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## Observational & Randomized Studies in Drug Safety: The Aprotinin Story

Dean A. Fergusson, MHA, PhD

Senior Scientist and Director, Clinical Epidemiology Program, Ottawa Hospital Research Institute

Director, University of Ottawa Centre for Transfusion Research

Associate Professor, Departments of Medicine, Surgery and of Epidemiology & Community Medicine, University of Ottawa

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# Disclosure

- No grants or consultant monies from manufacturers or distributors 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 16-20% of blood supply
- The HIV/HCV epidemic in the 1980's fueled a search for "transfusion alternatives" and "blood substitutes"

# Antifibrinolytic Agents in Cardiac Surgery

- Drugs act by inhibiting fibrinolysis (prevent the breakdown of clots)
- In turn, blood loss is reduced
- In turn, need for donated blood is reduced
- Administered peri-operatively
- Used since the 1970s, trials began in late 1980s
- Until 2006, aprotinin was the dominant antifibrinolytic in cardiac surgery
- Lysine analogues (TXA& EACA) seen as the cheaper and less effective cousin to aprotinin

**What about the effectiveness of aprotinin and lysine analogues?**

**1987 to 2001**

# Effectiveness of Aprotinin in Cardiac Surgery (1987 to 2001)

**Outcome:** proportion transfused

**Comparison:** placebo or nothing

**Patients:** low & high risk cardiac surgery

- **1994, 16 trials: OR 0.23 (0.16 to 0.33)**

Fremes SE et al. Ann Thorac Surg. 1994

- **1997, 45 trials: OR 0.31 (0.25 to 0.39)**

Laupacis A et al. Anesth Analg. 1997

- **2001, 54 trials: RR 0.70 (0.60 to 0.76)**

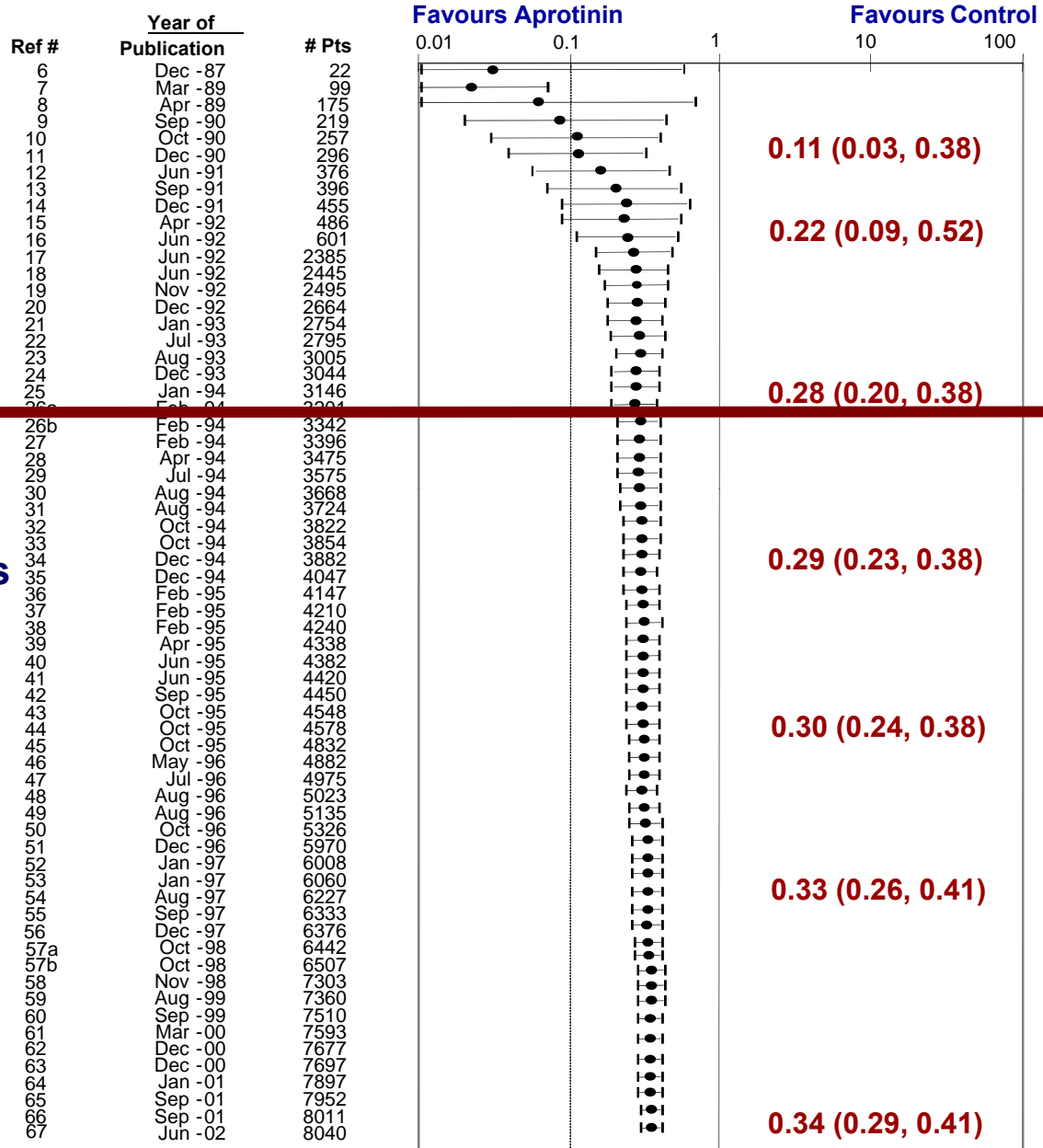
Henry DA et al. Cochrane Library, Vol. 4, 2001

