

Transfusion Medicine: 2008 Retrospective



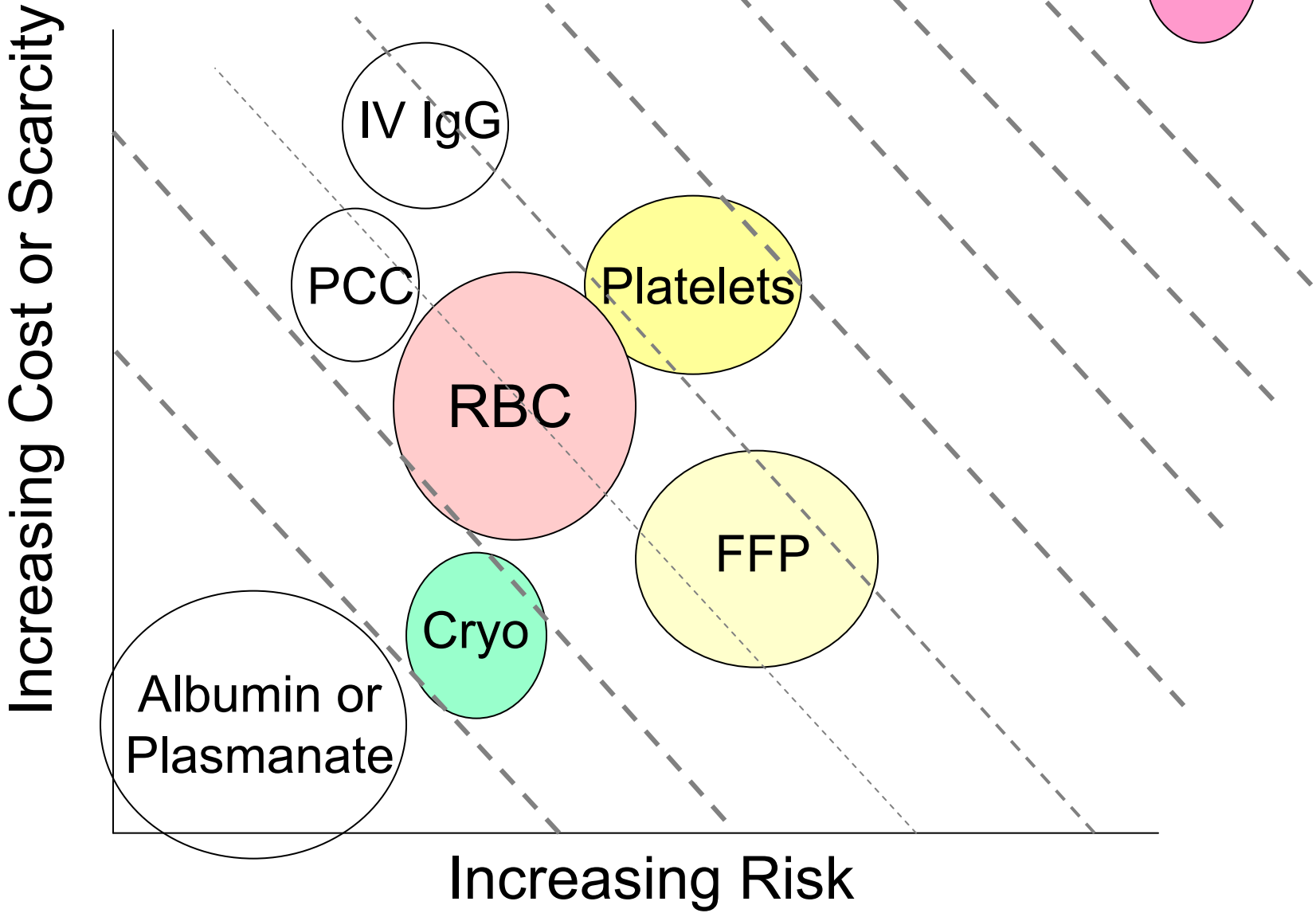
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Massachusetts General Hospital
Boston, MA

Topics for Today...

1. A new RCT on recombinant 7a as a rescue therapy for bleeding.
2. Hemoglobin-based RBC substitutes: where are they?
3. The “news” about fresh blood.

Which Blood Products Should We Audit ?

r7a



With thanks to Jeannie Callum, MD & Christine Cserti-Gazdewich, MD

Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial

Jaime Bosch, Dominique Thabut, Agustin Albillos, et al.

Hepatology 2008; 47: 1604-14.

Background for the r7a trial

- Among commonly treated illnesses, the lowest levels of factor 7 are found in advanced cirrhosis.
- UGI bleeding in cirrhosis carries high mortality and a “rescue” therapy is needed.
- In 2004, a multicenter RCT of r7a for the treatment of UGI bleeding in cirrhosis failed to demonstrate benefit, but in post-hoc analysis, the subgroup of patients with the most severe cirrhosis (Childs B & C) had statistically better outcomes in the r7a group.
- To explore this 2004 sub-group finding, a prospective RCT was organized that focused ONLY on patients with advanced cirrhosis.

The 2008 r7a RCT

Double-blind, RCT, in 31 hospitals and 12 nations.
Sponsored by NovoNordisk

Acute UGI bleed / cirrhosis and Child's B or C

Meet inclusion criteria and not multiple exclusion criteria

Placebo drug in identical packaging at time 0, 2, 8, 14 & 20 hours post endoscopy.

600 ug/kg r7a
(200 @ t=0 plus 4x 100 ug/kg at hours 2,8,14 & 20 post endoscopy.

300 ug/kg r7a
(200 @ t=0 plus 1x 100 ug/kg plus 3x placebo at same times post endoscopy.

Full standard Rx: somatostatin, vasopressin, antibiotics, transfusions, etc.

Outcome: failure to control bleeding in 24 hrs; re-bleed, death within 5 days.

Inclusion criteria

- Child's score ≥ 8
- Endoscopy shows active variceal bleeding
- Endoscopy within 6 hrs of ER admit
- First drug/placebo within 1 hr of endoscopy

Exclusion criteria

- Recent band ligation or sclerotherapy
- Unstable angina
- Peripheral vascular disease
- History of PE
- Known prior MI or stroke
- EKG evidence of cardiac ischemia
- DVT or portal vein thrombosis within 6 mos
- History of recurrent DVTs
- Advanced hepatocellular CA
- Pregnancy
- Known thrombogenic disorder
- Planned use of antifibrinolytic
- Planned use of dialysis or hemofiltration.

RCT of r7a: Sample size

- Based on the 2004 trial, the study was powered to allow detection of a 50% reduction (from 40% to 20%) in primary outcome:
 - Continued bleeding;
 - Re-bleed;
 - Death in first 5 days.
- ...with a power of 87% and a significance of 0.05.
- Two interim analyses were planned. After the first analysis, a “stop the trial” signal (based on futility) was obtained but “not communicated” to the study sponsor.
- The study continued to complete the planned enrollment of 258 patients.
- The primary comparison was Placebo vs 600 ug/kg

As expected from randomization, the groups were comparable

	Placebo n=86	600 ug/kg n= 85	300 ug/kg n=85
Age	54	55	55
Child's score (median)	10.5	11	10
INR	2.01 ± 0.52	2.04 ± 0.79	2.08 ± 0.86
Meld	18.5	17.4	18.0
Hct / Platelet	24 / 112,000	25 / 107,000	27 / 92,000
Oozing	72%	67%	69%
Spurting	28%	33%	31%

Results

	Placebo n=86	600 ug/kg n= 85	Odds ratio	P- value
Failure to stop bleed in 24 hrs	9%	9%	1.05 (0.36-3.07)	1.0
Re-bleeding	9%	4%	0.33 (0.08-1.42)	0.26
Death within 5 days	13%	12%	0.69 (0.24-1.95)	0.22
Failure on composite primary endpoint	23%	20%	0.8	0.37

Adverse events observed– no sig difference

	Placebo n=89	600 ug/kg n= 88	300 ug/kg n=88
Serious	44%	34%	47%
Fatal	34%	19%	35%
Arterial / MI	0	1	2
Venous	7	4	2

Change in INR

	Placebo n=89	600 ug/kg n= 88	300 ug/kg n=88
Baseline	2.01	2.04	2.08
At 24 hours	2.1	1.3	1.5

Author's conclusions from 2008 RCT of r7a

- There was no significant effect of treatment with 600 ug/kg of r7a compared with placebo on the composite endpoint.
- The overall incidence of adverse events were similar between the treatment groups.
- Rx with r7a had no notable effect on any of the coagulation-related safety parameters, except the INR which was lower in the r7a group, as expected.
- The trial did not confirm the findings from exploratory post-hoc analysis of the 2004 trial.

