

# Antifibrinolytic Therapy: Evidence, Bias, Confounding (and Politics!)

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**Abstract:** Cardiac surgery can be complicated by postoperative bleeding and a need for blood transfusion and surgical re-exploration. Anti-fibrinolytic drugs such as aprotinin and tranexamic acid may reduce bleeding risks but could possibly increase thrombotic complications. Aprotinin, in particular, has recently been implicated in at least two large observational studies, but this could be because it is more widely used in high-risk cardiac surgical patients. Observational studies are prone to several important sources of bias, in particular, confounding by indication (high-risk patients are more likely to receive aprotinin

and more likely to have postoperative complications, irrespective of their exposure to aprotinin). Although multivariate adjustment and propensity score-matching can adjust for confounding, there is no certainty that it removes all such bias. For all anti-fibrinolytic drugs, it remains unclear as to whether the beneficial effect on reduced bleeding outweighs a possible increased risk of thrombotic complications. Debate will continue until we have the results of definitive large randomized trials powered to detect a clinically important effect on outcome. **Keywords:** anti-fibrinolytics, aprotinin, evidence, bias. *JECT. 2007;39:308–310*

Complications of cardiac surgery include the competing risks of thrombosis [myocardial infarction (MI), stroke, and venous thromboembolism] and excessive bleeding (1,2). Excessive bleeding after bypass is arguably the most common complication of cardiac surgery, and this can delay completion of surgery, tracheal extubation, and intensive care discharge (2). Some patients require surgical re-exploration. About one half of all cardiac surgical patients receive a blood transfusion, and ~10% of all blood transfusions are used in cardiac surgery (3). Anti-fibrinolytic drugs such as aprotinin and tranexamic acid (TxA) may reduce bleeding risks but could possibly increase thrombotic complications after cardiac surgery.

There is strong evidence from meta-analyses of randomized trials that anti-fibrinolytic therapy with aprotinin reduces blood loss and the need for blood transfusion and re-operation for bleeding in many types of cardiac surgery (4,5). However, there are anecdotal reports (6–11), findings from small trials (12–14), and large observational studies (15,16) to suggest that anti-fibrinolytic drugs increase the risk of myocardial ischemia and thrombotic complications such as graft occlusion, MI, and renal dysfunction. Although aprotinin is the most frequent anti-fibrinolytic drug implicated, there is also some concern with  $\epsilon$ -aminocaproic acid (8,13) and desmopressin (5).

A large retrospective observational study involving 4374 patients undergoing coronary artery bypass graft (CABG) surgery found that aprotinin was associated with increased risk of renal impairment, MI, stroke, and death (15). In a similarly designed study, Karkouti et al. (16) reported on 898 patients undergoing high bleeding risk cardiac surgery, comparing aprotinin with TxA. Unlike the previous study, they found comparable rates of MI in the two groups, however, they did identify an association between aprotinin and renal dysfunction.

These publications have received widespread coverage in the media and have been applauded (17) and criticized (18–20) in the medical literature. Observational studies are prone to several important sources of bias (21–23). Because there is a lack of random allocation to groups, observational studies require some method(s) of balancing factors that may affect the outcome of interest. A recently developed and increasingly used method is the propensity score (24). Here, regression techniques can be used to estimate the probability that, based on that individual's potential confounders, that individual would be in the intervention group or comparison group. If all patients with a similar treatment probability are batched, the actual treatment group approaches that of random allocation—that is, propensity scoring attempts to recreate a random decision process.

However, propensity matching cannot alleviate all bias

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and confounding. In the above studies (15,16), the clinical indication for using aprotinin (as opposed to TxA or no anti-fibrinolytic) could be directly correlated with increased risk of renal impairment and MI—in other words, high-risk patients are more likely to receive aprotinin and are more likely to have postoperative complications. This is called confounding by indication. Multivariate adjustment and propensity matching techniques can only adjust for known, measured factors—you cannot adjust for what you do not know or have not measured (23). An illustration of such methods can be found in a controversial study published in 1996 (25), whereby the authors concluded that the use of a pulmonary artery catheter in intensive care was associated with increased mortality and increased utilization of resources. Subsequent large randomized trials could not replicate the findings of the observational study that had used propensity scores to adjust for confounding (26,27).

