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Evidence-based Transfusion Medicine: TRICC & BART Revisited

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Disclosure

- **No grants or consultancy monies from manufacturers of aprotinin, tranexamic acid, or epsilon-aminocaproic acid**
- **Principal Investigator on BART trial**
- **Published systematic reviews and editorials on the use of antifibrinolytics in cardiac and orthopedic surgery**

Is it right to say...

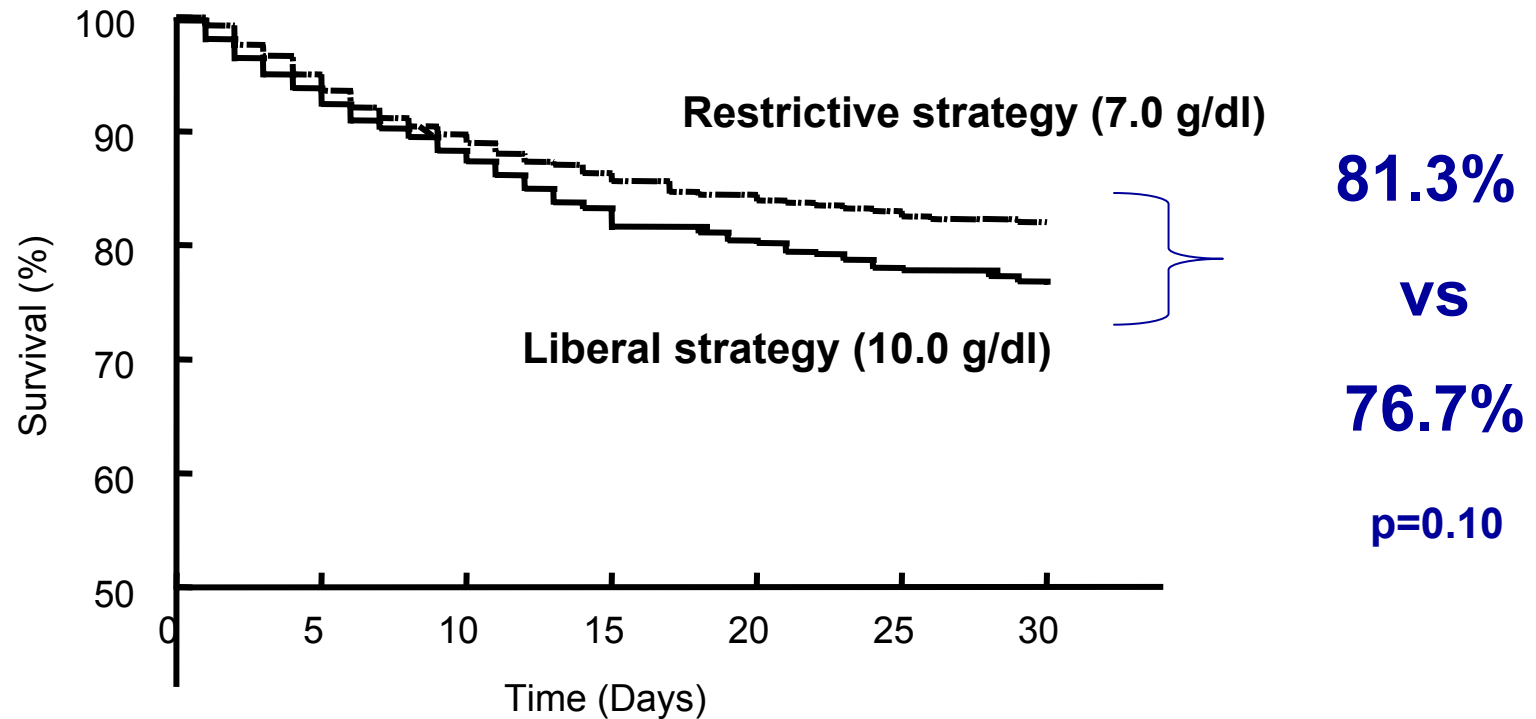
- **The safest transfusion is no transfusion**
- **The safest transfusion is the transfusion not given**
- **The best transfusion is the transfusion not given**

Raises two questions:

- **Show me the evidence?**
- **What is the comparison?**

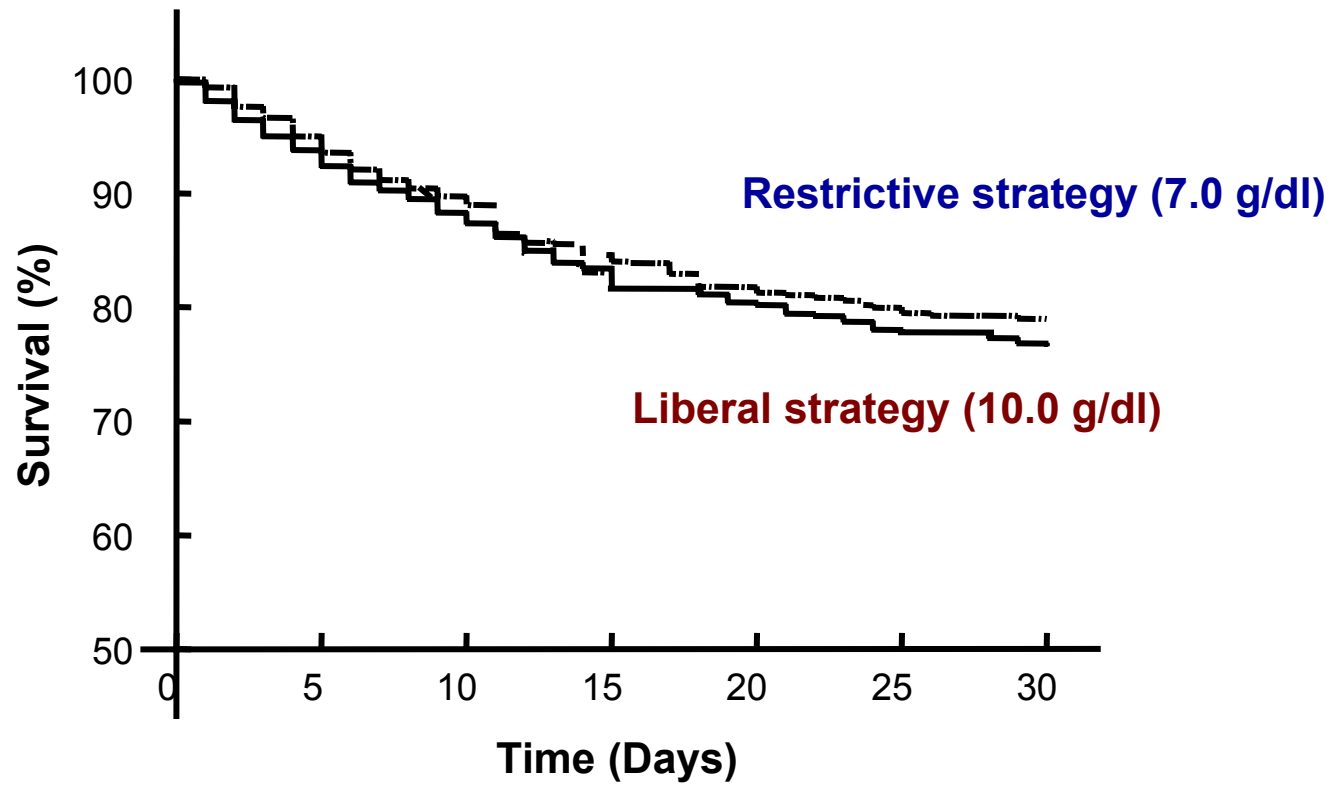
Why do RBCs still come under such scrutiny?