In Summary: Off-Label use of r7a

UGI bleed cirrhosis	Multicenter	n = 242	No benefit RBC use or survival
UGI bleed cirrhosis (chilids C & D)	Multicenter	n= 256	No benefit
Trauma (blunt)	Multicenter	n = 142	No benefit RBC use; survival
Trauma (penetrating)	Multicenter	n = 130	No benefit RBC use; survival
Trauma (USA)	Multicenter	n=1502 planned	Company closed for futility
Trauma (Global)	Multicenter	n= 576 planned	Company closed for futility

Off-label use of r7a (continued)

CNS bleed # 1	Multicenter	n = 399	No benefit on survival; Toxicity at doses that reduced hematoma growth
CNS bleed # 2	Multicenter	n= 841	No benefit on survival; reduced hematoma growth
Cardiac surgery	Multicenter	n = 172	Closed by company; ? Excess toxicity

Partial hepatectomy	Multicenter	n = 200	No benefit on blood loss or RBC use.
Liver txplant #1	Multicenter	n = 82	No benefit on blood loss or RBC use.
Liver txplant #2	Multicenter	n = 179	No benefit on blood loss or RBC use.
Major pelvic	Single center	n = 48	No benefit on blood loss.
Prostate	Single center	n = 36	Benefit~1-2 units RBCs

Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death

Charles Natanson, Steven Kern, Peter Lurie, Steven Banks, Sidney Wolfe

JAMA 2008; 299: 2304-12.

Cell-free hemoglobin-based RBC substitutes

Meta-analysis of 16 different trials

- Searched for all randomized trials
- 29 trials identified
- 16 excluded (health volunteers (5); duplicate reports (11))
- 13 trials analyzed
- Unpublished data from 3 other trials included.
- Mortality and myocardial infarction selected as endpoint.
- Relative risk of death or MI determined for control vs RBC-substitute.

Hemoglobin-based RBC Substitutes

Product	Company	Chemical alteration	P ₅₀ mmHg	Percent tetramer
HemAssist	Baxter	Cross-linking	32	> 99
Hemopure	Biopure	Pyridoxylation	32-38	< 5
Hemolink	Hemosol	Polymerization	34	30-40
Poly-heme	Northfield	Polymerization	26-30	< 1
Hemospan	Sangart	Pegylation	10	100

Constructing a Forest Plot

Is watching “American Idol” associated with having an MI ?

2004: 110 people randomly assigned to watch or not-watch TV.

Among 50 watching, 5 had heart attacks (10%)

Among 60 people NOT watching, 3 got heart attacks (5%)

Risk of MI (watching TV): $\frac{5}{50} = 10\%$

Risk of MI (NOT watching TV): $\frac{3}{60} = 5\%$

Relative Risk of MI (watching TV): $10\% / 5\% = \mathbf{2.0}$

Constructing a Forest Plot

2008: 1800 people randomly assigned to watch or not-watch TV.

