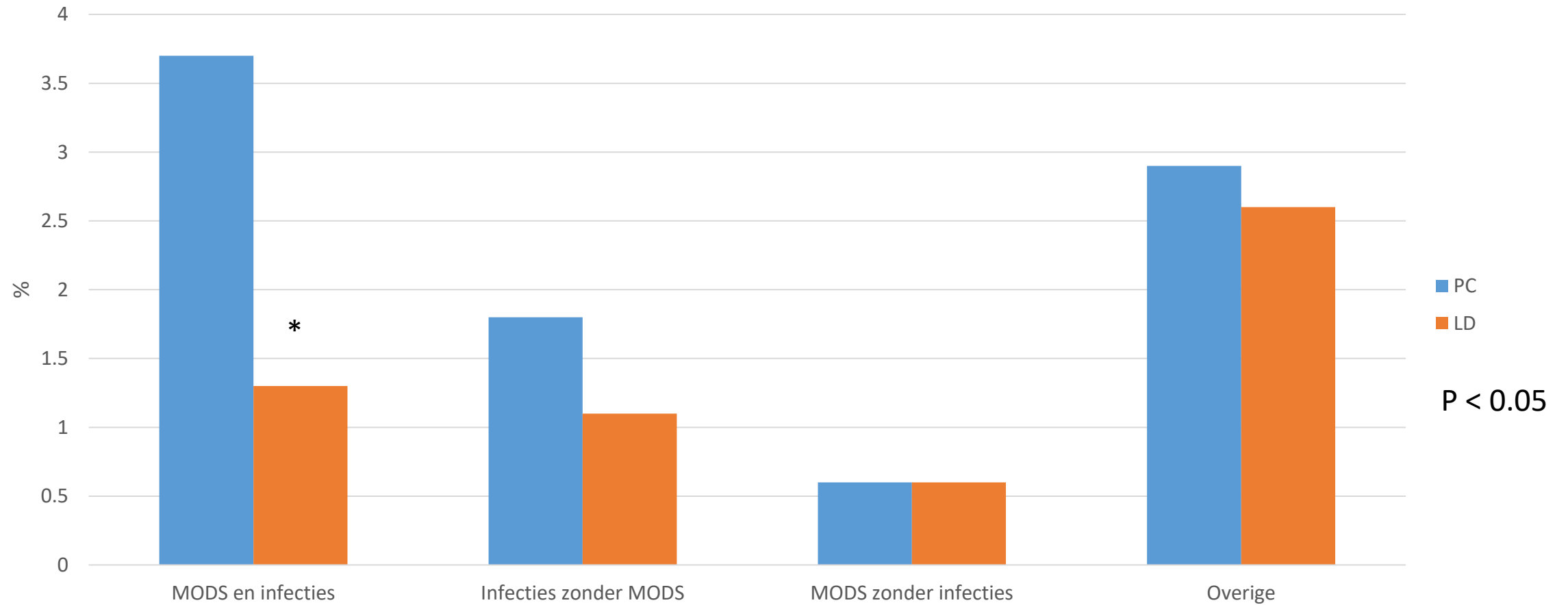
Y. M. Bilgin,*† L. M. G. van de Watering,‡ L. Eijssman,§ M. I. M. Versteegh,¶ M. H. J. van Oers* & A. Brand†‡
**Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands, †Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands, ‡Sanquin Blood Bank Southwest Region, Leiden, The Netherlands, §Department of Cardiothoracic Surgery, Academic Medical Center, Amsterdam, The Netherlands, and ¶Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands*

Received 18 October 2006; accepted for publication 22 January 2007

Met infecties: meer sterfte in PC groep



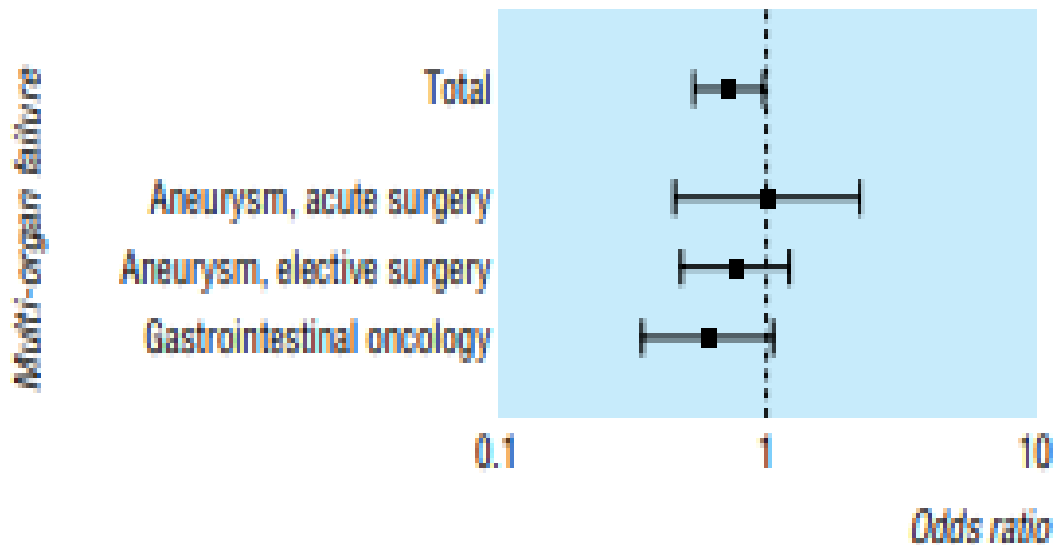
Oorzaken van sterfte



Hoe zit dat bij andere grote operaties?