The main culprit: the **TRICC** Trial of 838 patients

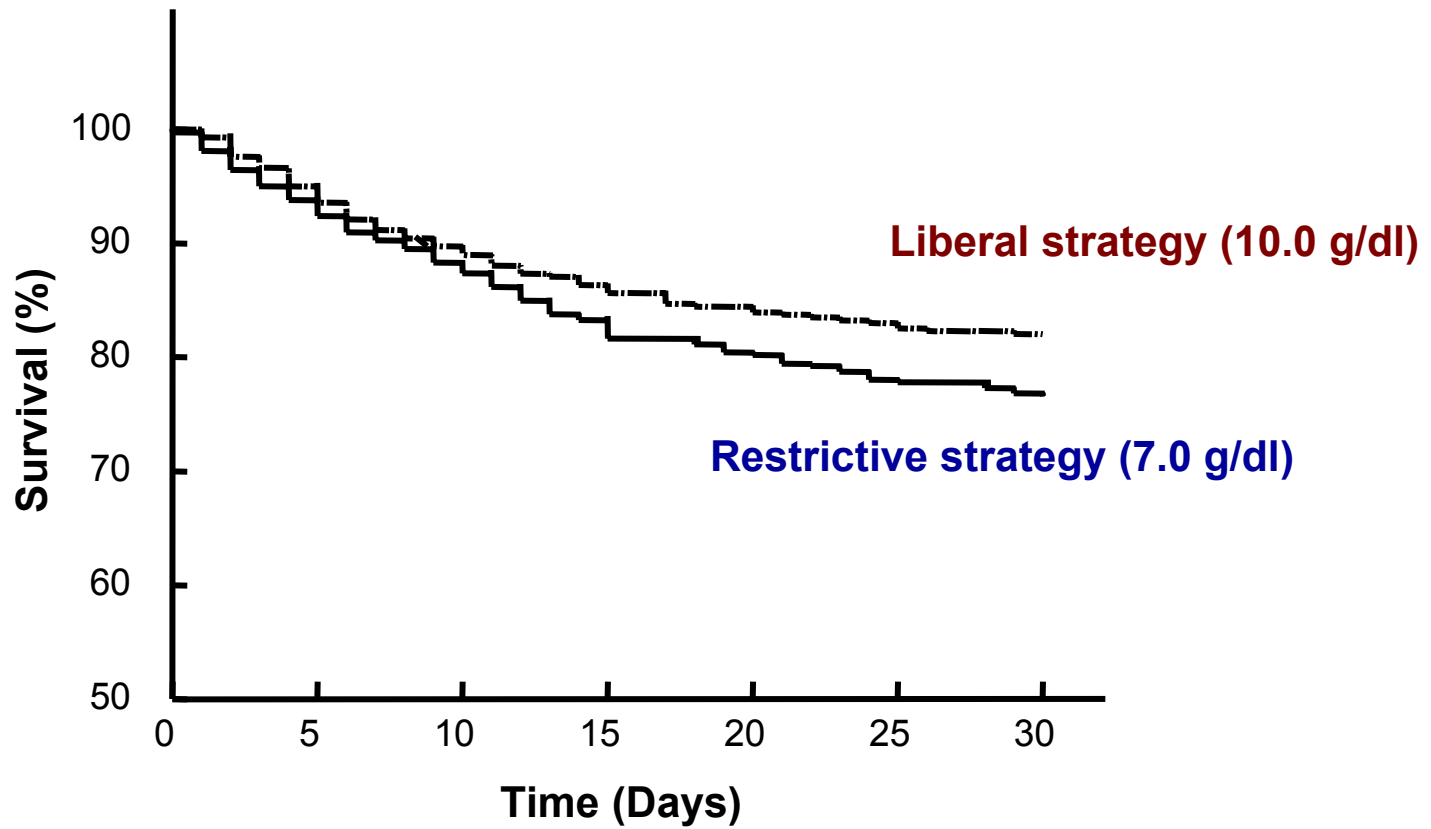


(Hebert, NEJM, 1999)