Among 800 watching, 40 had heart attacks

Among 1000 people NOT watching, 20 got heart attacks

$$\text{Risk of MI (watching TV): } \frac{40}{800} = 5\%$$

$$\text{Risk of MI (NOT watching TV): } \frac{20}{1000} = 2\%$$

$$\text{Relative Risk of MI (watching TV): } 5\% / 2\% = \mathbf{2.5}$$

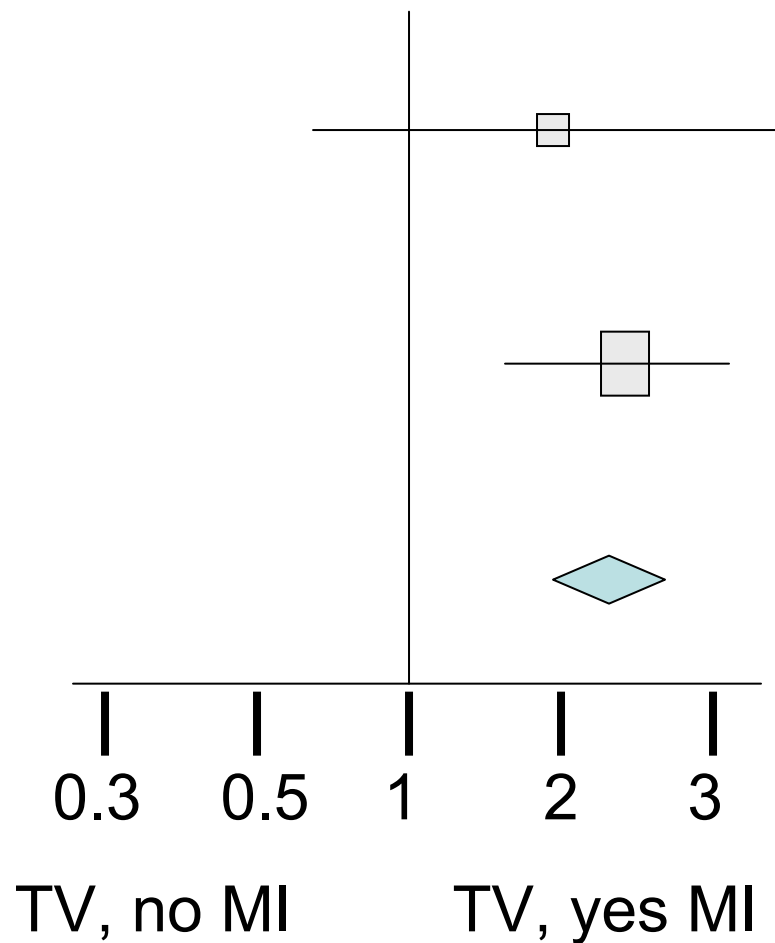
Constructing a Forest Plot

	Risk of MI (TV):	Risk of MI (NO TV):	RR
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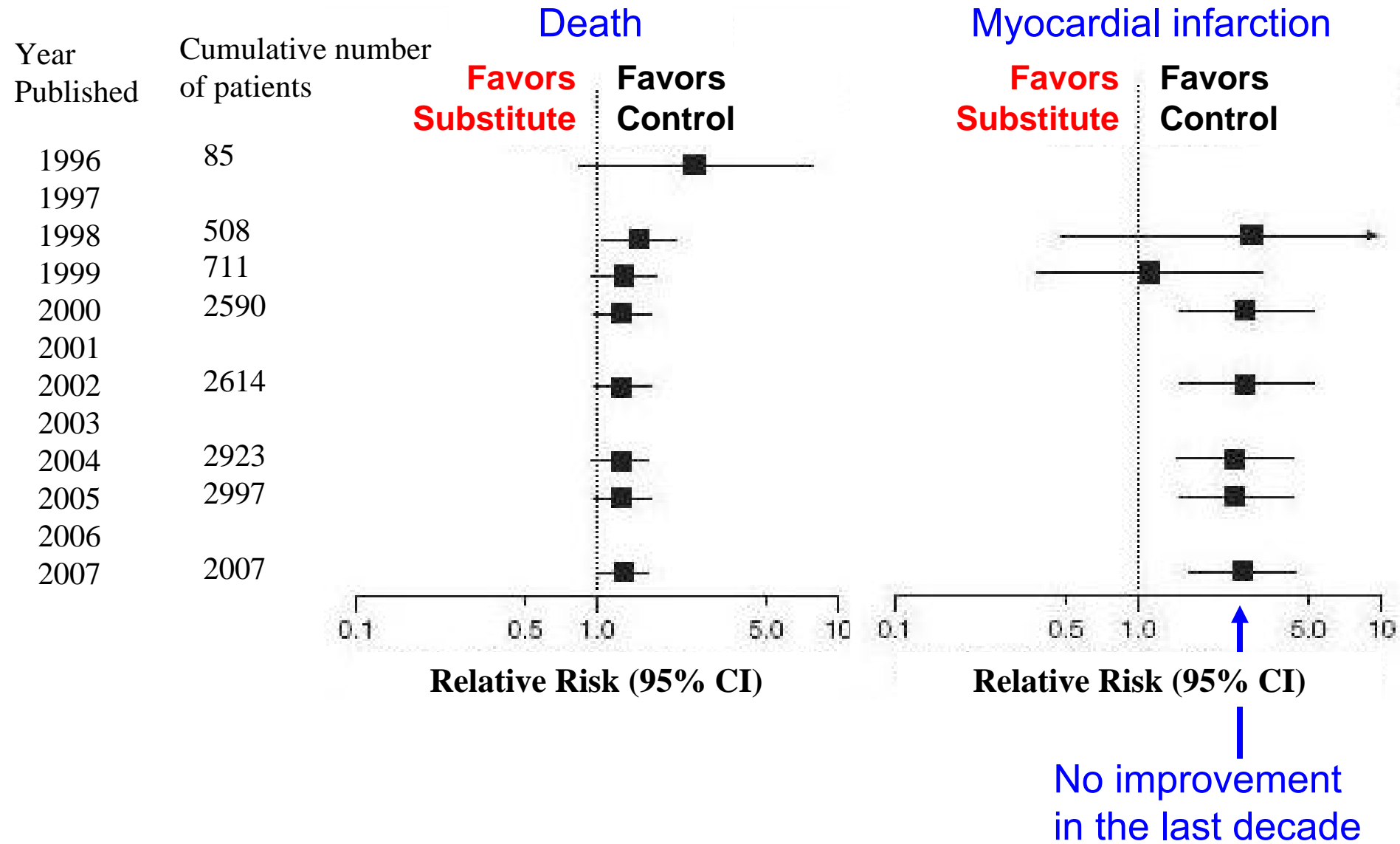
2004	$\frac{5}{50}$	$\frac{3}{60}$	2.0
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2008	$\frac{40}{800}$	$\frac{20}{1000}$	2.5
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Combined:	$\frac{45}{850}$	$\frac{23}{1060}$	2.44
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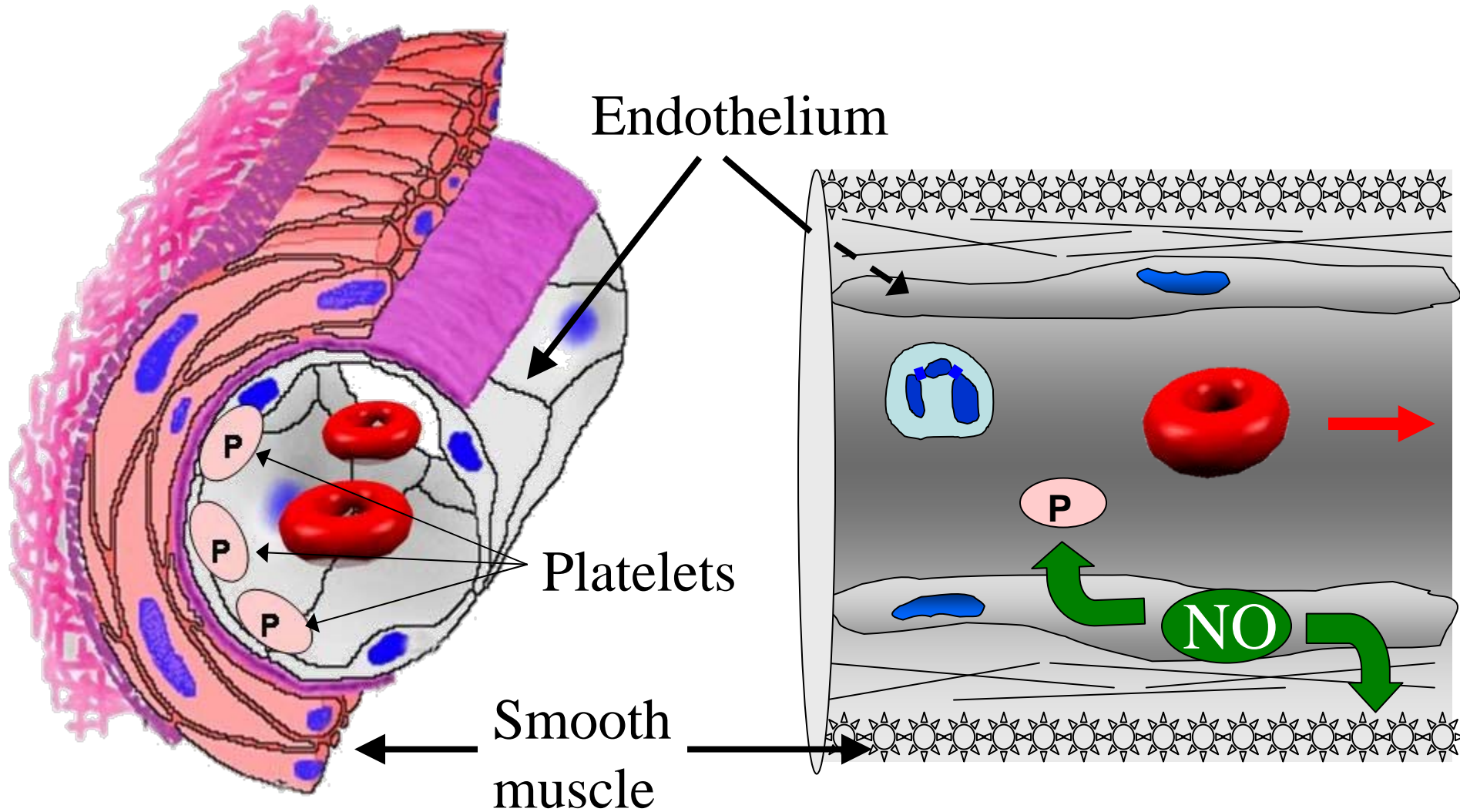
Relative Risk of Death or Myocardial Infarction over Time



Conclusions of JAMA meta-analysis

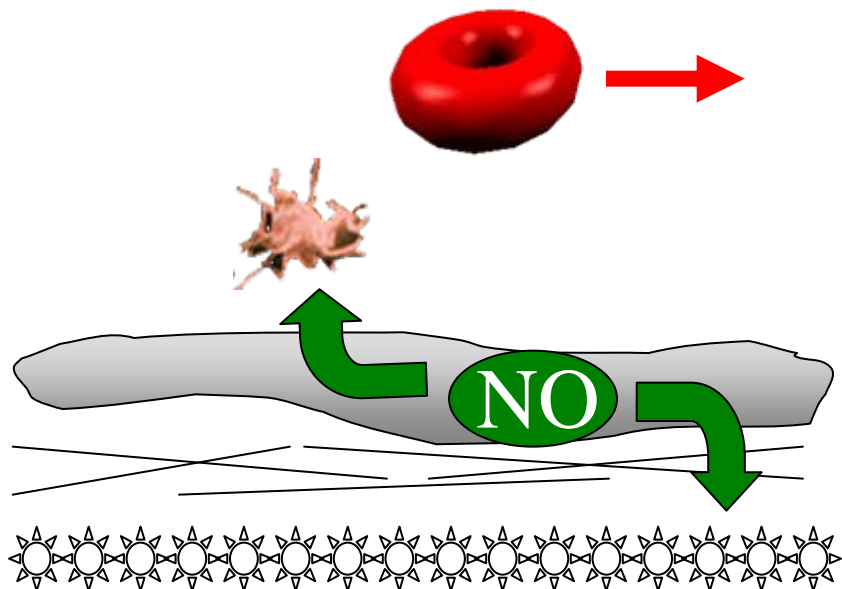
- Overall 30% increased relative risk of death
- A 2.7 *fold* increased risk of myocardial infarction
- Subgroups of patients or type of surgery (trauma, orthopedic, cardiac, stroke) showed similar results.
- Increased risks of hemoglobin-based substitutes have been consistent over time and were apparent by the year 2000.