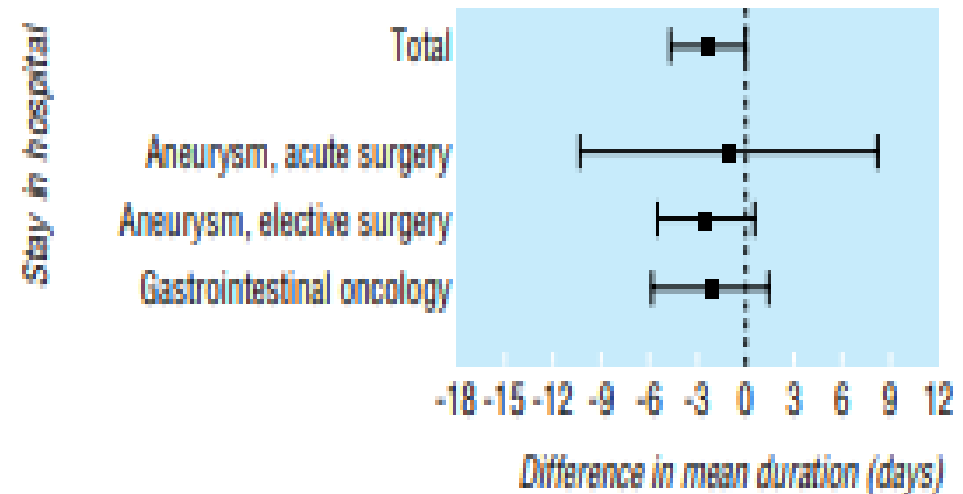
Effects of transfusion with red cells filtered to remove leucocytes: randomised controlled trial in patients undergoing major surgery

Joost A van Hilten, Leo M G van de Watering, J Hajo van Bockel, Cornelis J H van de Velde, Job Kievit, Ronald Brand, Wilbert B van den Hout, Robert H Geelkerken, Rudi M H Roumen, Ronald M J Wesselink, Ankie W M M Koopman-van Gemert, Jan Koning, Anneke Brand for Tactics (transfusion associated complications study)



MODS: 30% reductie in LD groep

- 19 ziekenhuizen in NL
- Aneurysma en gastro-intestinale kanker operaties
- N=1051
- 545 (52%) patienten kregen een transfusie
- Mediaan 4 (2-6) RBC's
- 254 (24%) patienten ≥ 4 eenheden RBC's



2.4 dagen minder ziekenhuisopname in LD groep

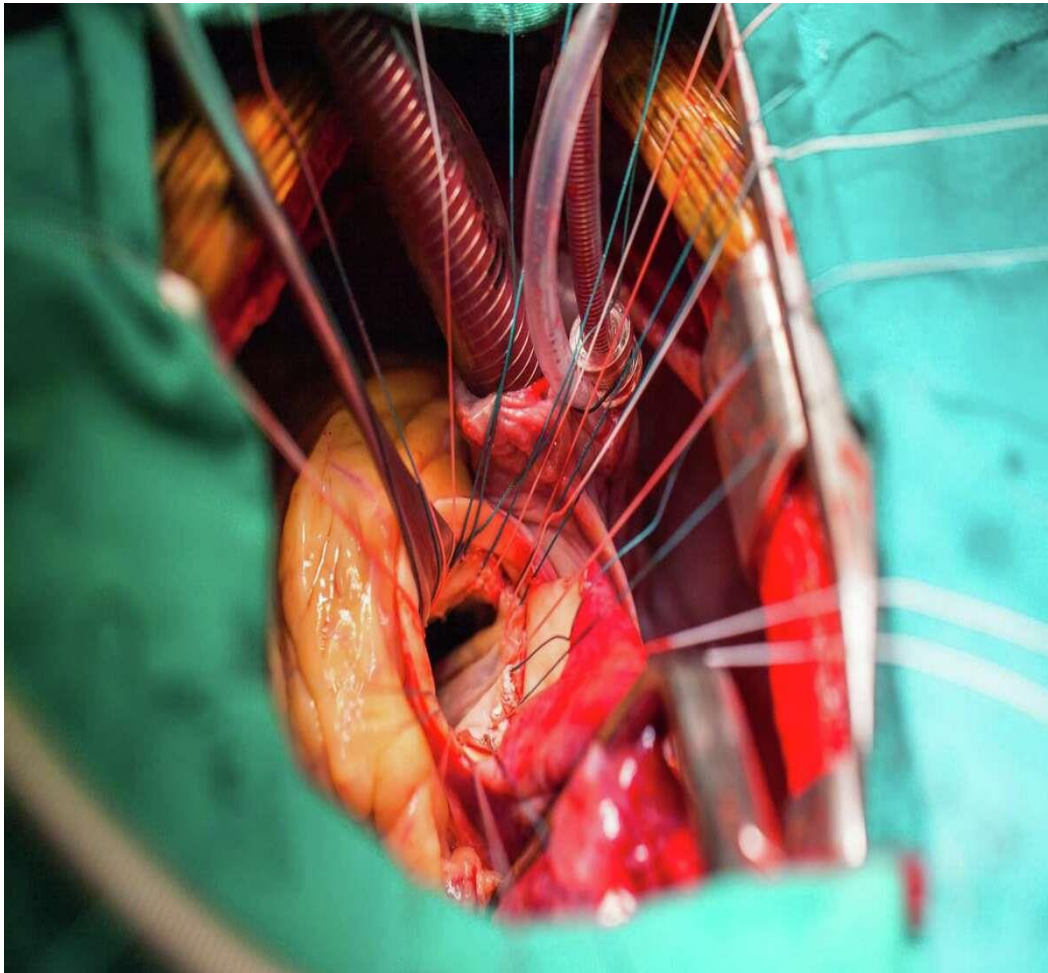
Mechanisme(n) TRIM ?