## Cumulative Meta-Analysis of all Placebo & Open-label Aprotinin RCTs

**Proven Efficacy**

**? Redundant Trials**

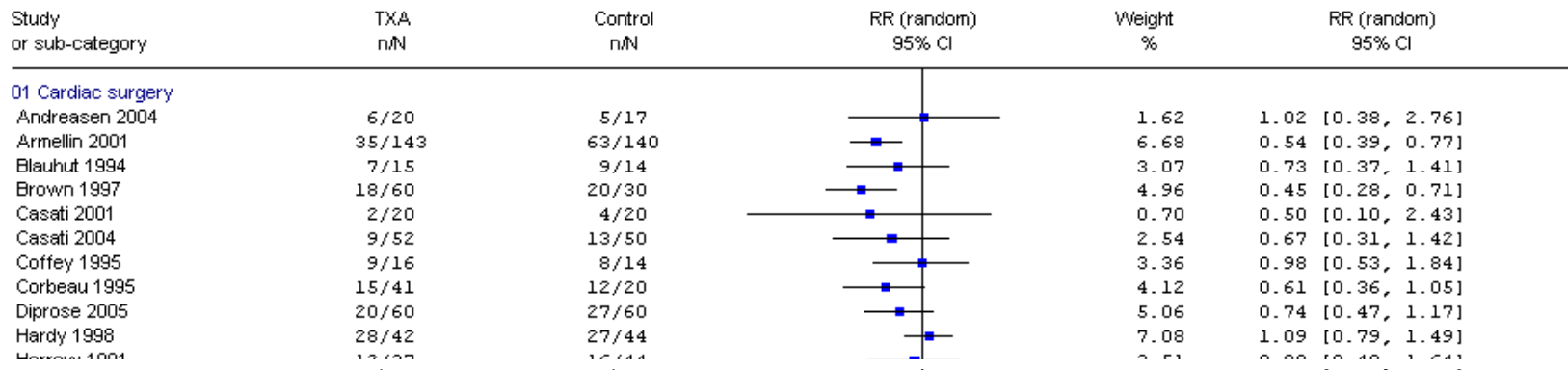
**? 5000 additional pts**



Odds Ratios with 95% Confidence Intervals

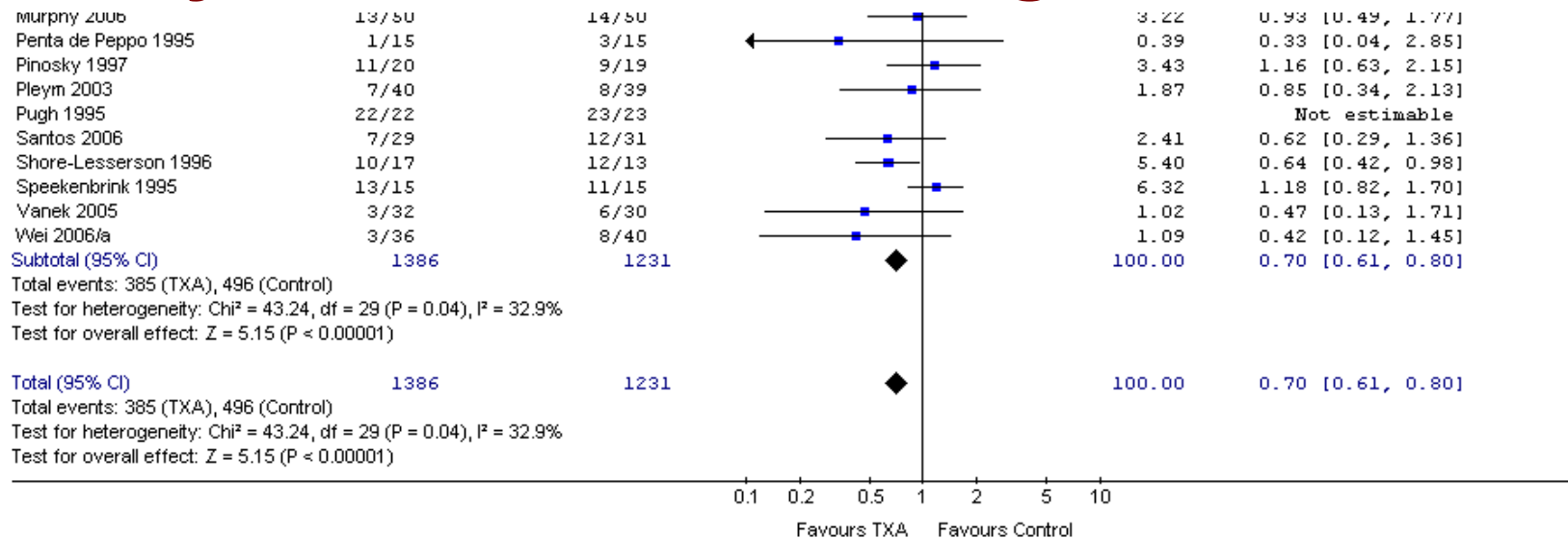
# Tranexamic Acid Placebo/Open-Label RCTs (n=30)

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 as aprotinin:**

**Many RCTs demonstrating effectiveness**



**What about safety of aprotinin?**

**1987 to 2001**

## **RCT Evidence of potential harm (up to 2001) Aprotinin vs Placebo/Open-label:**

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)