- Nitric Oxide: 1. relaxes platelets
2. relaxes smooth muscle (vasodilates)

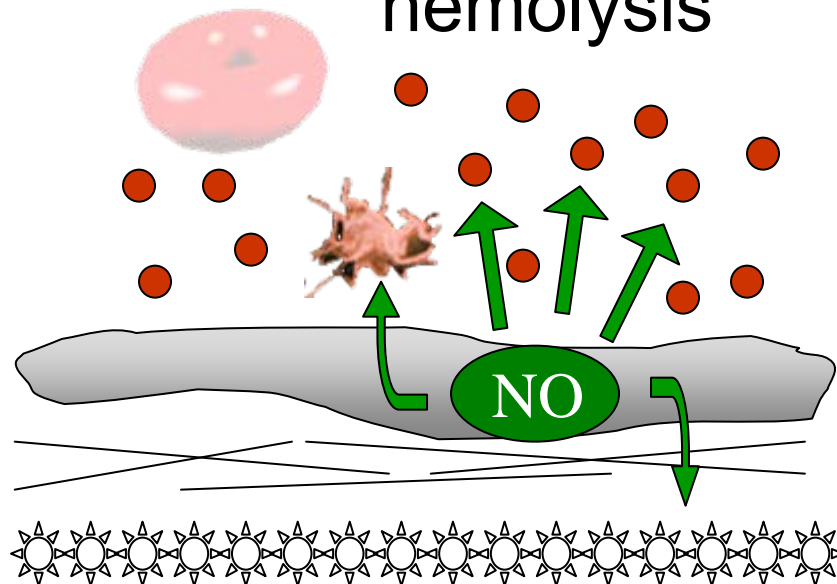


Nitric Oxide binds avidly to free hemoglobin

Normal



Intravascular hemolysis



Nitric Oxide depletion

Malaria

- Vasoconstriction & tissue ischemia
- Platelet activation
- Worsened cytoadhesion

RBC substitutes

- Renal vasoconstriction & hypertension

ABO hemolysis

Sickle cell

TTP, PNH

Others...

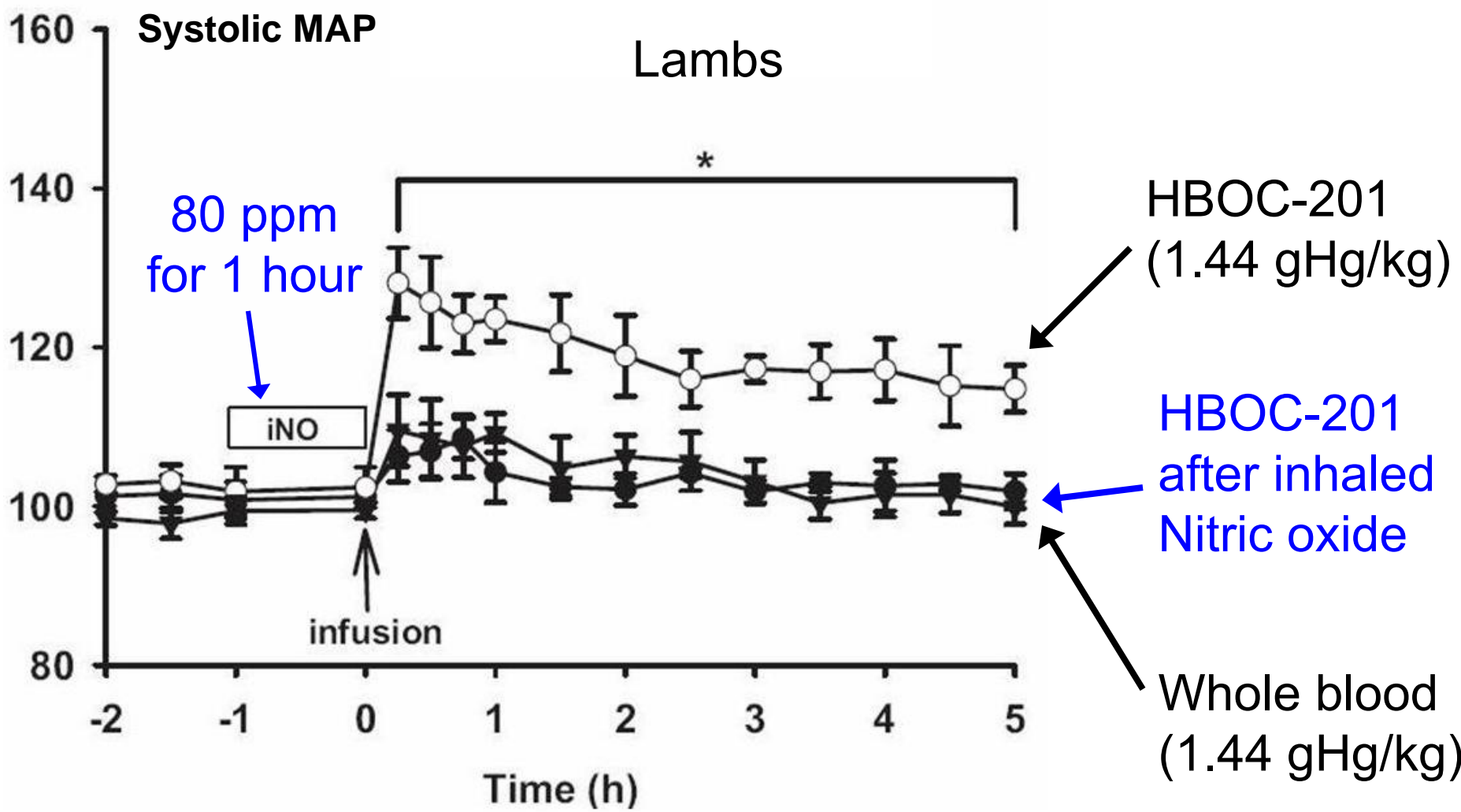
Inhaled NO enables artificial blood transfusion without hypertension

Yu B, Raher MJ, Volpato GP, Bloch KD, Ichinose F, Zapol WM.

Circulation. 2008; 117:1982-90.

Anesthesia Center for Critical Care Research of
the Department of Anesthesia and Critical Care,
Massachusetts General Hospital, Harvard
Medical School, Boston, MA 02114

Inhaled NO blocks hypertension from RBC substitute



Duration of Red-Cell Storage and Complications after Cardiac Surgery

Colleen Koch, Liang Li, Daniel Sessler, Priscilla Figueroa, Gerald Hoeltge, Tomislav Mihaljevic and Eugene Blackstone.

N Engl J Med 2008; 351: 1229-39.

RBCs are “good” for 42 days.