- Universele leukodepletie: 2001
- Geen nieuwe RCT's meer mogelijk

→ *Op zoek naar oorzaken TRIM*



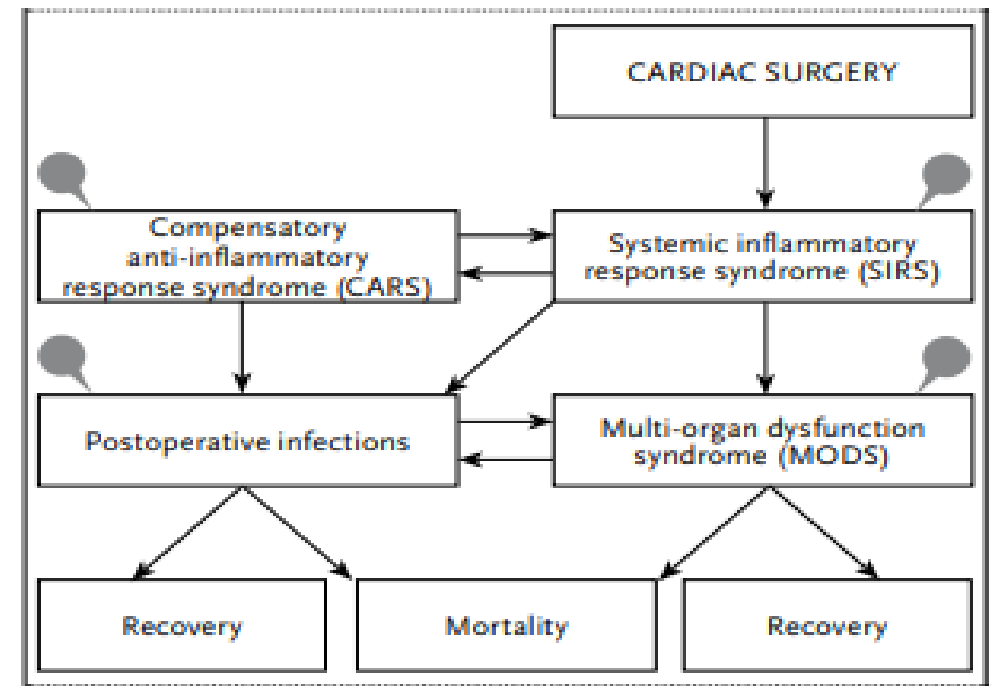
TRIM-effect vooral bij hartchirurgie ?



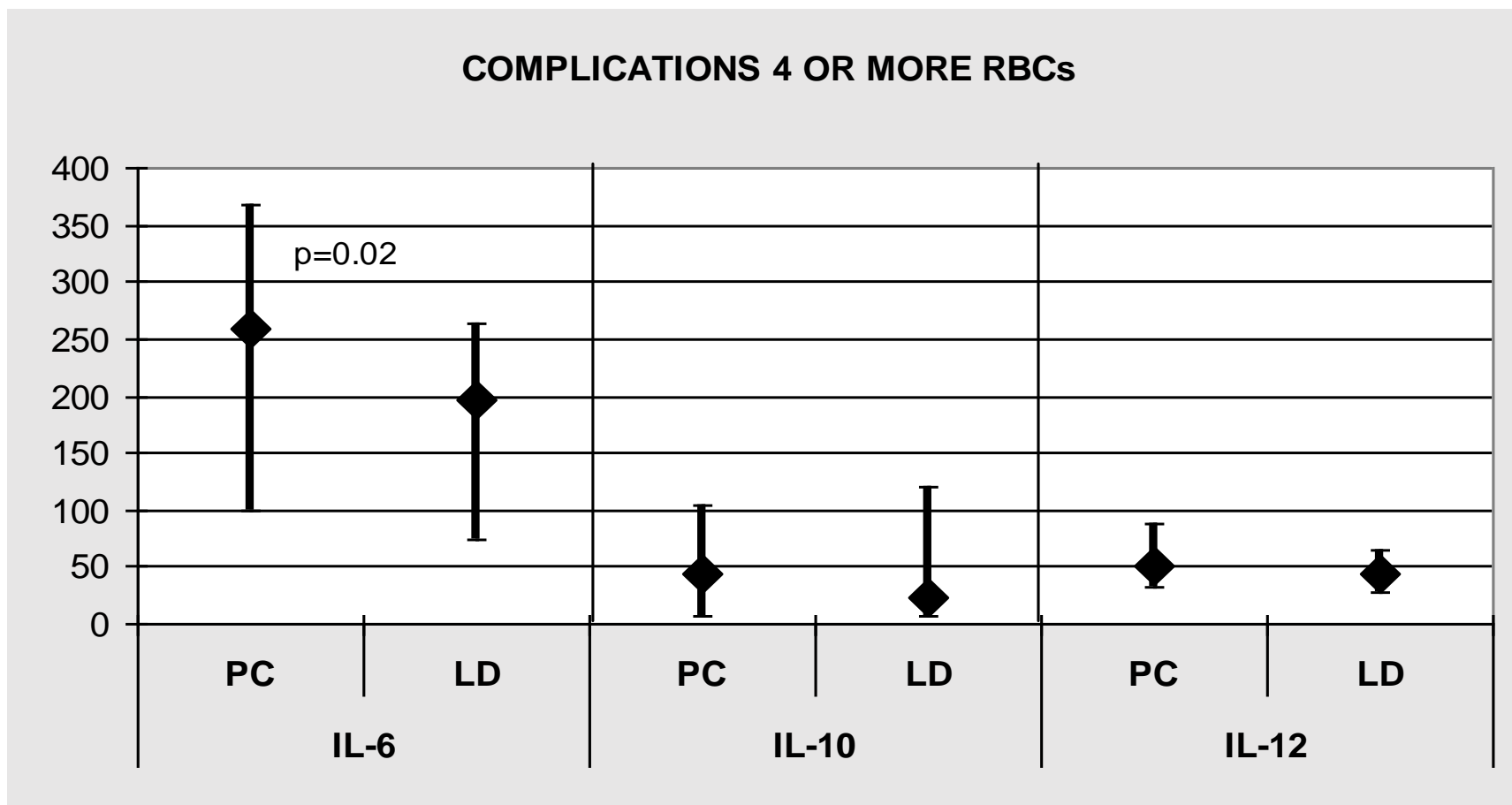
REVIEW

Transfusion-related immunomodulation: a second hit in an inflammatory cascade?

