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The Implications of Outcome Trials for Transfusion

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Disclosure of Relationships with Industry

- **received consultancy monies from Amgen, Novo Nordisk, Jansen Ortho, Ortho Biotech, Hemosol, Johnson and Johnson, and Lilly**
- **sat/sit on advisory boards for Amgen and Jansen-Ortho**
- **sit on Data and Safety Monitoring Boards for Novo Nordisk**
- **received unrestricted grants from J&J, Amgen, Ortho-Biotech, and Jansen Ortho**

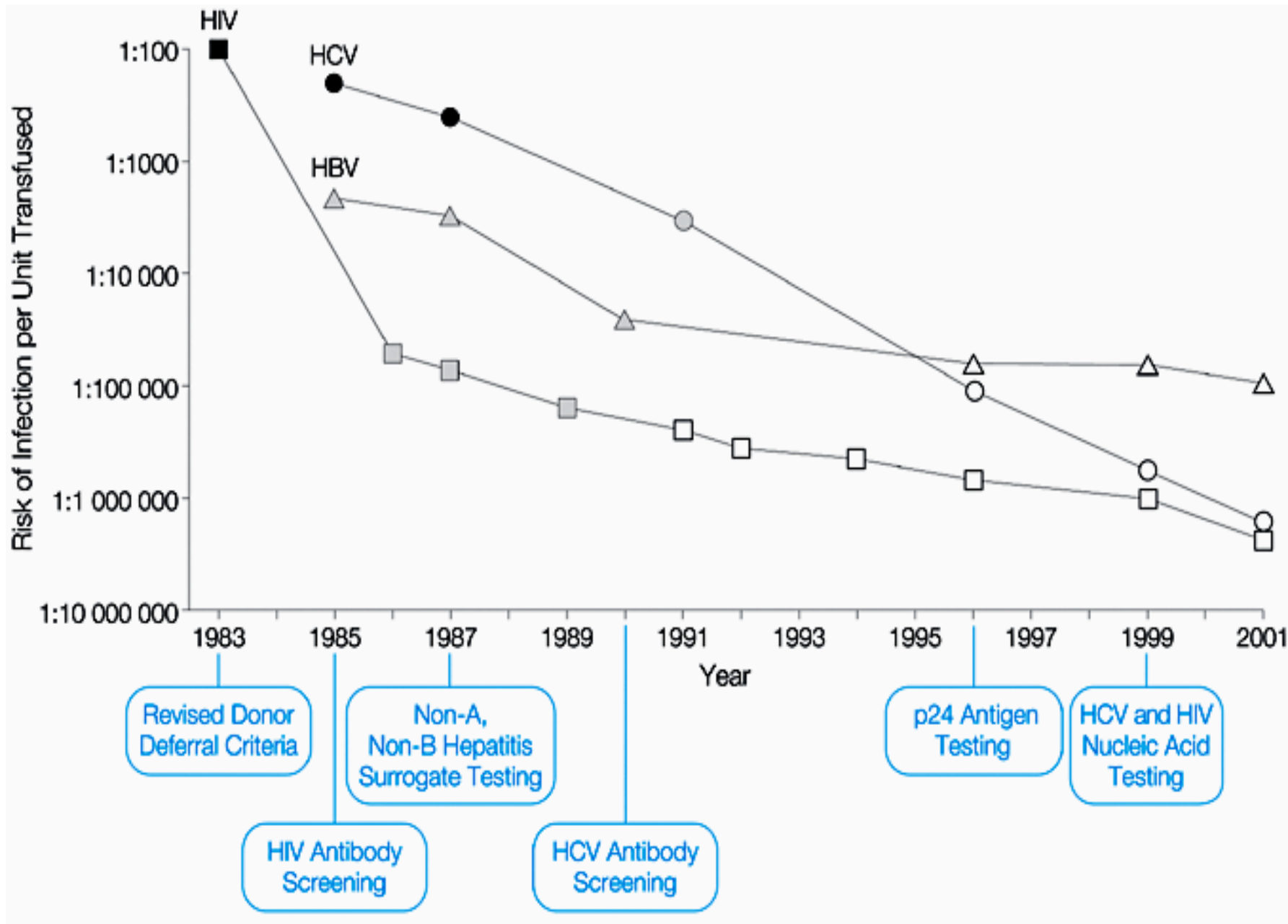
Topics to be covered

Studies assessing the “optimal” RBC product

- Leukoreduction
- Age of stored RBCs

Studies assessing transfusion minimisation/avoidance

- Transfusion triggers
- Pharmacologic/Non-pharmacologic
 - focus on aprotinin



Background

- While patients and physicians remain most concerned by the **transmission of viral diseases** through blood transfusions, there are other clinical consequences of RBCs
 - Alloimmunization to donor products
 - Bacterial contamination
 - Graft-versus-host disease
 - Transfusion reactions
 - **Immunosuppressive effects**

Can RBCs harm: data from observational studies

- > 50 retrospective studies document association between RBCs and **postoperative infections**
- Dose-response relationship between the number of RBCs and **postoperative infections** following colorectal surgery (Sher et al)
- Dose-dependent increase in **infections** in 9,598 consecutive hip fractures (Carson et al)

Putting risks in perspective

- In many countries, blood has never been safer
- Clearly, RBCs are an important supportive and life-saving measure for critically ill patients
- However, questions on it's efficacy and effectiveness remain

Do leukocytes matter?

Does age of stored blood matter?

When do we transfuse?

- **What are there consequences of over-transfusion?**
- **Under-transfusion?**
- **Risks and benefits of RBCs and alternatives/options need to be considered**

Leukoreduction

What is the independent effect of leukoreduction? Data from RCTs

D Fergusson, et al. A Meta-Analysis of Clinical Trials Evaluating Leukoreduced Red Blood Cell Transfusions in Surgical Patients. Can J Anesth 2004; 51(5): 417-424.

Study Characteristics

Year	Country	Surgical population	Type of filter	Type of control	Blinding	Time of randomization	Proportion randomized but NOT transfused**
1992 ¹⁴	Denmark	Colorectal	Bedside	Whole blood	No*	Pre-Operation	47%
1994 ¹⁰	Netherlands	Colorectal	Pre-storage	Buffy coat-depleted	No	Pre-Operation	?
1996 ¹¹	Denmark	Colorectal	Bedside	Buffy coat-depleted	No*	Pre-Operation	56%
1997 ¹²	Netherlands	Cardiac	Pre/Post-storage	Buffy coat-depleted	No	Pre-Operation	5%
1998 ¹⁵	USA	Gastrointestinal	Pre-storage	Standard	No	Pre-Operation	73%
2001 ¹³	Denmark	Colorectal	Pre-storage	Buffy coat-depleted	Patient, Investigators, and Physicians	Pre-Operation	55%
2002 ¹⁶	Netherlands	Mixture	Pre-storage	Buffy coat-depleted	?	Need for Transfusion	?
2002 ¹⁷	USA	Cardiac	Pre-storage	Standard	?	?	17%
2002 ¹⁸	UK	Cardiac	Post-storage	Standard & Buffy coat-depleted	Outcome Assessors	Pre-Operation	14%
2002 ¹⁹	USA	Mixture	Pre-storage	Standard	No	Need for Transfusion	2%

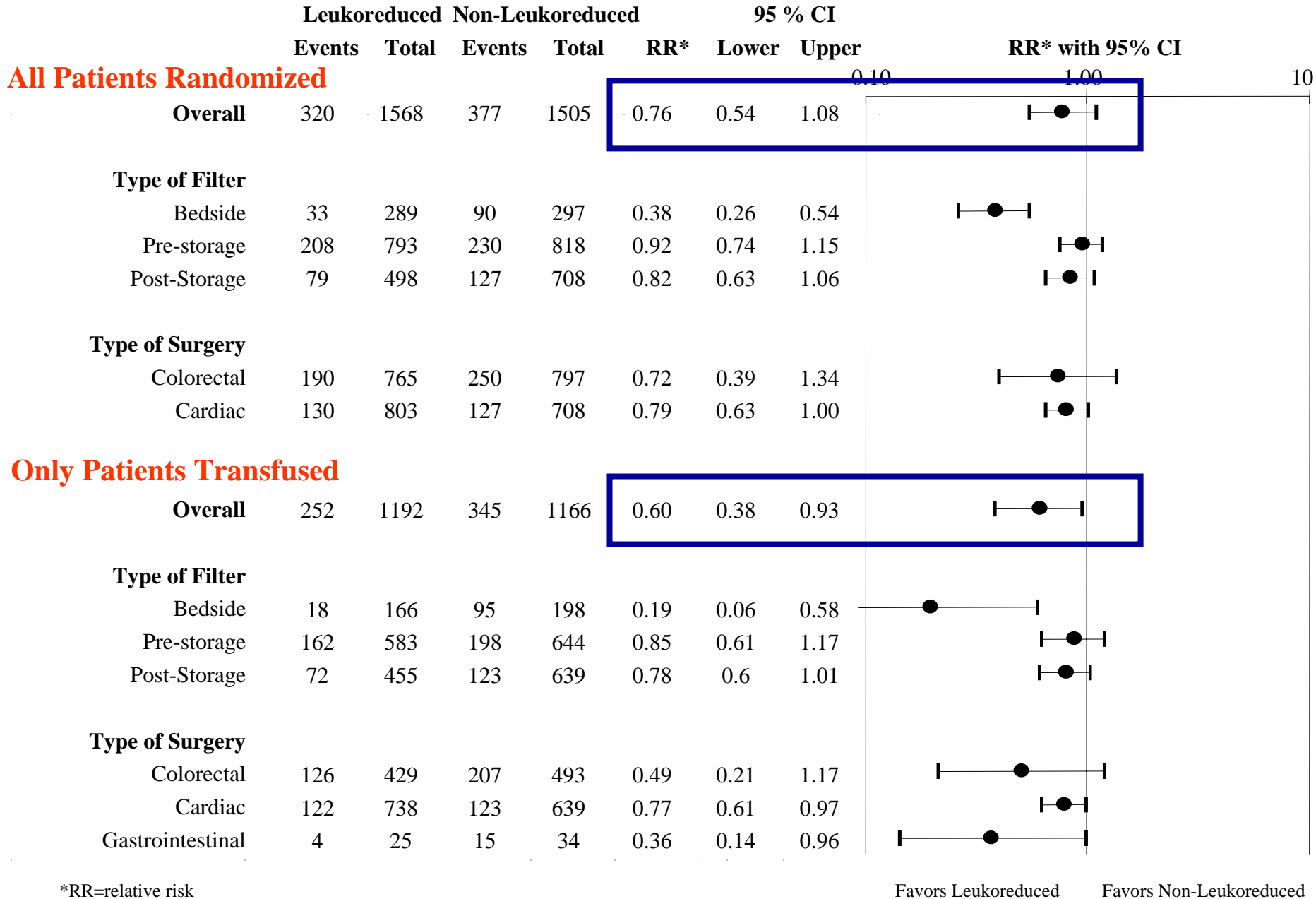
*publications report that physicians performing follow-up exams were blinded, however it is unclear whether they evaluated presence/absence of outcome on every patient