Day 0

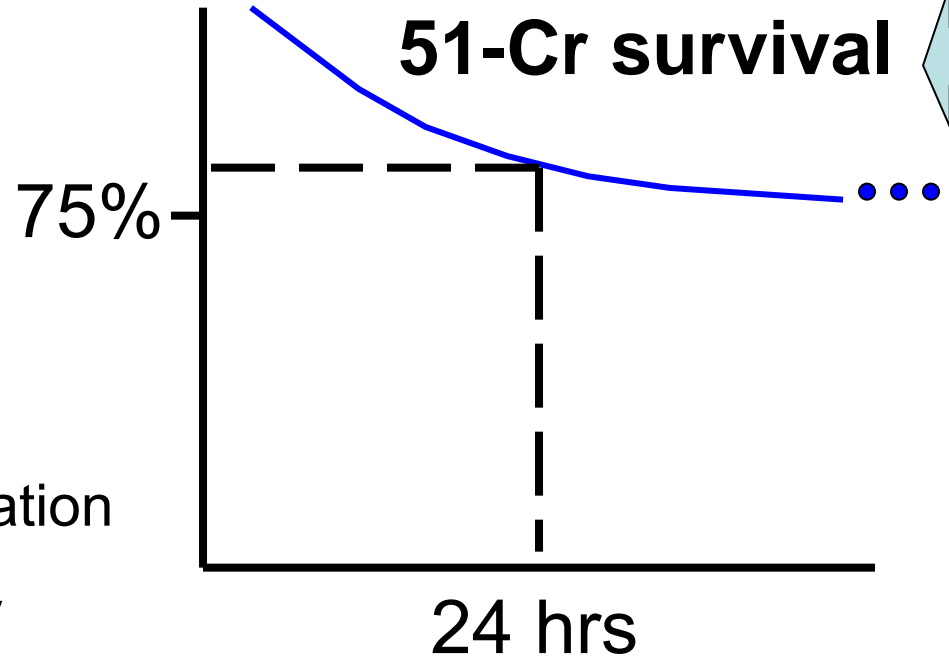


Day 42

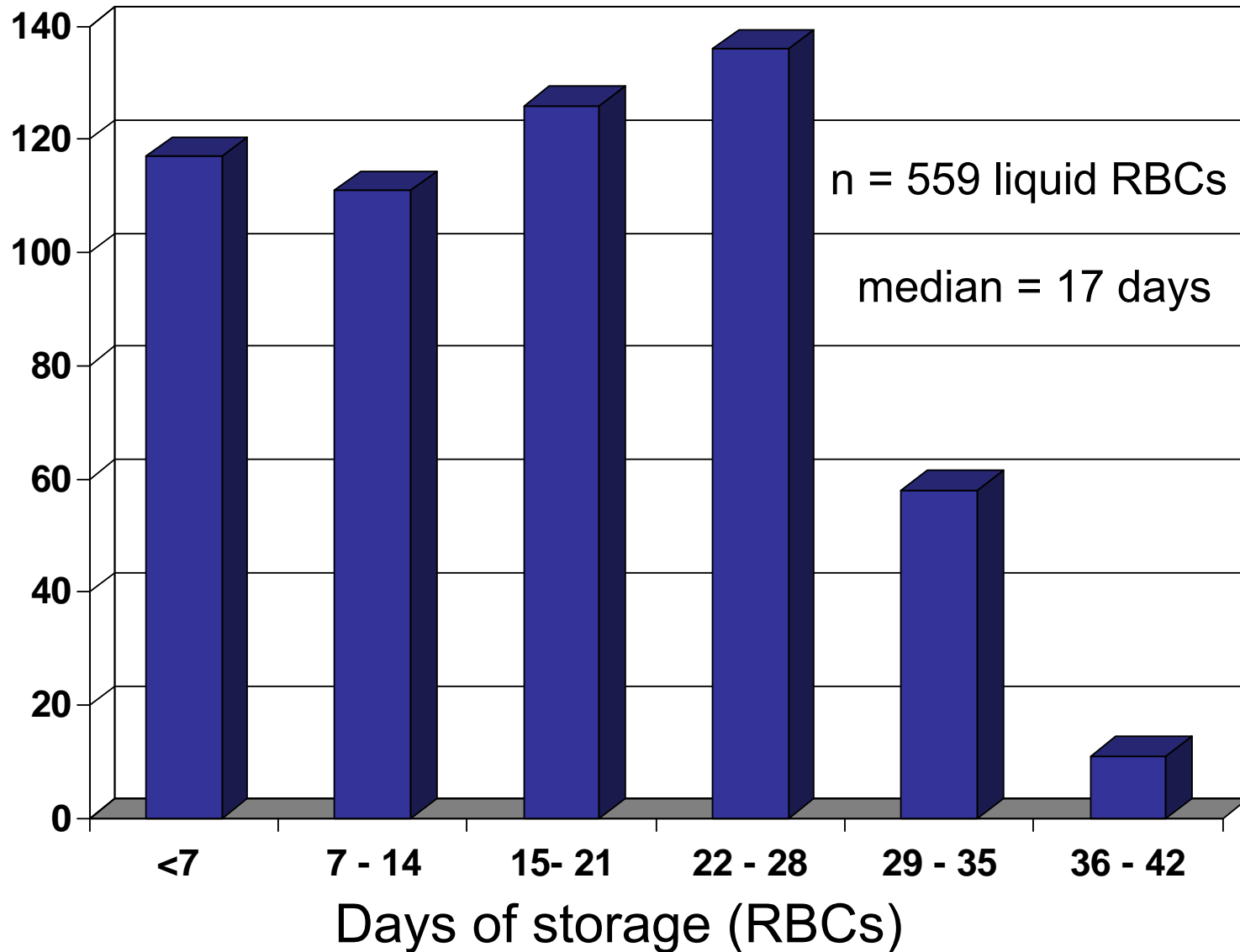


Shortcomings

- Presence at 24 hours
- Can accept loss of up to 25%
- No assessment of microcirculation
- No assessment of O₂ delivery



Distribution of RBCs at MGH (Feb 17, 2009)



103 units (19%) used the day before.

Koch CG *et al.* NEJM 2008;358:1229-39

Cardiac Surgery and Storage-age of RBCs

- Cleveland Clinic 1998 - 2006.
- Retrospective data.
- 2872 patients; 8802 RBCs stored < 14 days
- 3130 patients; 10,782 RBCs stored > 14 days.
- Survival was estimated by the Kaplan–Meier

Conclusion !

In patients undergoing cardiac surgery, transfusion of RBCs stored for > 14 days was associated with more complications and reduced short-term and long-term survival.

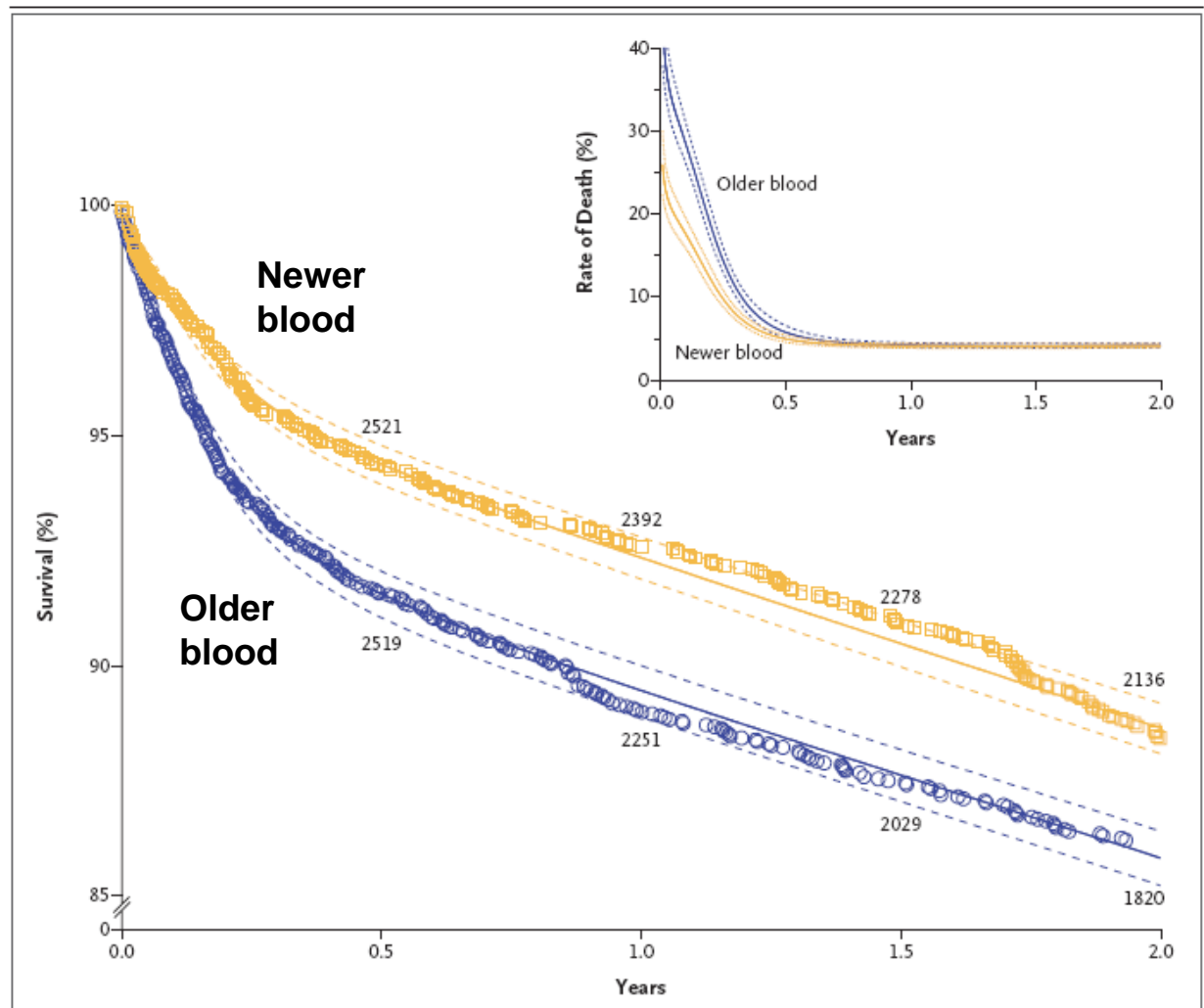


Figure 3. Kaplan–Meier Estimates of Survival and Death.

The curves show data from 2872 patients who were given exclusively newer blood (stored for 14 days or less) and 3130 patients given exclusively older blood (stored for more than 14 days). The numbers above and below the curves represent the numbers of patients who were alive and under follow-up observation in each group at that time. The solid lines of the same color represent estimated survival or the rate of death, and the dotted lines represent pointwise 95% confidence intervals. The nonparametric survival estimator (orange squares or blue circles), as determined by the Kaplan–Meier method, is superimposed on the parametric survival function estimator. In this unadjusted comparison, the percentage of patients receiving older blood who survived was lower than the percentage of those receiving newer blood who survived, especially during the initial follow-up period.