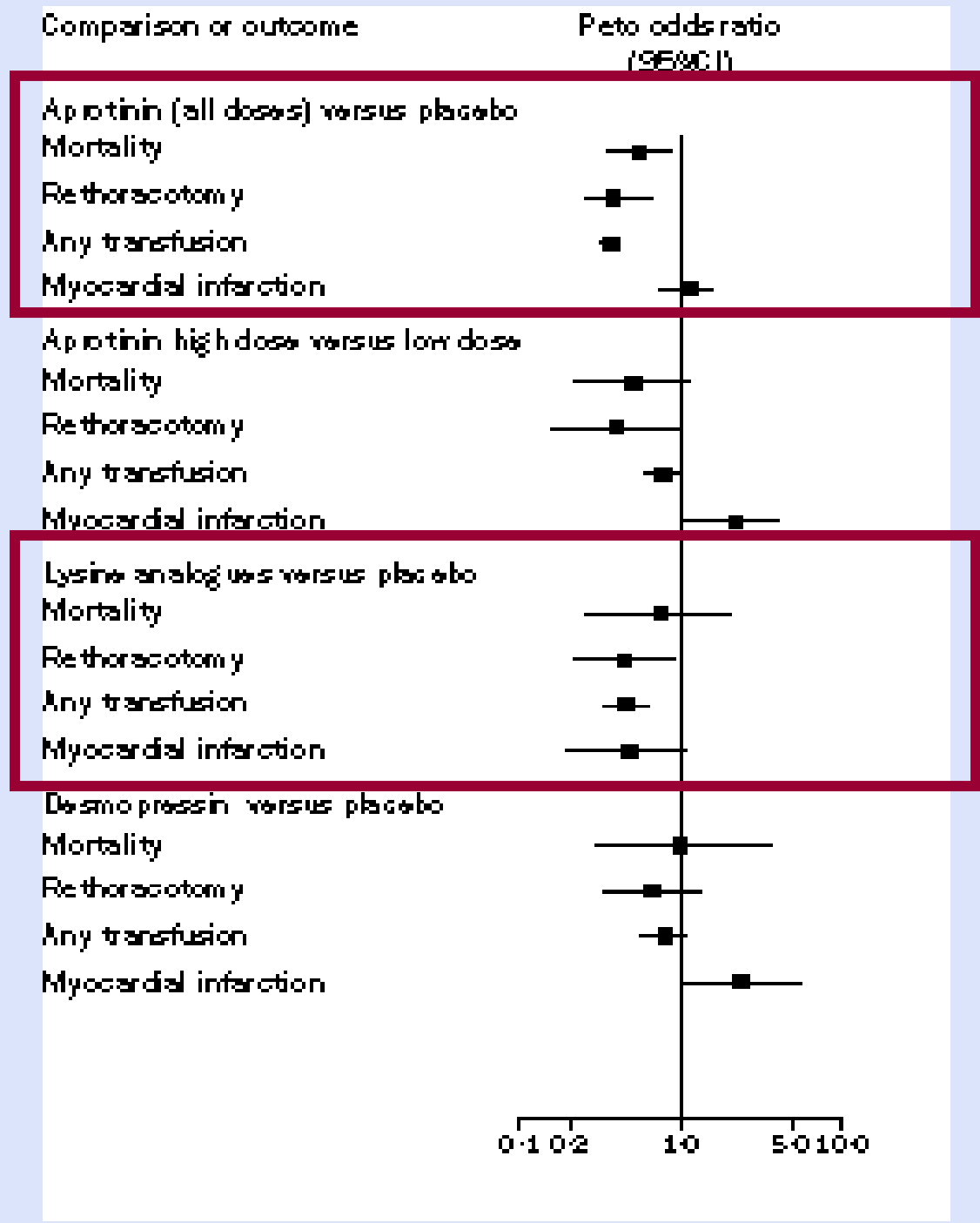
- Mortality RR=0.87, 95% CI 0.63-1.19
- Stroke: RR=0.43, 95% CI 0.16-1.19
- Renal failure: RR=1.19, 95% CI 0.79-1.79

Laupacis Systematic Review (Laupacis et al., 1997)

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

## Evidence of Renal Dysfunction/Failure (up to 2001)

- 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



Levi et al.  
Lancet, 1999

## As of 2001, what did we know?

- Antifibrics reduced transfusion compared to placebo/no control
- Head-to-head RCTs suggested TXA may be as effective
- Aprotinin placebo/open-label data suggested:
  - trend in benefit for mortality, re-op, and stroke
  - trend in an increase in renal dysfunction (not failure) and MI
  - data limited by a lack of reporting and/or adequate assessment
- Data remained an uncertain basis for replacing aprotinin with the cheaper lysine analogues in clinical practice
- All of above contributed to the need and design of BART

# *The BART Trial*

## Primary Question:

- Does aprotinin decrease massive postoperative bleeding by 3% (from 6% to 3%) in the initial 24 hours as compared to epsilon-aminocaproic acid or tranexamic acid in patients undergoing high-risk cardiac surgery?
- Secondary Outcomes (2 categories)
  - Fatal/life threatening (mortality, MI, stroke)
  - Serious morbidity (organ failure: kidney, lung, heart)

## Study Design:

- Randomized, double-blind, multi-centre randomized trial
- 3000 high-risk cardiac surgery patients

# Timeline

- Draft protocol written in 1999 and finalized in 2001
- Funded in 2001
- Enrollment began in September of 2002
- Based on DSMB recommendation, trial ended in October 2007 due to excess mortality in aprotinin arm

# 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)

NEJM, 2008

- **Aprotinin vs EACA: RR: 0.80 (95% CI, 0.59 to 1.07)**
- **Adjusted OR: 0.80 (95% CI, 0.58 to 1.11)**
- **Aprotinin vs TXA: 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 TXA: RR: 1.55, (95% CI, 0.99 to 2.42)
- Aprotinin vs EACA: RR: 1.52 (95% CI, 0.98 to 2.36)
- Aprotinin vs TXA or EACA: 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)