** based on patients randomized and eligible as defined in publication

? : not reported

Inappropriate point of randomisation has very important consequences

Postoperative Infection



*RR=relative risk

Favors Leukoreduced

Favors Non-Leukoreduced

Mortality

Leukoreduced Non-Leukoreduced
Events Total Events Total RR Lower Upper 95 % CI

RR with 95% CI

0.10 1.00 10

All Patients Randomized

Overall 173 2796 195 2801 0.71 0.45 1.13

Type of Filter

Bedside 10 289 5 297 2.06 0.71 5.94

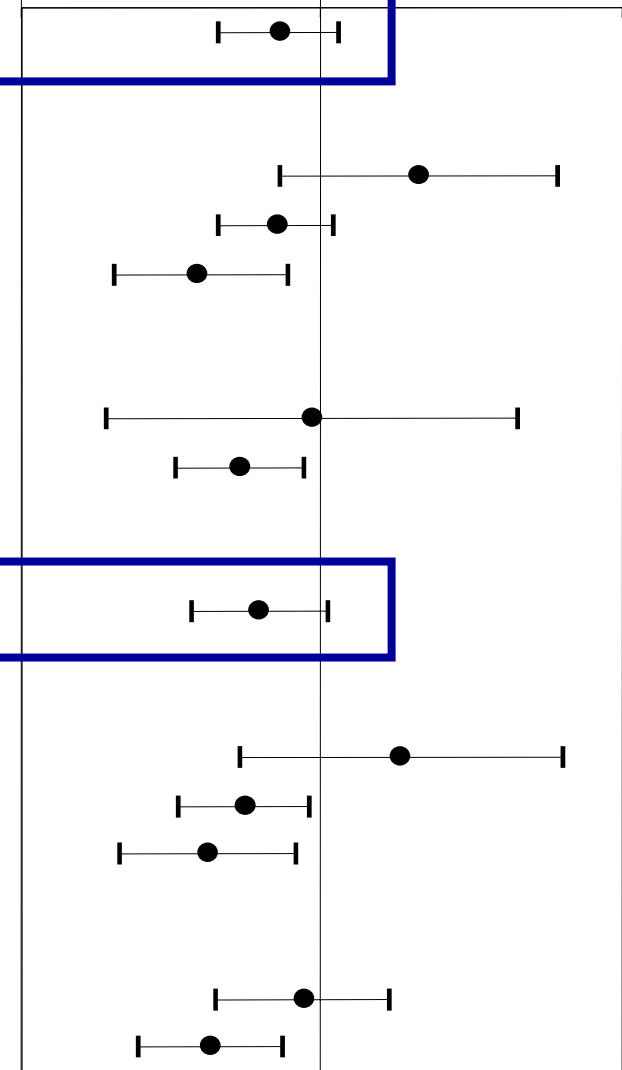
Pre-storage 152 2009 179 2102 0.70 0.45 1.08

Post-Storage 11 498 35 708 0.38 0.2 0.76

Type of Surgery

Colorectal 15 428 17 437 0.92 0.19 4.37

Cardiac 31 908 48 826 0.52 0.32 0.86



*RR=relative risk

Favors Leukoreduced Favors Non-Leukoreduced

With the available evidence...

- Countries have adopted universal leukoreduction (Canada, UK, France)
- Universal implementation limits design choice
 - RCT not feasible!
- With this restriction we conducted two studies to evaluate universal leukoreduction program

Clinical Effectiveness of Universal Leukoreduction in Critically Ill Adults

Hébert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA. 2003; 289 (15):1941-9.

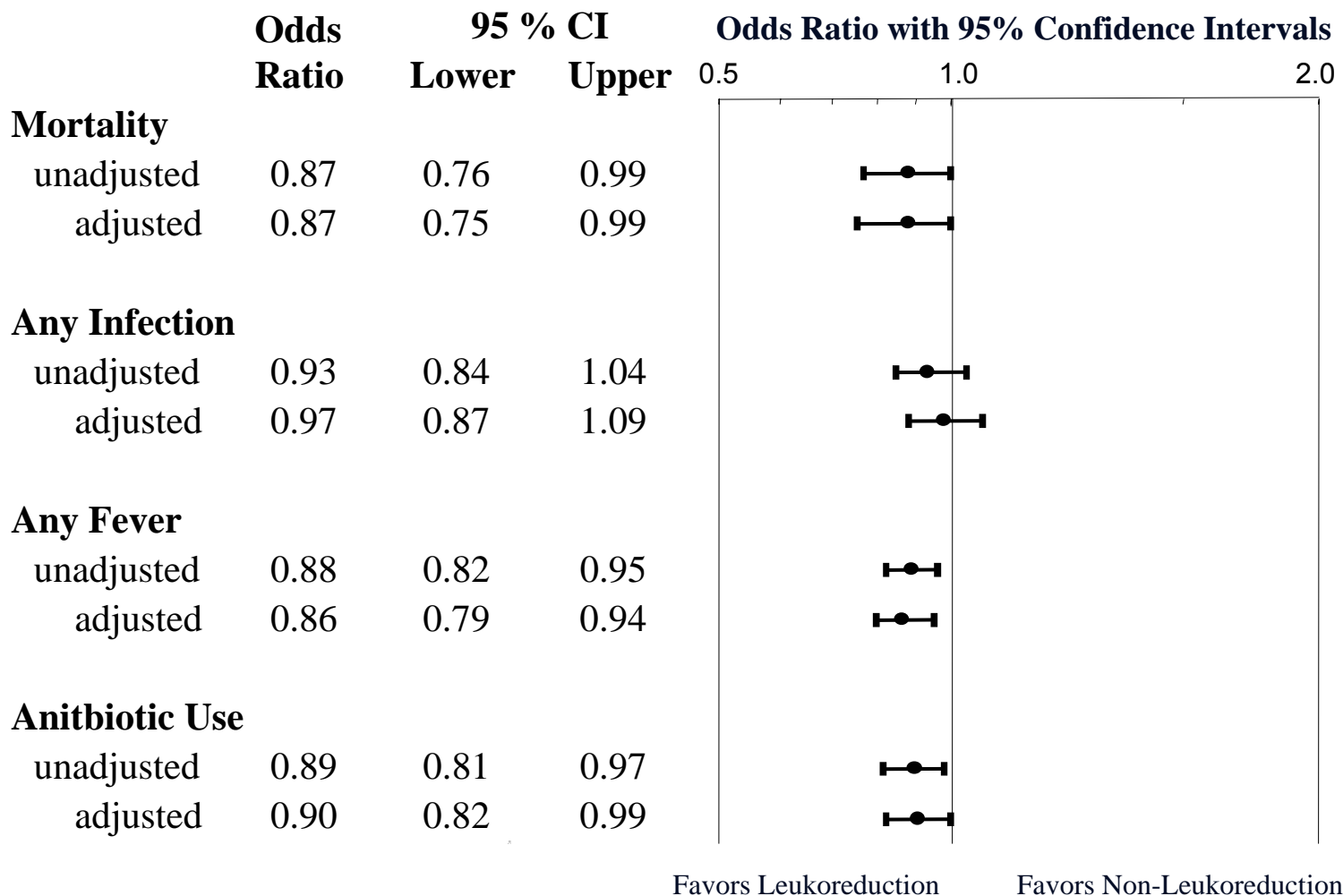
Study Design

- Study Design: Before and after retrospective cohort
- Study sites: 23 Centres from across Canada
- Study intervention: Universal pre-storage leukoreduction performed by Canadian Blood Services and Hema Quebec
- Study Period: 1 year before and 1 year after implementation of universal leukoreduction (August 1998 to August 2000)

Study population

- Total of 14,786 patients given RBCs following:
 - Cardiac surgery requiring cardiopulmonary bypass
 - 4,475 before/5,050 after
 - Postoperative critical illness and trauma
 - 1,715 before/1,815 after
 - Repair of hip fracture
 - 792 before/939 after

Odds Ratios for All Major outcomes in 14,786 Patients



Conclusions

- Significant reduction in mortality, fever, and antibiotic use
- No significant reduction in serious nosocomial infection
- All major and subgroup analyses show a consistent effect (and certainly no harm)
- As for mortality, for every 120 patients that receive leukoreduced blood, 1 death will be prevented
- Our study supports the adoption of a universal leukoreduction program

Clinical Effectiveness of Universal Leukoreduction in Neonates

Fergusson D, Hébert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. JAMA. 2003 Apr. 16; 289 (15):1950-6.