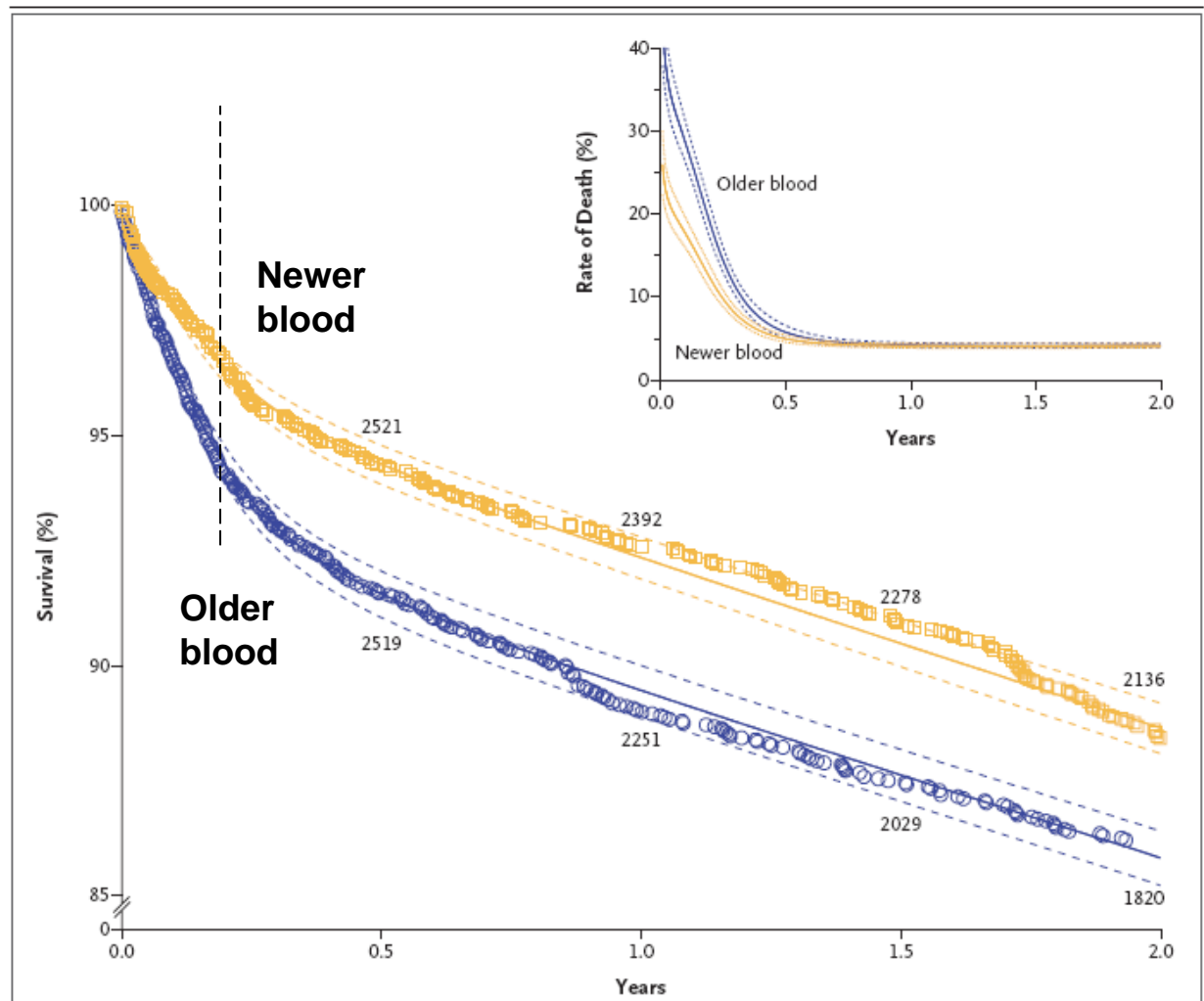


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RBC Storage in Cardiac Surgery Patients

Retrospective analysis of 6002 patients

More *complications* were also observed in the group receiving “older storage age” RBCs

Storage time:	<u>≤14d</u>	<u>>14d</u>	p-value
In-hospital mortality	1.7%	2.8%	0.004
Intubation > 72h	5.6%	9.7%	< 0.001
Renal dysfunction	1.6%	2.7%	0.003
MOF	0.2%	0.7%	0.007

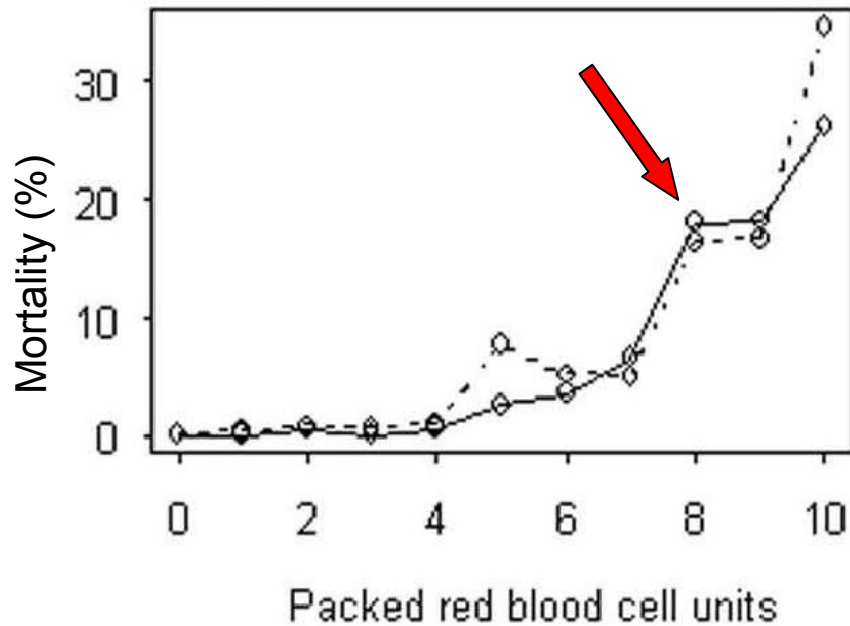
Is the comparison valid ?

Are the groups similar for features other than storage-age of RBCs?

Feature	< 14 days	> 14 days	p-value
Group O RBCs	53%	31%	< 0.001
Group O (pt)	51%	30%	< 0.001
WBC-reduction	36%	55%	< 0.001
Poor LV function	58%	63%	< 0.001
Mitral regurg	64%	67%	0.01
Peripheral vascular disease	54%	58%	0.002

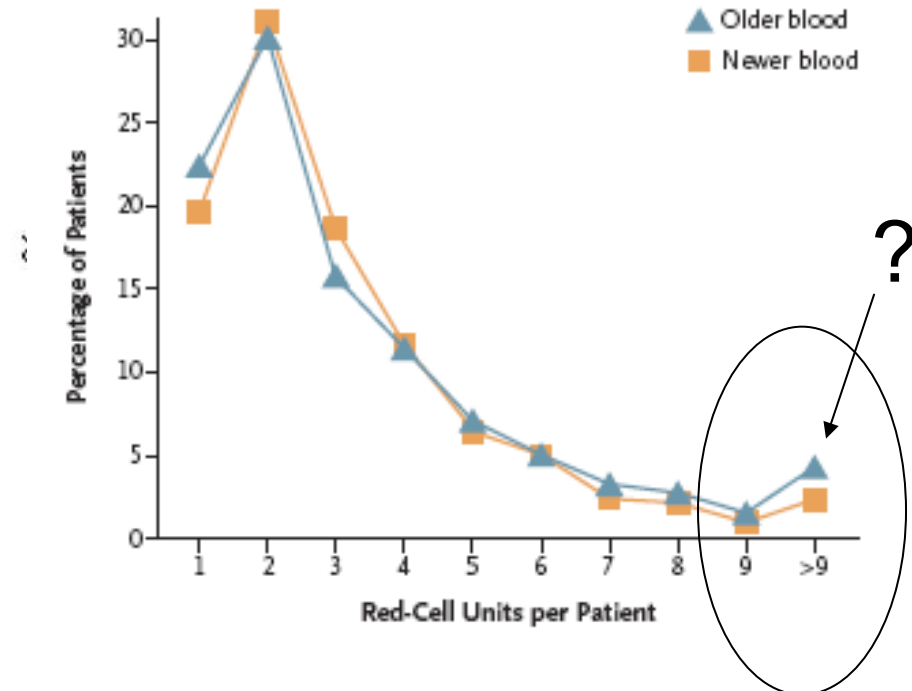
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Koch CG *et al. Crit Care Med* 2006;34:1608-16.