Y. M. Bilgin & A. Brand



Mediators bij aankomst op IC



Cytokines:

Pro-inflammatoir: IL-6, IL-12

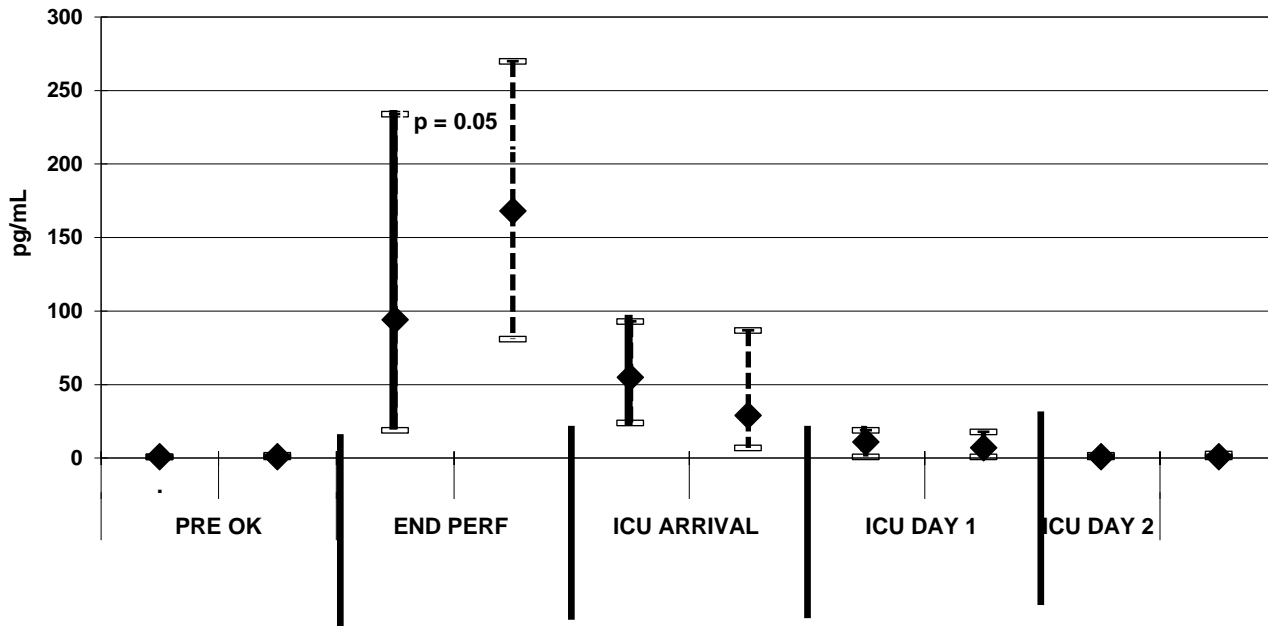
Anti-inflammatoir: IL-10

dank aan Jos Lorinser

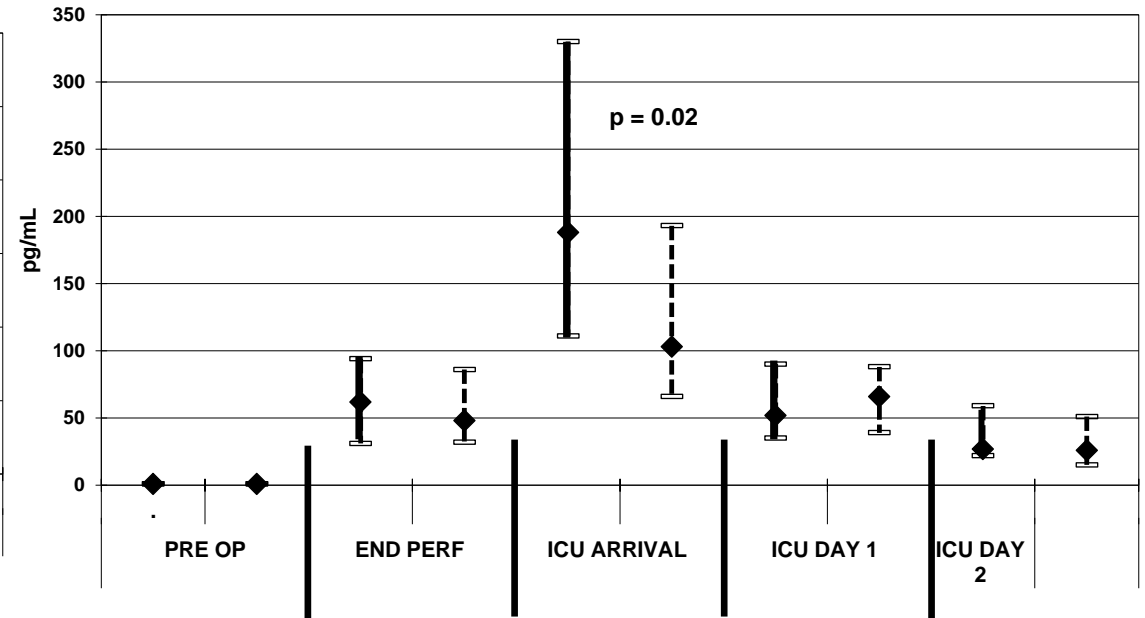
Crit Care Med 2011

Beloop van IL-10 en IL-6 na OK en op IC

IL-10 concentrations during ICU-stay



IL-6 concentrations during ICU-stay




LD: ---
PC: ____

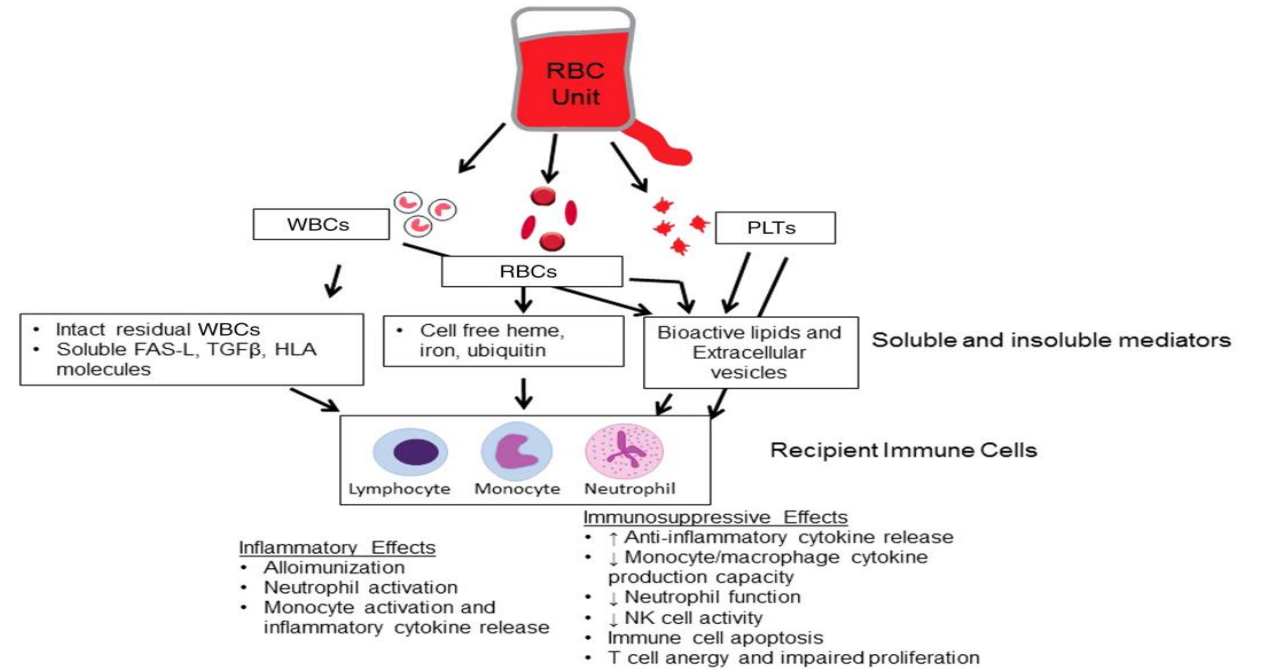
Anno 2022

- Allogene leukocyten: **XX**
- Nog steeds TRIM-effect aanwezig



Mechanisms of red blood cell transfusion-related immunomodulation