**Back to 2006**

**1 year prior to BART termination  
&  
2 years prior to publication**

# The publication of large observational studies

- Starting with Mangano, a number of large observational studies published since 2006
  - 5 compared aprotinin to “nothing”
  - 6 compared aprotinin to aminocaproic acid
  - 6 compared aprotinin to tranexamic acid
- Majority showed aprotinin increased serious morbidity and mortality
  - mortality, renal failure, stroke, and MI in particular
- Only a couple reported evidence of “effectiveness”
  - transfusion, re-ops for bleeding, massive bleeding, etc.

# The first and “most” influential (Mangano, NEJM 2006)

## Compared to receiving “nothing”, aprotinin:

- increased **renal failure** (OR= 2.59, 95%CI 1.36 to 4.95)
- increased **MI or Heart Failure** by 55% (P<0.0001)
- increased **stroke or encephalopathy** by 181% (p=0.0001)
  - **Above was inconsistent with RCT evidence in terms of either direction or magnitude of effect**

## Only “harm” presented

- No data on blood loss, proportion transfused, re-op rates, longer term mortality, massive bleeding
- This data is crucial for a meaningful comparison with RCT data

## Significant imbalances between the 2 groups were present

- CHF, renal disease, previous CABG, history of valve disease much higher in those that received aprotinin

## *Further observational studies after Mangano demonstrating harm*

- Mangano, JAMA 2007
  - Mortality with aprotinin increased compared to **no therapy**
  - Odds Ratio: 1.59 (0.76 to 3.34)
- Karkouti, Transfusion, 2006
  - Renal dysfunction increased from 17% to 24% (p=0.01) with aprotinin compared to **tranexamic acid**
  - Renal failure increased from 3.1% to 5.6% (p=0.08) with aprotinin compared to **tranexamic acid**
- Schneeweiss, NEJM 2008
  - Mortality with aprotinin increased compared to **EACA**
  - Propensity score-matched analysis: OR: 1.32 (1.08 to 1.63)
- Shaw, NEJM 2008
  - Mortality with aprotinin increased compared to **no therapy** or **EACA**
  - Hazard Ratio 1.32 (1.12 to 1.55)
  - Aprotinin associated with a larger risk-adjusted increase in the serum creatinine level (P<0.001)

# Concerns with the published observational studies

- Potential for significant confounding by indication
  - Patients that receive antifibs are different than those that receive nothing
  - Patients that receive aprotinin may be different than those that receive TXA or EACA
- Outcomes are confounded by patient prognosis, physician preference based on prognosis, and physician choices
  - can elaborate analysis account for these factors?
- Evaluating aprotinin versus “nothing” did not reflect the reality of antifibrinolytic practice in high-risk surgery
- Both potential risk and benefit data need to be provided

# Why we need to be concerned...

## Based on observational work

- Regulators placed alerts/warnings or suspended marketing authorization of aprotinin (before BART was stopped)
- Numerous lawsuits launched
- Aprotinin use decreased significantly
  - potential harm to those patients not offered alternative
  - what if no comparator?
- All of above impacted BART recruitment

Why was RCT evidence largely ignored or dismissed?