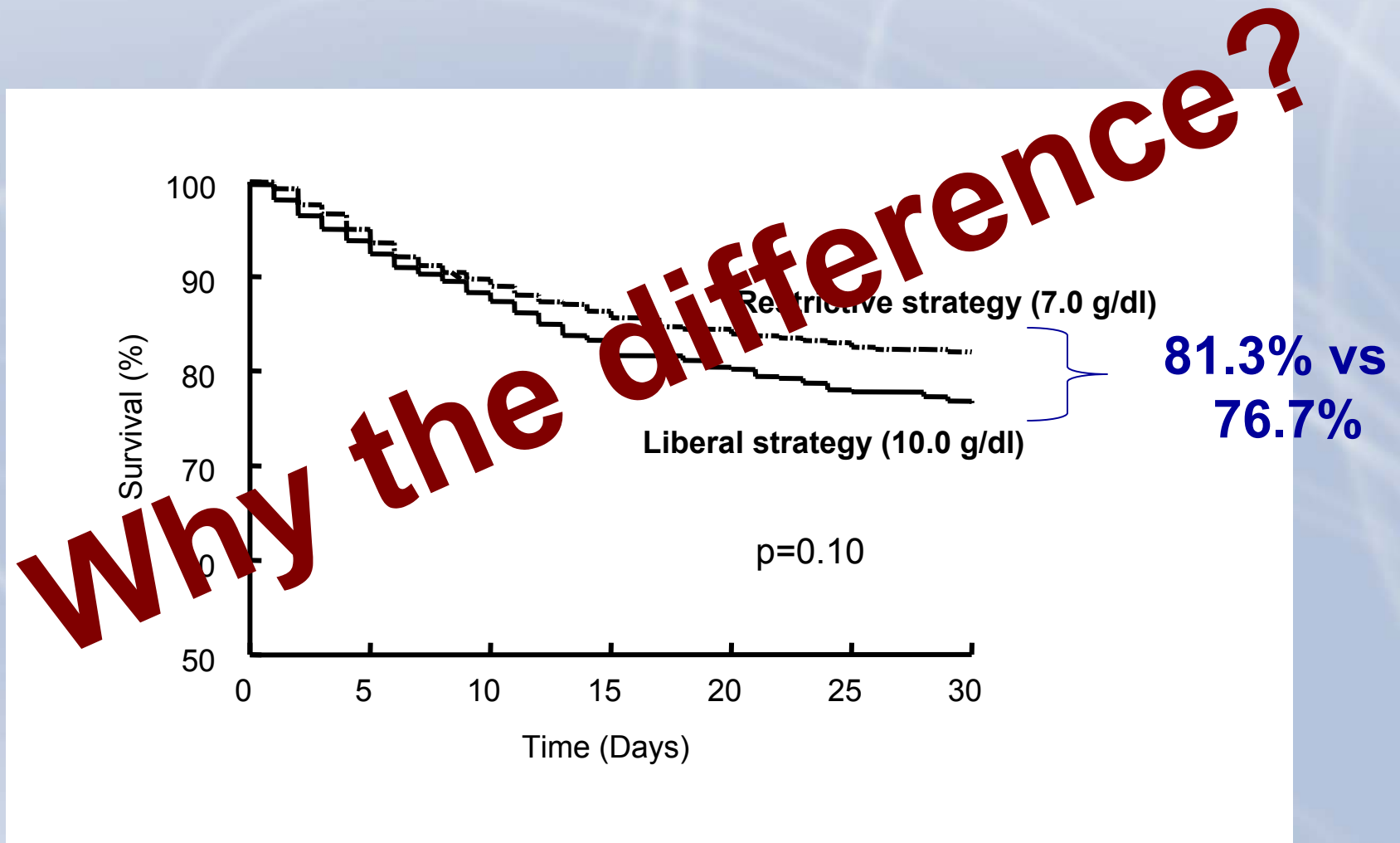
What if...



Or...



TRICC results raises a further question



(Hebert, NEJM, 1999)

Perspective

- TRICC measured 2 transfusion thresholds
- It did not measure RBCs vs no RBCs straight up
- The latter would answer the claim that “the best transfusion is the transfusion not given”
- But, is this feasible?

Back to Transfusion Thresholds

- Assessing when is it okay not to transfuse

Impetus for Evaluating Transfusion Thresholds

- Tolerating lower hemoglobin levels is a vital step towards reducing RBC exposure
- Effects of transfusion are not limited to the correction of the decreased O₂ supply
- Possible aggravation of ischemia by increasing blood volume and blood viscosity
- Moreover, patients with significant cardiovascular disease may not tolerate hemoglobin values below 80 to 100 g/L

Can we believe the large observational studies suggesting transfusions are harmful or **beneficial**?

- **Five of the “better” 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 elderly 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

Can we trust these studies?

Inferences from these studies are weakened because:

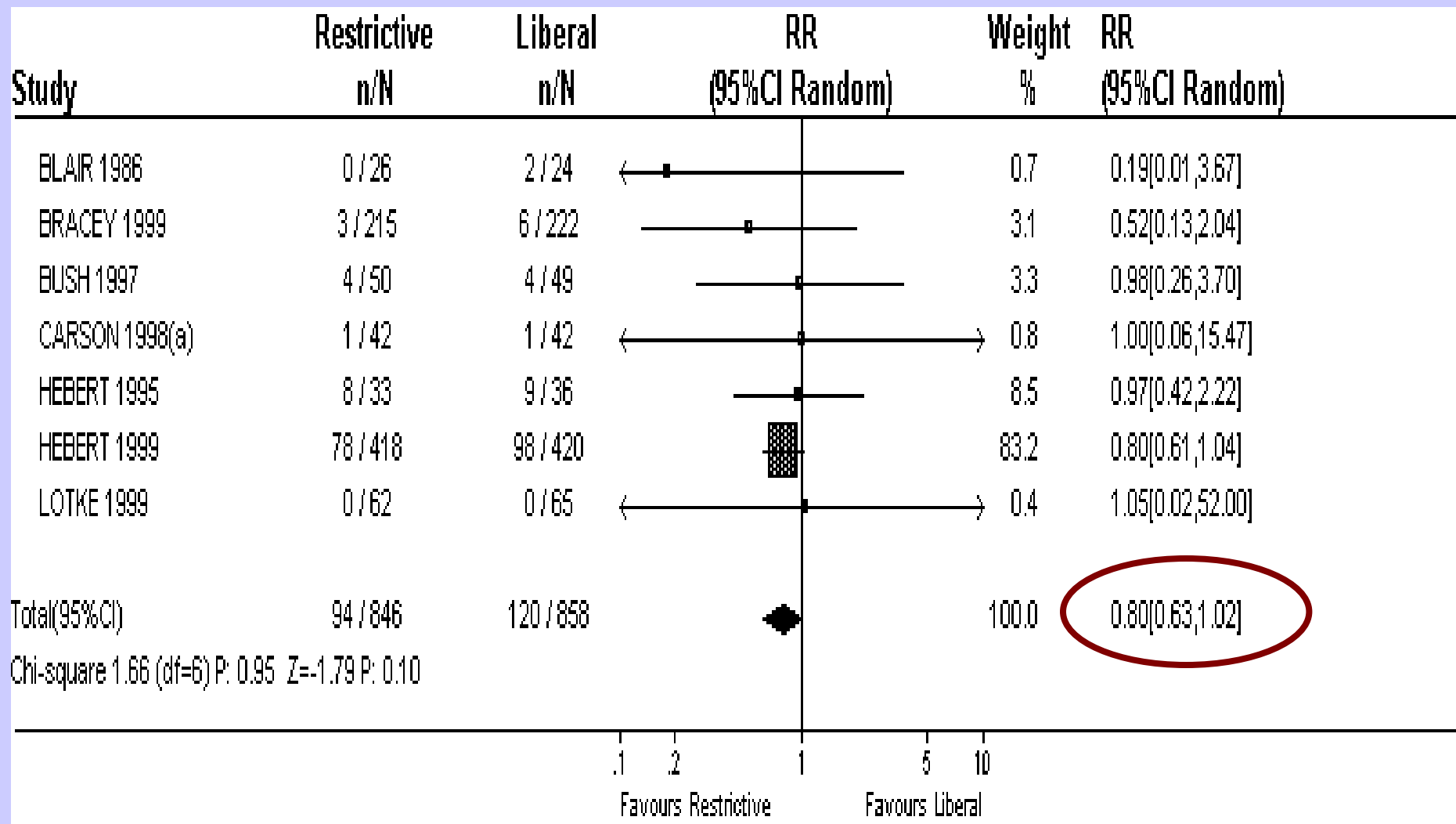
- Logic of transfusions always being harmful??
- Retrospective with limited data
- Minimal adjustment for confounding factors
- Timing of RBCs unknown
- Trigger unknown...admission hematocrit/nadir hematocrit
- **Main culprit: “Confounding by Indication”**
higher acuity → more aggressive care

