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Bleeding, Anti-fibrinolytics, Cardiac Surgery & the BART trial

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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**

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

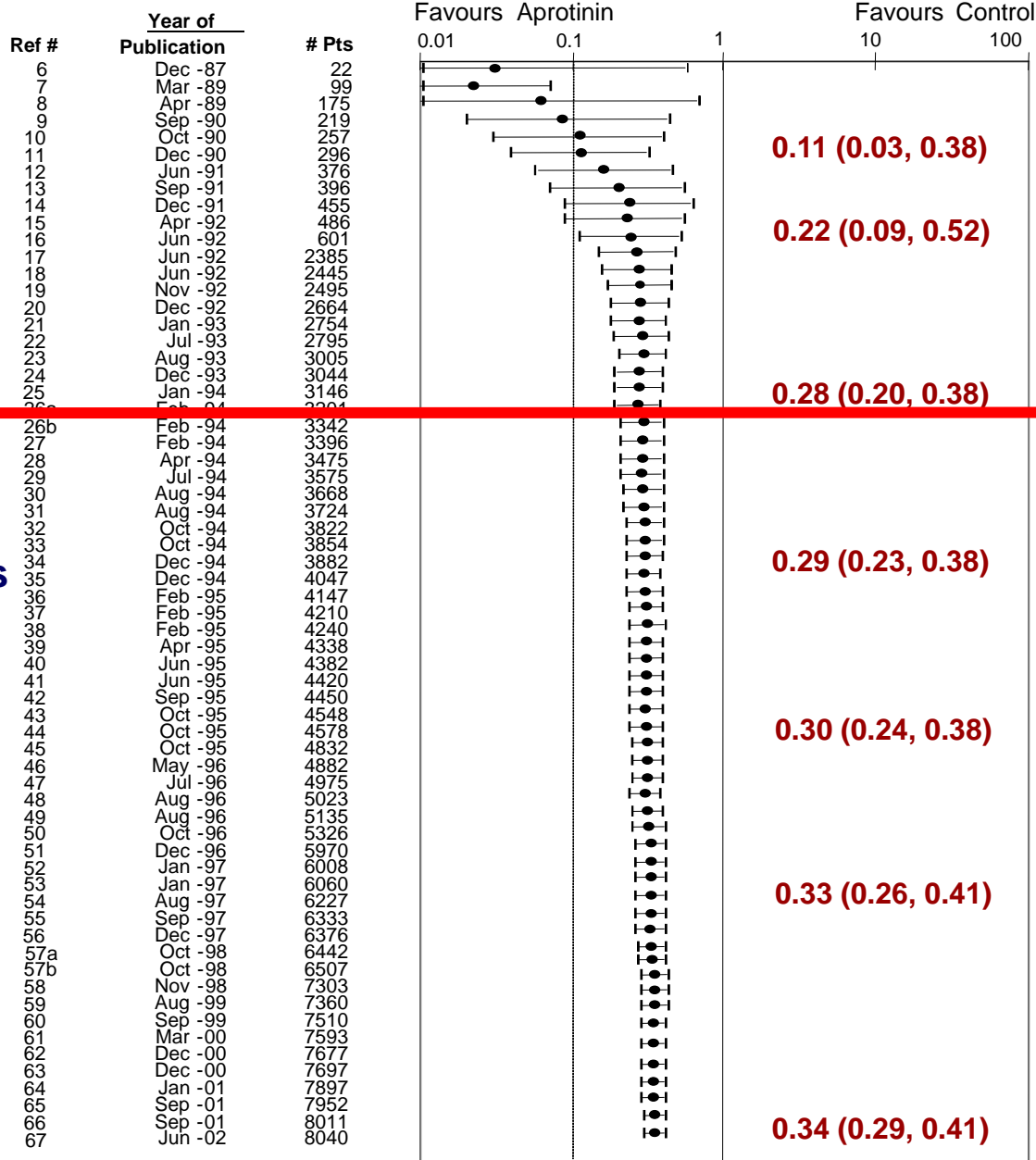
Background on Lysine Analogues

- 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

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?

Risk of Aprotinin

- **Known**
 - Anaphylaxis
- **Potential**
 - Renal dysfunction?
 - Aprotinin loves the kidneys
 - Thrombotic risk?
 - Mortality?
 - Downstream effects of renal and thrombotic effects
- **Also need to consider harm of not receiving aprotinin**
 - Re-op for bleeding
 - Death due to bleeding

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



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Ontario

Why did we undertake BART?

- **To definitively determine if aprotinin was superior**
- **To reduce significant practice variation**
- **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%)
= NNTH 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”
- 1 compared aprotinin to aminocaproic acid

- 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**
- Evaluating aprotinin versus “nothing” did not reflect the reality of practice (all 3 antifibs commonly used in high-risk surgery)

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 pragmatic 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



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