In an earlier study (2006) the same authors showed that most cardiac mortality was focused on the patients getting ≥ 8 units.



Koch CG *et al. NEJM* 2008;358:1229-39

In this study, the heavily transfused patients appear not to be balanced for younger vs older blood.

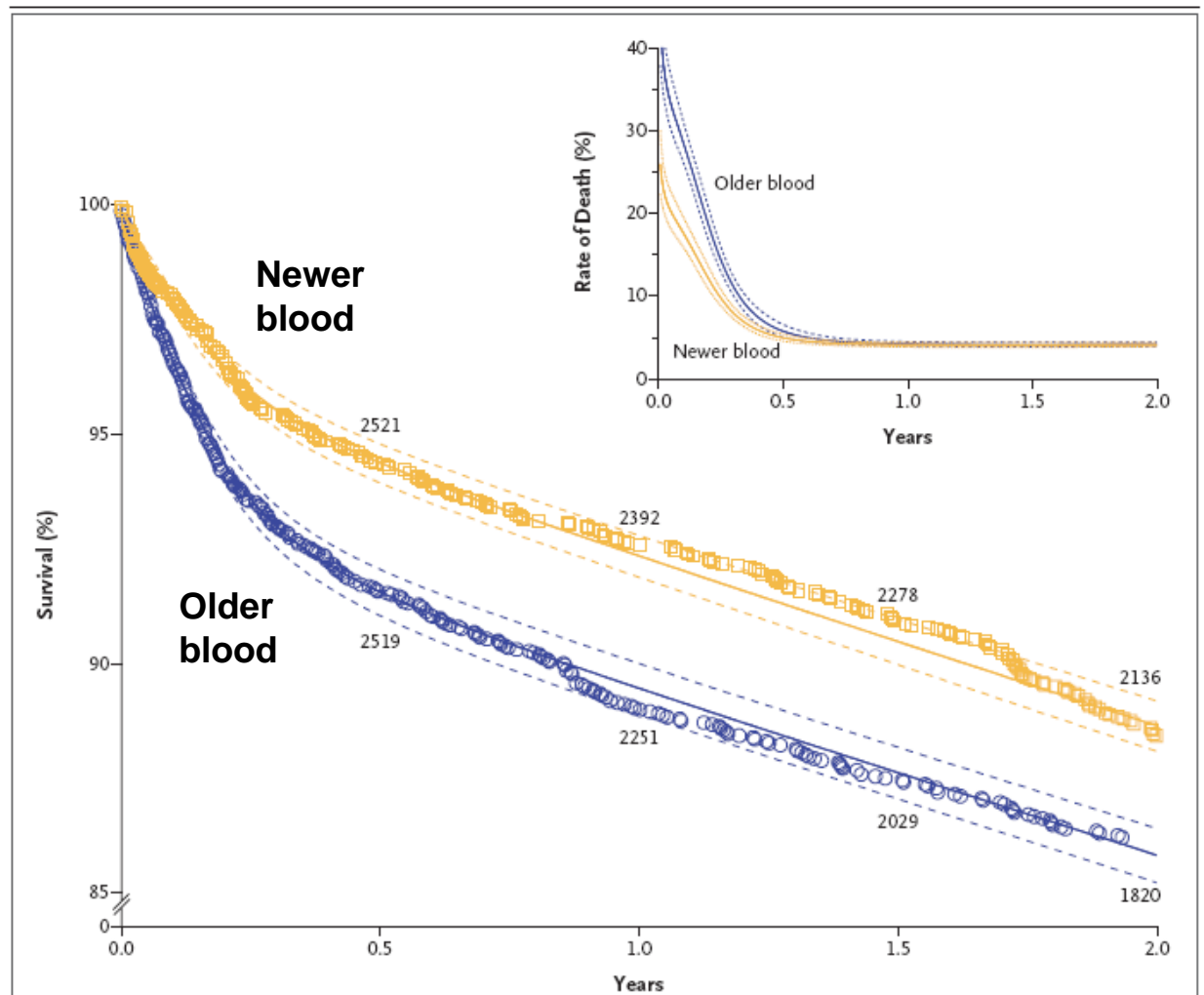


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Comparison of very different patient groups gives different results !

Data **un-adjusted** for differences in patient groups shown in Table 1 !