Methods

- **Design:** Retrospective before/after study
- **Sites:** 3 Canadian NICUs (Vancouver, Saskatoon, Toronto)
- **Intervention group:** all neonates <1250 g admitted to the NICU in the 18-month period following the introduction of leukoreduction
- **Control group :** all neonates <1250 g admitted to the NICU in the 18-month period prior to the introduction of universal leukoreduction.
- **Study Period:** Dec. 1998 thru to Dec. 2001

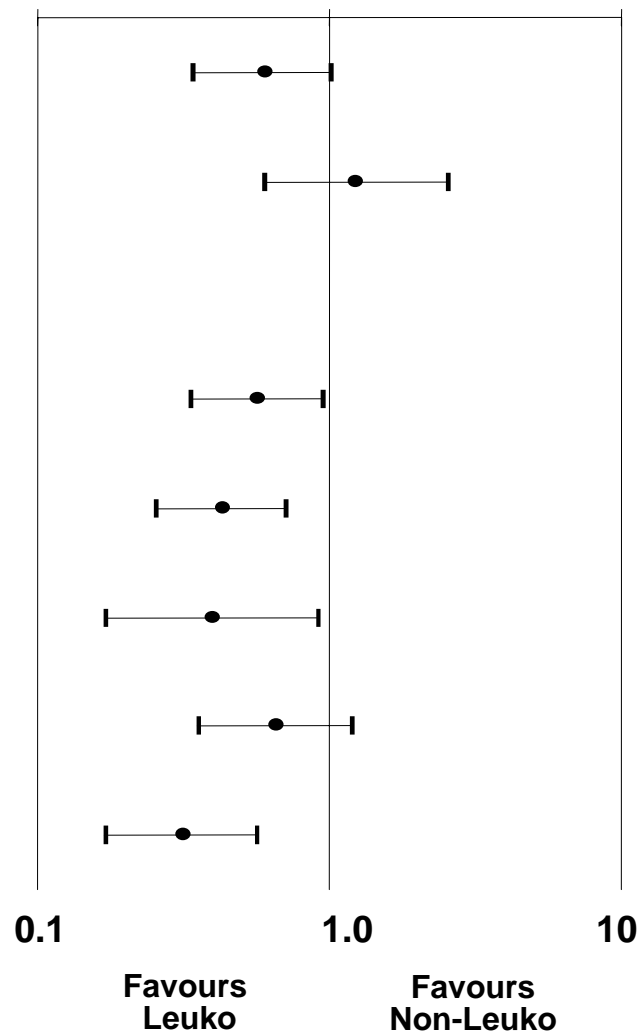
Adjusted Outcomes for the 515 Transfused Neonates

Primary Outcomes

	Odds Ratio	95% CI Lower	95% CI Upper
Bacteremia	0.59	0.34	1.01
Mortality	1.22	0.59	2.50

Major NICU Morbidities

	Odds Ratio	95% CI Lower	95% CI Upper
Retinopathy of Prematurity	0.56	0.33	0.93
Bronchopulmonary Dysplasia	0.42	0.25	0.70
Necrotizing Enterocolitis	0.39	0.17	0.90
IVH Grade III or IV	0.65	0.35	1.19
Any Major NICU Morbidity***	0.31	0.17	0.56



Conclusion

- For each 10 transfused neonates, leukoreduction was associated with the prevention of 1 major secondary complication of premature birth
- This clinical benefit was accompanied by an average decrease of 11 days of NICU stay
- The magnitude of these decreases represents substantial decreases in the cost in the care of these infants

Summary of Leukoreduction

- Solid evidence that it is effective
- Consistency across different patient populations
- Consistency across outcomes
- Adverse effects are minimal
- Cost-effectiveness?
- Mechanisms of action?
 - immunosuppressive or pro-inflammatory?
- Is a large, definitive RCT needed?

Age of RBCs Does it matter?

RBCs Day 5

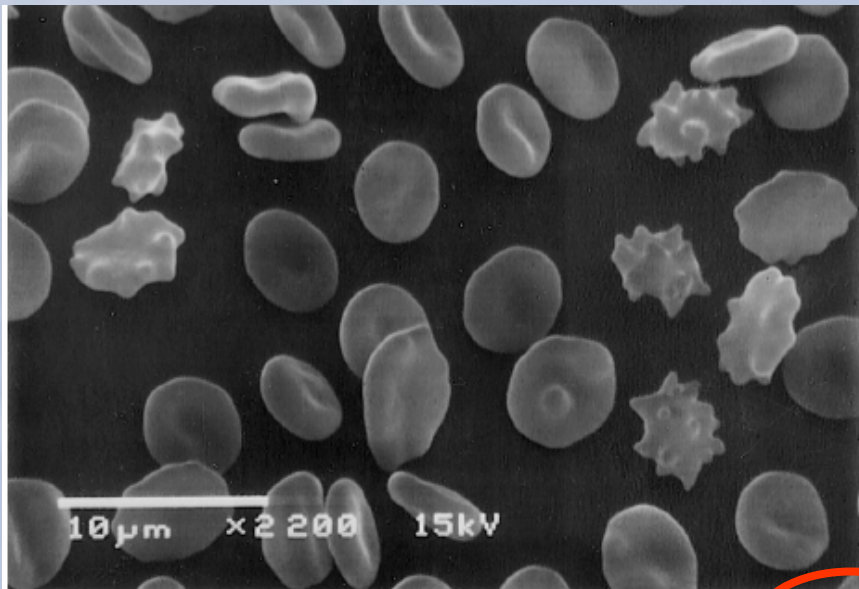


FIG. 1. Scanning electron microscope picture of RBC on the 5th day of storage. Original magnification 2200 \times . Discocytes dominate among the cell population, and only a few irreversibly changed RBC can be seen.

RBCs Day 14

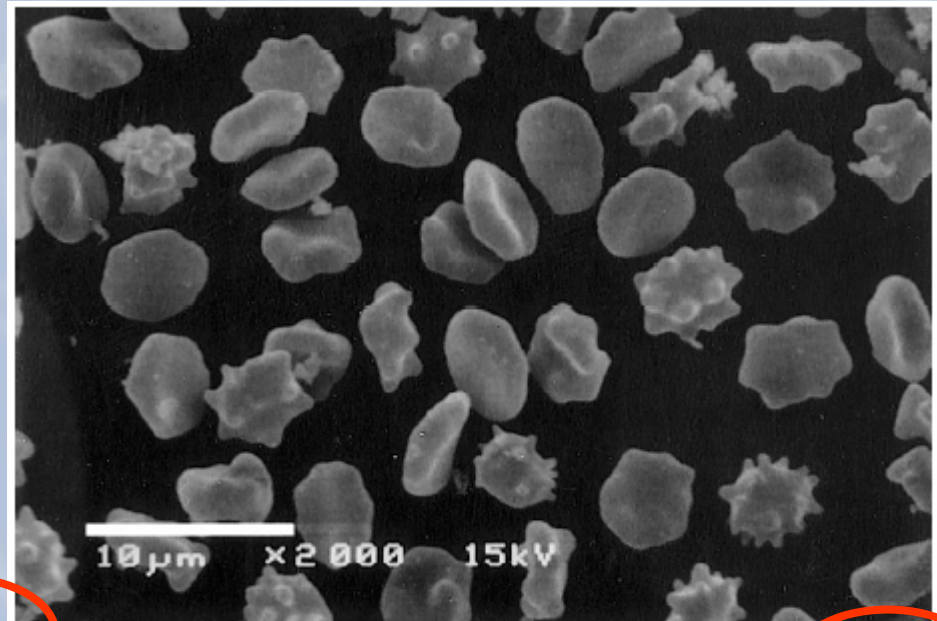


FIG. 2. Scanning electron microscope picture of RBC on the 14th day of storage. Original magnification 2000 \times . Numerous echinocytes and spherocytes can be seen.

Berezina LT et al. Influence of Storage on Red Blood Cell Rheological Properties. Journal of Surgical Research 102: 6-12, 2002

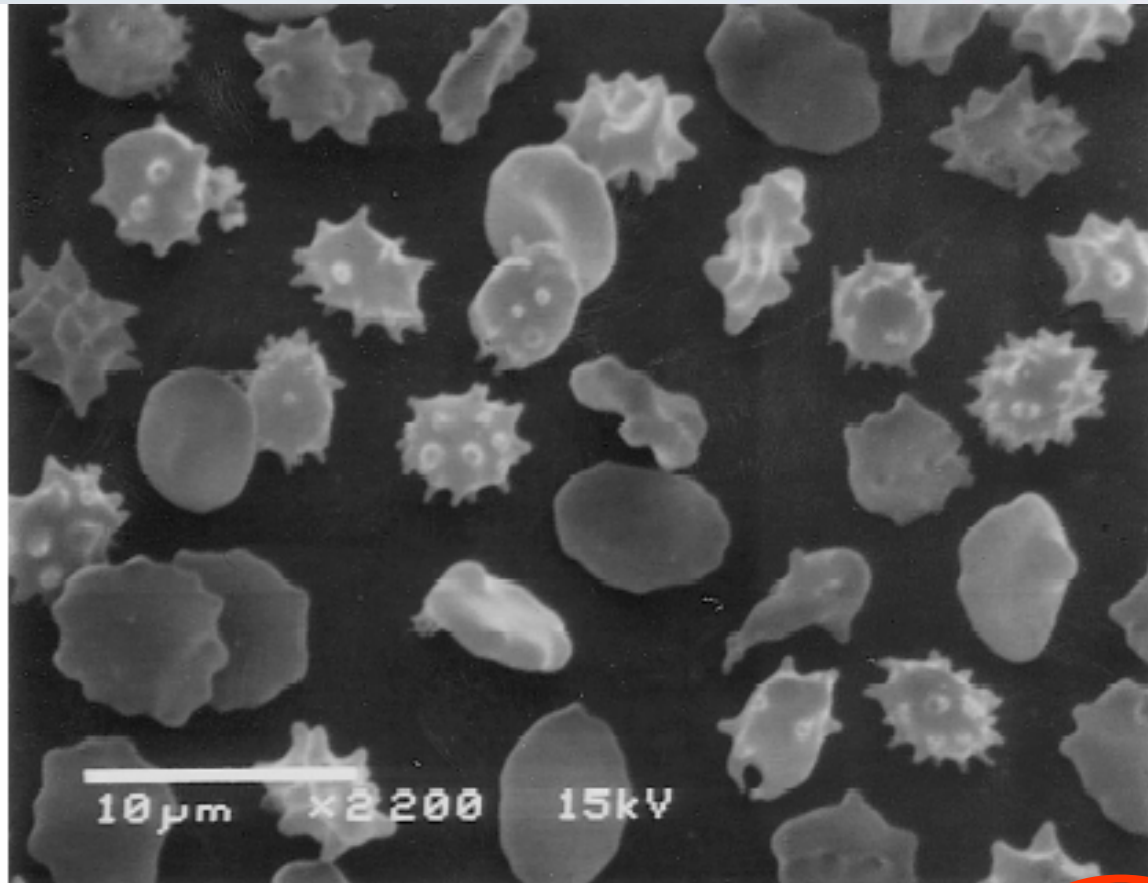
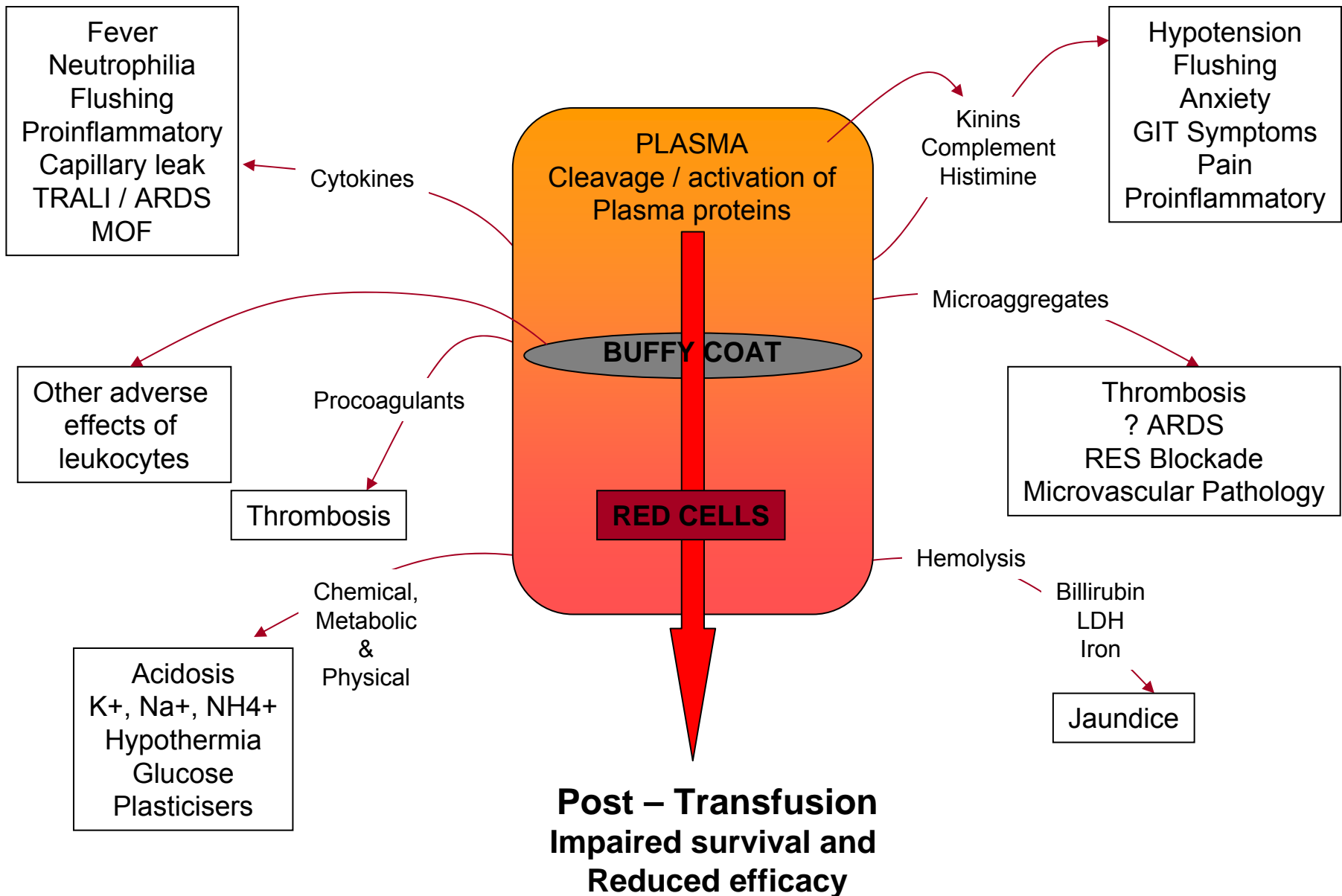