**Evidence
from
Randomized Controlled Trials**

Characteristics of 10 RCTs identified

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

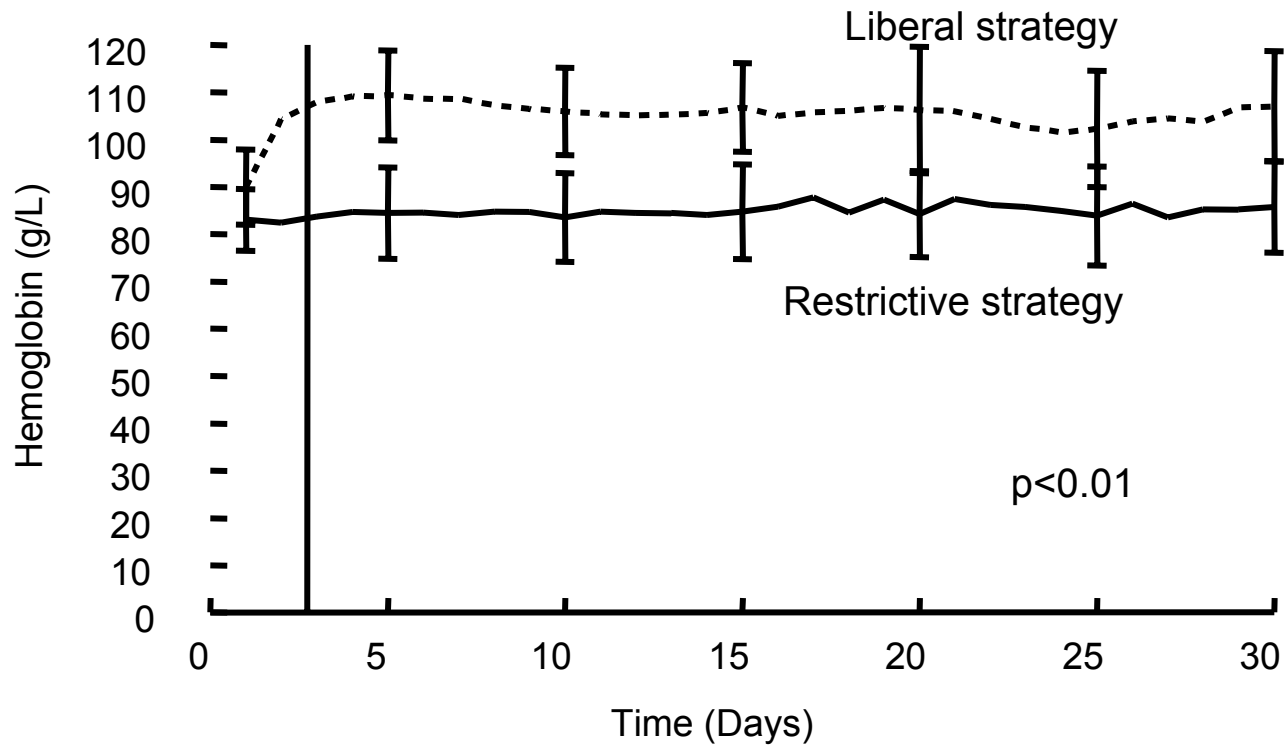
Setting: 25 ICUs across Canada

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)

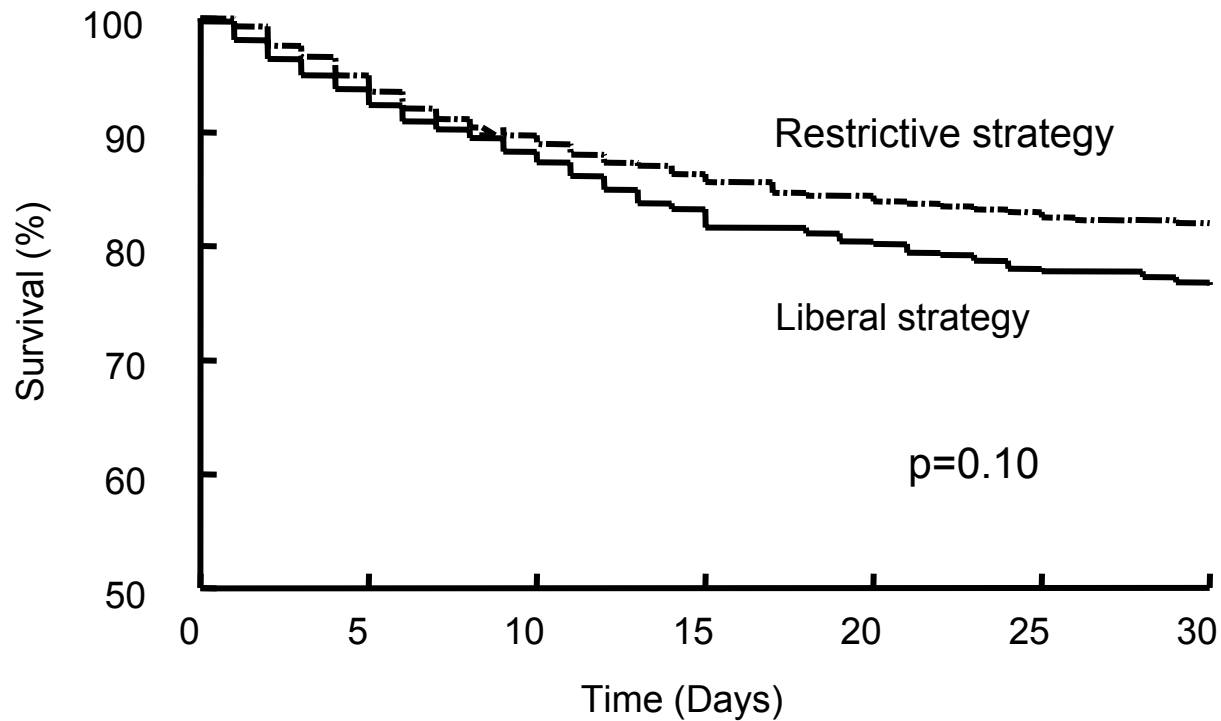
Intervention: 7.0 g/dl vs 10.0 g/dl hemoglobin trigger