Kenneth E. Remy,¹ Mark W. Hall,^{2,3} Jill Cholette,⁴ Nicole P. Juffermans,⁵ Kathleen Nicol,⁶ Allan Doctor,¹ Neil Blumberg,⁷ Philip C. Spinella,¹ Philip J. Norris ,^{8,9} Mary K. Dahmer,¹⁰ Jennifer A. Muszynski,^{2,3} for the Pediatric Critical Care Blood Research Network (Blood Net)



Effecten van plasma-en trombocytentransfusie?

Postoperative complications associated with transfusion of platelets and plasma in cardiac surgery

Yavuz M. Bilgin, Leo M.G. van de Watering, Michel I.M. Versteegh, Marinus H.J. van Oers, Eleftherios C. Vamvakas, and Anneke Brand

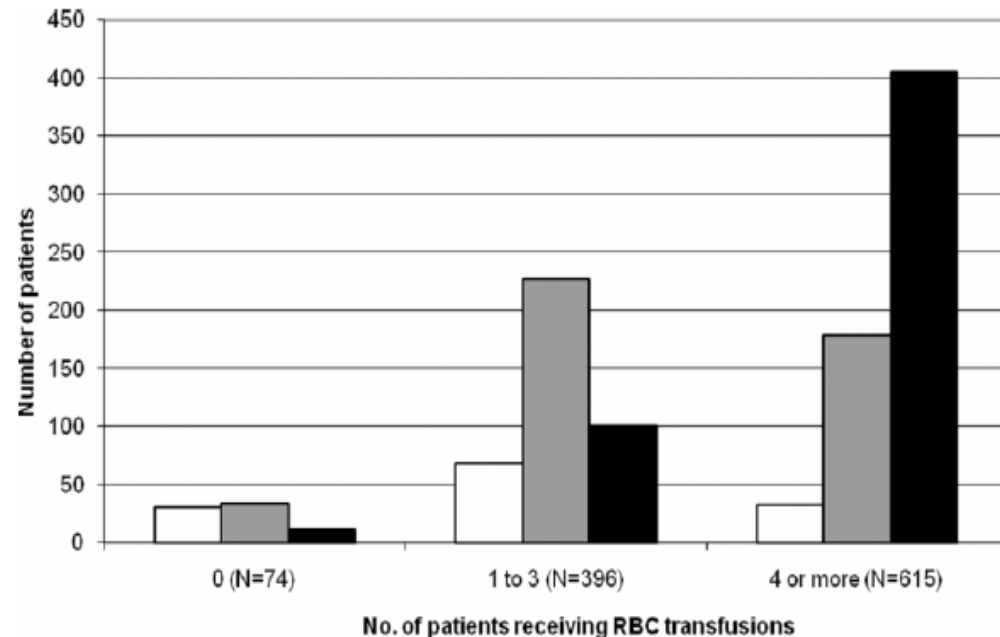


Fig. 1. Distribution of number of patients receiving RBC transfusions (0 [□], 1-3 [■], or ≥4 [■] units) with plasma transfusions (0, 1-3, or ≥4 units).