FIG. 3. Scanning electron microscope picture of RBC on the 42nd day of storage. Original magnification 2200 \times . Spherocytes and degenerated forms dominate among irreversibly changed cells.

Berezina LT et al. Influence of Storage on Red Blood Cell Rheological Properties. Journal of Surgical Research 102: 6-12, 2002

Clinical Consequences of the Storage Lesion



Retrospective Studies....

Prolonged cell storage and adverse outcomes

- In 698 ICU patients, association between the transfusion of aged blood (>14 days old) and **increased length of ICU** stay($p<0.01$)⁽¹⁾
- In severe sepsis, negative correlation ($r=-0.73, p<0.01$) between age of RBC units transfused and **survival** ⁽²⁾
- In 416 CABG pts, adjusted increase of 1% in the **risk of pneumonia** per day of average increase in the length of storage of RBCs⁽³⁾

(1) Martin et al, Clin. Inv. Med

(2) Purdy et al, Can J Anesth, 1997

(3) Vamvakas et al, Transfusion 1999 and 2000

RCTs...Prolonged cell storage and adverse outcomes

Study design: Single centre RCT

Study Population: 22 mechanically ventilated patients who required at least 2 units of RBCs

Intervention: Patients were allocated to leukodepleted red cells that were stored for either < 5 days or > 20 days

Outcomes: tissue oxygenation

Results: no difference in Pg-PaCO₂ gap, gastric intramucosal Ph and other oxygenation index parameters

Conclusion: findings do not support the use of fresh, leukoreduced RBCs

Walsh et al, CCM 2004 Med

RCTs....Prolonged cell storage and adverse outcomes The ABLE Pilot

Study Design: multicentre, pilot RCT

Study population: 66 cardiac surgical and critically ill patients

Intervention: Fresh (< 8 days) vs standard blood bank issue RBCs

Results:

- 9 patients did not receive RBCs
- In 57 patients, median storage times in fresh was 4 days vs 19 days in standard group ($p < 0.0001$)
- Life- threatening complication or death in 27% of fresh versus 13% of old ($p = 0.31$)

Hebert, Fergusson et al., Anesthesia And Analgesia, 2005

**Clinical Trials Assessing
Age of Blood:
One planned and one
underway**

ABLE Study Design

Principal Investigator: Paul Hebert (University of Ottawa)

Study Design: Randomized double-blind controlled clinical trial.

Setting: 50 tertiary care intensive care and trauma units. Study Sites in Canada, US, UK, France and Australia

Study Population:

- 6800 critically ill trauma victims who require at least one red cell unit within the first 24 hours of acute care
- Identify population at high risk of transfusion and mortality.

Outcomes

Primary outcome: 30-day all cause mortality.

Secondary outcomes:

- 1) Other mortality rates
- 2) Organ failure
- 3) Nosocomial infections
- 4) Quality of life using the SF-36 and costs of care.

Interventions

The Intervention

- Leukoreduced RBCs
- Definition of Fresh as 8 days or less
- Control group...standard-issue red cells (average age of 21 days)
- Limit blood groups to A & O

ABLE is a work in progress

- **Ongoing work modifying background and design**
 - incorporating feedback
- **Developing an inventory management strategy with blood banking community**
- **Discussion with distributors of blood products**
- **International collaboration with Australian, US, UK and European partners**
- **International meeting held in Toronto in June, 2006**
- **Submission to CIHR,NIH, MRC in planning stages**
- **\$12-15 million study**

Age of RBCs in Premature Infants (ARIPi) trial

Principal Investigator: Dean Fergusson (OHRI, Ottawa)

Objective:

- To determine if RBCs < 7 days old decrease major organ dysfunction in neonates admitted to the NICU and requiring at least one unit of RBCs compared to current standard practice
- Current practice: dedicated unit from a single donor used until outdate (35/42 days)

Age of RBCs in Premature Infants (ARIPi) trial

Study Design: Randomized double-blind controlled clinical trial

Setting: 6-8 Canadian NICUs

Study Population: 450 ELBW neonates (<1250 grams) who require at least one red cell transfusions

Outcomes: The primary outcome for this study will be a composite measure of major neonatal morbidities:

- necrotizing enterocolitis
- retinopathy of prematurity
- bronchopulmonary dysplasia
- intraventricular hemorrhage
- or death

Age of RBCs in Premature Infants (ARIPi) trial

- **Progress to date**

- received CIHR funding (April 2005)
- 4 sites actively enrolling
- >20 patients randomized to date (June 1st 2006 start)
- Another 4 sites are committed
- Endorsed by Canadian Neonatal Network

Summary of Age of Blood Evidence

- Evidence to date largely rests with animal and *in vitro* studies
- Clinical evidence is minimal!
- Given the potential repercussions on the blood system, we need to look at clinically meaningful outcomes (serious morbidity/mortality) across different patient populations
- **Requires large, definitive RCTs**

Studies assessing transfusion minimisation/avoidance

**How can we safely use less
blood**

Transfusion Triggers

Transfusion Triggers

- Tolerance of lower hemoglobin levels is a vital step towards reducing exposure to RBCs
- Effects of transfusion are not limited to the correction of the decreased O_2 supply
- We must consider possible aggravation of ischemia by increasing blood volume and blood viscosity
- Moreover, the margin of safety for DO_2 diminishes as hemoglobin levels decrease and patients with significant cardiovascular disease may not tolerate hemoglobin values below 80 to 100 g/L

**Are Low Hemoglobins
Associated
with Poor Outcomes?
(can we transfuse less?)**

Can we believe the large observational studies?

- **Five Retrospective Cohorts**

- 1,958 Jehovah's witnesses from 10 centres⁽¹⁾
- 9,958 patients with hip fracture⁽²⁾
- 4470 critically ill patients⁽³⁾
- 78,974 patients with acute MI⁽⁴⁾
- 24,112 patients in patients with acute coronary syndromes

(1) Carson JL, et al. Lancet 1996;348:1055-60.

(2) Carson, et al. JAMA 1998;279:199-295.

(3) Hebert et al, Am Rev Resp Crit Care, 1997

(4) Wu et al, NEJM, 2001

(5) Rao et al, JAMA, 2004

What about recent NEJM and JAMA studies?

“Blood Transfusion in Elderly Patients with Acute Myocardial Infarction”

Wen-Chih Wu et al N Engl J Med 2001; 345: 1230-6

Objectives:

- to determine the risk associated with anemia in elderly patients with acute MI
- to determine the effectiveness of RBC transfusion in elderly patients

What did Wu et al. find?

- Higher mortality rates with lower admitting Hct
- Transfusions associated with decreased mortality following MI with Hct < 33%
- But, transfusions associated with increased mortality with higher Hct.