Outcomes: 30 day all-cause mortality and organ failure

Hemoglobins over time

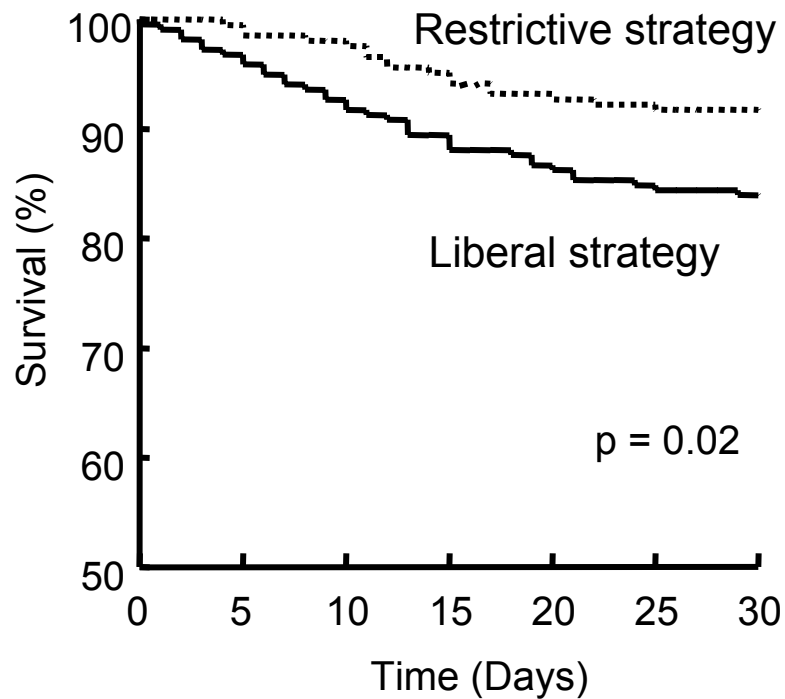


Survival of all patients over 30 days

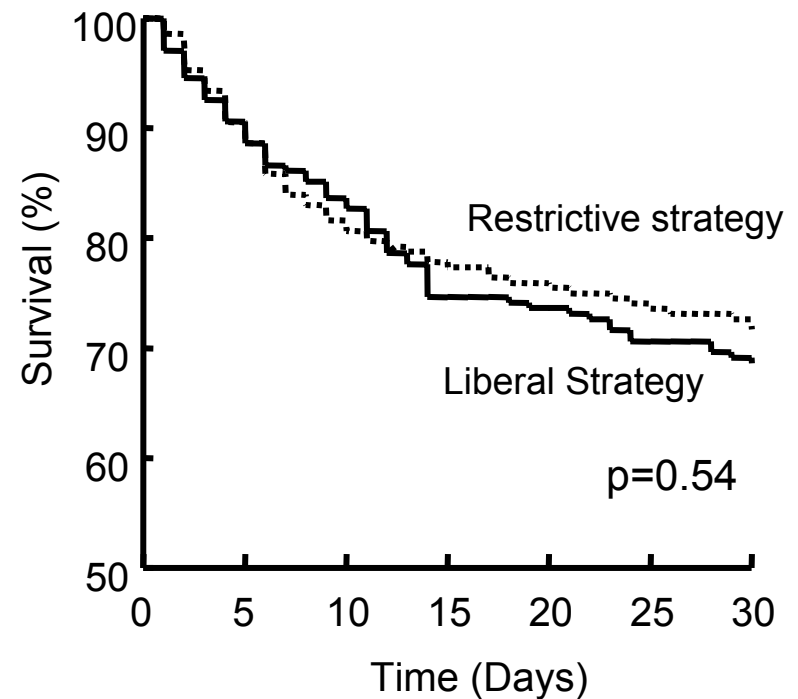


Survival according to disease severity

APACHE II \leq 20



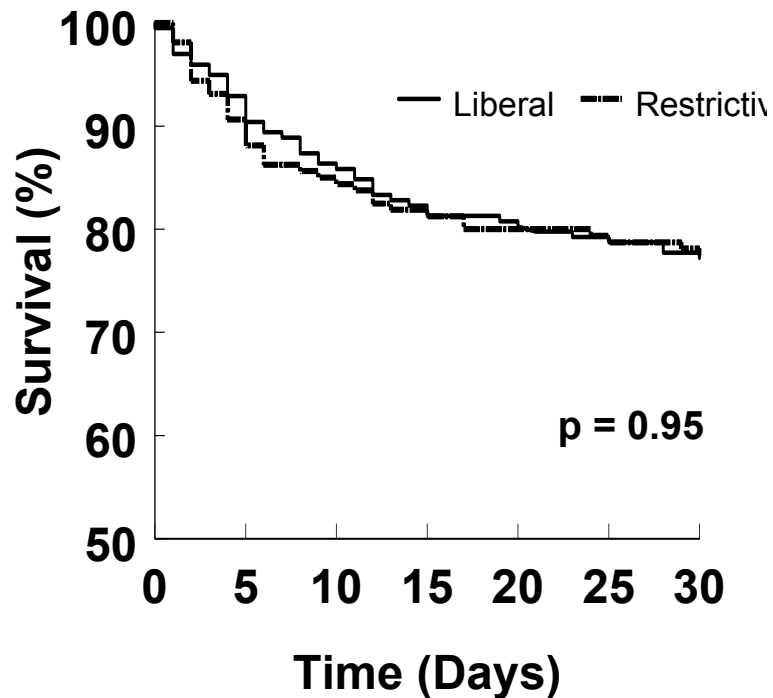
APACHE II $>$ 20



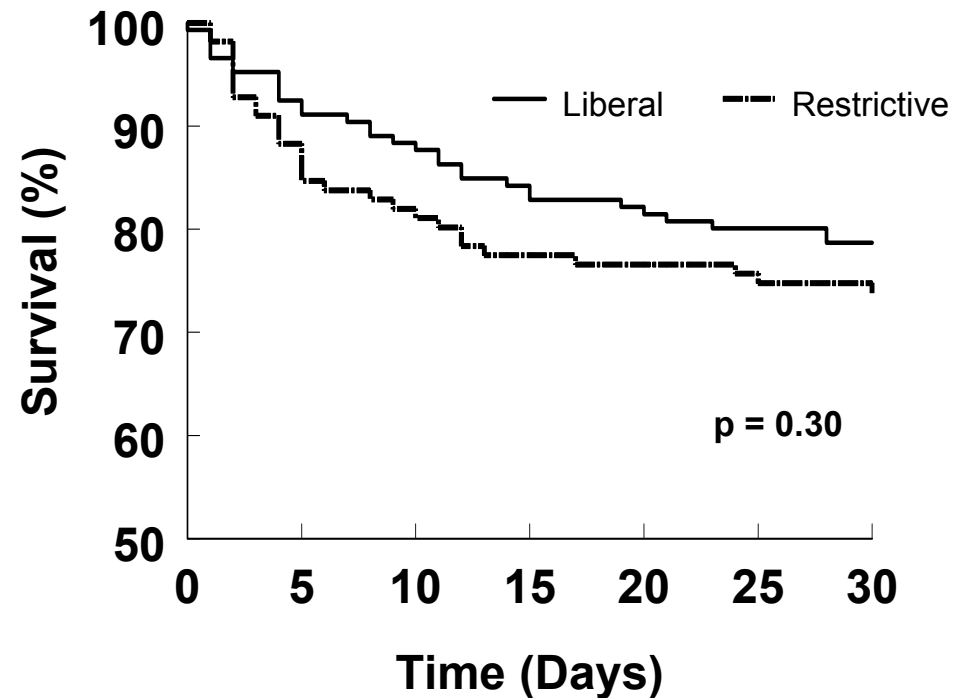
Complications during the ICU Stay

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

Patients with cardiovascular diseases (n=357)



Patients with Ischemic Heart Disease (n=257)



Other RCTs Since the Systematic Review

- **PINT Trial in Neonates**
- **Bell Trial in Neonates**
- **Transfusion Triggers in the Pediatric ICU**
- **FOCUS Study**
- **Cardiac trial underway in Canada (pilot)**
- **Cardiac trial underway in the UK**

TRIPICU Study (critically ill pediatric patients)

- **New or progressive multiple-organ failure**
 - Low Hgb: 12%
 - High Hgb: 12%
- » Lacroix et al., NEJM, 2007

PINT Trial (critically ill neonates <1000g)

- **Death Or Severe Morbidity**
 - Low Hgb: 165/223 (74%)
 - High Hgb: 159/228 (70%)
 - Odds ratio: 1.3 (0.8, 2.0)
- » Kirpalani et al., Journal of Pediatrics, 2006

Bell Trial (preterm infants in the NICU)

- Thresholds based on respiratory support**
- 1° outcome not explicitly stated**
 - More neurological adverse events in low hgb group

Recent threshold trials suggest NO untoward effect of RBCs

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/Canada

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 (MI and infection)

Transfusion Thresholds Summary

- 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 suggest no untoward effects of restrictive thresholds
 - **Or suggest no adverse effects of RBCs?**