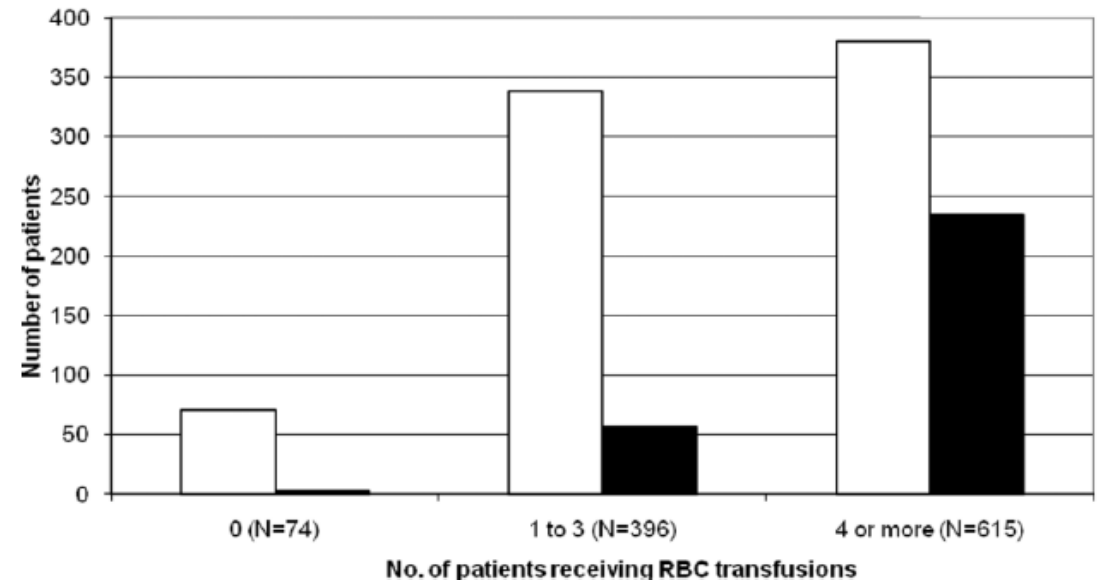


Fig. 2. Distribution of number of patients receiving RBC transfusions (0, 1-3, or ≥4 units) with (■) or without (□) PLT transfusions.

Multivariate analyse : sterfte

TABLE 5. Results of multivariate analyses (MVA) for overall mortality and deaths occurring in the presence (or absence) of infections

Risk factors	Mortality			Mortality with infection			Mortality without infection		
	MVA OR	MVA 95% CI	p value	MVA OR	MVA 95% CI	p value	MVA OR	MVA 95% CI	p value
Study (first/second)	0.61	0.31-1.22	0.16	0.66	0.26-1.64	0.37	0.60	0.24-1.49	0.27
Age (years)	1.05	1.02-1.08	0.003	1.07	1.02-1.11	0.01	1.02	0.99-1.06	0.18
Sex (male/female)	1.55	0.90-2.66	0.12	1.41	0.67-2.94	0.37	1.87	0.90-3.88	0.10
Type of surgery (CABG/valve/both)	1.30	0.86-1.98	0.22	1.31	0.75-2.29	0.34	1.26	0.73-2.19	0.41
Cardiopulmonary bypass time (hr)	1.39	1.08-1.78	0.01	1.15	0.82-1.61	0.42	1.80	1.34-2.43	<0.001
Number of RBC transfusions	0.99	0.94-1.06	0.84	1.05	0.98-1.12	0.15	0.93	0.84-1.02	0.11
Randomization arm (BCD/LD)	1.80	1.04-3.13	0.04	2.12	1.01-4.58	0.05	1.36	0.70-2.77	0.40
Number of PLT transfusions	1.37	1.12-1.68	0.002	1.29	1.03-1.61	0.03	1.14	0.93-1.41	0.22
Number of plasma transfusions	1.14	1.06-1.23	<0.001	1.11	1.01-1.21	0.02	1.10	1.01-1.21	0.04

- **Mortaliteit met infecties ($p < 0.05$):**

- Randomisatie (LD/PC)
- Aantal trombo transfusies
- Aantal plasma transfusies

- **Mortaliteit zonder infecties ($p < 0.05$):**

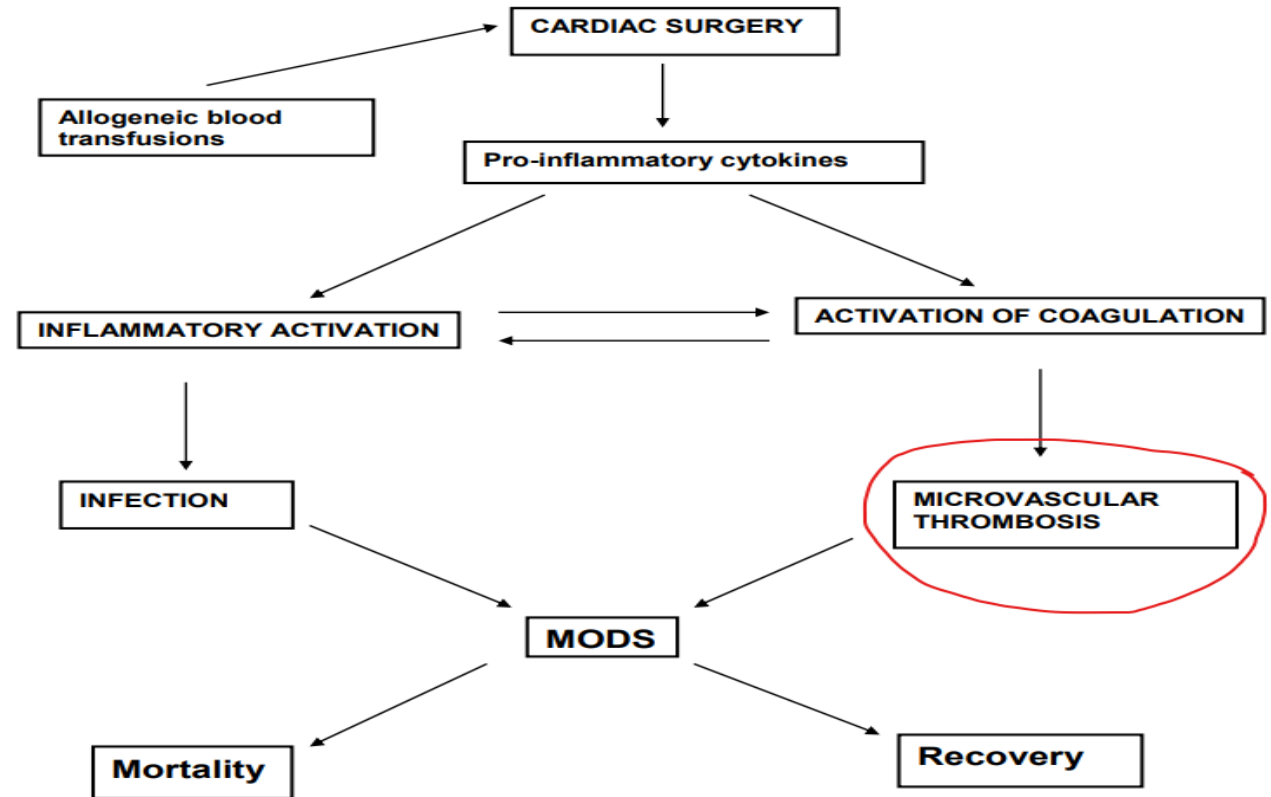
- Aantal plasma transfusies
- CPB tijd

TRIM: NOT FINISHED YET

- TRIM: multifactorieel
- “Second hit” of meerdere hit’s ?
- Effect op coagulatie ?
- Interactie coagulatie – inflammatie ?