Mortality in transfused vs non-transfused patients

	Hct	OR (95% CI)*	
RBCs save lives	5.0 – 24.0%	0.22 (0.11 -0.45)	
	24.1 – 27.0%	0.48 (0.34 -0.69)	
	27.1 – 30.0%	0.60 (0.47 -0.76)	
	30.1 – 33.0%	0.69 (0.53 -0.89)	
	33.1 – 36.0%	1.13 (0.89 -1.44)	
	36.1 – 39.0%	1.38 (1.05 -1.80)	
	39.1 – 48.0%	1.46 (1.18 -1.81)	

*OR adjusted for clinical factors, medication use, and predictors of transfusion

“Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes”

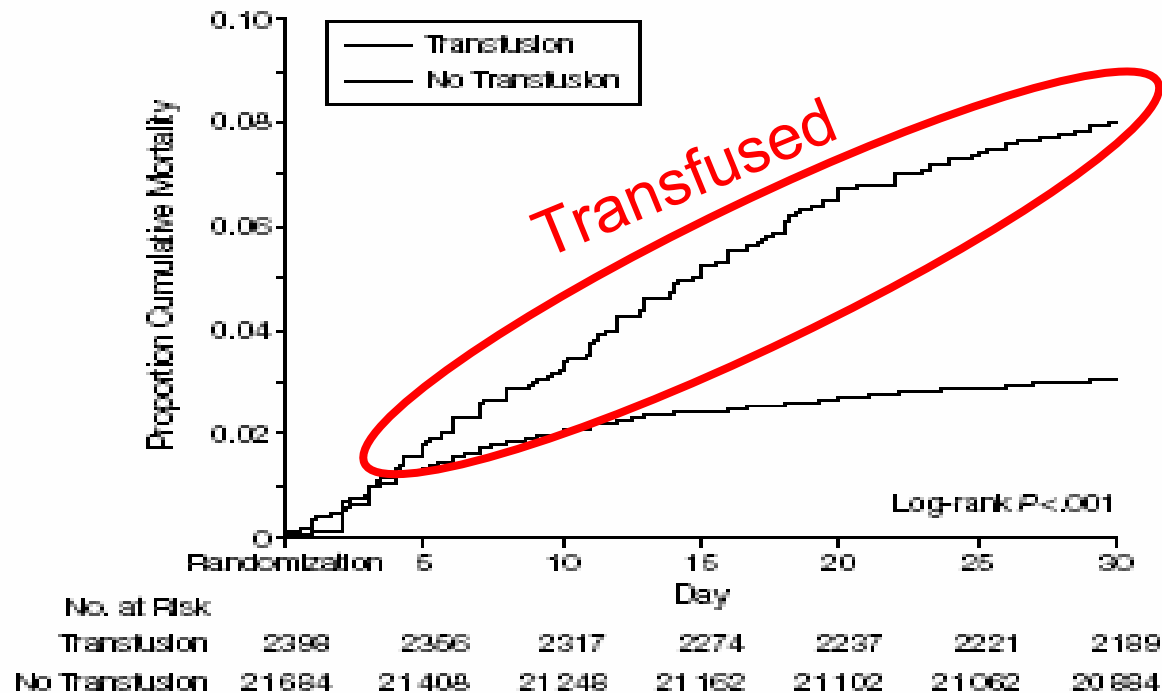
Rao et al. JAMA. 2004; 292(13):1555-62.

Objective:

- to determine the association between blood transfusion and mortality among patients with acute coronary syndromes who develop bleeding, anemia, or both during their hospital course

Risk of Death in 24,112 transfused versus non-transfused from 3 RCTs

Figure 1. Kaplan-Meier Estimates of 30-Day Mortality Among Patients Who Did and Did Not Receive Blood Transfusion



Survival data were missing for 3 patients who received transfusion and for 27 patients who did not receive transfusion.

Risk of Death in 24,112 transfused versus non-transfused from 3 RCTs

Table 4. Adjusted Predicted Probabilities of 30-Day Death With and Without Transfusion by Nadir Hematocrit Value

	Nadir Hematocrit, %*			
	20	25	30	35
Adjusted odds ratio (95% CI)†	1.59 (0.95-2.66)	1.13 (0.70-1.82)	168.64 (7.49-3797.69)	291.64 (10.28-8273.85)

Abbreviation: CI, confidence interval.

*Nadir hematocrit value was incorporated into the multivariable logistic regression model as a continuous variable. The association between nadir hematocrit value and 30-day mortality was evaluated using restricted cubic splines. Because the association followed 2 lines, 1 below and 1 above a nadir hematocrit value of 25%, a linear spline transformation with a nadir hematocrit value of 25% as the knot point was used. Nadir hematocrit values in the table are sample values above and below 25%.

†Adjusted for US vs non-US site, age, race, weight in kilograms, diabetes mellitus, systolic and diastolic blood pressure, heart rate at baseline, time from symptom onset to hospitalization, prior stroke, prior myocardial infarction, sex, history of angina prior to qualifying episode, hypertension, hyperlipidemia, family history of coronary artery disease, history of congestive heart failure, peripheral vascular disease, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, Killip class, baseline hematocrit, maximum creatine kinase ratio at baseline, chronic renal insufficiency, ST-segment elevation or depression on initial electrocardiogram, β -blocker use at baseline, calcium channel blocker use at baseline, nitrate use at baseline, and current smoking.

Hebert & Fergusson, JAMA, 2004

Do Transfusions Get to the Heart of the Matter?

How do Rao and Wu studies compare?

- Both studies document harm from RBC transfusion with hematocrits exceeding 33%
- Reasons for differences at hematocrits < 33%
 - Different population (younger and aggressively treated in Rao study)
 - Different data acquisition: primary data collection vs administrative database
 - Different statistical techniques
 - Different event rates

What's wrong with these studies?

Inferences from these studies are weakened because:

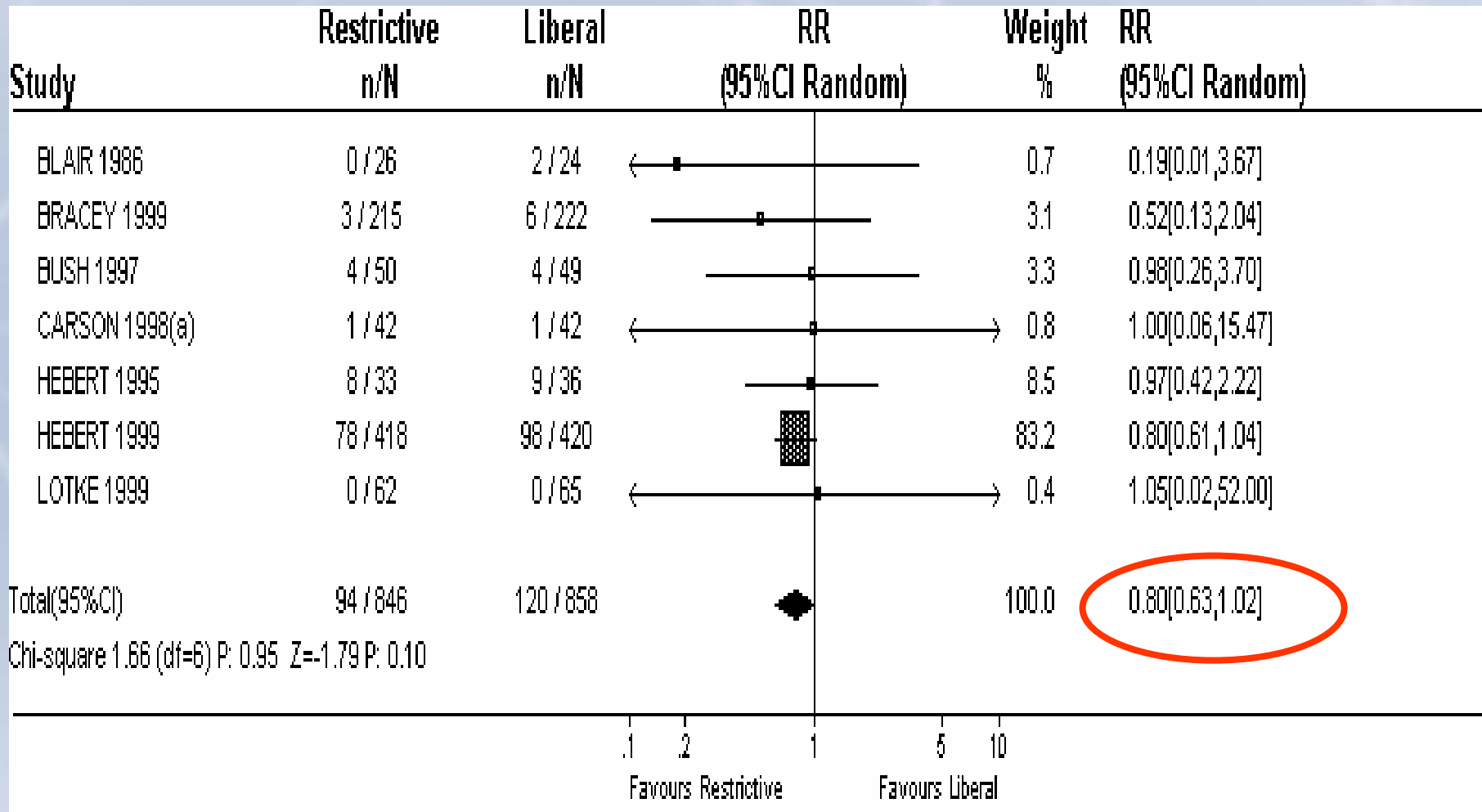
- Retrospective study with limited data
- Minimal adjustment for confounding factors
- Timing of RBCs unknown
- Trigger unknown...admission hematocrit/nadir hematocrit
- **Main culprit: “Confounding by Indication”**
higher acuity → more aggressive care

**How about evidence
from
Randomized Controlled Trials?**

What about RCTs?

Author	Year	N	Setting	Hb (in g/dL)
Topley	1956	22	Trauma	11.3 vs 15.6
Blair	1986	50	GI Bleed	2 U vs 8U
Fortune	1987	25	Trauma	10.0 vs 13.0
Weisel	1992	27	CABG	10.0 vs 12.0
Johnson	1992	39	CABG	8.3 vs 10.7
Hebert	1995	69	ICU	7.0-9.0 vs 10.0 -12.0
Bush	1997	99	Vascular	9.0 vs 10.0
Carson	1998	84	Hip Fx	10.0 vs Symptoms
Bracey	1999	428	CABG	8.0 vs.9.0/symptoms
Hebert	1999	838	ICU	7.0 vs 10.0

Does a Restrictive Strategy Decrease all Cause Mortality?