- Results of FOCUS and UK Cardiac Trial are eagerly anticipated!

Conclusions

- **If we accept “the gap” of harm, need to consider what is responsible**
 - Leukoreduction? – likely contributes
 - Age of blood? – no evidence
 - Other unmeasured effects? – beyond evaluation??
- **Surprisingly, despite millions of units collected, processed, and administered, there is very little evidence on when and where RBCs are effective/ineffective and what constitutes the optimal RBC product**

Two issues to keep in mind

- **What if FOCUS and Cardiac threshold trials demonstrate:**
 - No difference between thresholds
 - Or a benefit of more RBCs
- **Although not addressed today, we need to keep the risk/benefit of RBCs in perspective with respect to alternatives**
 - Drugs and non-drug technologies also have their own risk/benefit ratios
 - Need definitive RCTs to evaluate

***Antifibrinolytics in Cardiac Surgery:
BART in perspective***

Cardiac Surgery and Blood Transfusion

- **>1,000,000 cardiac surgeries worldwide**
- **High-risk cardiac procedures (repeat and combined procedures) account for 25% of total cardiac surgeries**
- **These procedures present a high risk of bleeding**
- **Cardiac procedures consume 16% of blood supply**
- **The HIV/HCV epidemic in the 1980's fueled a search for therapies to minimize the need for transfusion**

Background on Aprotinin

- Aprotinin, an antifibrinolytic, is a serine proteinase inhibitor used to reduce perioperative blood loss
- By reducing blood loss, it reduces the need for allogeneic (donated) blood transfusion
- Administered peri-operatively
- Used in the 1980's and trialled in late 1980's
- Until 2006/7, most often drug used for preventing blood loss in cardiac surgery in North America and Europe
- Approved by FDA in 1993