# Conclusions – Clinical

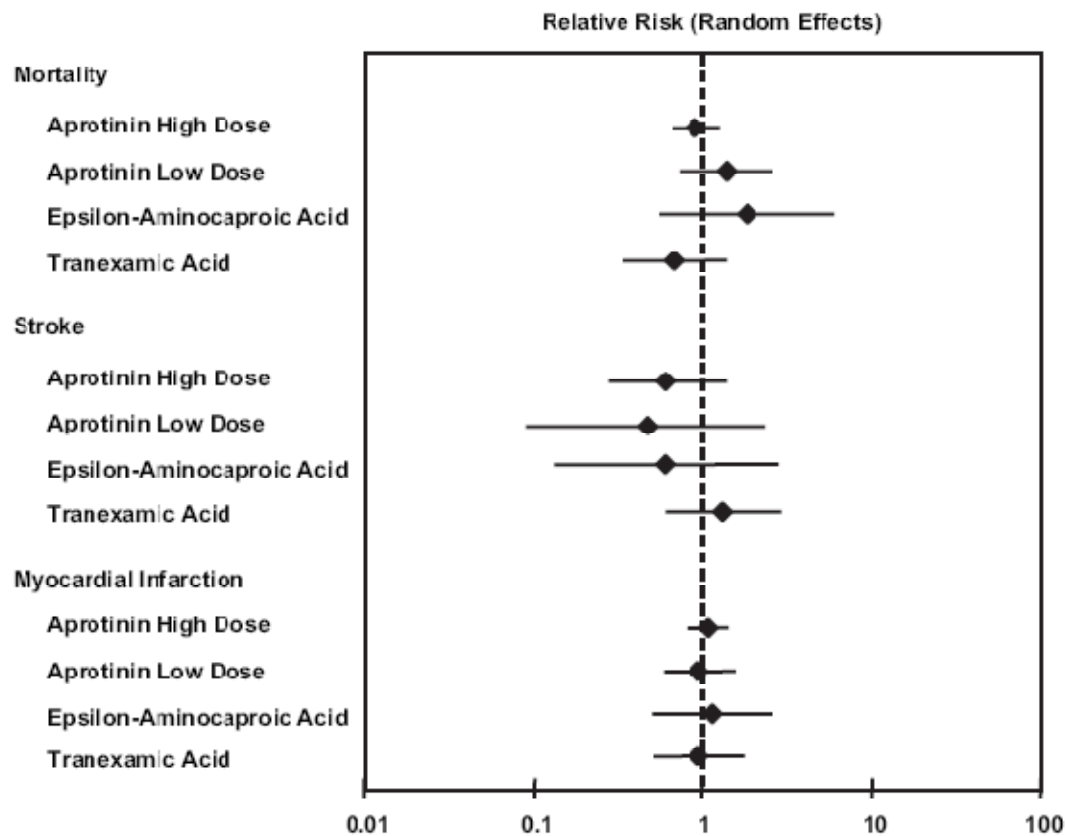
## What BART can help answer

- Effectiveness of aprotinin compared to TXA & EACA in terms of massive bleeding
- Safety of aprotinin compared to TXA & EACA in terms of mortality and serious morbidity
- Results applicable to a purposively chosen high-risk patient population

## What BART cannot help answer

- Safety of aprotinin compared to “nothing”
- Effectiveness (massive bleeding) of aprotinin compared to “nothing”
- Effectiveness and safety in low risk cardiac surgery (e.g. primary CABG)
- For the above, meta-analyses of RCTs remain the most robust estimates