Transfusion Requirements in Critical Care (TRICC)

Hebert PC, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med.* 1999;340(6):409-17

Purpose:

To determine if a restrictive and liberal red cell transfusion strategy are equivalent in terms of effects on mortality and morbidity in volume resuscitated critically ill patients

TRICC Study

Study design: Multicentre RCT

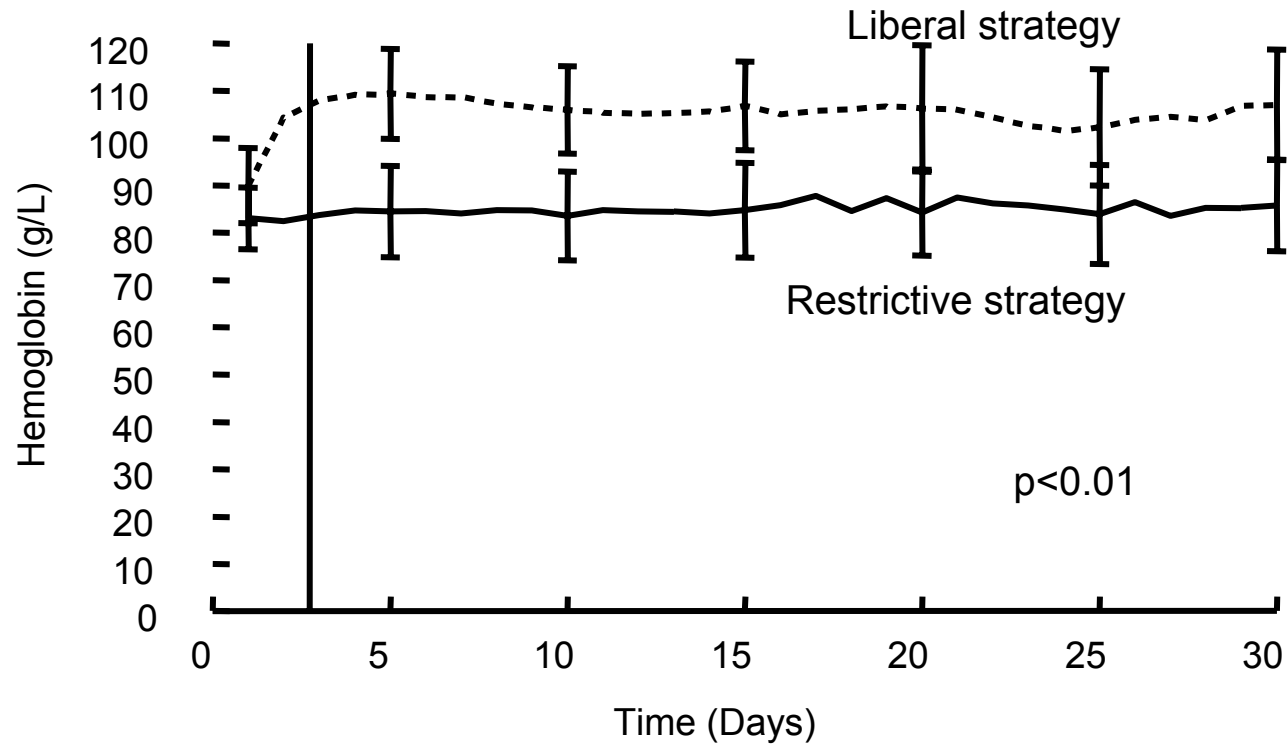
Setting: 25 ICUs across Canada

Study Population: Included Hb < 9.0 g/dl within 72 hrs and excluded patients with active blood loss (3.0 g/dl decrease or >3 unit transfusion in 12 hrs)

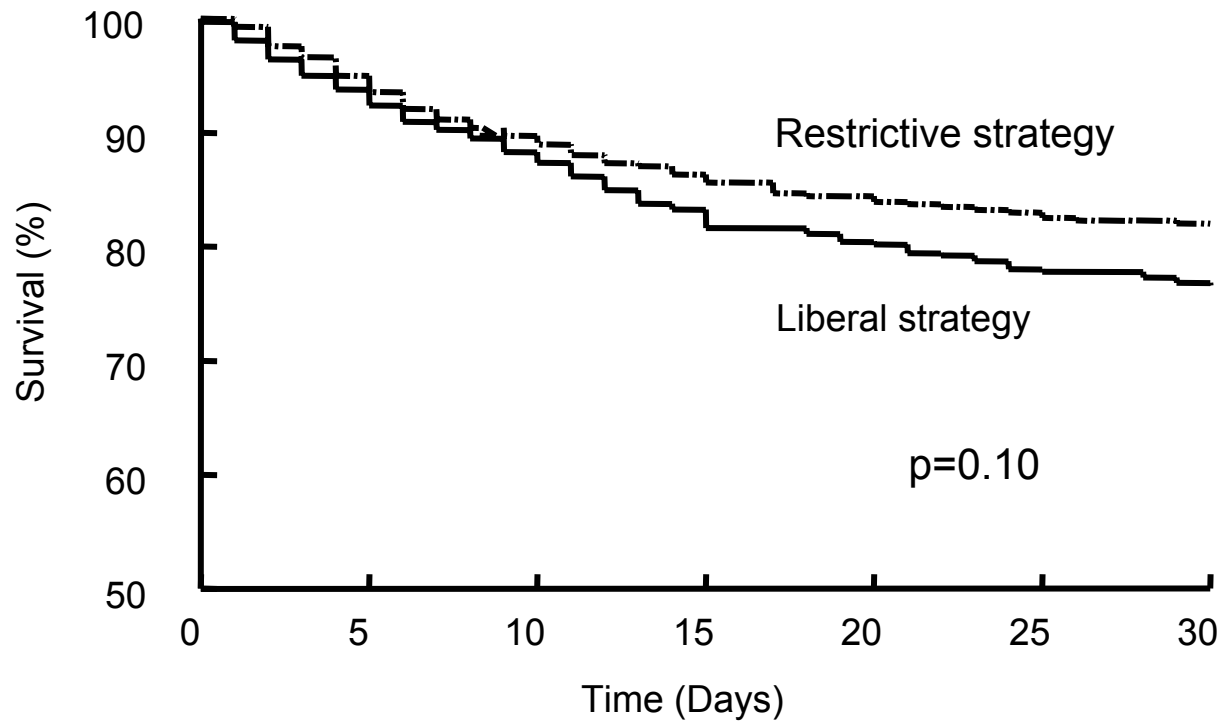
Intervention: 7.0 g/dl vs 10.0 g/dl hemoglobin trigger