FIGURE 2 RELATION BETWEEN ALLOGENEIC BLOOD TRANSFUSIONS, INFLAMMATION AND COAGULATION



Stolling-markers na transfusie (1)

Tuinman et al. *Critical Care* 2011, **15**:R59
<http://ccforum.com/content/15/1/R59>

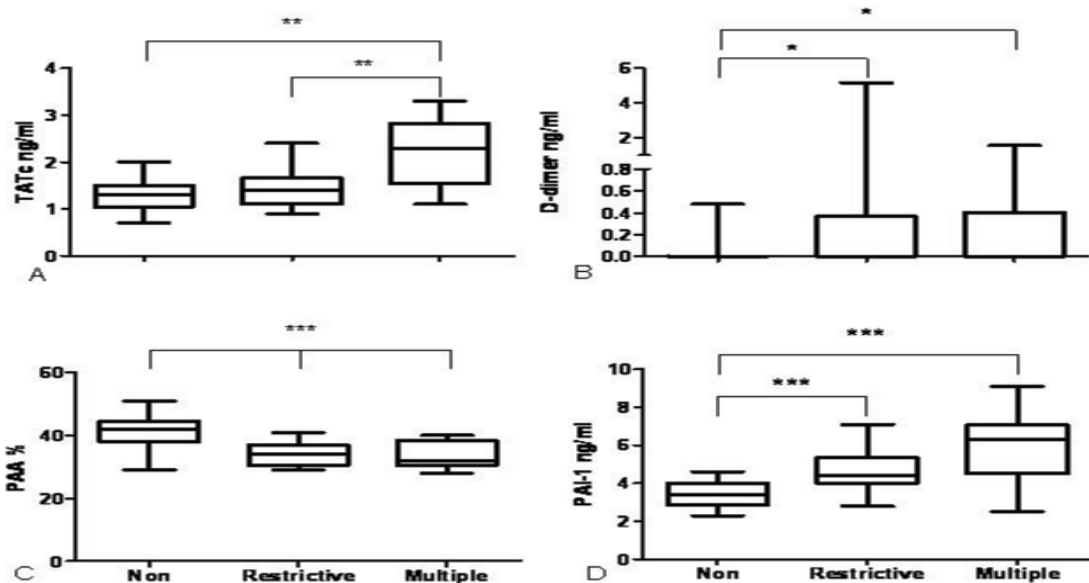


RESEARCH

Open Access

Blood transfusion during cardiac surgery is associated with inflammation and coagulation in the lung: a case control study

Pieter R Tuinman^{1*}, Alexander P Vlaar¹, Alexander D Cornet⁴, Jorrit J Hofstra¹, Marcel Levi², Joost CM Meijers³, Albertus Beishuizen⁴, Marcus J Schultz¹, AB Johan Groeneveld⁴, Nicole P Juffermans¹



Na (multi)pele RBC transfusies:

- Verhoogde D-Dimeer en TATc
- PAA-1 toegenomen PAA% verlaagd

Na transfusie van RBC's:

- Activatie van coagulatie
- Verminderde fibrinolysis

Stolling-markers na transfusie (2)

ORIGINAL ARTICLE

Vox Sanguinis 2021

Effect of red blood cell transfusion on inflammation, endothelial cell activation and coagulation in the critically ill

Lisa van Manen^{1,2} | Maïke E. van Hezel^{1,2} | Margit Boshuizen^{1,2} |
Marleen Straat¹ | Angelique M. E. de Man³ | Charlotte Dekimpe⁴ |
Karen Vanhoorelbeke⁴ | Robin van Bruggen² | Nicole P. Juffermans^{1,5}

- Inflammatie en coagulatie hoog op IC
- Stijging van vWF 24 u na RBC bij sepsis op IC

TABLE 3 Level of biomarkers of endothelial cell activation and inflammation before transfusion, within hour after transfusion and 24 h after transfusion

Biomarker	Reference value	Before transfusion median (IQR)	1 h after transfusion median (IQR)	24 h after transfusion median (IQR)	p-value
vWF ag (%)	50%-150%	478 (338-597)	481 (348-614)	526 (395-623)	0.009
ADAMTS13 ag (%)	50%-150%	40.4 (31.8-53.6)	43.9 (31.7-54.7)	40.8 (31.4-52.2)	0.06
vWF/ADAMTS13 ratio		11.6 (7.2-18.0)	11.7 (7.0-18.1)	12.1 (8.4-17.2)	0.98
sICAM-1 (ng/ml)	60-218	462 (324-605)	448 (334-601)	453 (337-609)	0.83
sTM (ng/ml)	0.5-5.7	7.6 (5.9-11.3)	7.6 (5.4-11.2)	7.5 (5.2-11.1)	0.26
Syndecan-1 (ng/ml)	50-100	2.9 (2.3-3.6)	2.9 (2.3-3.7)	2.9 (2.1-3.7)	0.94
TNFa (pg/ml)	0-16	11.5 (9-15.3)	12 (8.7-16)	12.5 (9-14.8)	0.09
IL-6 (pg/ml)	5-15	46.2 (18.2-75.3)	43.3 (18.1-71.4)	35.2 (18.2-64.4)	0.32

→ Toename (bestaande) endotheel-activatie tgv RBC transfusie

Transfusie en trombose bij hartchirurgie?