## Brown et al., Circulation, 2007

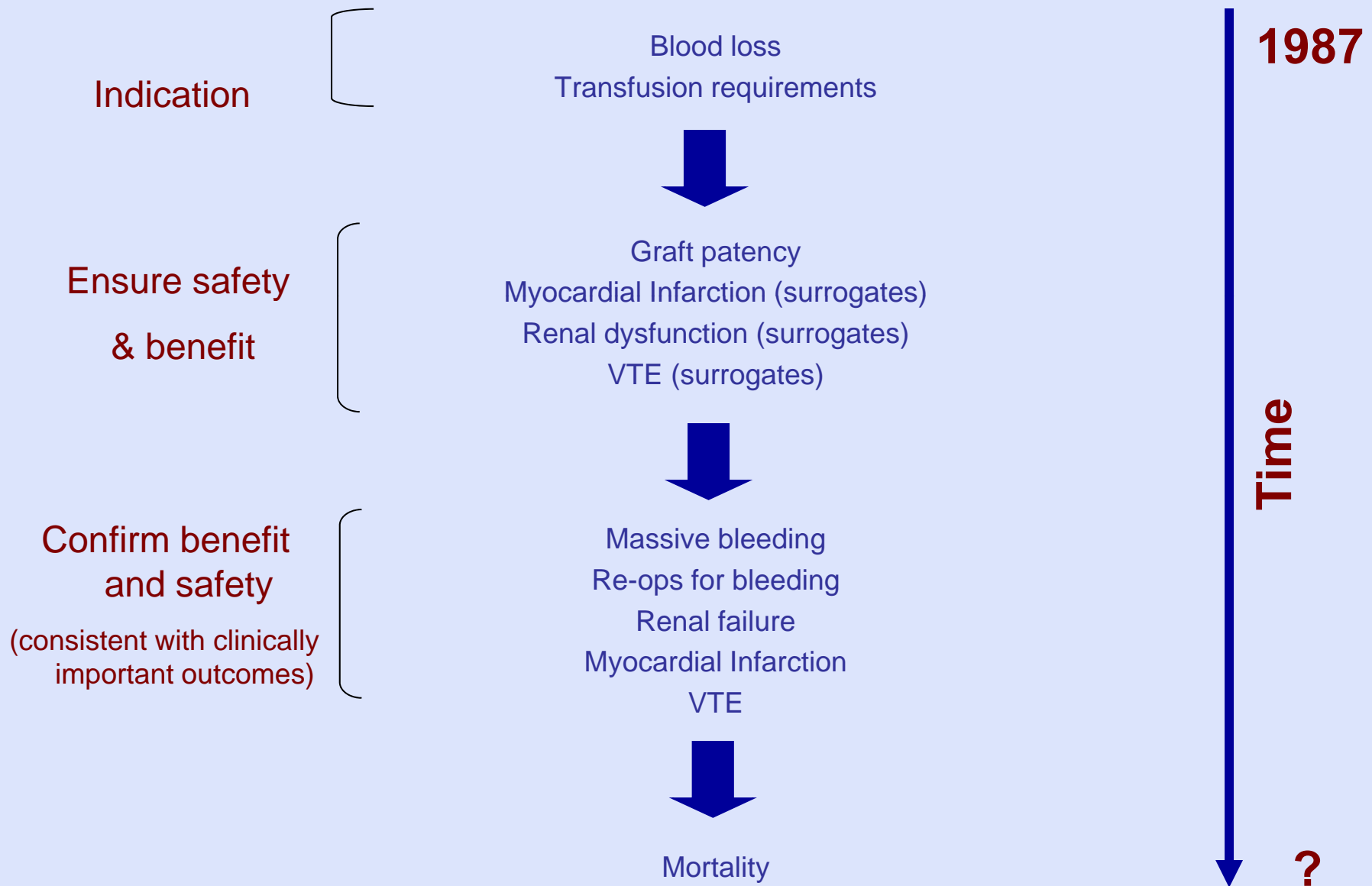


**Figure 4.** Adverse outcomes by antifibrinolytic agent compared with placebo. The RRs of adverse outcomes (mortality, stroke, and myocardial infarction) by antifibrinolytic agent vs placebo are plotted. The RR (diamond) and 95% CIs (horizontal bars) summarize the effect using a random-effects model. Effects left of 1.0 favor the antifibrinolytic agent over placebo; effects to the right favor placebo over antifibrinolytic agent. When the horizontal bars cross 1.0, the effect is not significantly different from the comparison group; this is the case for all agents for all adverse events (mortality, stroke, myocardial infarction) plotted here.

# Conclusions- Methods

- Choice of control is vital in both intervention & observational research (apples to apples/like with like)
- The threat of **confounding by indication** in acute care settings (surgery, ICU) requires thoughtful attention in comparative effectiveness research
  - Need to ensure that those patients receiving a treatment are “like” those that do not or those that receive an alternative
    - this is Epidemiology 101
- The reality is that **clinically important outcomes + greater treatment choices = larger trials**
  - thus, the leap to incorporating harms as a co-primary or secondary outcomes is not large