Outcomes: 30 day all-cause mortality and organ failure

Hemoglobins over time

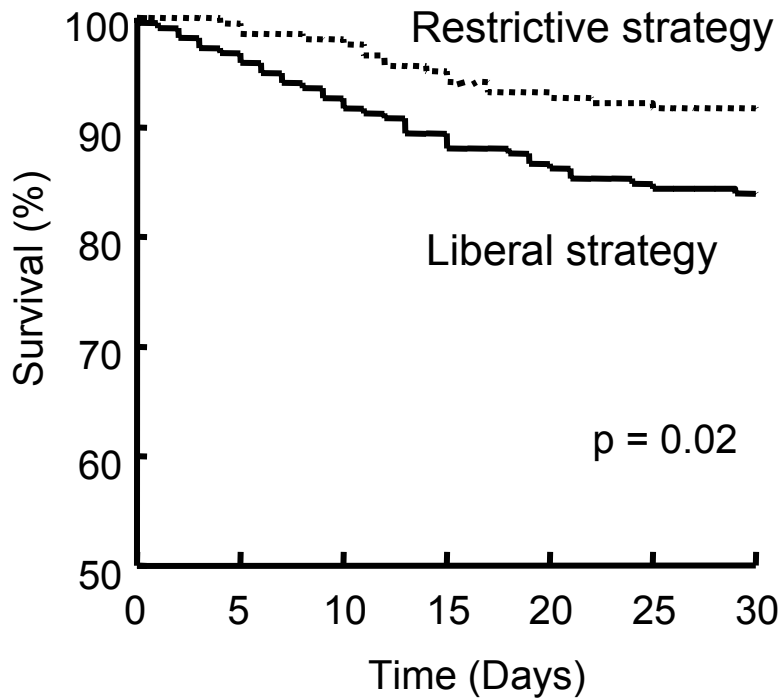


Survival of all patients over 30 days

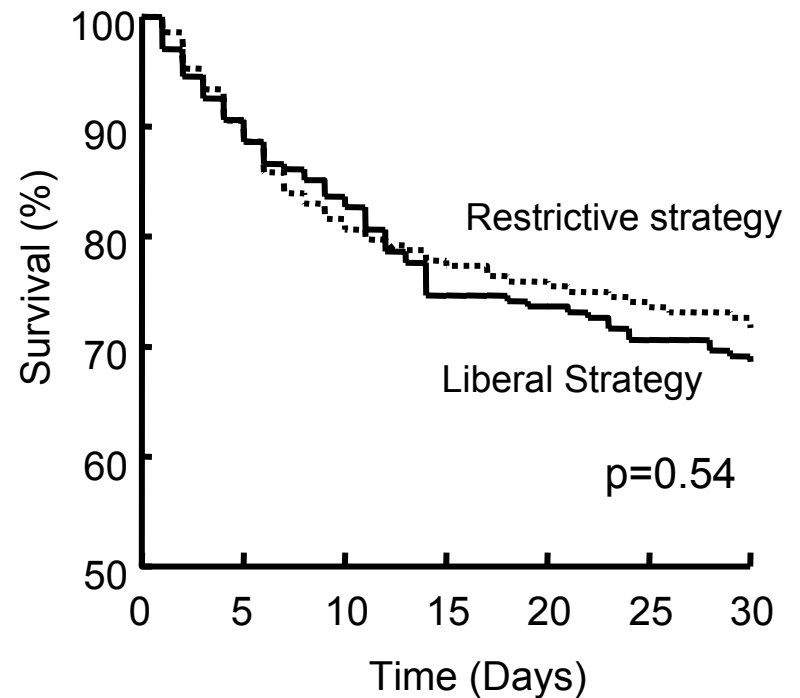


Survival according to disease severity

APACHE II \leq 20



APACHE II $>$ 20



Complications during the ICU Stay

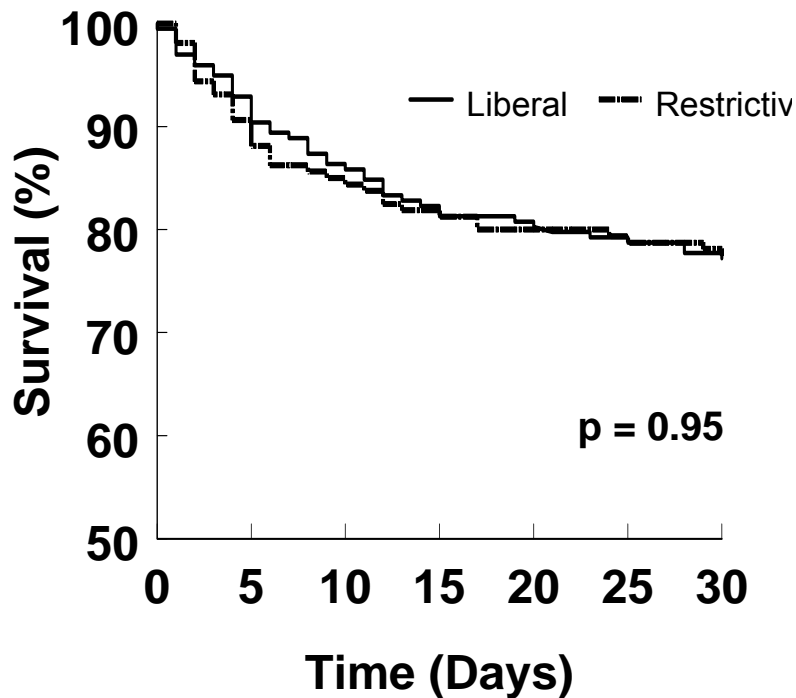
Complication	Liberal (n=420)	Restrictive (n=418)	P Values
<i>Cardiac No. (%)</i>	88 (21.0)	55 (13.2)	<0.01
Myocardial Infarction	12 (2.9)	3 (0.7)	0.02
Pulmonary Edema	45 (10.7)	22 (5.3)	<0.01
Angina	9 (2.1)	5 (1.2)	0.28
Cardiac Arrest	33 (7.9)	29 (6.9)	0.6
<i>Pulmonary No. (%)</i>	122 (29.1)	106 (25.4)	0.22
ARDS	48 (11.4)	32 (7.7)	0.06
Pneumonia	86 (20.5)	87 (20.8)	0.92

Ancillary Questions from the TRICC trial

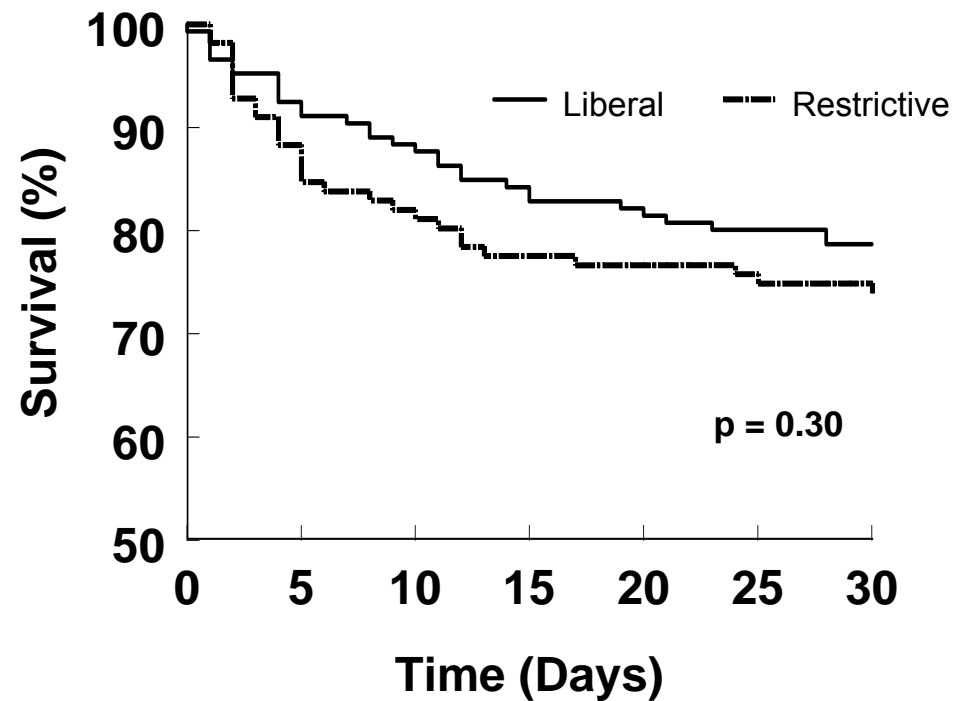
- **Do the results apply to patients with cardiac disease?**
 - Can we resolve the Wu/Rao debate?
- **What about multiple trauma and head injury victims?**

*What about subgroup analyses from
the TRICC Trial?*

Patients with cardiovascular diseases (n=357)



Patients with Ischemic Heart Disease (n=257)



Other Trigger Trials

- **PINT Study**
- **Transfusion Triggers in the Pediatric ICU**
- **FOCUS Study (Carson)**

**THE PREMATURE INFANTS IN NEED OF TRANSFUSION (PINT) STUDY: A
RANDOMIZED, CONTROLLED TRIAL OF A RESTRICTIVE (LOW) VERSUS
LIBERAL (HIGH) TRANSFUSION THRESHOLD FOR EXTREMELY LOW BIRTH
WEIGHT INFANTS**

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ELIZABETH V. ASZTALOS, MSc, FRCP(C), NANCY HEDDLE, MSc, MORRIS A. BLAJCHMAN, MD, FRCP(C),
ABRAHAM PELJOWSKI, MD, FRCP(C), ANGEL RIOS, MD, MEENA LACORTE, MD, ROBERT CONNELLY, MD, FRCP(C),
KEITH BARRINGTON, MB, FRCP(C), ROBIN S. ROBERTS, M.TECH, FOR THE PINT INVESTIGATORS*

Objective To determine whether extremely low birth weight infants (ELBW) transfused at lower hemoglobin thresholds versus higher thresholds have different rates of survival or morbidity at discharge.

The Journal of Pediatrics • September 2006

Prematures In Need of Transfusion (PINT) RCT

- **General Objective:** To evaluate risks and benefits of blood transfusion in support of infants <1000 g BW
- **Primary Objective:** To determine whether a lower or a higher Hb transfusion threshold leads to differences in clinically relevant outcomes

Outcomes of PINT Trial

	Low Hb (n=223)	High Hb (n=228)	OR 95% CI
Death before discharge	48/223 (22%)	40/228 (18%)	1.3 (0.8, 2.2)
Bronchopulmonary Dysplasia (BPD)	105/179 (59%)	108/193 (56%)	1.2 (0.7, 1.8)
Retinopathy of Prematurity (ROP) Stage 3 or 4	34/184 (18%)	33/196 (17%)	1.2 (0.7, 2.0)
Brain Injury (Parenchymal density/PVL/VE enlargement)	40/216 (19%)	45/217 (21%)	0.8 (0.5, 1.4)
Death Or Severe Morbidity	165/223 (74%)	159 (70%)	1.3 (0.8, 2.0)

Kirpalani et al., Pediatric Academic Societies Meeting, LB15, San Francisco, 2004

PINT Conclusions

- In infants <1000g BW, there is little evidence of benefit or harm from either a higher or lower threshold, for clinically relevant outcomes
- PINT data support conservative transfusion regimens
- Resulted in fewer transfusions (mean units 4.9 vs. 5.7, p-value 0.07)

Transfusion Triggers in Pediatric ICUs

Principal Investigator: Jacques Lacroix (Hopital Ste. Justine, Universite de Montreal)

Study Population

- 660 Critically Ill Children
- Hb \leq 95 g/L within the first 7 days after PICU admission.
- Age \geq 3 days after birth (at term) or \leq 14 years old.

Design: Multi-centre Non-Inferiority RCT

Intervention

Liberal Strategy: trigger of 95 g/L and target range 110 – 120 g/L

Restrictive Strategy: trigger 70 g/L and target range 85 – 95 g/L

Outcomes

New or worsening of Organ Dysfunction (MODS) post-randomization

Functional Outcomes in cardiovascular Patients undergoing Surgical Hip Fracture Repair (FOCUS)

Principal Investigator: Jeff Carson (University of Medicine & Dentistry of New Jersey)

Study Population: patients with CV disease that have undergone surgical repair of hip fracture

Design: Multi-centre RCT, 2600 patients, 25 centres in the US

Intervention:

Liberal Strategy: trigger of 100 g/L and maintain above 100 g/L

Restrictive Strategy: symptoms of anemia

Outcomes:

- Primary: functional recovery (ability to walk ten feet without human assistance 60 days post-op)
- Long term survival, nursing home placement, post-op complications

Transfusion Triggers: Summation

- TRICC has demonstrated that you can adopt a transfusion threshold of 70 g/L and maintain critically ill patients between 70 and 90 g/L
- Patients with acute MI and unstable angina may possibly benefit from Hb > 80 g/L
- Further trials are needed in patients with cardiac disease
- PINT and TRIPICU study suggests restrictive strategy tolerated in premature infants
- Need research into potential mechanisms underlying transfusion effects