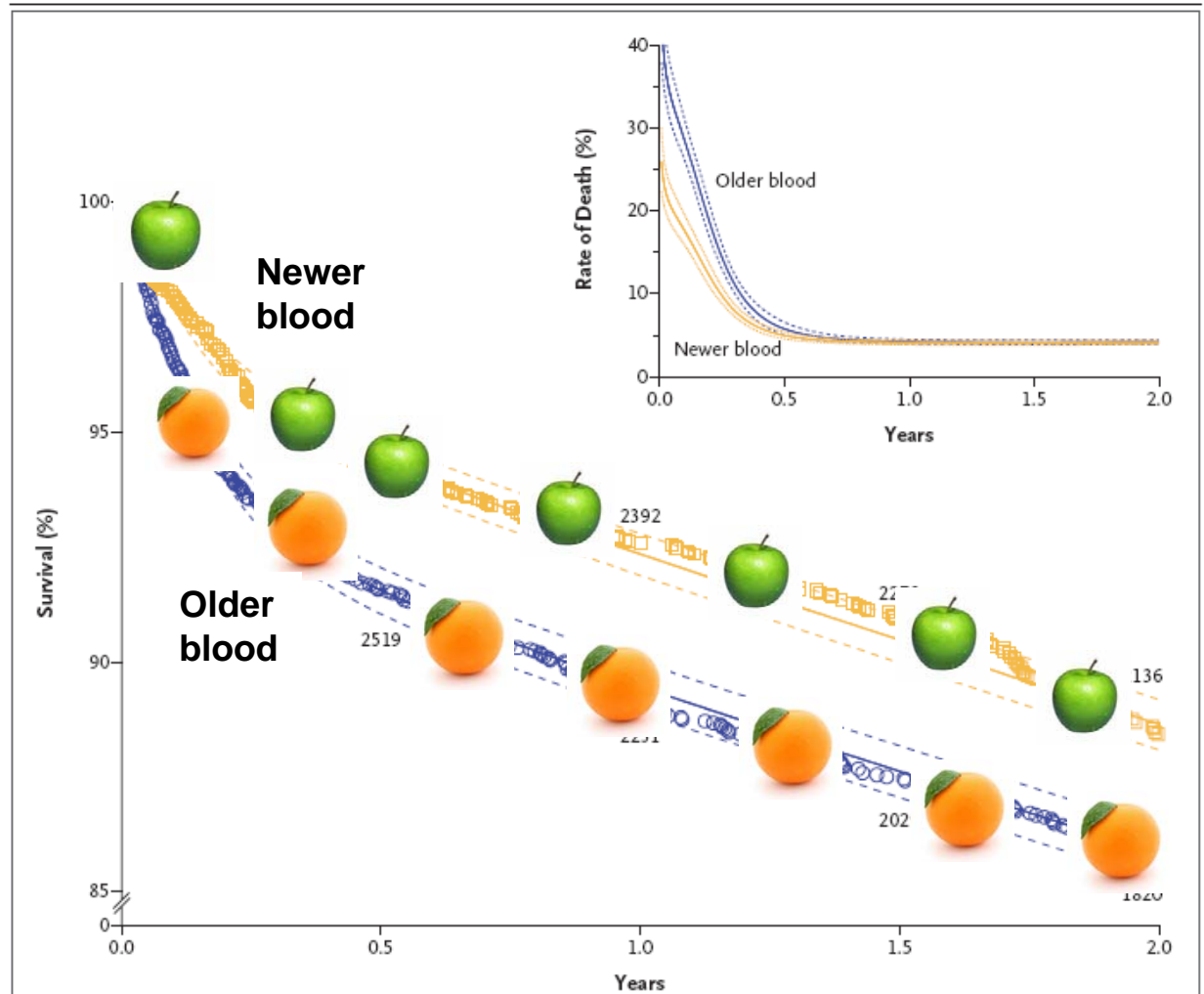


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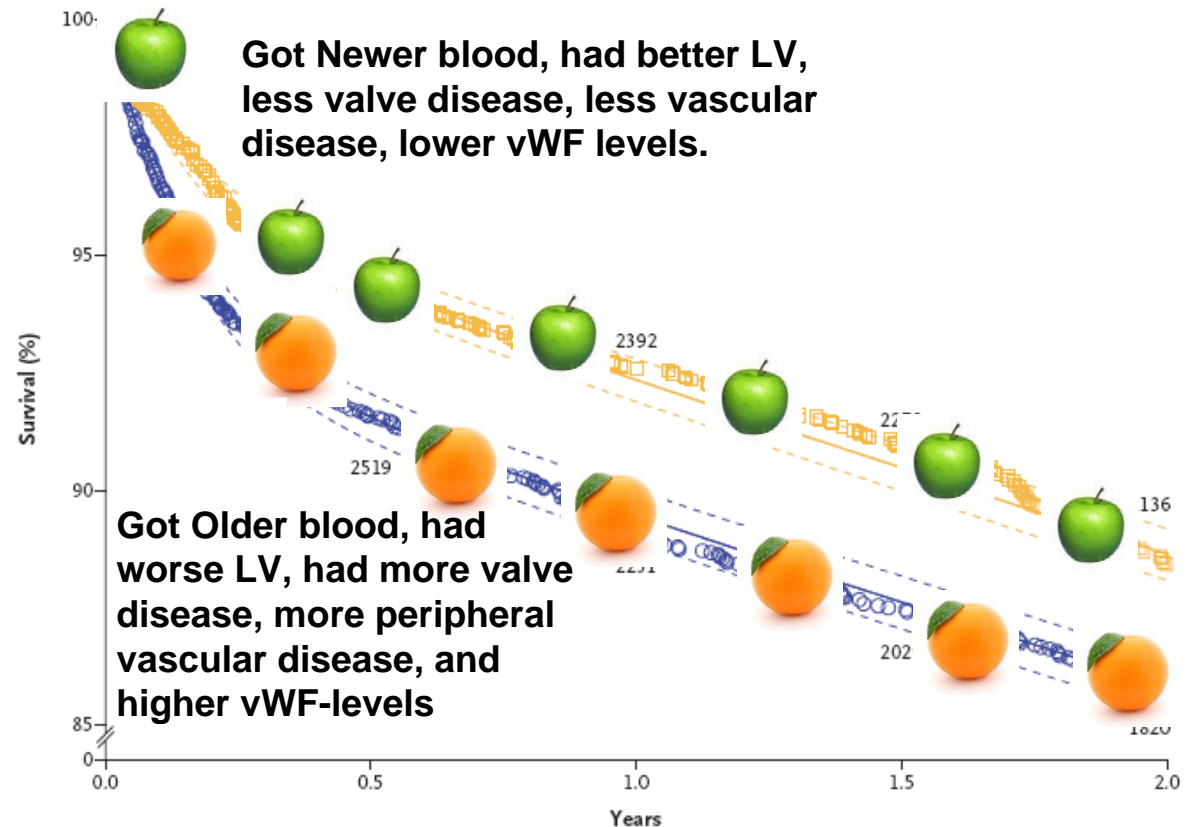


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Duration of Red-Cell Storage and Complications after Cardiac Surgery

Koch CG *et al. NEJM* 2008;358:1229-39

Weaknesses of this work....

- Retrospective design
- Comparisons between heterogeneous groups (Table 1)
- Treated storage-age as a dichotomous variable
- Displayed unadjusted survival
- No plausible mechanism explains divergence of survival curves long after senescence of transfused cells
- Mortality concentrated to heavily transfused patients who were not balanced between the two groups and who have other clinical confounders.

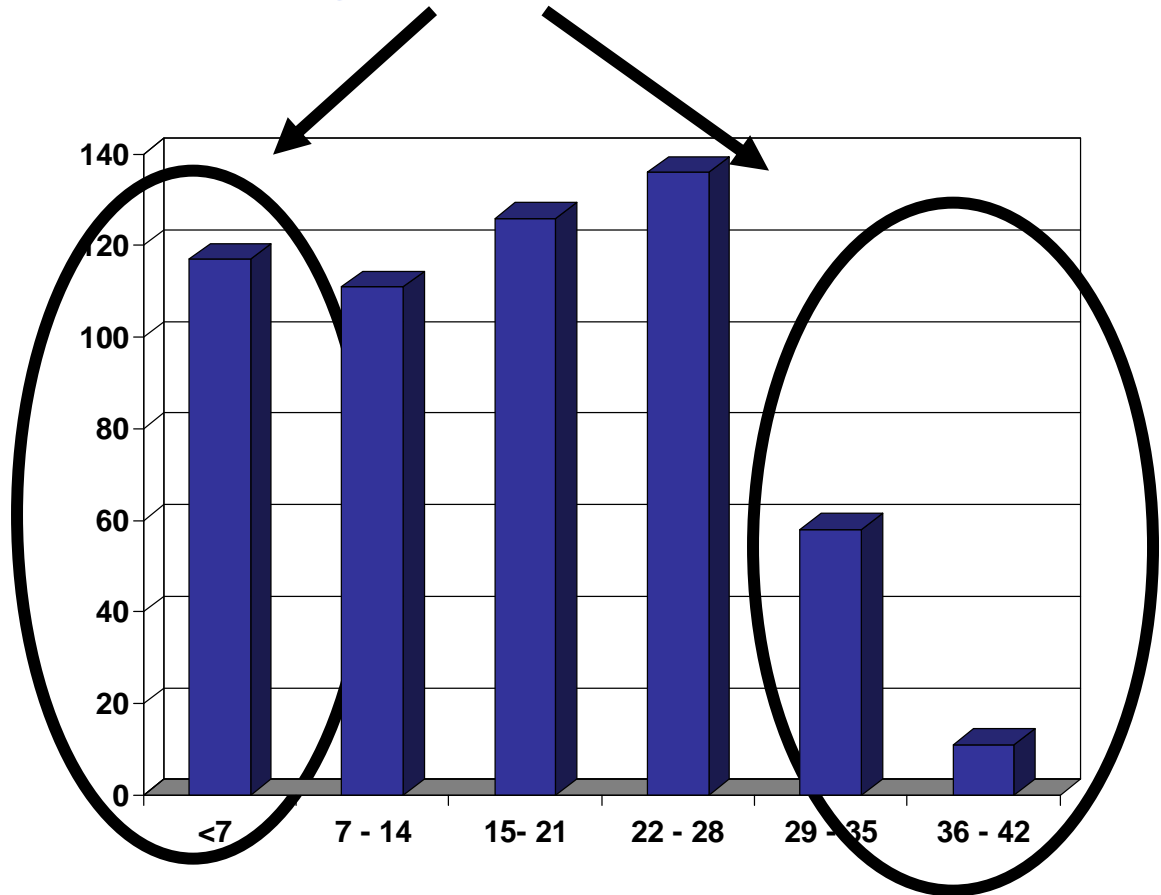
What *should* be done to answer the question...

Randomize patients to receive either one of the 2 “tails” of the RBC age distribution.

* Prospective RCT

* Stratify for ABO group

* Treat # of RBCs transfused as a continuous variable



3 kinds of studies reviewed today...

1. A multicenter prospective RCT on use of r7a as a rescue therapy for variceal bleeding in patients with advanced cirrhosis.
2. A meta-analysis of prior RCTs using hemoglobin-based RBC substitutes.
3. A retrospective study of the association between RBC storage age and outcomes.

Conclusions of Today's Presentation

- Medicine is advanced by new technology, but not all new technology is safe and effective.
- Concepts which seem to be “obviously good” (fresh blood) or “more modern” (recombinant clotting factors or RBC substitutes)... may prove to be of either ineffective or harmful.
- Post-hoc analyses of single studies (2004 r7a study) can produce misleading results that are not confirmed in a true RCT.
- Collections of case reports, anecdotes, and retrospective studies (Koch paper in NEJM) carry inherent intellectual flaws and are no substitute for prospective RCTs.

Mulago Hospital, Kampala, Uganda

1500 bed teaching hospital
Largest in nation.

Support for the Laboratory:

- * Direct gifts
- * “Keep the T-shirt” (Blood donors)



Mulago Hospital Children's Fund

sdzik@partners.org

Sunny Dzik,
Mass General Hospital,
Boston