Thrombosis Research 136 (2015) 1204–1210



Contents lists available at ScienceDirect

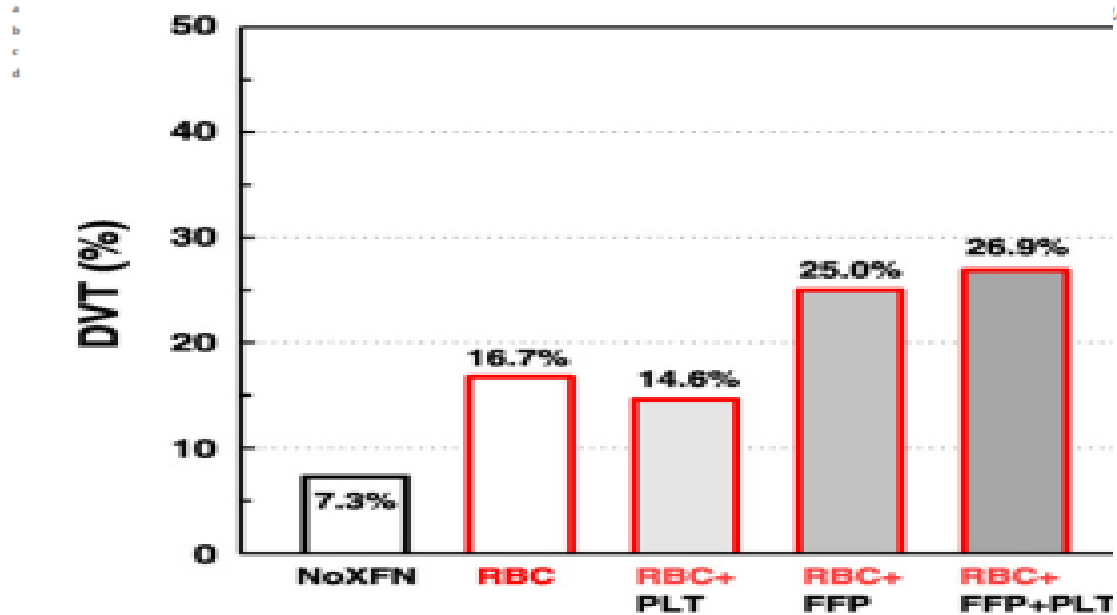
Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Role of blood transfusion product type and amount in deep vein thrombosis after cardiac surgery☆

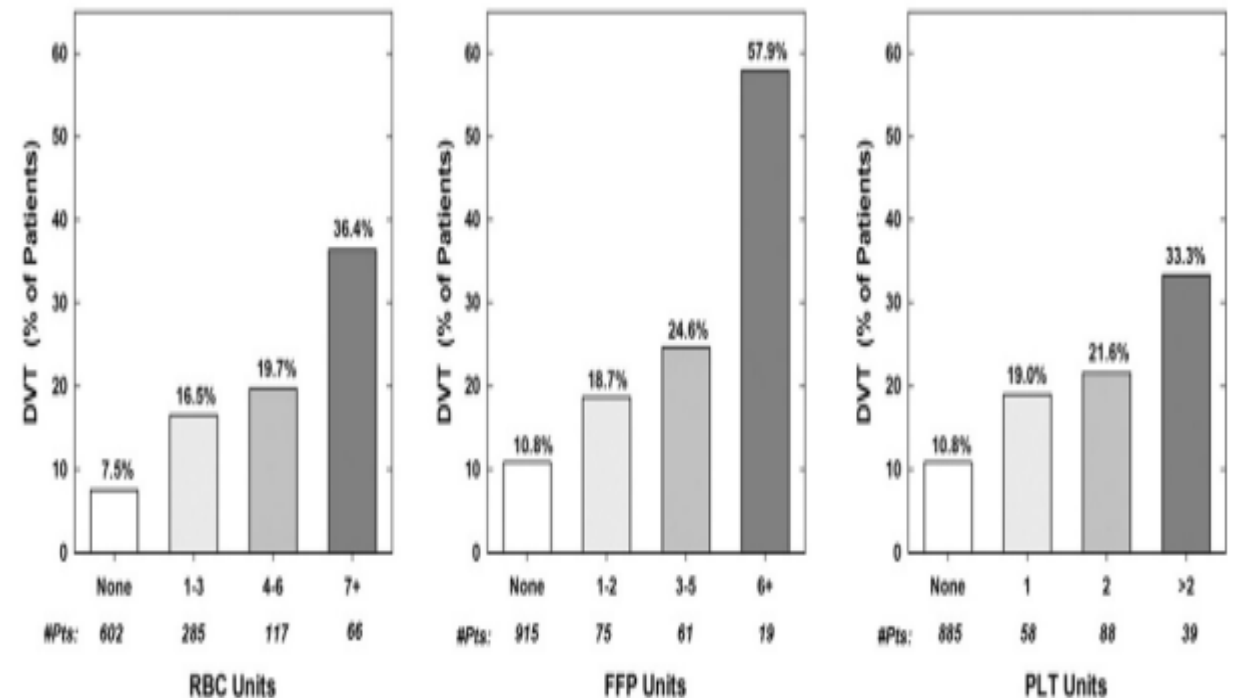
Lama Ghazi ^a, Thomas A. Schwann ^b, Milo C. Engoren ^{c,d}, Robert H. Habib ^{a,*}



- N= 1070 patienten
- 139 (13%) patienten DVT

L. Ghazi et al. / Thrombosis Research 136 (2015) 1204–1210

121



CONCLUSIE

- *Anno 2022 TRIM-effect: nog niet opgehelderd*
- *Allogene leukocyten: belangrijke factor bij TRIM-effect bij hartchirurgie*
- *“Second-hit” model ?*
- *Meerdere hit’s aanwezig ?*
- *Effect transfusie op inflammatie maar ook op coagulatie-systeem ?*



CONCLUSIE

- *Anno 2022 TRIM-effect: nog niet opgehelderd*
- *Allogene leukocyten: belangrijke factor bij TRIM-effect bij hartchirurgie*
- *“Second-hit” model ?*
- *Meerdere hit's aanwezig ?*
- *Effect transfusie op inflammatie maar ook op coagulatie-systeem ?*



TRIM vervangen door TRIC (Transfusion-related inflammation and coagulation) ???

“Het is beter een genie te zijn uit liefde dan om kwart voor drie”

Leo Vroman

Uit proefschrift van Anneke Brand (1979)