Technologies to reduce the exposure to allogeneic RBCs

Interventions that potentially decrease blood transfusions

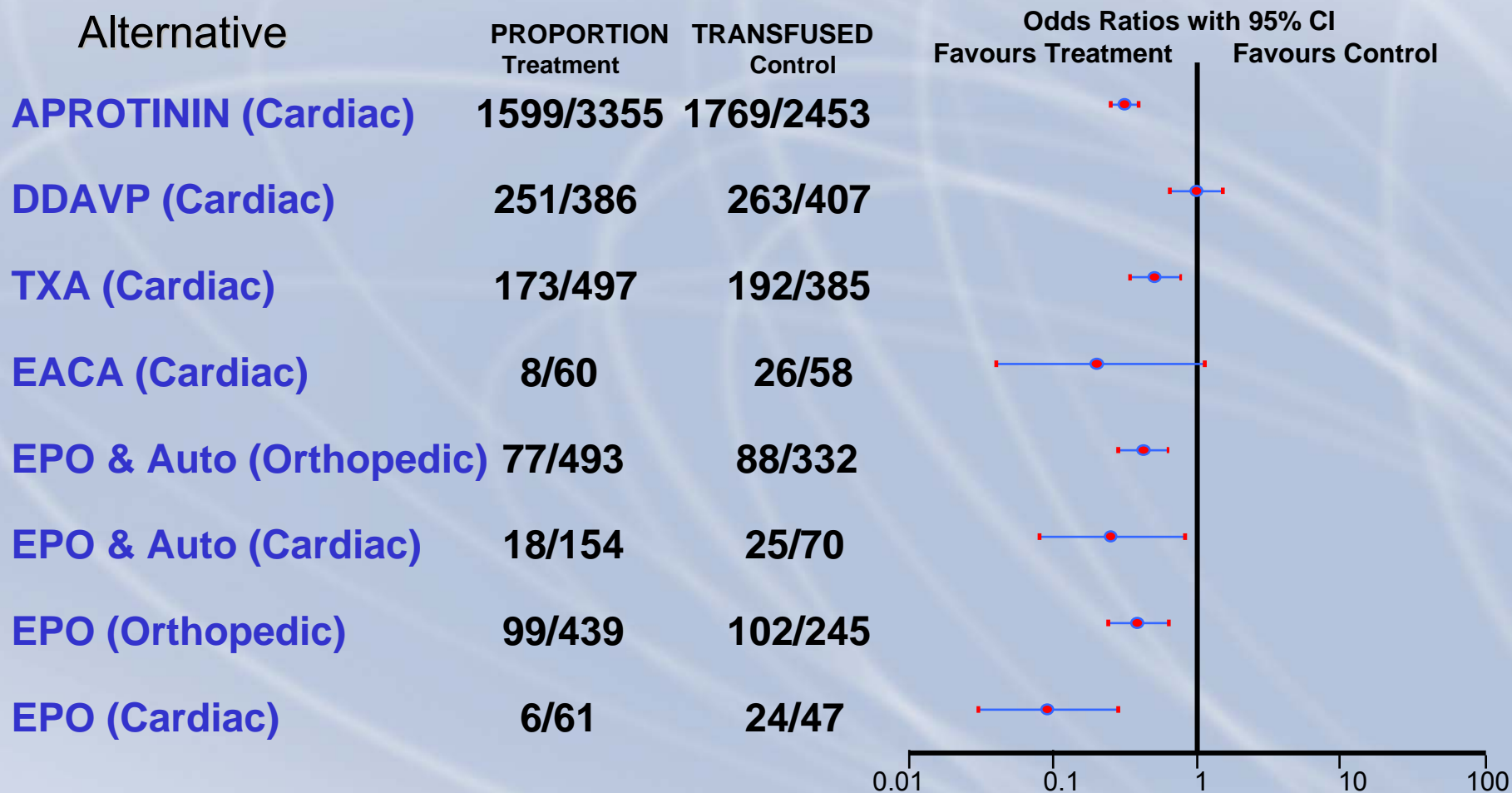
Pharmacological intervention

- **Antifibrinolytic agents**
 - serine protease inhibitors(Aprotinin)
 - lysine analogues (tranexamic acid and Amicar)
- **DDAVP**
- **Enhanced RBC production- Erythropoeitin**

Non-pharmacological interventions

- **Restrictive transfusion strategies**
- **Autologous pre-donation**
- **Normovolemic hemodilution**
- **Cell salvage**

What Drugs decrease exposure to RBCs?



Laupacis and Fergusson, Anesth Analg., 1997, Transfus Med., 1998

Aprotinin Risks

Aprotinin versus Placebo/No intervention: Adverse Events

Pooled trial data (Smith et al., 1996)

- Stroke: 2.4% vs 1.0% in aprotinin patients (p=0.027)

Cochrane Systematic Review (Henry et al., 2001)

- Mortality RR=0.87, 95% CI 0.63-1.19
- Stroke: RR=0.43, 95% CI 0.16-1.19
- Renal failure: RR=1.19, 95% CI 0.79-1.79

Laupacis Systematic Review (Laupacis et al., 1997)

- MI: OR=1.15, 95% CI 0.82-1.53

Antifibrinolytics versus Placebo: Adverse Events

Aprotinin (all doses) vs placebo

Mortality (1.5% v. 2.8%)

Rethoracotomy (1.8% v. 5%)

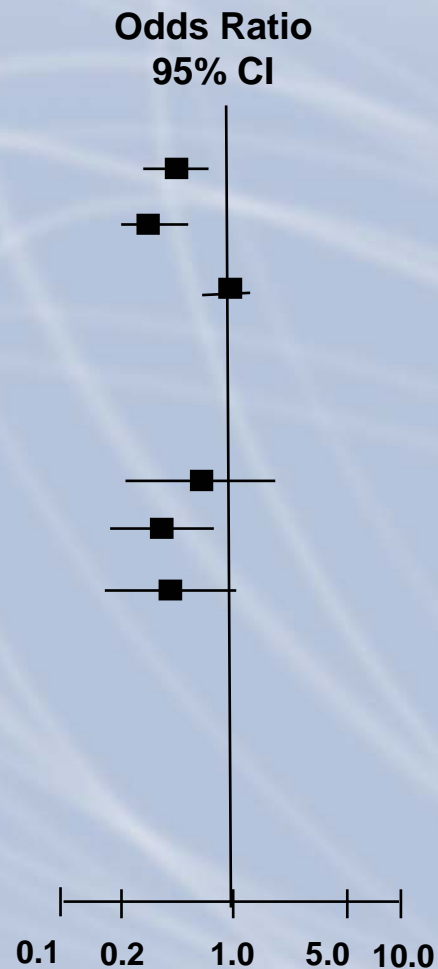
Myocardial infarction

TXA/EACA vs placebo

Mortality

Rethoracotomy

Myocardial infarction



Levi et al., Lancet 1999

Evidence of Renal Dysfunction in Cardiac Surgery

- **Three trials (Lemmer 1995, Cosgrove 1992, Swart 1994) reported a trend of a mild to moderate increase in serum creatinine but NO increase in irreversible renal failure or need for dialysis**
- **Lemmer showed that the changes were transient at 4 to 6 weeks follow-up**
- **One trial (D'ambra 1996) reported increase in renal function (creatinine > 44.2 $\mu\text{mol/L}$) in 30% of high-dose aprotinin, 14% of low-dose aprotinin, and 8% of placebo patients**

Conclusion from Adverse Event Data

- No informative data from head to head comparisons
- From placebo-controlled studies:
 - **Sparse/incomplete data on whether aprotinin increases significant MI and renal failure**
 - **Data suggests that aprotinin reduces mortality, stroke, and re-op for bleeding rates**

And along comes Mangano...

ORIGINAL ARTICLE

The Risk Associated with Aprotinin in Cardiac Surgery

Dennis T. Mangano, Ph.D., M.D., Iulia C. Tudor, Ph.D., and Cynthia Dietzel, M.D.,
for the Multicenter Study of Perioperative Ischemia Research Group
and the Ischemia Research and Education Foundation*

ABSTRACT

RESULTS

In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio, 2.34; 95 percent confidence interval, 1.27 to 4.31). Similarly, use of aprotinin in the latter group was associated with a 55 percent increase in the risk of myocardial infarction or heart failure ($P < 0.001$) and a 181 percent increase in the risk of stroke or encephalopathy ($P = 0.001$). Neither aminocaproic acid nor tranexamic acid was

Mangano Design

- **Multi-centre, multi-national, observational cohort**
- **Evaluated four groups of patients undergoing coronary-artery bypass surgery with cardiopulmonary bypass**
 - patients that received aprotinin, tranexamic acid, epsilon-aminocaproic acid, or no agent
- **A total of 4,374 patients were evaluated**
- **Used propensity-adjusted analysis to help control for differences between groups**

Mangano Results

Overall

- Aprotinin increased the odds of renal failure, MI, heart failure, and stroke compared to control patients
- A non-statistically significant increase in mortality with the use of aprotinin compared to control was observed

However,

- In patients undergoing complex surgery, no statistically significant associations were demonstrated between aprotinin and cardiovascular and cerebrovascular events compared to control patients
- Analysis looking at aprotinin versus EACA or TXA not provided
- **NO** data on proportion transfused, re-op rates, longer term mortality, massive bleeding

How do we assess the effectiveness of a technology?

- The gold standard in establishing **benefits** and **harms** is the randomized controlled trial
- Only study design where causality can be shown
 - Observational designs cannot
 - Single arm interventional studies can not
 - Studies with historical controls can not

How can we account for differences between Mangano and Systematic Reviews of RCTs

- Confounding by indication
- Patient populations (Mangano included angioplasty patients)
- Lack of reporting in clinical trials
- Different definitions used in trials
- Mangano used composite endpoints versus single condition reporting in trials

The need for large, definitive RCTs

- **Evidence of efficacy and safety of aprotinin is much greater than any other transfusion avoidance alternative**
- **Nonetheless, further trials are necessary to definitively confirm clinically meaningful benefits and harms**
 - Clearly defined and carefully measured
- **Because of rarer endpoints, large trials are necessary**
 - BART trial underway (3000 pts)

To summarize

- Aprotinin, unequivocally, effective at reducing blood transfusion/avoidance and blood loss
- Evaluation of adverse events from randomized clinical trials suggests that aprotinin reduces mortality, stroke, and need for re-operation due to bleeding
- Lack of evidence with respect to MI and renal failure
- Mangano article runs counter to evidence provided by RCTs
- Mangano article suffers from serious methodological/analytical limitations
- Overall, no definitive data to suggest that aprotinin should be abandoned in cardiac surgery

Areas where there is sufficient evidence:

- **Optimal RBC product to transfuse**
 - Leukoreduction effectiveness data is solid and consistent
- **Transfusion triggers**
 - ICU patients can tolerate threshold of 70 g/L and be maintained between 70 and 90 g/L
 - Safe to transfuse less
- **Alternatives...**
 - Aprotinin, TXA, EACA all effective at reducing proportion transfused in Cardiac Surgery, and Orthopedic Sx (aprotinin)
 - Cell Salvage effective in Orthopedics in reducing proportion transfused
 - PAD across a number of surgeries effective for reducing proportion transfused

Areas where we need RCTs:

- **Optimal RBC product to transfuse**
 - Age of RBCs - underway
- **Transfusion triggers**
 - Patients with ischemic heart disease
 - Postoperative (esp. cardiac)
- **Alternatives...**
 - Comparative studies with antifibrinolytics and non-pharmacologic interventions
 - with clinically meaningful outcomes

Areas where we need RCTs:

- **Optimal RBC product to transfuse**
 - Age of RBCs - underway
- **Transfusion triggers**
 - Patients with ischemic heart disease
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- **Alternatives...**
 - Comparative intervention
 - with clinically meaningful outcomes

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