There are inconsistencies in the Mangano data (20), and the results are not supported by other high level evidence. Three meta-analyses of randomized trials have found that anti-fibrinolytic therapy reduces blood loss, the need for blood transfusion, and re-operation for bleeding in many types of cardiac surgery (5,28,29). Levi et al. (5) did a systematic review and meta-analysis of 72 trials (8409 patients) of anti-fibrinolytic drug therapies. They found that there was a significant decrease in perioperative blood loss and blood transfusion, but also a beneficial effect on the need for re-operation and overall mortality. Specifically, treatment with aprotinin decreased mortality almost twofold [odds ratio (OR), 0.55; 95% confidence interval (CI): 0.34–0.90] compared with placebo. Treatment with aprotinin and with lysine analogs decreased the frequency of re-operation (OR, 0.37; 95% CI, 0.25–0.55 and OR, 0.44; 95% CI, 0.22–0.90, respectively). Aprotinin and lysine analogs did not increase the risk of perioperative MI, but desmopressin was associated with a twofold increase in the risk of MI. Recently, published guidelines from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists have critiqued the latest evidence and made up-to-date recommendations for use of anti-fibrinolytics in cardiac surgery (4).

However, despite the reassurance of numerous clinical trials, even pooled analyses (5,28,29) have insufficient power to identify uncommon but serious adverse outcomes from anti-fibrinolytic therapy (17). Subgroup analyses from a large multicenter trial suggested aprotinin could increase the risk of graft thrombosis in patients with poor distal coronary perfusion (12). Possible factors associated with increased thrombotic complications include insufficient heparinization (30), use of low-dose aprotinin (31), small caliber coronary anastomoses (30), anti-thrombin deficiency (32), and factor V deficiency (33). However, there is also evidence that aprotinin inhibits various pro-

thrombotic pathways and has anti-platelet activity (34). These mechanisms have been used to explain the reduction in cerebrovascular events seen with aprotinin in a meta-analysis of clinical trials (32). Also, aprotinin has been shown to reduce myocardial ischemia-reperfusion injury (35). TxA does not share aprotinin's capacity to inhibit thrombin production (36).

Anti-fibrinolytics are recommended for re-operative and other complex cardiac surgery. However, it is not yet clear whether these drugs provide any benefit beyond limiting blood loss (37) and, for aprotinin at least (4,5), re-exploration for postoperative bleeding. For all anti-fibrinolytic drugs, it remains unclear whether the reduced bleeding outweighs the risk of increased thrombotic complications.

At present, however, there is insufficient evidence to make any reliable statements regarding risks and benefits of aprotinin or TxA in most cardiac surgical procedures (29). Two ongoing large randomized trials should provide some answers (38,39).

#### **The Canadian BART Study**

This trial is studying blood conservation using anti-fibrinolytics in cardiac surgery (38). They are comparing aprotinin with the lysine analogs (TxA or  $\epsilon$ -aminocaproic acid) in 3000 patients. The primary aim is to measure the effect on excessive bleeding and need for blood transfusion.

#### **The Australian ATACAS Trial ([www.atacas.org.au](http://www.atacas.org.au))**

The ATACAS Trial is a randomized, double-blind, trial testing whether aspirin, TxA, or both can reduce mortality and/or major morbidity after CABG surgery (39). It is being conducted by the ANZCA Trials Group and is designed to answer two clinically important questions:

- i. Should aspirin be continued up until the day of CABG surgery?
- ii. Should TxA be used for all at-risk CABG surgeries?

The trial is recruiting 4600 CABG (on-pump or off-pump) patients, comparing TxA vs. placebo and aspirin vs. placebo, in a factorial design, aiming to detect a 30% or greater reduction in major complications or death ( $\alpha = 0.05$ ,  $\beta = 0.10$ ).

#### **CONCLUSIONS**

Anti-fibrinolytics reduce bleeding after cardiac surgery, and this probably reduces the need for blood transfusion (28,29). Possible thrombotic risks associated with aprotinin, such as MI and stroke, may or may not be shared by other anti-fibrinolytic drugs (29). Should anti-fibrinolytic therapy (aprotinin or TxA) be used more widely, selec-

tively, or not at all? Debate will continue until we have the results of definitive large randomized trials.

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