# A logical evolution of relevant and meaningful outcomes in Phase ≥III trials: the case of aprotinin in cardiac surgery

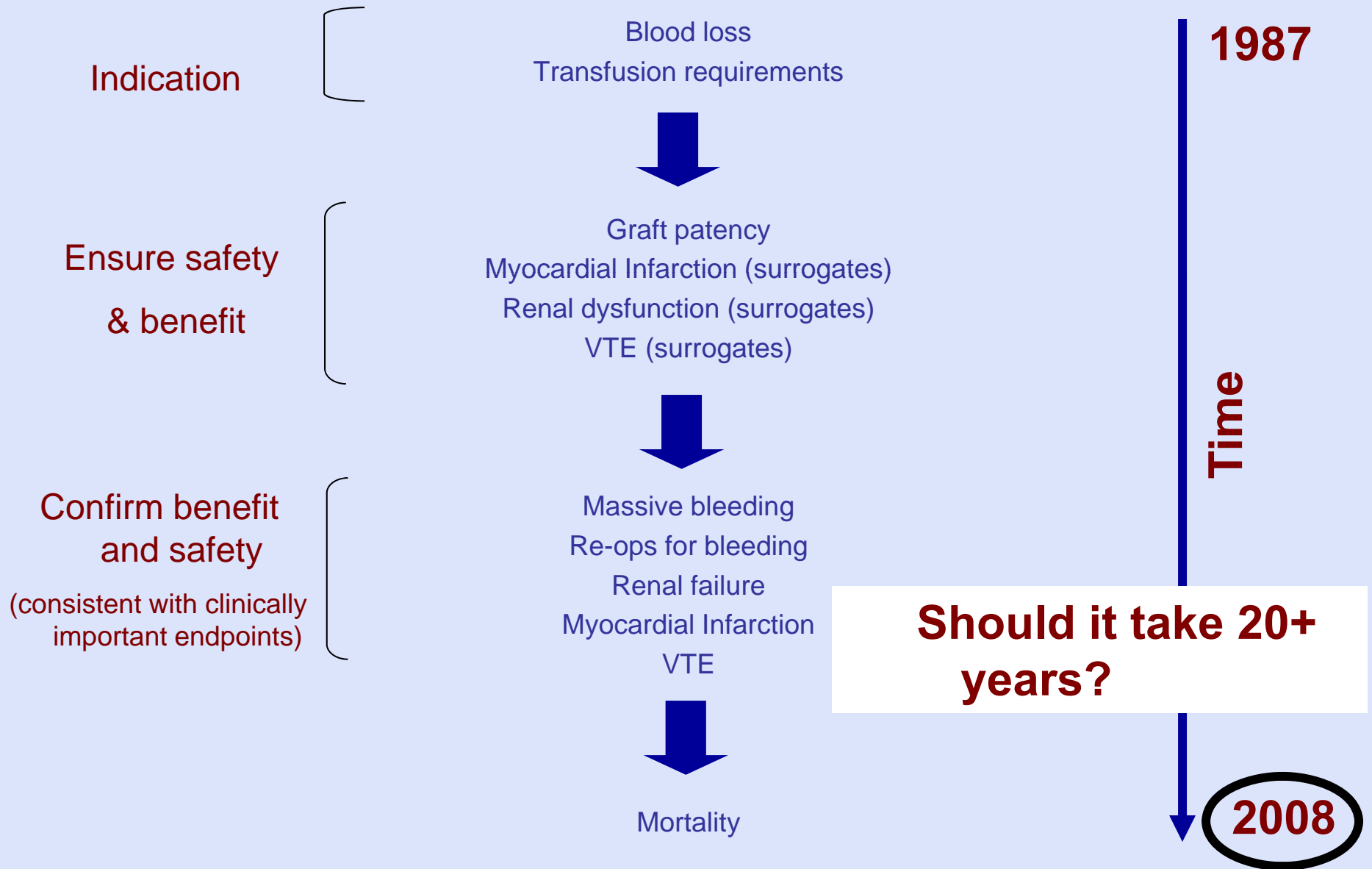


# Evidence from aprotinin trials 1987-2006

- 64 trials in total
- 49 (77%) had blood loss or transfusion requirements as the primary objective (1987 to 2006)
- 15 (23%) provided a primary an outcome or objective other than blood transfusion or blood loss
  - 9 evaluated graft patency/MI as a primary objective
  - 6 coagulation parameters
- No trial had the primary objective of assessing allergic reactions, massive bleeding, mortality, re-ops, or other serious thrombotic events

Fergusson et al., Clinical Trials, 2005

# A logical evolution of relevant and meaningful outcomes in Phase ≥III trials: the case of aprotinin in cardiac surgery



# Final Thoughts

- BART provides an example of why we need large trials with clinically important outcomes
- Rather than conducting many small RCTs and/or observational studies, we need to plan and conduct large rigorous trials to assess concurrently harms & benefits
- As per the last slide, timing is important
  - Regulators/Funders/Sponsors play an important role
  - 3000-patient comparator trial could have started enrollment in the late 1980s/early 1990s
    - Consider in light of the thousands of patients randomized to placebo in the numerous redundant small aprotinin trials