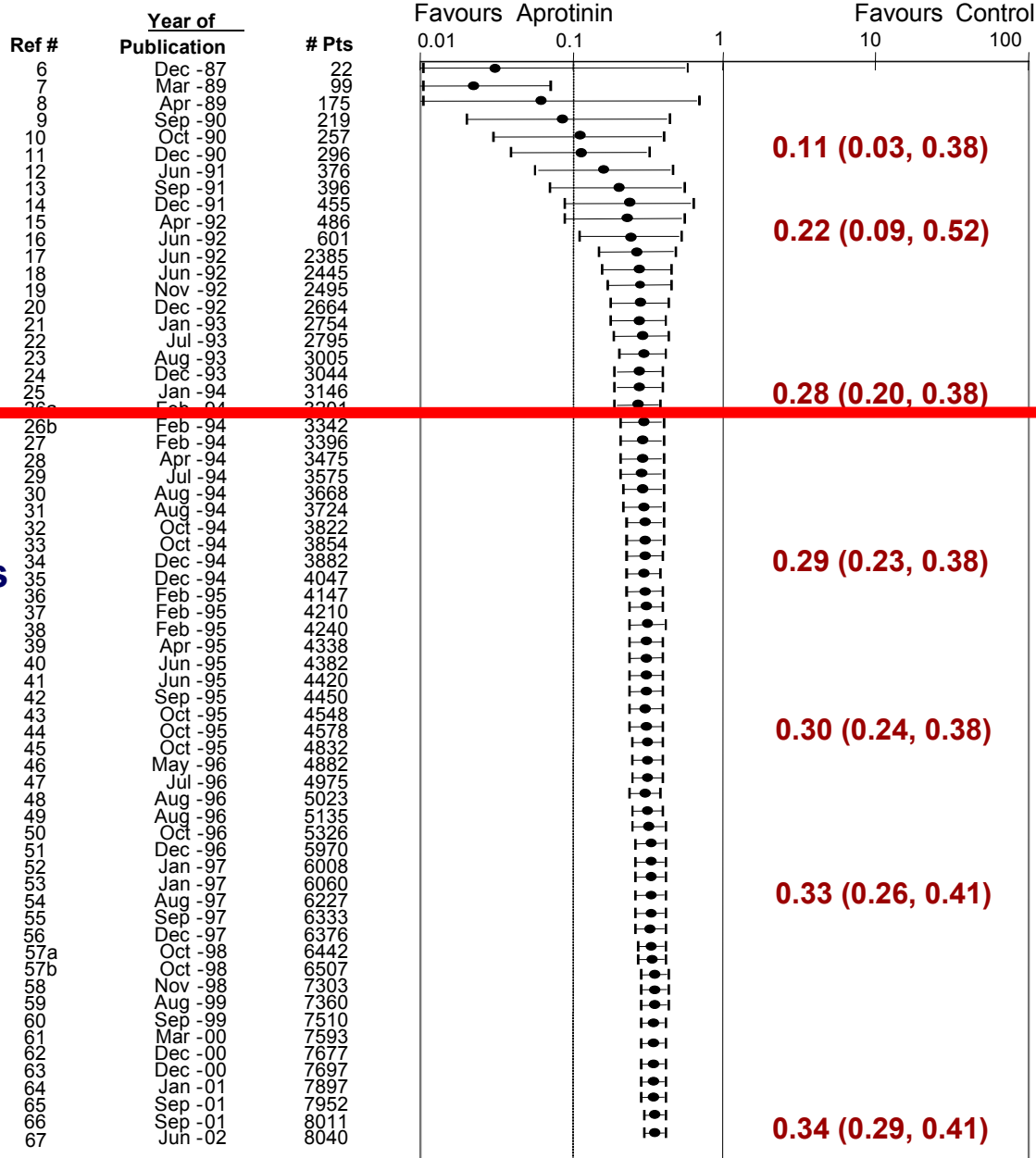
Background on Lysine Analogues

- Epsilon-Aminocaproic and Tranexamic acid
- Drugs inhibit the proteolytic activity of plasmin and the conversion of plasminogen to plasmin by plasminogen activators (inhibits fibrinolysis, thus reducing blood loss)
- Used since the early 1990's to reduce blood loss and need for transfusion
- Seen as the cheaper and less effective cousin to aprotinin
 - **Not by all, but by most**

1987 to 2001

***What did we know about the effectiveness of
aprotinin and lysine analogues?***

Odds Ratios with 95% Confidence Intervals



Proven Efficacy
(need for RBCs)

Redundant Trials?
> 5000 additional pts

Tranexamic Acid (30 studies)

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (Version 02)
 Comparison: 10 Tranexamic Acid vs Control (Blood Transfusion & Blood Loss) - Cardiac Surgery
 Outcome: 01 No. Exposed to Allogeneic Blood



**Same Story:
 Many trials demonstrating effectiveness**

What about safety of aprotinin?

SAEs/Harm

Aprotinin versus Placebo/No intervention:

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

***What about head-to-head comparisons of
aprotinin vs TXA and EACA?***

Transfusion Avoidance

- Pooled Relative Risk (>1 favours aprotinin):
 - Aprotinin vs TXA: 1.08 (95% CI 0.88 to 1.32)
 - Aprotinin vs EACA: 1.14 (95% CI 0.84 to 1.55)

Re-Operations

- Pooled Relative Risk (>1 favours aprotinin):
 - Aprotinin vs TXA: 0.98 (95% CI 0.51 to 1.88)
 - Aprotinin vs EACA: insufficient data

Carless, BMC Cardiovascular Disorders,

As of 2001, what did we know?

- Effectiveness and history of aprotinin well-established
- Aprotinin was the drug of choice
- Head to head trials suggest TXA may be as effective
- Analysis of all cause mortality, MI and stroke were uninformative
- Data remained an uncertain basis for replacing aprotinin
- Sounds like the right time for a definitive comparator trial!



BART

Blood Conservation using
Antifibrinolytics in a Randomized Trial



CIHR IRSC

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en santé du Canada



Ontario

Why did we undertake BART?

- **To definitively determine if aprotinin was superior**
- **To determine if Aprotinin is worth the cost (\$1500 vs \$300 vs \$4)**
- **Pharmaceutical companies would NOT fund comparative studies**
- **No pressure from regulators to conduct head-to-head study**

Our Primary Question:

- Does aprotinin decrease massive postoperative bleeding by an ARR of 3% (from 6% to 3%) compared to epsilon-aminocaproic acid or tranexamic acid in patients undergoing high-risk cardiac surgery?

Study Design:

- Double-blind multi-centre randomized trial
- 19 centres across Canada

Study Population

- Targeted cardiac surgical patients at **high risk of death, massive hemorrhage and life threatening complications**
- Increased risk was based upon the type of procedure, defined as surgical interventions with:
 - an average mortality at $\geq 2X$ the norm for bypass surgery
 - risk of re-operation $> 5\%$

Patients randomized to:

- **Aprotinin** ("high-dose-scheme"): 2 million units loading dose + 2 million units CPB pump prime + maintenance infusion of 500,000 units per hour
OR
- **Tranexamic acid**: 30mg/kg loading dose + 2mg/kg pump prime + 16mg/kg/hr maintenance infusion
OR
- **Epsilon-aminocaproic acid**: 10g loading dose + 2g/hr maintenance infusion (no pump prime)

Primary Outcome (Composite)

- Massive bleeding: blood loss from chest tubes $>1.5L$ over any 8 hour period in first 24 hrs post-op
- Massive transfusion: replacement of >10 units in first 24 hrs post-op
- Death due to hemorrhage
- Re-operation for hemorrhage and tamponade
- **Met outcome if any 1 of 4 reached**

Secondary Outcomes

Two major categories of clinical outcomes:

Fatal / Life-threatening

- 30-day all-cause mortality
- Myocardial Infarction
- Stroke (focal neurologic deficit lasting more than 24 hours)

Serious

- Renal dysfunction/Failure (increase in creatinine, dialysis preceded by a doubling of creatinine)
- Prolonged invasive mechanical ventilatory support (>48 hours)
- Prolonged low output state (need for vasopressors, balloon pump or ventricular assist device for >48 hours)

Timeline

- **Protocol written in 1999**
- **Funded in 2001 by Ontario MoH and CIHR**
- **Patient enrollment began in September of 2002**
- **Trial ended on October 16th, 2007**

BART Results

- **Randomized 2,468 high risk cardiac surgical patients**
- **2,331 patients were included in our main ITT analysis**
 - 781 received aprotinin
 - 770 received tranexamic acid
 - 780 received aminocaproic acid

Fergusson, NEJM, 2008

Primary Outcome: Massive Bleeding

Components	Aprotinin (N=780)	Tranexamic Acid (N=770)	Aminocaproic Acid (N=780)
	<i>number of events (percent)</i>		
Bleeding from chest tubes	41 (5.3)	58 (7.5)	65 (8.3)
Massive transfusion	16 (2.1)	17 (2.2)	22 (2.8)
Death due to hemorrhage	11 (1.4)	8 (1.0)	4 (0.5)
Reoperation for bleeding	43 (5.5)	62 (8.1)	64 (8.2)
Any massive bleeding	74 (9.5)	93 (12.1)	94 (12.1)

- **Aprotinin vs Aminocaproic acid: RR: 0.80 (95% CI, 0.59 to 1.07)**
- **Adjusted OR: 0.80 (95% CI, 0.58 to 1.11)**

- **Aprotinin vs Tranexamic acid: RR: 0.79 (95% CI, 0.59 to 1.05)**
- **Adjusted OR: 0.78 (95% CI, 0.56 to 1.08)**

30-day Mortality

- A total of 108 of 2331 patients (4.6%) died within 30 days after study randomization
 - 47 (6.0%) in the aprotinin group
 - 30 (4.0%) in tranexamic acid
 - 31 (3.9%) in aminocaproic acid
- Aprotinin vs Tranexamic acid: RR: 1.55 (95% CI, 0.99 to 2.42)
- Aprotinin vs Aminocaproic acid RR: 1.52 (95% CI, 0.98 to 2.36)
- Aprotinin vs lysine analogues: RR: 1.53 (95% CI, 1.06 to 2.22)

Table 5. Major Secondary Outcomes.

Adverse Event	Aprotinin		Tranexamic Acid		Aminocaproic Acid		Aprotinin vs. Tranexamic Acid	Aprotinin vs. Aminocaproic Acid
	<i>no. of patients</i>	<i>events (%)</i>	<i>no. of patients</i>	<i>events (%)</i>	<i>no. of patients</i>	<i>events (%)</i>	<i>relative risk (95% CI)</i>	
Stroke	759	22 (2.9)	753	28 (3.7)	768	22 (2.9)	0.78 (0.45–1.35)	1.01 (0.57–1.81)
Myocardial infarction	717	33 (4.6)	727	28 (3.9)	735	20 (2.7)	1.19 (0.73–1.95)	1.69 (0.98–2.92)
Deep-vein thrombosis or pulmonary embolism	712	9 (1.3)	718	8 (1.1)	729	7 (1.0)	1.00 (0.99–1.01)	1.00 (0.97–1.01)
Respiratory failure	771	96 (12.5)	769	100 (13.0)	776	98 (12.6)	0.96 (0.74–1.24)	0.99 (0.76–1.28)
Cardiac shock	772	112 (14.5)	769	112 (14.6)	778	119 (15.3)	1.00 (0.78–1.27)	0.95 (0.75–1.20)
Renal failure								
Preexisting condition								
Any	770	129 (16.8)	766	137 (17.9)	774	132 (17.1)	0.94 (0.75–1.17)	0.98 (0.79–1.23)
Doubling of baseline creatinine level	772	49 (6.3)	766	34 (4.4)	773	38 (4.9)	1.43 (0.93–2.19)	1.29 (0.86–1.95)
Postoperative creatinine level >150 µmol/liter	772	119 (15.4)	767	125 (16.3)	775	124 (16.0)	0.95 (0.75–1.19)	0.96 (0.76–1.21)
Postoperative dialysis	773	24 (3.1)	769	24 (3.1)	778	21 (2.7)	0.99 (0.57–1.74)	1.15 (0.65–2.05)
New condition								
Any	770	102 (13.2)	766	97 (12.7)	774	100 (12.9)	1.05 (0.81–1.36)	1.03 (0.79–1.33)
Doubling of baseline creatinine level	772	47 (6.1)	766	31 (4.0)	773	35 (4.5)	1.50 (0.97–2.34)	1.34 (0.88–2.06)
Postoperative creatinine level >150 µmol/liter	772	92 (11.9)	767	86 (11.2)	775	93 (12.0)	1.06 (0.81–1.40)	0.99 (0.76–1.30)
Postoperative dialysis	773	16 (2.1)	769	19 (2.5)	778	11 (1.4)	0.84 (0.43–1.62)	1.46 (0.68–3.13)

Interpretation

- **We found an absolute 2.5% increase in massive bleeding with the use of TXA or EACA (9.5% vs 12%)
= **NNT of 40 patients****
- **We found an absolute 2% increase in mortality for patients administered aprotinin (4% vs 6%)
= **NNT of 50 patients****
- **Without question, harm trumps benefit**

Need to go back to 2006

- A number of large observational studies were published from 2006 to 2008
- All showed aprotinin was harmful in terms of serious morbidity and mortality
- Most studies compared aprotinin to “nothing”
- Contradicted all the trial evidence

Concerns with ALL Observational Studies

- Potential for significant confounding by indication (apples & oranges)
- Outcomes confounded by patient prognosis, physician preference based on prognosis, and physician choices
 - **No amount of elaborate analysis can account for these factors**

Big picture, why we need to be concerned?

- FDA issued warning for aprotinin
- Health Canada and Bayer issued a public communication highlighting potential risk
- Other regulatory agencies did the same
- All based on observational work, not trial evidence!

Conclusions

- **BART provides an example of why we need large trials with clinically important outcomes (benefits and harms)**
- **Rather than conducting many small, redundant RCTs and observational studies**
- **Clearly, the Regulators play an important role (HC, FDA)**
 - They could and should have asked for the 3000 patient trial back in the early 1990s

Thank you!

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